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Risk Assessment Of Cardiovascular Disease In Vitamin D Deficient Patients Visiting Tertiary Care Hospital, Peshawar, Khyber Pakhtunkhwa, Pakistan

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Abstract

Coronary illness (CVD) is as yet one of the greatest worldwide medical problems, so it's critical to completely comprehend the gamble factors that add to it. This study analyzes the connection between Low vitamin D levels and the risk of cardiovascular illness for ideal gastrointestinal calcium retention and bone mineralization, vitamin D is a fundamental Prohormone. The specific reasons for cardiovascular problems are as yet unclear, albeit a few Speculations remember direct impacts for the heart and vasculature, downregulation of the renin- angiotensin-aldosterone framework, and improved glycemic the executives. Tissues containing vitamin D receptors incorporate cardiomyocytes, endothelium, and vascular smooth muscle. There is mounting proof that proposes lack in vitamin D might be impeding to cardiovascular wellbeing. To study the result of vitamin D deficiency on cardiac enzymes. And to see whether vitamin D supplementation have any beneficial effect on the levels of cardiac enzymes in CVD patients.The data of vitamin D serum levels were collected form 120 patients that were diagnosed with cardiovascular disease. The data was divided into two main groups that is G1 (low vitamin D levels)G2 (normal to high vitamin D levels) The study reveals a concerning frequency of vitamin D deficiency among cardiac patients, with 68% exhibiting low levels. In contrast, a smaller but notable percentage, 15% of patients, demonstrated ptimal vitamin D levels. This research shows a high correlation between incident and common cardiovascular disease risk factors and vitamin D levels and consequences, as well as a significant frequency of vitamin .D deficiency in the general healthcare population

Introduction

Vitamin D has generally been connected to the metabolism of bones. It is fundamental for protecting

calcium homeostasis by working with the stomach's physiologic retention of calcium. The assurance
of the vitamin D receptor's far and wide articulation (VDR) in practically every sort of human cell,
including immunological, vascular, and heart cells, suggests that vitamin D-interceded impacts
stretch out past outer muscle tissues. Subsequently, there has been a lot of study done on vitamin D's
conceivable job in the etiology of various constant non-skeletal issues, including malignant growth,
immune system and viral illnesses, and cardiovascular sicknesses (CVD). (Cosentino et al, 2021).
The normal illnesses and driving reason for death universally, especially in Western countries, are
cardiovascular (CV) issues like myocardial localized necrosis, coronary conduit sickness, or stroke,
as well as CV risk. This features the meaning of explaining vitamin D's capability corresponding to
CVD. (Oberoi, D et al, 2019).

Historical perspective

In 1922, McCollum et al. observed that vitamin D was the treatment for rickets, a bone condition
that causes skeletal irregularities and bone uneasiness in young people. The advantages of daylight
in lessening rickets were known well before McCollum's revelation of vitamin D. The 1930s saw
the explanation of the atomic designs of nutrients D2 and D3. The designs of 1, 25(OH) 2 D and
25(OH) D were portrayed in the mid-1970s and late 1960s, separately. Reports about vitamin D
excess, especially in youths, during the center of the twentieth century cast uncertainty on the
nutrient, and up until the 1970s, some figured it might try and be the reason for CVD. Robert Scragg
proposed in 1981 that low UV-B illumination and a correspondingly low vitamin D status throughout
The colder time of year might be the reason for the higher predominance of CVD.

Metabolism and physiology of vitamin D

At the point when vitamin D is consumed, it is joined with chylomicrons, which are then taken up
by the lymphatic framework and circled. Nutrient D2 from the food and nutrient D3 from skin blend
tie to egg whites and vitamin D restricting protein (DBP). Vitamin D is conveyed to the liver, where
25(OH) D is created by vitamin-D-25-hydroxylases, and 1, 25(OH) 2D is delivered by 25-
hydroxyvitamin D-1α inside the liver. After 1, 25(OH) 2D isolates from DBP and courses in the
flow, it ties to the intracellular atomic vitamin D receptor, where it can play out various physiological
assignments and control its own levels. While Keratinocytes express 1, 25-hydroxycholecalciferol

and 1α-hydroxylase (CYP27B1) and 25-hydroxylase (CYP27A1) in the epidermis, in spite of the
way that the liver and kidney are the essential organs answerable for blending 1, 25-
hydroxycholecalciferol and 25-hydroxycholecalciferol. Notwithstanding, since the covering is the
objective tissue and is where vitamin D causes development capture and animates keratinocyte
separation, the skin's capacity to make 1,25(OH)2 D3 is restricted. (Aljack, H., Abdalla, M. 2019).

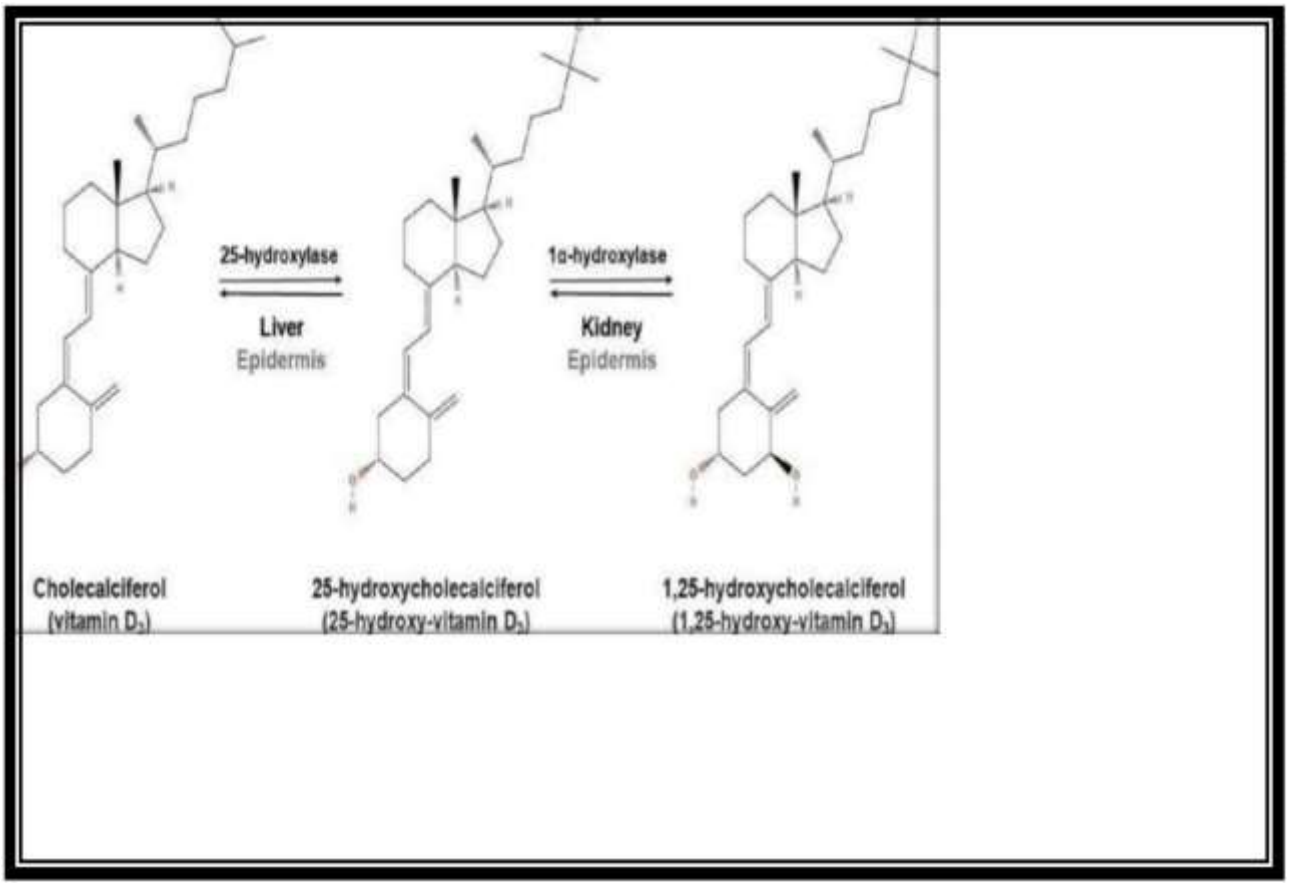

Figure 1.1: Metabolism of vitamin D

Graph shows how people produce 1, 25-hydroxy-cholecalciferol, frequently known as 1, 25-
hydroxyvitamin D3. Nutrient D3, cholecalciferol, is first different to 25-hydroxycholecalciferol by
25-hydroxylase. In the liver and kidney, 1α-hydroxylase thusly changes over this 25-hydroxyvitamin
D3 to 1, 25-hydroxycholecalciferol (1, 25-hydroxyvitamin D3). Regardless, both of the two
reactions can happen in the skin. (Savanelli, M. C., et al 2016)

VDR is available in basically all human tissues and cells, with the biggest amounts being found in
tissues associated with calcium homeostasis. Moreover, different tissues and cells have 25(OH) D
movement which empowers the kidney to wipe out 1, 25(OH) 2D. Certain components, like the phase of cell development or provocative flagging atoms, control the chemical in specific tissues. 1,

25(OH) 2D can likewise be catabolized by extra-renal tissues When 1, .25(OH) 2D enacts vitamin
D receptors, both genomic and non-genomic pathways in these tissues are significantly actuated
organically. (Porto, C. et al, 2018).

Grouping of vitamin D deficiency

The half-life of 25(OH) D, which is utilized to characterize vitamin D status in the blood, is two to
about a month. The Establishment of Medication (IOM) report orders vitamin D lack as indicated
by levels under 12 ng/mL (increase by 2.496 to change over ng/mL to nmol/L) and 20 ng/mL as
adequate, while the Endocrine Society Rules propose that degrees of 25(OH) D <20 ng/mL are
insufficient and levels of 30 ng/mL are adequate. These classes basically center around results
connected with bones since there is as of now inadequate information to give suggestions on CVD
or other persistent problems. (Sun, H., Long S.R., 2019).

Prevalence rate of vitamin D deficiency

It is regularly perceived that vitamin D deficiency and insufficiency are successive; as a matter of
fact, levels of under 30 ng/mL are found in over portion of the world's population. (AL Mheid, I., et
al 2017). Many factors should be thought about while surveying the risk of lack of vitamin D, like
maturing, female sex, hazier skin pigmentation, less sun openness, occasional vacillations, and
distance from the equator. Changes in way of life, less time spent in the sun, and, less significantly,
air contamination are the primary drivers of the expanded pervasiveness of low vitamin D levels.
(Hiemstra,T et al 2019). It ought to be referenced that past investigations of 25(OH) D levels among
research facilities and between tests showed a significant level of heterogeneity in the revealed
results. Hence, this features the requirement for normalizing 25(OH) D estimations and issues an
admonition against looking at vitamin D level and there shorts got from different examination.
(Zitterman, A et al 2021).

Sources of vitamin D

Sunlight

The fundamental and regular wellspring of vitamin D is sun openness. Your skin makes vitamin D
when it is presented to daylight. The sun's UVB beams make the skin begin creating vitamin D.
Contingent upon their skin type, the hour of day, and their area, many individuals can get by with
only 10 to 30 minutes in the sun a few times each week. (Nitsa, A., Toutoutza, M. 2018).

Fortified Foods

A few food sources are invigorated with vitamin D to assist with people meet their everyday prerequisites. Normal invigorated food varieties include:

Milk and Dairy Items: Numerous dairy items, like milk, yogurt, and a few cheeses, are frequently strengthened with vitamin D.

Orange juice: A few brands of squeezed orange are invigorated with vitamin D.

Cereals and Breakfast Food sources: Certain grains and breakfast food sources might be sustained with vitamin D. (Costanzo, S et al, 2018).

Supplements

There are a few unique kinds of vitamin D enhancements available, like nutrient D2 (ergocalciferol) and vitamin D3 (cholecalciferol). The ideal structure is D3, as it brings vitamin D steps up in the blood more actually than different structures. (Wang, T., Sun, H., 2019).

Ideal Levels of vitamin D

The ideal level of vitamin D can change, yet a typical reference range for complete 25-hydroxyvitamin D (25(OH) D), is frequently viewed as between 20 to 50 ng/mL (or 50 to 125 nmol/L). However, ideal levels can rely upon individual medical issue (Nalbant, A. t al 2017).

Testing of vitamin D level

Testing for vitamin D levels typically involves measuring the concentration of 25-hydroxyvitamin D in the blood. This test is known as the 25(OH) D blood test. Vitamin D is important for bone health, immune function, and overall health. The test can help diagnose vitamin D deficiency, determine the severity of the deficiency, and guide treatment decisions. (Verdoia, M. et al 2021).

Preventive strategies for vitamin D deficiency

Hypothetically, there are a few methodologies of improving the vitamin D level of the people who are in danger. Without an inquiry, openness to UVB beams from the climate is the essential normal wellspring of vitamin D. Hence, week by week UVB openness ought to be a standard piece of drives to upgrade vitamin D levels. (Gachemba, Y. M et al 2022). For the individuals who can't invest a lot of energy outside or who find it challenging to get vitamin D from sun openness, vitamin D-rich food sources and enhancements are particularly useful. (Cubbon, R.M et al 2019).

Disease prevention

25(OH) D concentrations should be at least 75nmol/l in order to prevent diseases. (Jorge, A. J. L 2018).

Diseases related with vitamin D deficiency

Lack of vitamin D can add to different medical conditions, as vitamin D assumes a significant part in a few physiological capabilities inside the body. Here are a few infections and conditions related with lack of vitamin D. (Wimalwansa, S. J et al 2018).

Osteoporosis and Osteopenia

Vitamin D is fundamental for calcium ingestion, and lacking levels can prompt diminished bone mineral thickness, expanding the risk of osteoporosis (fragile bones) and osteopenia (lower than typical bone thickness). (Alghamdi, S. J. H., Omer, E. O 2020).

Rickets

Rickets is a youth sickness portrayed by delicate, weak bones. It's principally brought about by a deficit vitamin D, calcium, or phosphate. Vitamin D is significant for the legitimate mineralization of developing bones. (Ghassab, O. K et al 2021).

Osteomalacia

Osteomalacia is a condition in grown-ups described by softening of the bones, prompting torment and muscle shortcoming. It is many times brought about by an extreme and delayed lack of vitamin D. (Musogiuri, G., Annweiler. C 2017).

Muscle Weakness and Pain Lack of vitamin D has been connected to muscle shortcoming and agony, and it might add to conditions like myopathy and fibromyalgia.

Increased Risk of fall and Fractures

Low vitamin D levels have been related with an expanded risk of falls and cracks, especially in more seasoned group. (Musogiuri, G., Annweiler. C 2017).

Type 2 Diabetes

There may be a connection in between vitamin D insufficiency and a higher chance of type 2 diabetes, according to certain research. Still, further investigation is required to make a firm link.

Cardiovascular Disease

The conceivable connection between vitamin D inadequacy and cardiovascular problems is as yet being examined. Low vitamin D levels have been connected in specific examinations to an expanded risk of coronary illness. (Wang, T. J. et al 2008).

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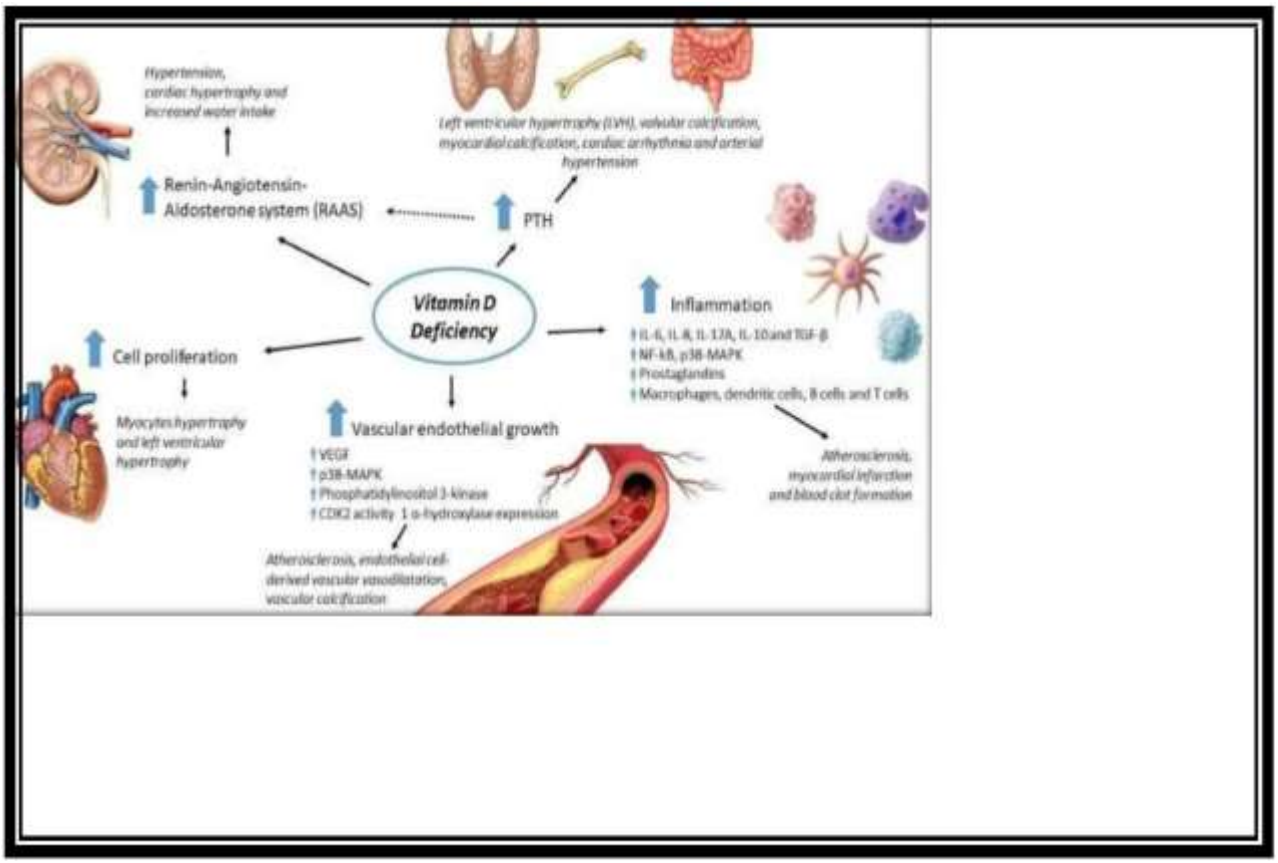

Figure 1.2: Vitamin D deficiency

Cardiovascular disease

A gathering of sicknesses that influence the heart or veins is alluded to as cardiovascular infection
(CVD). A general word incorporates various sicknesses, and it is a main worldwide reason for
morbidity and mortality. (Soh, V et al 2021).

Vitamin D and Stroke

An interference of blood stream to the mind, whether from bleeding (hemorrhagic stroke) or
impediment (ischemic stroke), brings about a stroke. (Anderson, J. L., May, H. T 2010).

Vitamin D and Peripheral Artery Disease (PAD)

The vascular wall may likewise incorporate vitamin D receptors, showing that vitamin D lack might
add to the etiology of blood vessel illness Low vitamin D level was connected to a speedier
weakening in practical exhibition in individuals with fringe vascular sickness, yet not to death.
(Levin, A., & Li, Y. C. 2005).
In people with occlusive and aneurysm tic corridor sickness, vitamin D deficiency was essentially successive, autonomous of laid out cardiovascular gamble factors. Furthermore, it showed a
significant relationship with the level of vascular sickness and atherosclerotic markers, including

carotid supply route, lower leg brachial record, and high touchy C responsive protein. (Verdoia, M.,
et al 2021). It was recommended that an autonomous blood vessel wall activity intervenes the
relationship between low vitamin D level and vascular illness. Serious lack of vitamin D prompts a
fiery climate and a debilitated versatile safe reaction, which thusly advance insulin obstruction and
vascular brokenness. (Judd, S. E., & Tangpricha, V. 2019).

Arrhythmias

These are irregularities in the heart's beat, for example, atrial fibrillation or ventricular tachycardia,
which can build the gamble of stroke or cardiovascular breakdown. (Siadat, Z. D., Kiani,
K.2012).

Vitamin D and Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone framework (RAA) controls extracellular liquid volume balance
in light of aldosterone discharge and vascular opposition due to the development of angiotensin II.
(Nemerovski, C. W., et al 2009). Various examinations led on people and creatures have shown that
vitamin D smothers the creation of the renin quality by means of bringing down RAA movement.
By means of a cis-DNA component in the renin quality advertiser, vitamin D represses the RAA
framework and controls the qualities engaged with renin union. (Kheiri, B., et al 2018).

Atherosclerosis

Since the VDR is expressed in the vasculature, one could be enticed to guess that vitamin D may
likewise offer security against vascular sicknesses, like endothelial brokenness and atherosclerosis.
(Mozos, I.,&Marginean, O, 2015). In light of exploratory review, vitamin D might have a few
potential vasculoprotective advantages by means of advancing nitric oxide (NO) age, restraining the
development of macrophage froth cells, or lessening endothelial cell grip particle articulation. This
is in accordance with results from observational examinations that connected diminished vitamin D
levels and endothelial brokenness to expanded blood vessel firmness. (Kienreich, K., et al 2013).
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Vitamin D Receptors in Cardiovascular Tissues

Vitamin D is engaged with the guideline of calcium and phosphate digestion, and it has receptors in different tissues, including the cardiovascular framework. Studies recommend that vitamin D might assume a part in vascular wellbeing, circulatory strain guideline, and the counteraction of atherosclerosis. (Drechsler, C., Pilz, S., 2010).

Vitamin D and Atrial Fibrillation

Vitamin D might raise the risk of atrial fibrillation (AF) through direct consequences for the chamber or aberrant control of cardiovascular risk factors. Irritation, which is connected to low vitamin D levels, has an urgent impact in the etiology of AF (Pilz, S., Gaksch, M., 2013). As a matter of fact, it has been seen that patients with Raised C-receptive protein readings had a two-overlap expanded possibility of creating AF. Besides, in light of the fact that RAAS enactment influences both underlying and electrical atrial redesigning as well as the guideline of fiery reactions, low vitamin D levels might raise the gamble of a (AF). Low vitamin D are consequently connected to a further developed phase of left atrial fibrosis. (Scragg, R., Stewart, A. W., 2017).

Mechanisms for the cardiovascular effects of vitamin D deficiency

The consequences of preclinical and clinical examinations showing the advantageous impacts of vitamin D and its analogs on fibrinolysis, blood lipids, thrombogenicity, endothelium recovery, and smooth muscle cell expansion were validated by late countrywide investigations. These examinations likewise showed an interaction between significant cardiovascular risk factors and truncated 25(OH) D levels. These discoveries propose that 25(OH) D might have medical advantages, some of which might be related with the cardiovascular framework, that are inconsequential to calcium digestion. (Hashemi, S. M et al 2015). The preventive impact of calcitriol on blood vessel calcification and atherosclerotic sores might be credited to various systems. In the first place, vitamin D receptors are communicated by vascular smooth cells. With a sudden calcium imbuement into the cells, calcitriol forestalls the expansion of these cells. Also, raised serum parathyroid chemical (PTH) levels are the outcome of low calcitriol levels. Because of expanded heart contractility and myocardial calcification, overabundance PTH levels may, to some extent partially, add to cardiovascular sickness. Third, research on mice has exhibited that calcitriol hinders

the arrival of provocative cytokines such IL-6, IL-10, and tissue putrefaction factor-α (TNF-α). There
is developing proof nowadays that fiery components are significant to the vascular affront's turn of events.
Fourth, the rennin-angiotensin-aldosterone framework (RAAS) is adversely directed by calcitriol,
an endocrine go between. The control of circulatory strain, electrolytes, and volume hemostasis is to
a great extent subject to the RAAS. Treatment with calcitriol brings down angiotensin II levels,
plasma rennin movement, and pulse. Fifth, vascular calcification might be worked with by
osteogenic processes and the relocation and multiplication of vascular smooth muscle cells, which
may at last prompt thrombogenesis. 6th, vitamin D affects insulin responsiveness and is related with
metabolic condition and diabetes. (Alkhatatabeh, M. J., et al 2017).

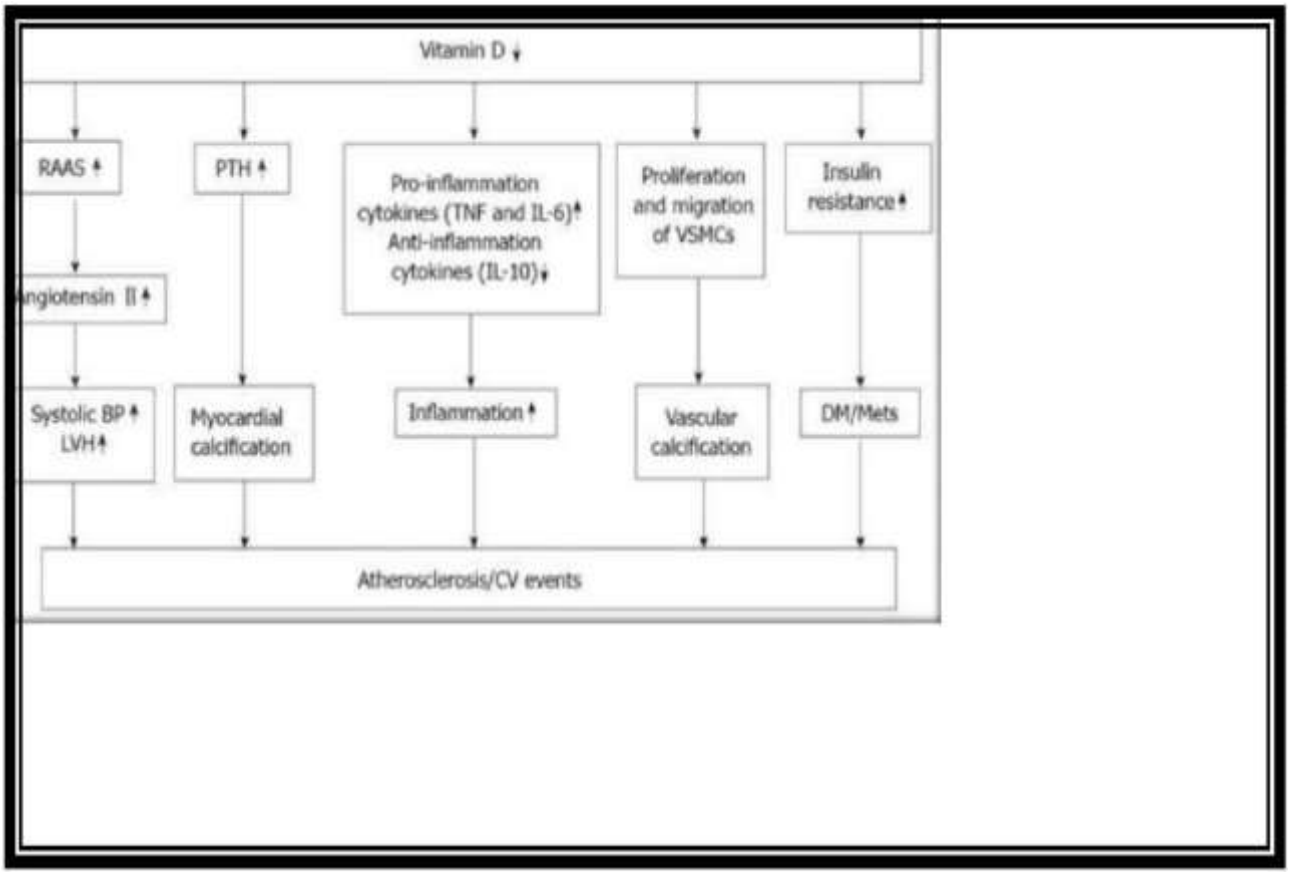

Figure 1.3: Mechanisms for the cardiovascular effects of vitamin D deficiency

The progressions in the calcium digestion of cells and the framework are connected to fundamental
hypertension. There is an expansion in intracellular cytosolic calcium focuses yet a reduction in
extracellular ionized or ultrafiltrable calcium levels. Hypertensive subjects will quite often lose more
calcium through renal discharge and consume less calcium through diet than individuals with
standard pressure. (Ruwanpathirana, T., Reid, c. M., 2014). Concentrates on in the study of disease

transmission have shown that there is a negative relationship between diastolic circulatory strain and
serum 25(OH) D levels. Controlling 5 μg of vitamin D every day to normotensive patients didn't
modify their pulse in clinical preliminaries. Then again, some exploration has shown that giving
hypertension patients 0.75 or on the other hand 1.0μg of vitamin D/d will bring down pulse. At the
point when 20μg of vitamin D/d was taken on a transient premise, diastolic pulse was emphatically brought down. Patients with moderate hypertension showed a lessening in both the diastolic and
systolic circulatory strain following a month and a half of UV-B openness. Apparently reestablishing
expanded intracellular calcium levels to predictability is an urgent move toward bringing down
circulatory strain, which assists with making sense of why calcium-channel blockers are useful for
hypertensive people. (Dziedzie, E. A., et al 2021). Diminished adenylate cyclase movement can
prompt a development of intracellular free calcium, a lessening in calcium re-take-up into the
sarcoplasmic reticulum, and an expansion in pulse and vascular reactivity. Since intracellular
adenylate cyclase action is calcitriol-reliant, expanding the chemical's action might bring down the
measures of free cell calcium. (Sunbul, M., et al 2015).
Significant risk factors for the improvement of arteriosclerosis incorporate hyperlipidemia, diabetes,
and an expansion in blood clotting factors, blood thickness, and leukocyte sums. Arteriosclerosis is
increasingly more obviously demonstrated to be a poor quality foundational incendiary infection.
(Mirhosseini, N., Rainsbury, j., 2018). Raised degrees of serum C-receptive protein act as a huge
indicator of both provocative reactions and the probability of creating arteriosclerosis. The
development of C-responsive protein is constrained by TNF-α, IL-6, and IL-10. IL-6 and IL-10 have
been displayed in creature examinations to hurry arteriosclerosis. In vitro, calcitriol can portion
conditionally restrain the arrival of IL-6 and TNF-α.in human people between TNF-α and 25(OH)
D levels. (Nourouzi, H., Ziaie, N., 2019).

Renal Implication of Vitamin D Deficiency Related to Cardiovascular Pathology

The kidneys are engaged with the creation of the metabolically dynamic type of vitamin D since
they are the site of the subsequent hydroxylation, which is started by parathyroid chemical.
Phosphate levels impact the renal hydroxylation of vitamin D through adverse criticism circle.
Shortages in 1, 25-dihydroxyvitaminD affect the calcium, phosphate balance in people with renal

hindrance. Patients with constant renal sickness have a higher risk of cardiovascular issues when
contrasted with those with ordinary kidney capability. Besides, it has been shown that there are
numerous relationship between lacking vitamin D and poor CV results in patients with renal
sickness. (Bouillon, R. et al 2019).
Low-slung vitamin D levels and high parathyroid chemical were related with mortality in patients
with constant renal ailment, generally because of cardiovascular causes. While thinking about
dynamic vitamin D, (J-DAVID), a randomized preliminary with the subsequent essential results in
hemodialysis patients: coronary mediations, lower appendage vein mediation, and cardiovascular
occasions that are deadly or nonfatal, will most likely give significant data about cardiovascular
occasions in patients with stage 5 constant kidney sickness. Also, vascular calcifications were
tracked down in tentatively uremic rodents with low vitamin D levels. Patients with stage 5 ongoing
renal illness are related with an expanded gamble of cardiovascular mortality. (Mihos, C. G., et al
2017).
The utilization of warfarin, treatment for renal osteodystrophy, and different components of the
uremic milieu may all play a part in the beginning of this disease. Patients with persistent renal
disappointment who were vitamin D insufficient showed weakened stream intervened dilatation and
expanded atherosclerotic injuries with blood vessel hardening. (Cortese, F., et al 2022)

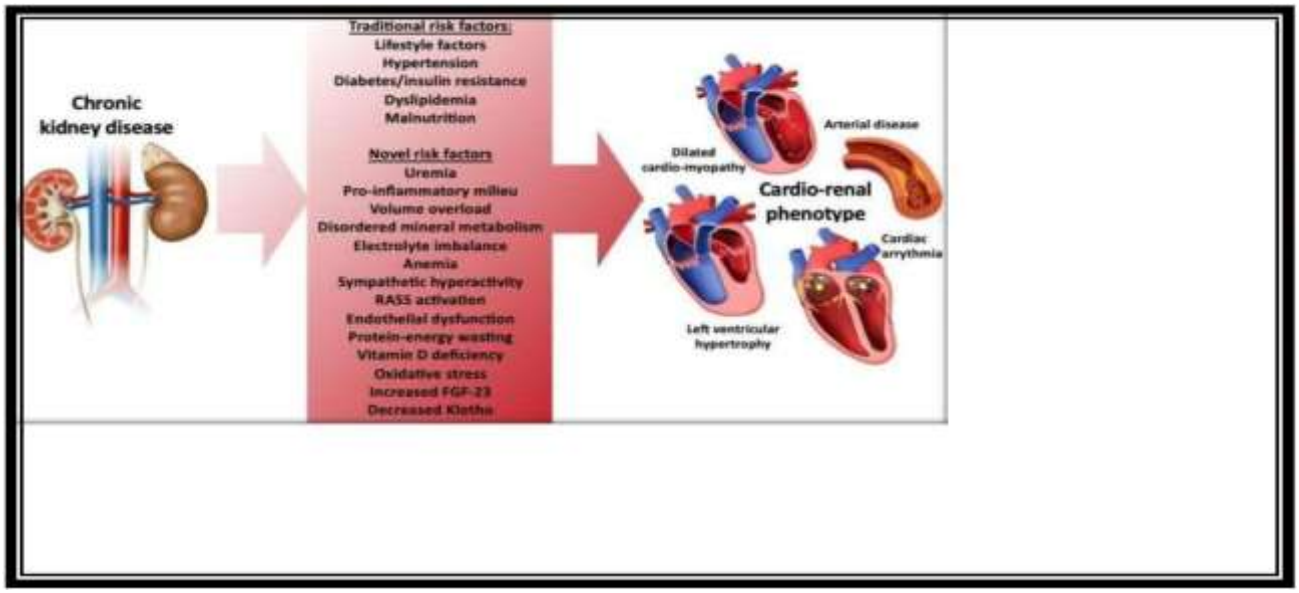

Figure 1.4: Chronic Kidney disease related to cardio renal phenotype

Molecular effects of vitamin D on the myocardium
Vitamin D likewise controls the outflow of myosin, a critical contractile protein of the myocardium.

These consequences for myosin quality articulation might be mostly liable for the connections
tracked down in rodents between vitamin D status and heart contractility. Besides, a review
exhibiting that vitamin D is essential for ideal mitochondrial capability in chicken hearts shows that
vitamin D controls the energy digestion of the heart. (Nemerovski, C. W., et al 2009).

Direct effect of vitamin D on myocardial structure

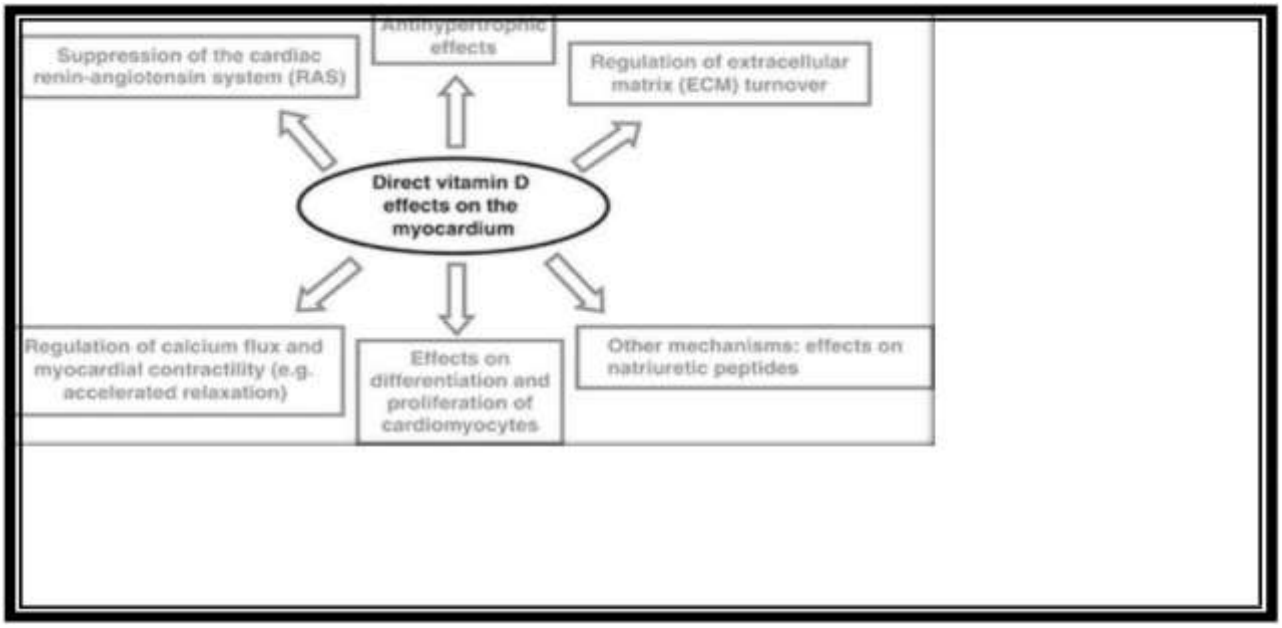

Figure 1.5: Direct vitamin D effects on the myocardium.

Effects of vitamin D indirectly on the heart.

By several indirect impacts on the myocardium, vitamin D lack may likewise be connected to
myocardial ailments. These results remember disturbances for calcium homeostasis, conventional
cardiovascular risk factors, atherosclerosis, contaminations, or immune system processes.

Figure 1.6: Effects of vitamin D indirectly on the heart.

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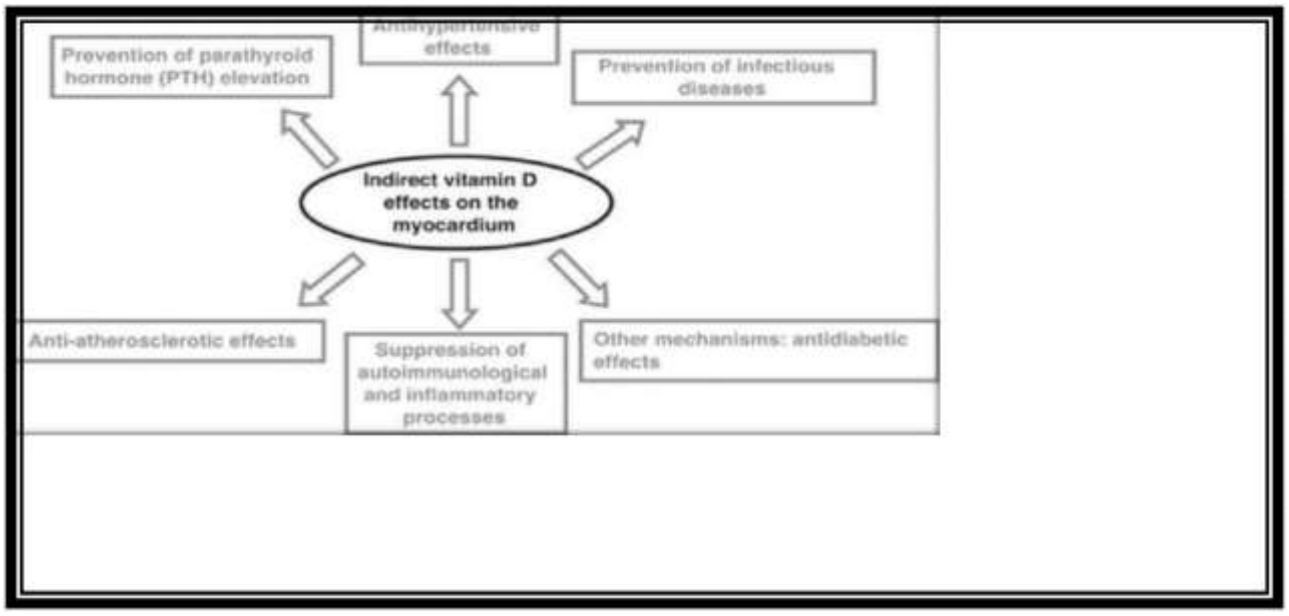

CHAPTER 2
MATERIAL AND METHODS

Study design
Data were randomly gathered as part of a randomized control trial to observe the association between vitamin D insufficiency and heart disease.

Study site
The research was done in the cardiac departments of two tertiary care hospitals in Peshawar, the Hayatabad Medical Complex (HMC) and the Khyber Teaching Hospital (KTH).

Study duration
The study was directed from 28 September 2023 to 25 January 2024 in cardiac department.

Study approval
The study was permitted by the Ethical committee of the above-mentioned hospitals. Informed consent was required from all the subjects who contributed in the study keeping ethical considerations and privacy of data in sight.

CERTIFICATE OF CONSENT
Mr. /Ms.: Resident of have read the
questionnaire given to me:
I allow them to ask any question about the research. I will properly answer and voluntarily
participate in the research.
Date:
Signature:
Thumb print:

Study population
This study includes sample of 120 individuals with cardiovascular disease, spanning all age groups
and gender
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MTI - HAYATABAD MEDICAL COMPLEX
OFFICE OF THE CHAIRMAN
Hospital Research and Ethical Committee (IREB)

Doc. No:	HMC-QAD-F-XX
Version No:	00
Date:	6/9/2022

APPROVAL CERTIFICATE

The Ethical Review Board of the Hayatabad Medical Complex has reviewed the under mentioned Synopsis/Article in accordance with the declaration of Helsinki (2013) and found it to meet the requirements and be approved.

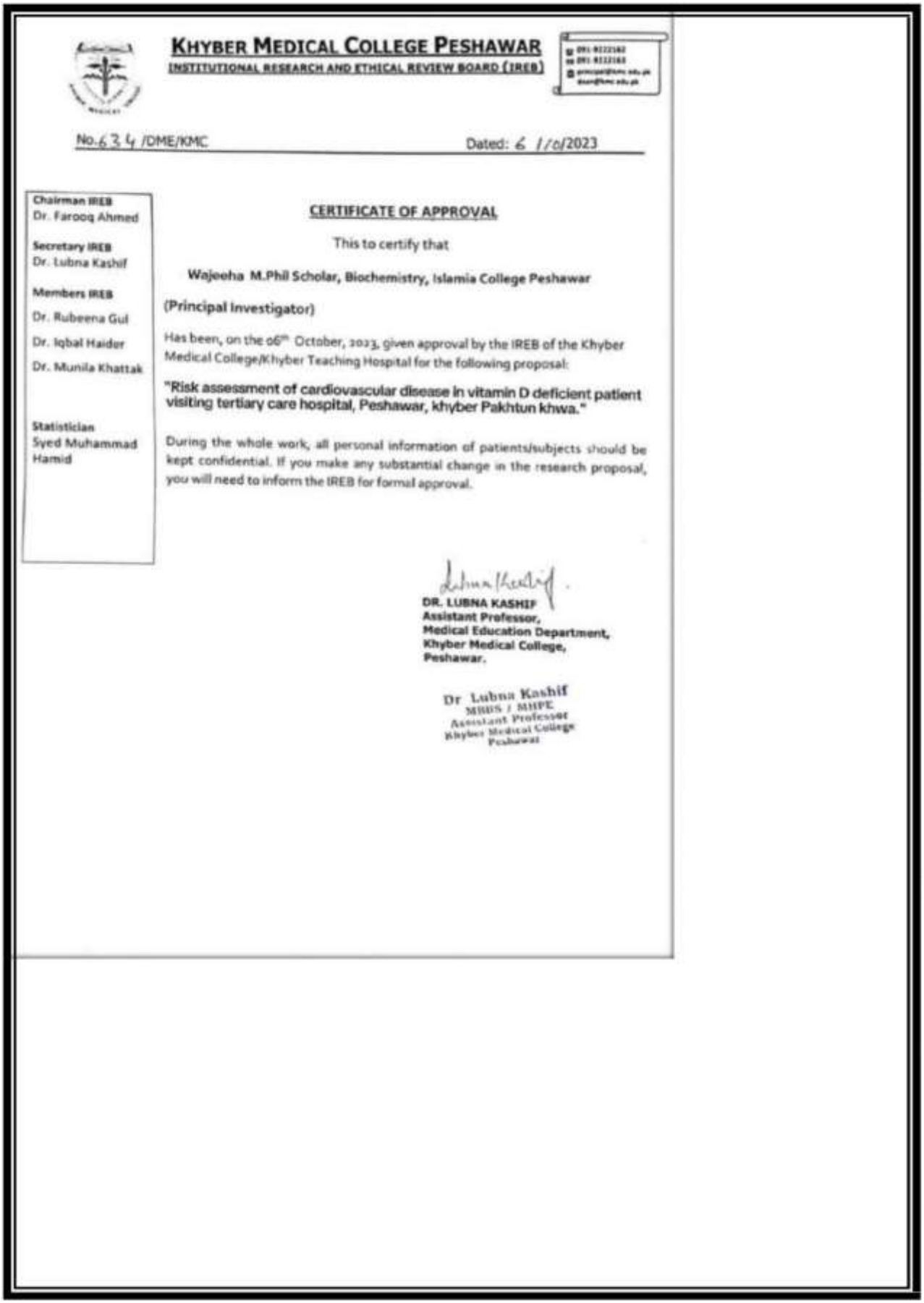
Approval No:	**1592.**
Synopsis / Research Article	Risk assessment of cardiovascular disease in vitamin D deficient patient visting tertiary care hospitalPeshawar, Khyber pakhtun khwa.
Investigators / Authors	**Wajeeha Fayaz.**
Approval Date	27 Sep 2023.
IREB Decision	Approved.

Standard conditions of Approval Apply.

The Principal Researcher is required to notify the Secretary of the Ethical Committee about:

- Any significant change to the project and the reason for that change, including an indication of ethical implication (if any).
- Serious adverse effects on participants and actions are taken to address those effects.
- Any other unforeseen events or unexpected developments that merit notification.
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project.
- Provide the progress report / Final report / discontinuation report.

Chairman IREB / Secretary
Professor Dr. Wajid Ali Akhunzada
Chairman
Institutional Research & Ethical Board
Hayatabad Medical Complex Peshawar



KHYBER MEDICAL COLLEGE PESHAWAR
INSTITUTIONAL RESEARCH AND ETHICAL REVIEW BOARD (IREB)

No.634 /DME/KMC Dated: 6 /10/2023

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Dr. Iqbal Haider
Dr. Munila Khattak

Statistician
Syed Muhammad Hamid

CERTIFICATE OF APPROVAL

This to certify that

Wajeeha M.Phil Scholar, Biochemistry, Islamia College Peshawar

(Principal Investigator)

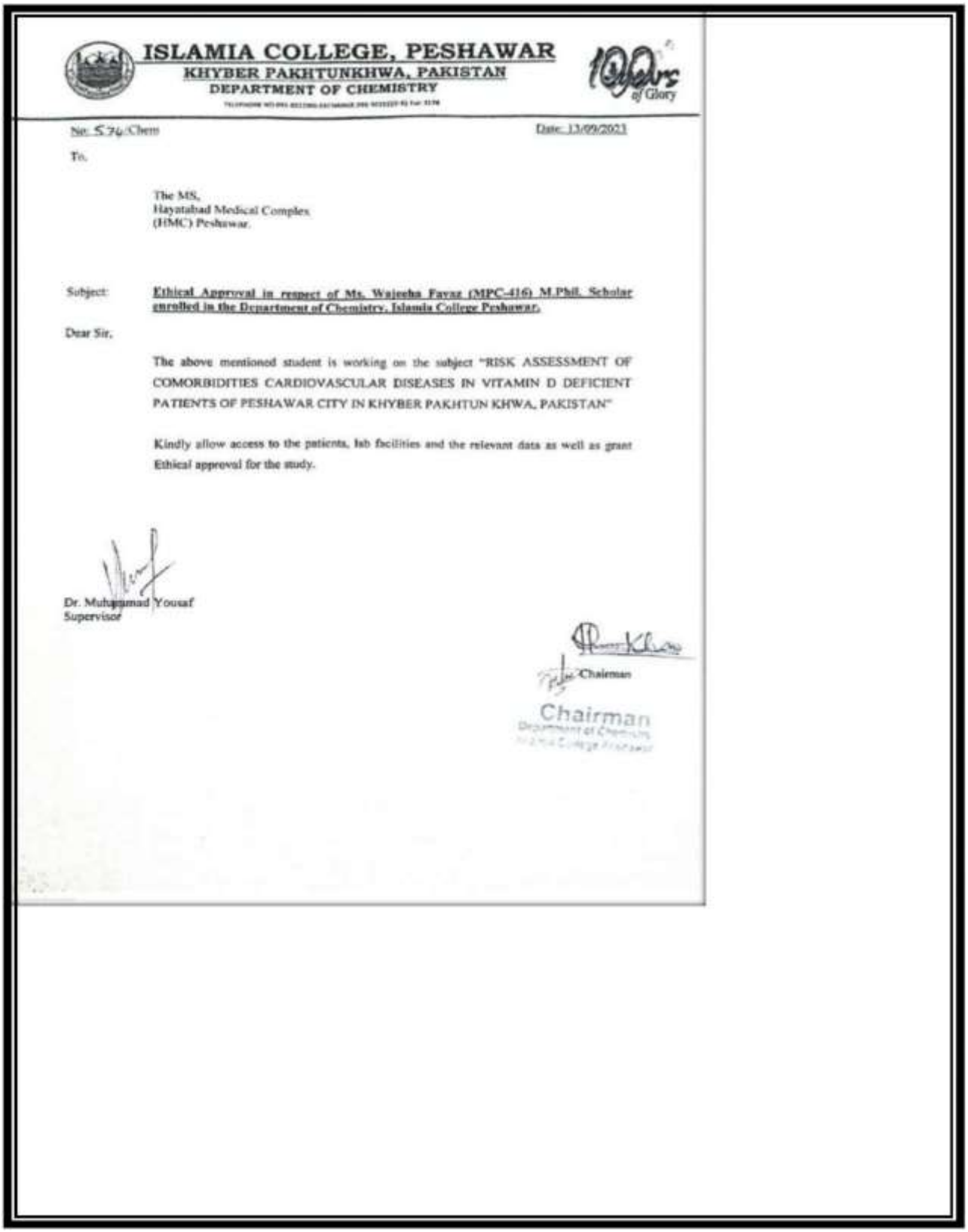
Has been, on the 06th October, 2023, given approval by the IREB of the Khyber Medical College/Khyber Teaching Hospital for the following proposal:

"Risk assessment of cardiovascular disease in vitamin D deficient patient visiting tertiary care hospital, Peshawar, khyber Pakhtun khwa."

During the whole work, all personal information of patients/subjects should be kept confidential. If you make any substantial change in the research proposal, you will need to inform the IREB for formal approval.

DR. LUBNA KASHIF
Assistant Professor,
Medical Education Department,
Khyber Medical College,
Peshawar.

Dr Lubna Kashif
MBBS / MHPE
Assistant Professor
Khyber Medical College
Peshawar



ISLAMIA COLLEGE, PESHAWAR
KHYBER PAKHTUNKHWA, PAKISTAN
DEPARTMENT OF CHEMISTRY

100 Years of Glory

No: S 74 /Chem

Date: 13/09/2021

To,

The MS,
Hayatabad Medical Complex
(HMC) Peshawar.

Subject: **Ethical Approval in respect of Ms. Wajeeha Fayaz (MPC-416) M.Phil. Scholar enrolled in the Department of Chemistry, Islamia College Peshawar.**

Dear Sir,

The above mentioned student is working on the subject "RISK ASSESSMENT OF COMORBIDITIES CARDIOVASCULAR DISEASES IN VITAMIN D DEFICIENT PATIENTS OF PESHAWAR CITY IN KHYBER PAKHTUN KHWA, PAKISTAN"

Kindly allow access to the patients, lab facilities and the relevant data as well as grant Ethical approval for the study.

Dr. Muhammad Yousaf
Supervisor

Chairman

Chairman
Department of Chemistry
Islamia College Peshawar

Collection of data

Data was assembled through face to face interviews and the finish of a pre-made, organized survey
that incorporated different elements of interest. Using surveys, patients were addressed for
segment, dietary, clinical, and family ancestry data. To decide the family background of every

member, inquiries concerning whether a parent, uncle, grandfather, or grandmother had coronary
illness were inquired.

Collection of blood samples

According to standard protocols the blood of samples of all (120) patients were taken in a
sample tube which was centrifuged and was further taken for analyzing the level of vitamin
D and cardiac enzymes i.e. (CK, AST, LDH)

Procedure

Determination of vitamin D

Firstly, the injection site was sterilized with an antiseptic. Then the blood sample from patient was
taken by venipuncture technique.
After withdrawing the needle, pressure was applied for a specific duration before applying
the bandage to cover the puncture site.
Then the blood sample was centrifuged at an appropriate speed and time to separate the
serum or plasma from the cellular components.
In the end the blood sample was examined in laboratory by a portable analyzer "Alinity I on
chemiluminescent micro particle immunoassay (CMIA) principle" (Nong, K., Liu, Y., Fang, X.,
2022)

Determination of LDH

Lactate dehydrogenase (LDH) in serum can be separated into five different isoenzymes based upon their
electrophoretic mobility. Each isoenzyme is a tetramer composed of two different subunits. The subunits
are designated heart (H) and muscle (M), based upon their polypeptide chains. The five isoenzymes are
thus: HHHH, HHHM, HHMM, HMMM, MMMM. This method measures total LDH activity in serum.
Elevations can occur in megaloblastic anemia, carcinoma, shock, muscular disorders, nephrotic
syndrome, cirrhosis, myocardial or pulmonary infarction, leukemia, hemolytic anemia and non-viral
hepatitis. As this list implies, LDH in the serum can be from a wide variety of tissues, including heart,
liver, muscles and kidneys. The Roche method of LDH measurement is derived from the formulation
recommended by the International Federation of Clinical Chemistry (IFCC) and is optimized for
performance and stability. In the presence of cofactor NAD+, LDH converts L-lactate to pyruvate.
NAD+ is reduced to NADH during this reaction. The initial rate of NADH formation is directly
proportional to the catalytic LDH activity and is determined by measuring the increase in absorbance at
340 nm. This is a kinetic (Rate-A) reaction (Hague Road Indianapolis,2011)

Determination of AST

The LX20 uses an enzymatic rate method to measure the AST activity in serum or plasma. In the reaction, the AST catalyzes the reversible transamination of L-aspartate and α-ketoglutarate to oxaloacetate and L-glutamate. The oxaloacetate is then reduced to malate in the presence of malate dehydrogenase with the concurrent oxidation of NADH to NAD. The system monitors the rate of change in absorbance at 340 nm over a fixed time interval. The rate of change in absorbance is directly proportional to the AST activity in the sample. AST measurements are used in the diagnosis and treatment of certain types of liver and heart diseases. (Beckman Synchron, et al 2001)

Determination of CK

The DxC800 use an enzymatic rate method to determine CK activity in serum or plasma. In the reaction, the CK catalyzes the transfer of a phosphate group from the creatine phosphate substrate to adenosine diphosphate (ADP). The subsequent formation of adenosine triphosphate (ATP) is measured through the use of two coupled reactions catalyzed by hexokinase (HK) and glucose-6-phosphate dehydrogenase (G6PD) which results in the production of ß-Nicotinamide Adenine Dinucleotide (reduced form) (NADH) from ß-Nicotinamide-Adenine Dinucleotide (NAD). The system monitors the rate of change in absorbance at 340 nm over a fixed time interval. The rate of change in absorbance is directly proportional to the activity of CK in the sample. Measurements of creatine kinase are used in the diagnosis and treatment of myocardial infarction, skeletal muscle diseases, and diseases of the central nervous system. (Beckman Coulter Synchron et al 2007)

Statistical analysis

Version 29.0 of the (SPSS) software was used to tabulate, compute, and examine the collected data. The frequency and percentage distribution of descriptive statistics were employed.

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CHAPTER 3

RESULT AND DISCUSSION

Table 3.1: Base line characteristics

Variables	**Response options**	**Frequency (n)**	**%**	**P-value**
Gender	Male	79	65.8	**0.000**
Female	41	34.1		
Age	<18	22	18.3	**0.010**

18 – 45			35	29.1	
> 45			54	45	
BMI		Normal < 25	36	30.2	**0.000**
Over weight 25 -29.9			59	49.1	
Obese 30			24	20.3	
Educational status		Educated	44	36.6	**0.000**
Uneducated			56	46.6	
Socioeconomic Status		Good	21	17.5	**0.010**
Poor			63	52.5	
Satisfactory			36	30	

Table 3.1outlines the basic demographic data, including age, gender distribution, socioeconomic
position and educational status. Males made up 65.8% of the sample, while females made up
34.1%. A considerable proportion of participants (45%), were 45 years of age or older. There was no significant difference in the participants' educational status.

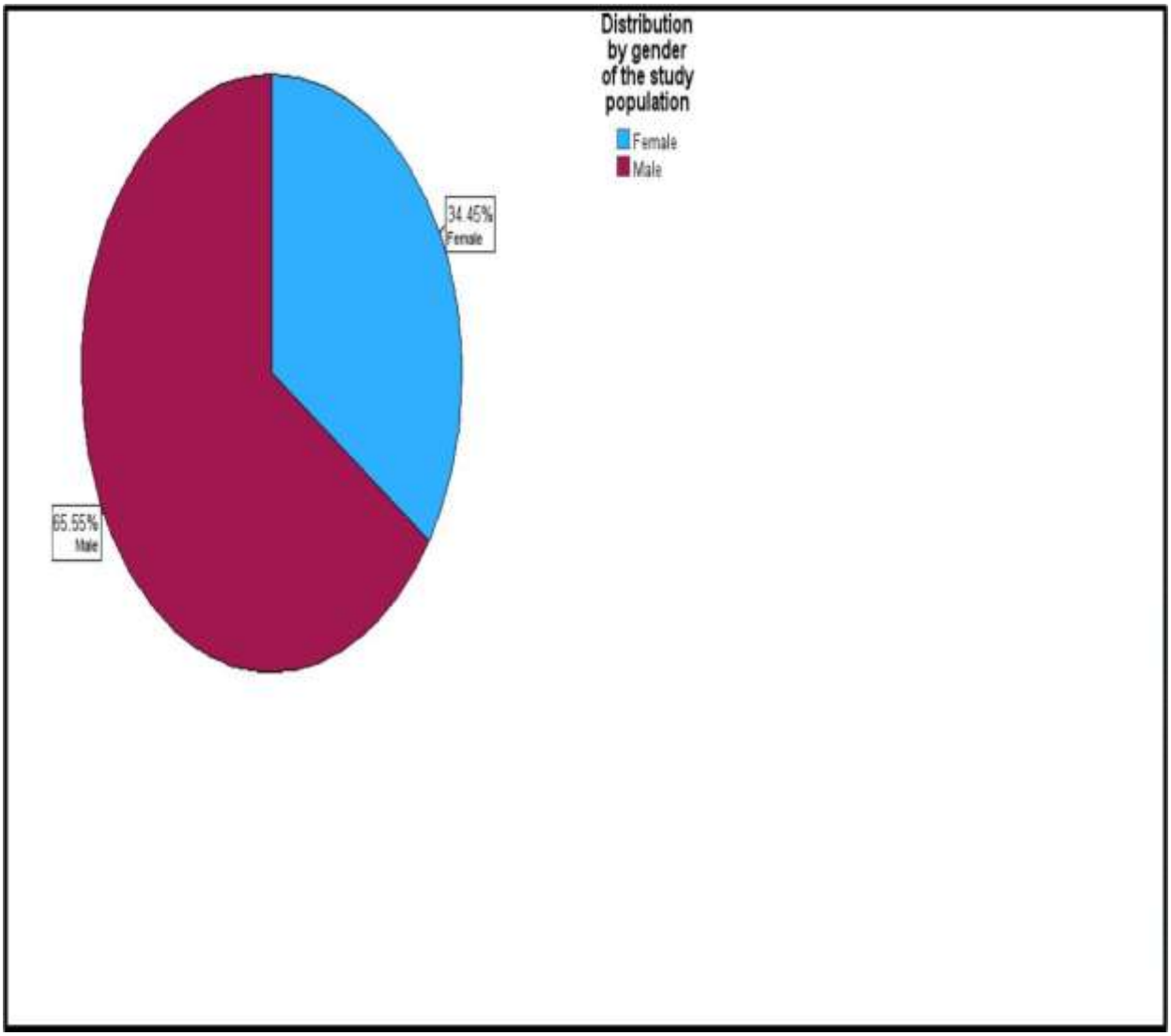


Figure 3.1: Distribution by gender (n=120)

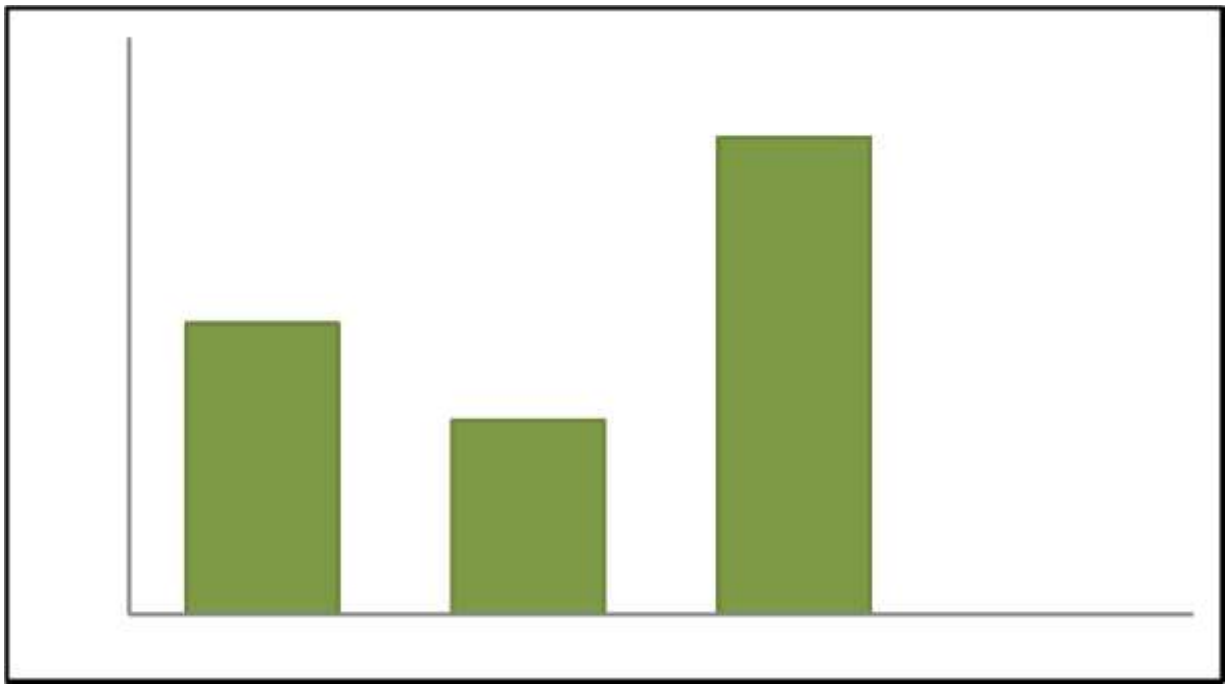
60.00%
50.00%
40.00%
30.00% 54.17%

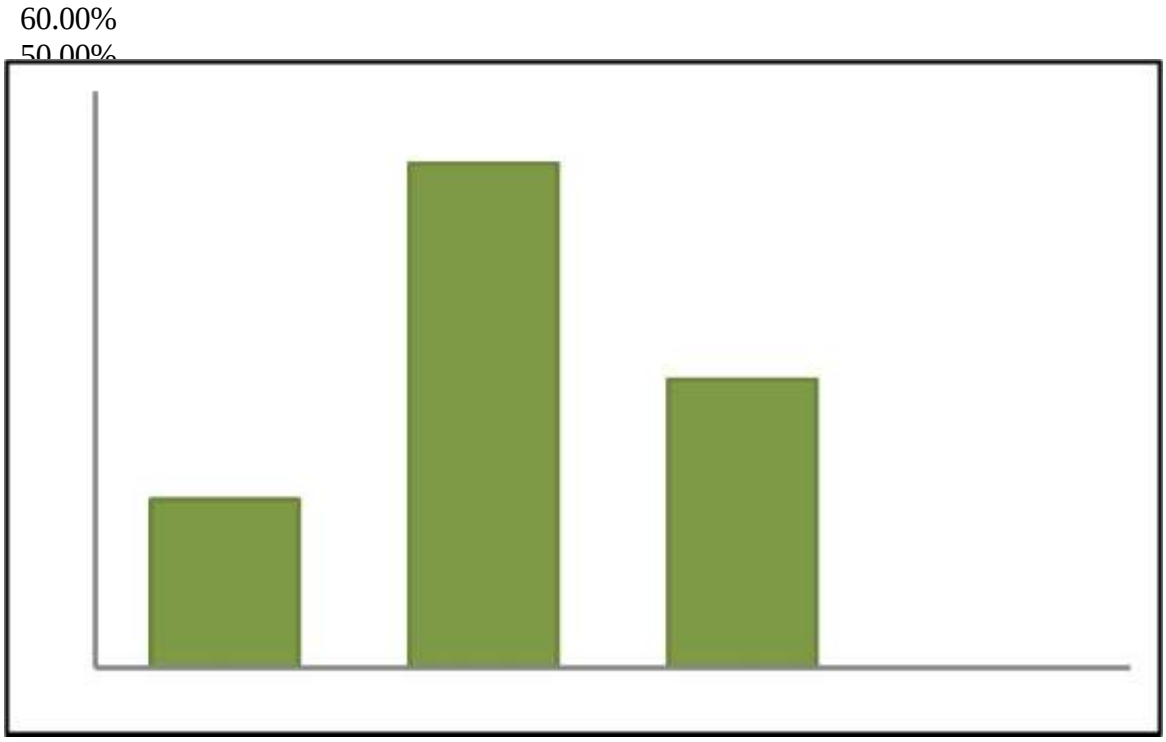
20.00%
10.00% 20.00% 25.83%

0.00%
<18 18-45 >45

Figure 3.2: Percentage distribution of age group among the study population (n=120)

33





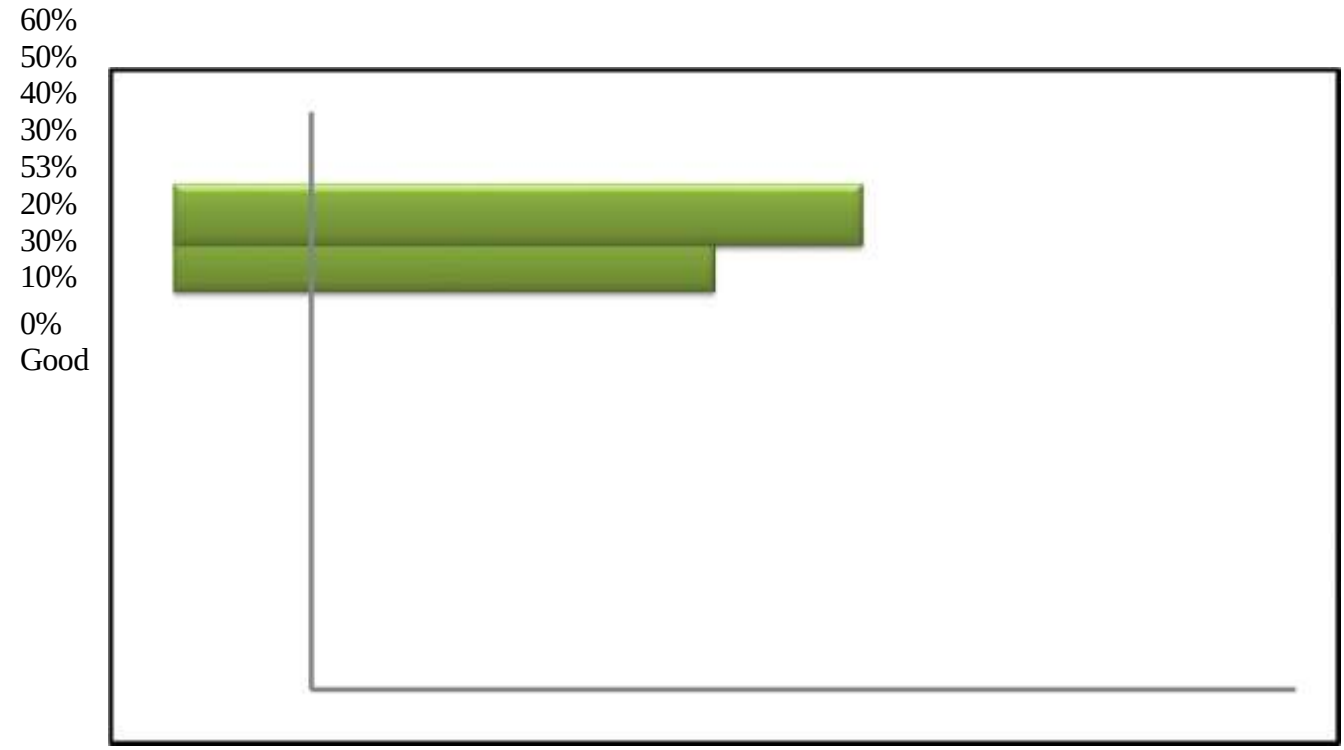


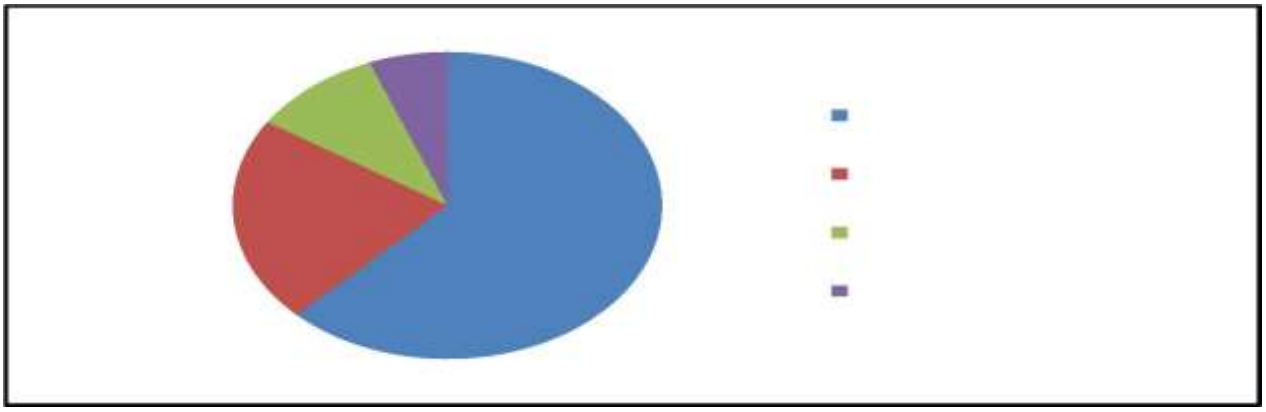
Figure 3.5: Socioeconomic status of participants

35

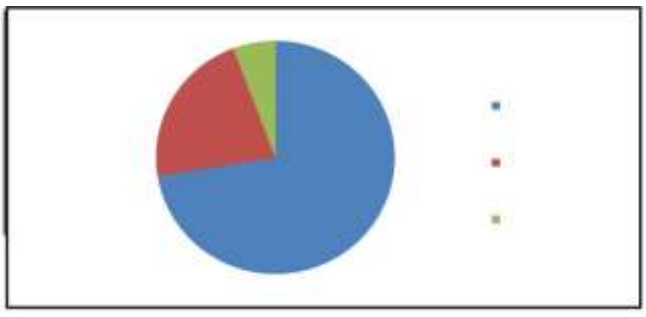
Table 3.2: Medical History of the study participants

Variables	**Response Option**	**Frequency (n)**	**Percent (%)**
Comorbidity	Chronic Kidney Disease	26	21.6
Diabetes Mellitus	12	10	

	Chronic obstructive pulmonary disease	7 5.8	
Cardiac Disease in family history	Have a family history of cardiac disease	43 35.2	
	Don‟t have a family history of cardiac disease	77 64.71	
Regular Physical Activity	Have regular physical activity routine	35 29.1	
	Don‟t have regular physical activity routine	85 70.8	
Effect of Vitamin D rich food and Supplement	Yes 32.5		39



No	81	67.5	
Effect of CVD on other organs	Brain 0.0		0
Lungs	7	5.8	
Kidneys	26	21.6	
Awareness of vitamin D deficiency associated with CVD	Awareness of vitamin D deficiency associated with CVD	6 5	
	No Awareness of vitamin D deficiency associated with CVD	114 95	
Age at which CVD was diagnosed	<18-30 45		54
30->50	66	54	
36			



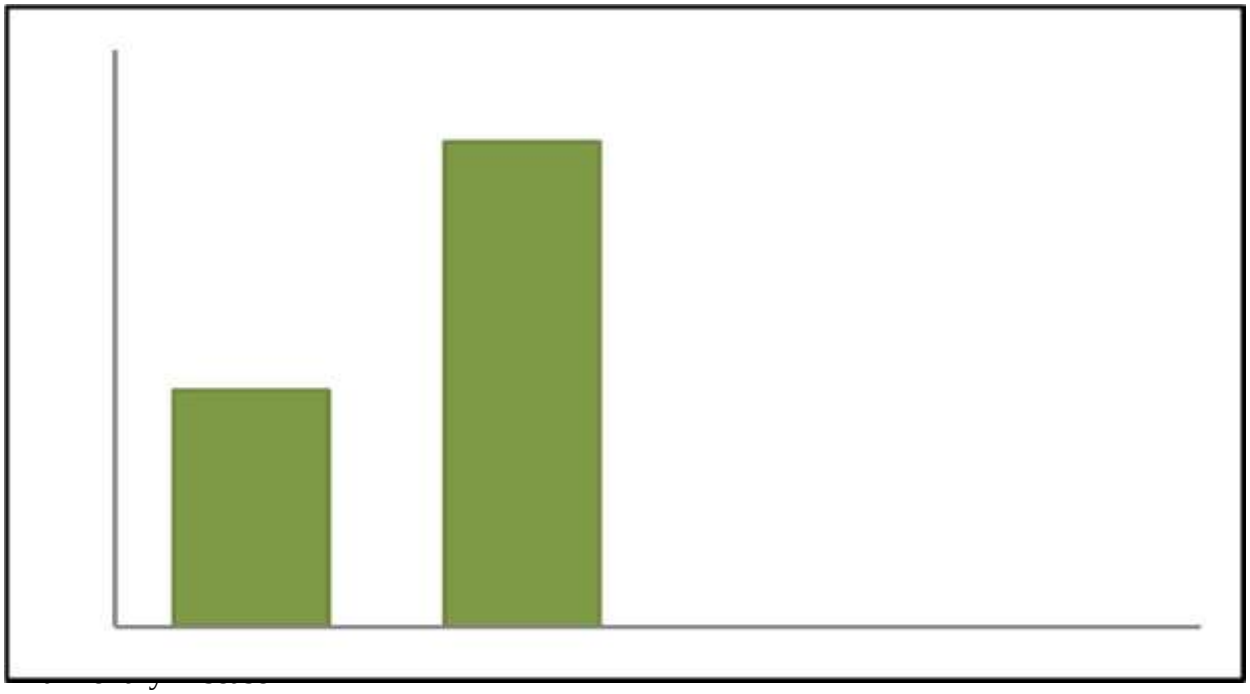


Figure 3.6: Percentage distribution of comorbidity of cardiovascular disease of study
Participants.

6%
22% No Effect
Kidney
72% Lungs

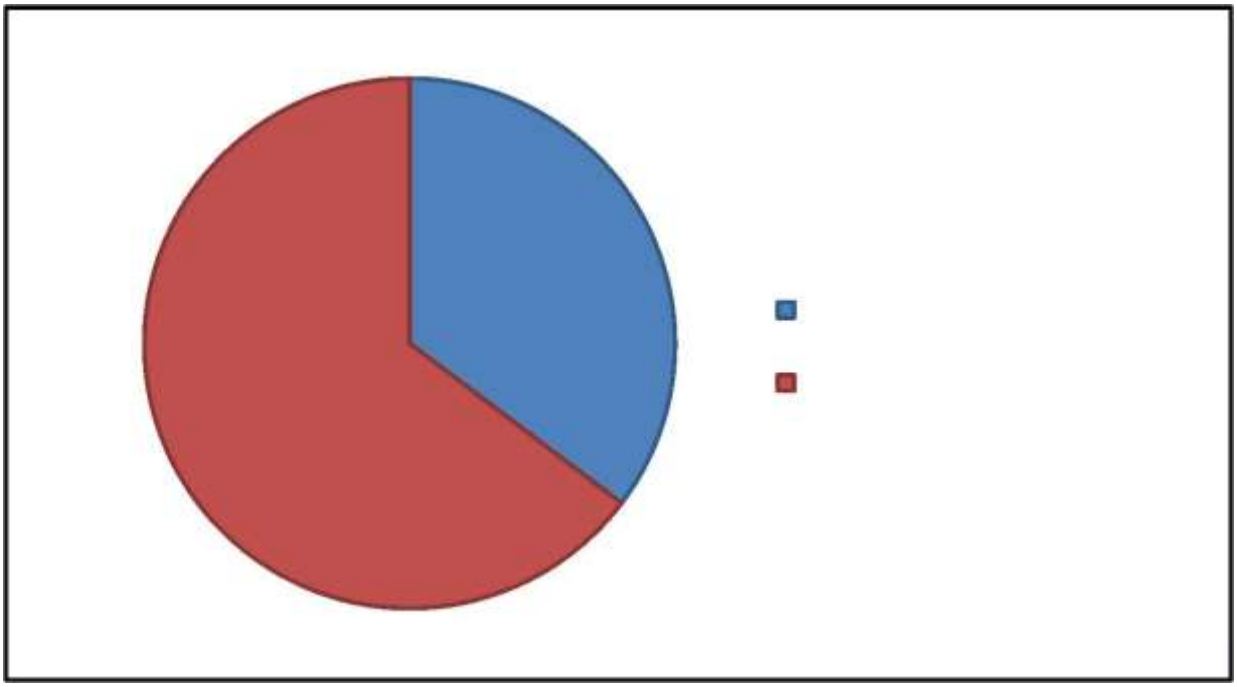


Figure 3.7: Percentage distribution of effect of CVD on other organs of study participants.

37
80.00%
70.00%
60.00%
50.00%

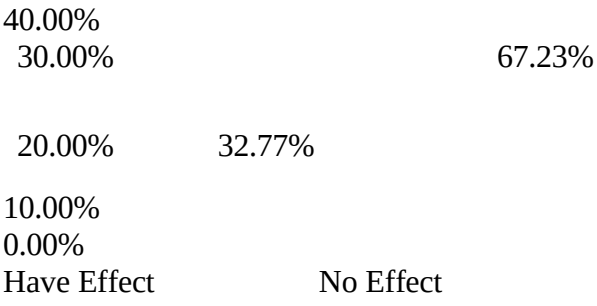


Figure 3.8: Percentage distribution of effect of vitamin D Supplements on the level of cardiac enzymes of the study population (n=120)

Figure 3.9: Percentage distribution of cardiac disease in family history

38**Table 3.3 Descriptive statistics**

Parameter	**N**	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Age in years	120	14	85	49	21
BMI (Kg/m$^{2)}$	120	18	59	28	11
Vitamin D level (ng/mL)	120	21	55	33	9
CK (mg/dL)	120	400	1807	873	415.7
LDH (mg/dL)	120	400	998	625	187.6
AST (mg/dL)	120	180	830	472	224.3

Table 3.3 outlines the descriptive statistics for age, BMI, vitamin D, and various cardiac Enzymes levels are provided. The average age of participants was approximately 49 years with the BMI of 28, indicating a predominantly overweight sample. The vitamin D level had mean value of 33 which is lower to normal in range. Whereas cardiac Enzymes including CK, LDH, AST had mean values 873,625 and 472 respectively.

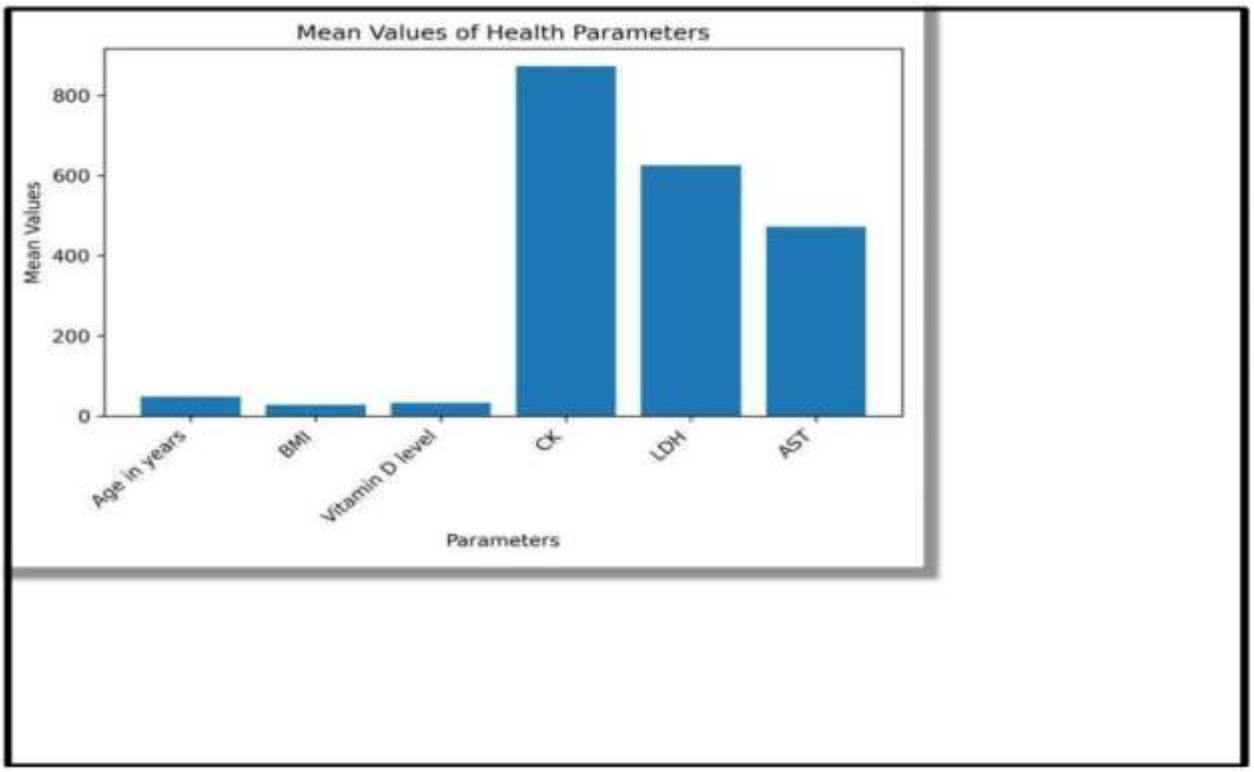


Figure 3.10: Mean values of health parameters

Table 3.4 Laboratory parameters (vitamin D, Cardiac Enzymes) of the study participants

Laboratory parameters	Response options	Frequency	Percentage
Vitamin D (ng/ml)	Low (20-40 ng/mL)	68	56.67
	Very low(< 20 ng/mL)	33	27.50
	Optimal(40-80 ng/mL)	19	15.83
CK (mg/dl)	Normal(30-170 mg/dL)	4	3.3
	Borderline (170-250mg/dL)	18	15.6
	High (>250 mg/dL)	82	68.3
LDH (mg/dl)	Normal (140-280mg/dL)	8	6.6
	Borderline (280-370mg/dL)	44	36.6
	High (>370mg/dL)	68	56.6
AST	Normal (10-36 mg/dL)	11	9.1
	Borderline (40-80 mg/dL)	38	31.6
	High (>80 mg/dL)	71	59.1

Table 3.4 presents the distribution of biomarker levels (Vitamin D, CK, LDH, and AST) among
research participants. Each biomarker is categorized into different ranges representing normal,
borderline, and high levels. The frequencies and percentages are provided for each category.
Notably, the majority of participants have biomarker levels within the low range for Vitamin D, CK,

and AST, while LDH levels show a higher proportion in the borderline and high ranges indicating potential health concerns.

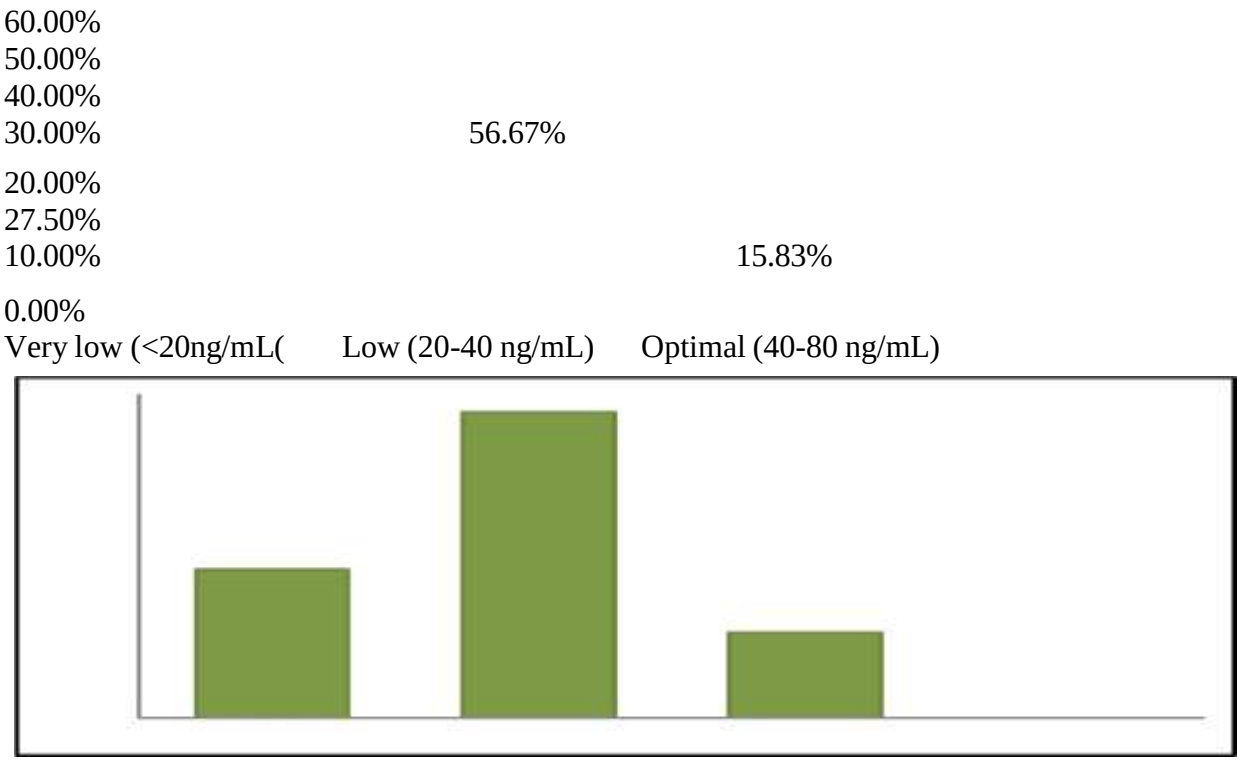


Figure 3.11: Frequency and percentage distribution of vitamin D level among the study population (n=120)

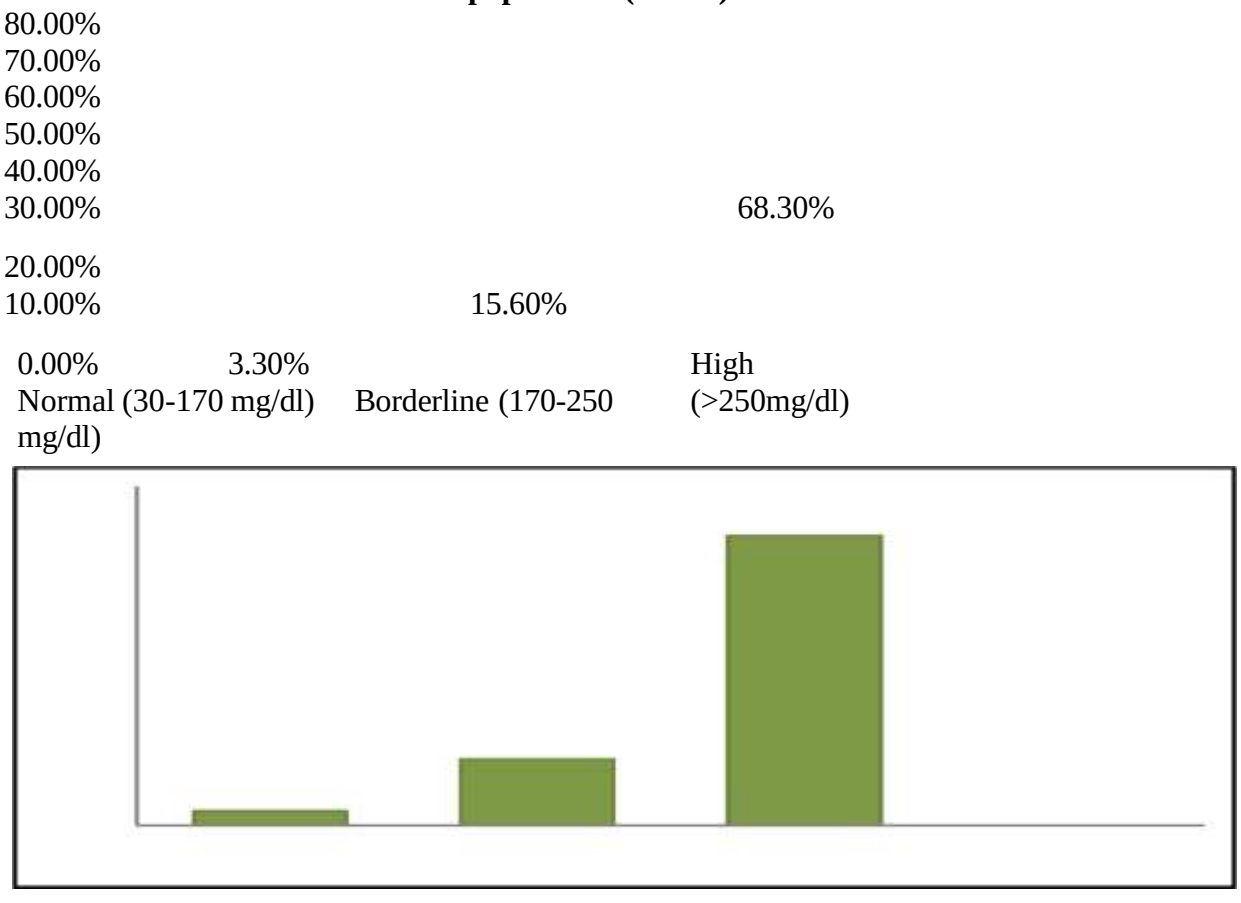


Figure 3.12: Frequency of level of Creatine kinase (CK) of study participants

42

60.00%
50.00%
40.00%
30.00% 56.60%
20.00% 36.60%
10.00%
0.00% 6.60%
Normal (140-280mg/dl) Borderline (280-370 High (>370mg/dl)

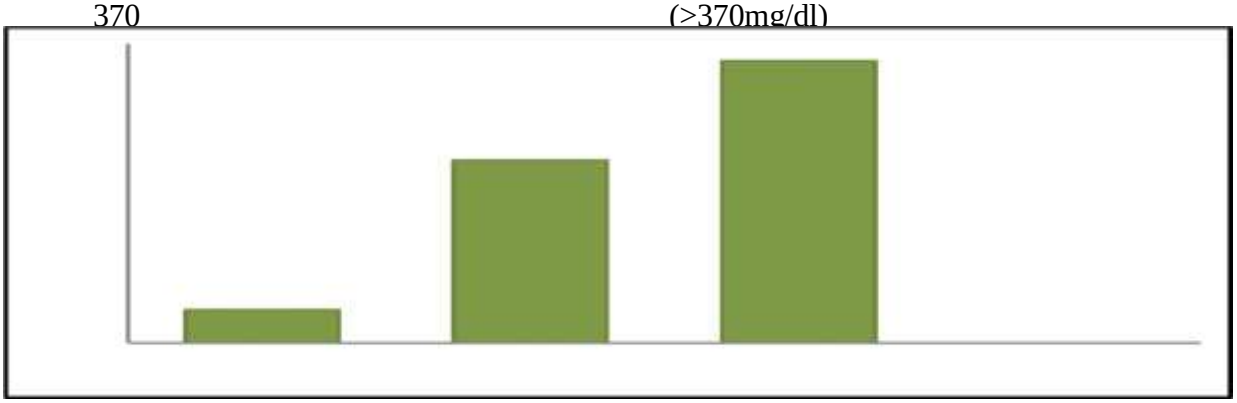


Figure 3.13: Frequency of level of lactate dehydrogenase (LDH) of study participants

70.00%
60.00%
50.00%
40.00%
30.00% 59.10%
20.00%
31.60%
10.00%
9.10% 0.00%
Normal (10-30 mg/dl) Borderline (40-80 mg/dl) High (>80 mg/dl)

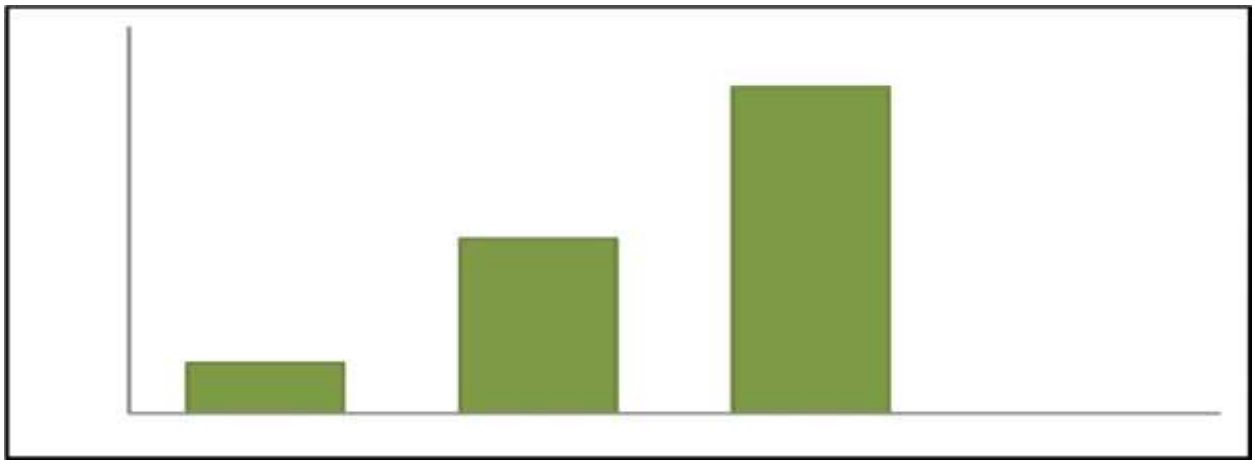


Figure 3.14: Frequency of level of Aspartate aminotransferase (AST) of study participants

DISCUSSION

The frequency of vitamin D absence in this population has been uncovered in this research that

examined vitamin D levels among cardiac patients.
According to Michelle et al. 2015, numerous studies including high-risk populations for CV
illness have highlighted vitamin D insufficiency (< 50 nmol/L 25-hydroxy vitamin D), indicating
that little vitamin D status may be theoretically substantial and curable risk factor. In a 5.4-year
follow-up, normotensive participants with blood concentration of < 37.5 nmol/L of 25-hydroxy
vitamin D showeda 62% growth in CV disease risk compared to those with greater levels in an
observational trial by Waang and colleagues. Similarly, Dobnig et al. found that the highest risk
of sudden cardiac death was seen in patients within the lowermost quartiles of either 1, 25-
dihydroxy or 25-hydroxy vitamin D (<51pmol/L) among 3258 patients mentioned for coronary
angiography.
In this research 68% of Patients exhibited Low Vitamin D Levels: The majority of cardiac
patients, constituting 68% of the cohort, demonstrated low vitamin D levels. This observation
raises awareness about the high incidence of vitamin D deficiency within the cardiac patient
population. 27% of Patients had Very Little Vitamin D Levels: A significant subset of patients,
accounting for 27% of the total, presented with very low vitamin D levels. This highlights a
concerning quantity of individuals with a pronounced lack, emphasizing the need for targeted
interventions to address and rectify these deficiencies.15% of Patients demonstrated Optimal
Vitamin D Levels: A smaller yet notable percentage, comprising 15% of the patients, exhibited
optimal vitamin D levels. Therefore it can be said that a lack of vitamin D increases the risk of
cardiovascular events and represents a separate cardiovascular risk factor.
Comparisons of traits between the sexes for conventional cardiovascular risk factors, metabolic
disorders and cardiovascular disease, cardiovascular agents, and cardiovascular and all-cause
mortality.The frequency of atrial fibrillation was substantially more in males than in women
(25.6% vs. 15.4%,p = 0.04). (Yi Zhang 2016)
Interestingly, the research demonstrates a significant gender difference in the incidence of
cardiovascular disorders with men being more susceptible than women. However the study
found that women had a lower rate of cardiovascular disease (34%) compared to men, who had
the greatest percentage (66%).
According to Lakatta. E.G. et al. (2016) cardiovascular disease, including hypertension and

atherosclerosis, which cause heart problem and stroke, is the major reason of death for more
than 40% of fatalities in those 65 years of age and older. In the similar age variety, near 80% of
all cardiovascular deceases take place. Therefore, the primary risk aspect for CV disease is age
itself.
Because interactions occur among age-associated cardiovascular variations in health and specific
pathophysiologic mechanisms that cause a disease, the medical symptoms and diagnosis of some
cardiovascular disorders possibly change in adults with innovative oldness.
Notably, the study reveals a notable age related pattern, with individuals aged over 45 exhibiting
higher percentage (54%) of cardiovascular disease compared to those under 45. Younger
individuals particularly those aged <18 (20%) and >18-45(25%) generally experienced a lower
prevalence of cardiovascular disease.
According to R Scragg et al. (2017) large population-based the results of this RCT are consistent
with those of previous Mendelian randomization experiments and RCTs on vitamin D
supplementation, showing that vitamin D supplementation at the dosage and occurrence we
utilized do not avert CVD
In this research in a sample group of 120 patients it was noted that a substantial proportion,
constituting 67% of patients, reported feeling no discernible effect from vitamin D
supplementation or an increased eating of vitamin-D rich foods in connection to cardiovascular
health. Conversely 32% of patients reported a positive and noticeable impact on their
cardiovascular health after incorporating vitamin D supplementation and vitamin D rich foods
into their routines. However it is still unclear if taking supplements of vitamin D can lower the
risk of CV disease or lessen its severity.
Exploring the prevalence of family history of cardiovascular disease within the cohort. The
findings revealed diverse perspectives among the participants. Remarkably, 36% of the study
participants acknowledged having a family history of cardiovascular disease. This
acknowledgement implies that a notable portion of the sample population recognizes the
presence of cardiovascular condition among their relatives. Contrastingly, a mainstream of
participants constituting 64%, stated that they did not have a family history of cardiovascular
disease A substantial correlation between conventional CVD risk variables and obesity. For all

racial/ethnic and gender groupings, there was a similar correlation between obesity and risk
factors for CVD. An intriguing discovery revealed that, although the proportion of Chinese
American partakers who were overweight or obese was lower than that of other groups, a

comparable correlation was noted between increased body size and the effects of CVD Chinese
Americans. Burke, G. L. (2018).
Exploring the intricate relationship between body weight and the prevalence of cardiovascular
disease within the cohort, the study categorized patients into three distinct weight groups:
overweight, normal weight and obese.
It was observed that: 49% of overweight patients were diagnosed with cardiovascular disease,
30% of normal weight patients exhibited cardiovascular disease, 20% of obese patients presented
with cardiovascular disease.
The prevalence of cardiovascular disease appears to be notable advanced in overweight
individuals in comparison to both normal weight and obese counterpart.

CONCLUSION

In conclusion our all-encompassing analysis of cardiovascular health factors uncovers
important subtleties among various populations. Given that vitamin D deficiency is highly
predominant among cardiac patients, specific interventions may be necessary to address this
nutritional component as a separate cardiovascular risk factor. The significance of customized
risk assessments is highlighted by gender differences, age-related trends, and the influence of
family history. Moreover, the complex connection between cardiovascular illness and body
weight emphasizes the value of holistic methods to weight control. Together, these results
advance our knowledge of cardiovascular health and lay the groundwork for specialized
therapies and individualized treatment plans. However it's uncertain if taking supplements of
vitamin D can lower the menace of cardiovascular disease or lessen its effects. The findings
major message is that CVD due to vitamin D deficit is a worldwide health problem that has not
been thoroughly examined or analyzed in order to fully comprehend its scope and prevalence.47

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