Dissertation on

SERUM PHOSPHATE AS A MARKER OF CAROTID INTIMAL MEDIAL THICKNESS IN NON-DIABETIC CHRONIC KIDNEY DISEASE PATIENTS

Submitted in partial fulfilment for the degree of

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CERTIFICATE

This is to certify that the dissertation entitled "**SERUM PHOSPHATE AS A MARKER OF CAROTID INTIMAL MEDIAL THICKNESS IN NON-DIABETIC CHRONIC KIDNEY DISEASE PATIENTS"** is a bonafide original work done by **Dr.BADRI SRINIVASAN K**, in partial fulfilment of the requirements for M.D.GENERAL MEDICINE BRANCH – I examination of The Tamilnadu Dr.M.G.R Medical University to be held in 2019, under my guidance and supervision in 2018

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I hereby solemnly declare that the study **"SERUM PHOSPHATE AS A MARKER OF CAROTID INTIMAL MEDIAL THICKNESS IN NON-DIABETIC CHRONIC KIDNEY DISEASE PATIENTS"** is done by me at Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai during 2018 under the guidance and supervision of **Prof.P.VASANTHI M.D.,** This dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai towards the partial fulfilment of requirement for the award of M.D. Degree in General Medicine (Branch I).

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ABBREVIATIONS

- CKD - Chronic kidney disease
- HDL - High density lipoprotein
- LDL - Low density lipoprotein
- IDL - Intermediate density lipoprotein
- KDIGO - Kidney Disease Improving Global Outcomes
- eGFR - estimated Glomerular Filtration Rate
- ACR - Albumin Creatinine Ratio
- AER - Albumin Excretion Rate
- AKI - Acute Kidney Injury
- RAAS - Renin Angiotensin Aldosterone System
- BP - Blood Pressure
- DM - Diabetes Mellitus
- HTR - Hypertensive Retinopathy
- ACE-I - Angiotensinogen Convertase Enzyme Inhibitor
- ARB - Angiotensin Receptor Blocker
- BMI - Body Mass Index

- Hb - Haemoglobin
- IV - Intravenous
- SC - Subcutaneous
- TSAT - Transferrin saturation
- PTH - Parathormone
- CVD - Cardio-Vascular Disease
- LV - Left Ventricle
- CIMT - Carotid IntimalMedialThickness
- AGE - Advanced Glycation End product
- ESA - Erythropoietin Stimulating Agent
- GIT - Gastrointestinal Tract
- FGF 23 - Fibroblast Growth Factor 23
- Na-Pi - Sodium-phosphate cotransporter
- RRT - Renal Replacement Therapy
- FGFR1 - FGF Receptor 1
- Apo B - Apolipoprotein B
- Apo A - Apolipoprotein A

- PEW - Protein Energy Wasting
- CERA - Continuous Erythropoietin Receptor Activator
- MDRD - Modification of Diet in Renal Disease
- EPI - Epidemiology Collaboration
- SNGFR - Single Nephron GFR
- FSGS - Focal Segmental Glomerulosclerosis
- NSAIDs - Non-steroidal Anti-inflammatory Drugs
- TIBC - Total Iron Binding Capacity
- CAD - Coronary Artery Disease
- PD - Peritoneal Dialysis
- HD - Hemodialysis
- ESRD - End Stage Renal Disease
- TGF - Transforming Growth Factor
- CRP - C- Reactive Protein

INTRODUCTION

AIMS AND OBJECTIVES

REVIEW OF LITERATURE

MATERIALS AND METHODS

OBSERVATION AND RESULTS

DISCUSSION

CONCLUSION

SUMMARY

BIBLIOGRAPHY

ANNEXURE

INTRODUCTION

Chronic kidney disease patients are generally at increased risk for accelerated atherosclerosis. Cardiovascular disease and stroke are the most common causes of mortality in CKD patients with the risk being 10-20 times more than the general population.

Atherosclerosis assessed by means of measurement of thickness and stiffness of arterial walls is far advanced in CKD patients.

Advanced age, systemic hypertension, smoking and dyslipidaemia are the most significant risk factors for accelerated arteriosclerosis in the general population. It is not clear whether the risk factors for arteriosclerosis in the non-uremic population is comparable to that of arteriosclerosis in the uremic population.

Though increased serum phosphate concentration is a significant risk factor for vascular calcification, an advanced form of atherosclerosis, the association between serum phosphate concentration and arterial wall thickness in CKD is not clear.

In this study carotid intimal media thickness being a direct marker of atherosclerosis which is measured using B mode ultrasound of carotid artery is compared with serum phosphate levels in non-diabetic CKD patients and also correlation with other factors such as age, sex, stage of CKD, haemoglobin, serum albumin, serum calcium, urine PCR, LDL cholesterol, fundoscopic and echocardiographic findings is studied.

AIMS AND OBJECTIVES

- To study the relation between serum phosphate and carotid artery intimal medial thickness in non-diabetic chronic kidney disease patients in a tertiary care institute.

- Factors such as age, sex, stage of chronic kidney disease, haemoglobin, serum albumin, serum calcium, serum phosphorus, LDL cholesterol, calcium-phosphate product, urine protein creatinine ratio, fundus examination and echocardiographic findings are compared with carotid artery intimal medial thickness.

REVIEW OF LITERATURE

CKD

As defined byKDIGO

CKD is defined as abnormalities of kidney structure or function, present >3 months, with implications for health and CKD is classified based on cause, GFR category and albuminuria category.

It is a clinical syndrome that occurs due to irreversible loss of renal function leading to disturbances in various metabolic, endocrine, excretory and synthetic function causing accumulation of non – protein nitrogenous substances which leads to metabolic derangements presenting as distinct clinical manifestations.

End stage renal disease is described as a terminal stage of CKD,in which without any replacement therapy patients could not survive and would result in death.

Markers of kidney damage (1 or more for more than 3 months)

Albuminuria (AER 30mg/d or more ; ACR 30mg/g or more)

Urinary sediment abnormalities

Electrolyte and other abnormalities due to tubular disorders

Abnormalities detected by histology

Structural abnormalities detected by imaging

History of renal transplantation

Decreased GFR (for >3 months)

GFR <60ml/min/1.73 m^2 (GFR categories G3a – G5)

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

ALBUMINURIA IN CKD

Category	ACR	Description
A1	<3 mg/mmol	Normal to mildly increased
A2	3-30 mg/mmol	Moderately increased (CKD)
A3	>30 mg/mmol	Severely increased (CKD)

If GFR <60 ml/min/1.73 m^2 or markers of kidney damage present, determination of duration of kidney disease by reviewing history and previous documents done

- If >3 months then CKD is confirmed.
- If not >3 months then CKD is not confirmed and tests should be repeated as patient may have AKI, CKD or both.

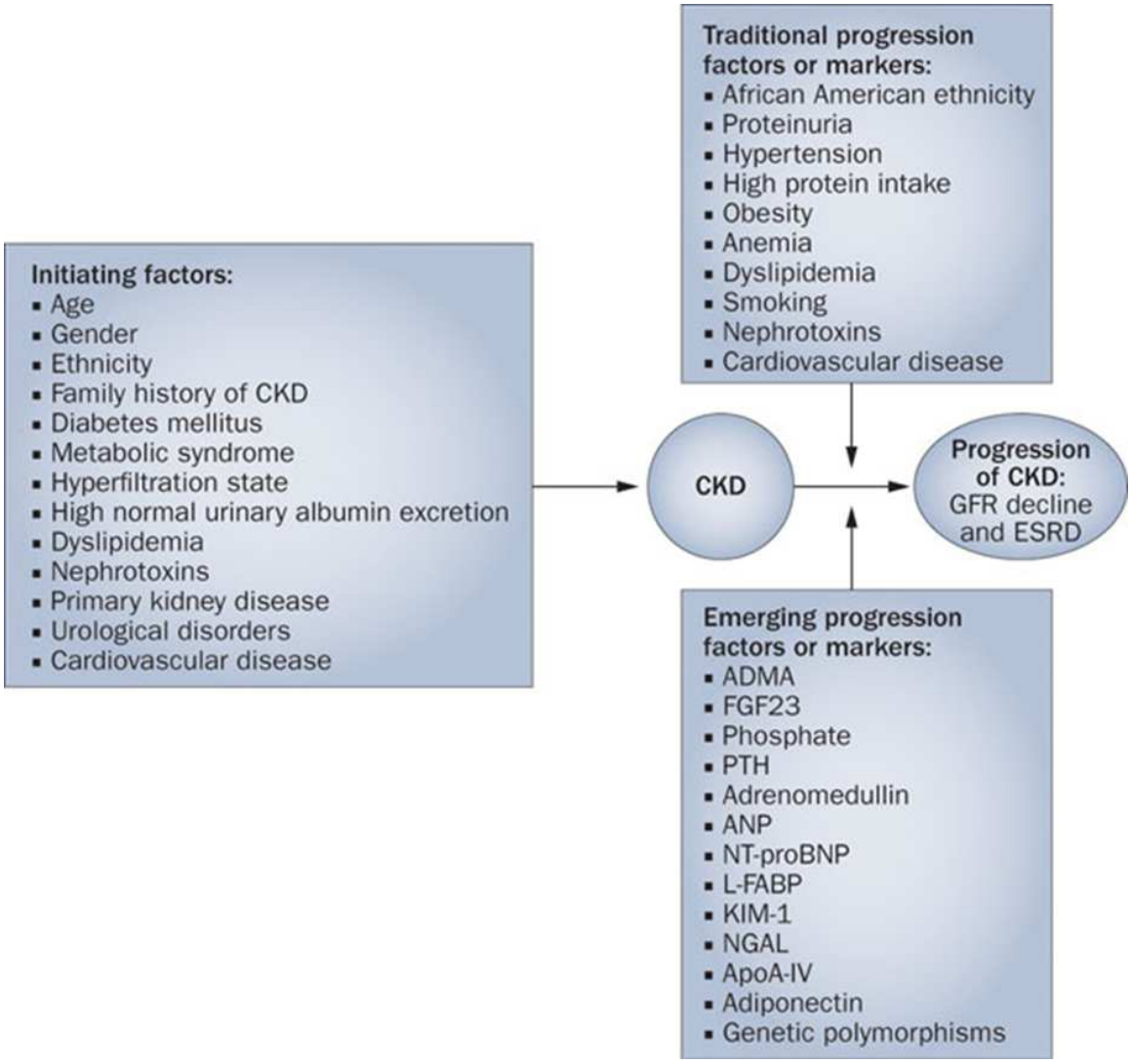
PROGRESSION OF CKD

CKD progression is defined as:

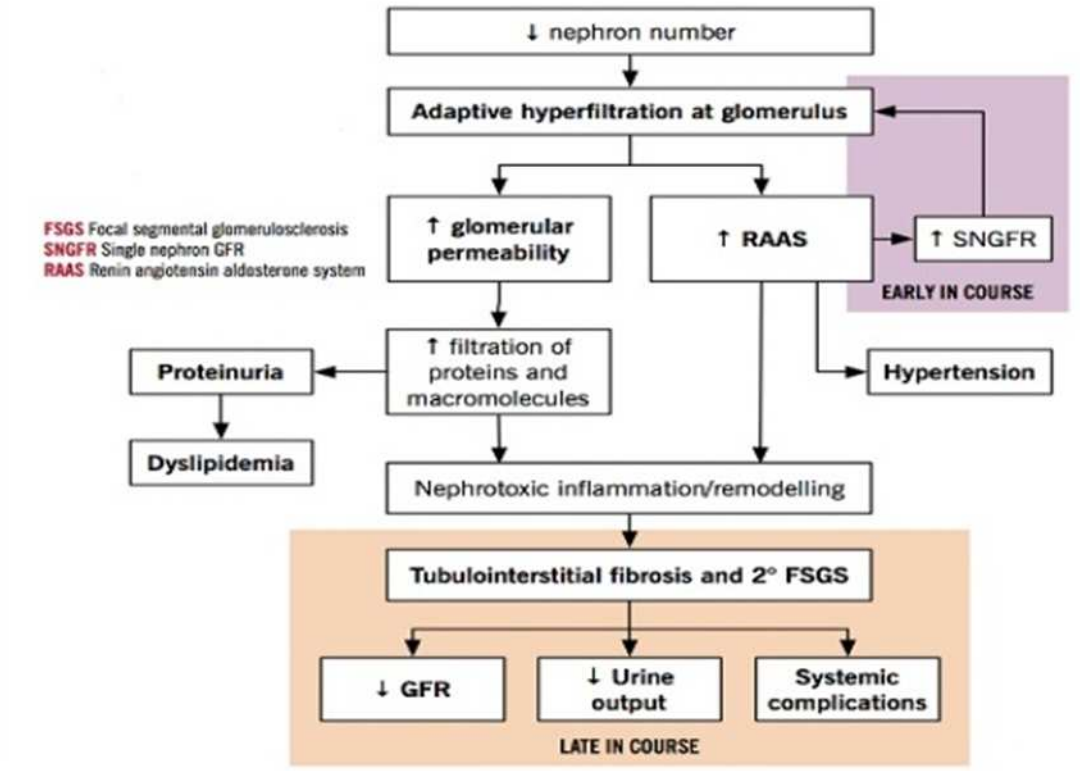
- Drop in GFR of 25% or greater from baseline
- Sustained fall or decline in eGFR by >5ml/min/1.73 m^2 / year

The confidence in assessing progression increases by increase in number of serum creatinine measurements and duration of follow up

RISK FACTORS FOR INITIATION AND PROGRESSION OF CKD



PATHOPHYSIOLOGY OF PROGRESSION OF CKD



PREVENTION OF CKD PROGRESSION

1. BP management

- BP agents and targets should be individualised based on age, other co-morbidities, coexistent cardiovascular disease and tolerance to treatment
- Postural change in BP should be checked during every follow-up of CKD patients taking BP lowering drugs
- In CKD patient with urine albumin excretion of <30mg/24 hrs target BP should be <140/90 mm Hg
- In CKD patient with urine albumin excretion of >30mg/24hrs target BP should be <130/80 mm Hg
- An ARB/ ACE-I should be used in diabetic CKD adults with urine albumin excretion of 30-300mg/24 hrs
- An ARB/ACE-I should be used in CKD adults of any etiology with urine albumin excretion of >300mg/24hrs
- Antihypertensive treatment in children with CKD is started if BP is persistently > 90^{th} percentile
- Children with CKD who are proteinuric should have their BP lowered to <50^{th} percentile according to age, sex, height unless signs of hypotension are present
- ARB/ACE-I to be used in children irrespective of proteinuria.

2. Protein intake is restricted to 0.8g/kg/day in GFR <30ml/min/1.73 m^2

3.Target HbA1c should be 7% or less.

4.Salt restriction to <2g% amounting to 5g of sodium chloride

5.BMI to be maintained between 20-25 and physical activity of at least 30 minutes for 5 times a week

6.Smoking abstinence is necessary.

GFR MEASUREMENT

Glomerular filtration rate is the rate of filtrate produced by all the nephrons of both kidneys in a minute.

Creatinine clearance is defined as the volume of blood plasma cleared of creatinine per unit time which is a useful measure for approximating GFR.

Glomerular filtration rate (GFR) is equal to the Clearance Rate when any solute is freely filtered and is neither reabsorbed nor secreted by the kidneys.

Cockcroft-Gault formula

$$GFR_{Cockcroft} = \frac{(140 - age) \times mass\ (kg)\ [\times 0.85 \text{ if female }]}{72 \times serum\ creatinine\ (mg/dl)}$$

MDRD formula

The 6-variable (or original, or equation 7) MDRD formula

$eGFR = 170 \times SCr^{-0.999} \times age^{-0.176} \times SUN^{-0.170} \times SAlb^{0.318} \times 0.762\ (\text{if female}) \times 1.180\ (\text{if black})$

The 4-variable (or abbreviated, or modified) MDRD formula

$eGFR = 186.3 \times SCr^{-1.154} \times age^{-0.203} \times 0.742\ (\text{if female}) \times 1.212\ (\text{if black})$

The ID-MS traceable MDRD formula

$eGFR = 175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742\ (\text{if female}) \times 1.212\ (\text{if black})$

CKD-EPI Formula

CKD-EPI formula for estimating GFR

$GFR_{(ml/min)} = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times (0.993)^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$

where κ = 0.7 for females, 0.9 for males
α = -0.329 for females, -0.411 for males
Scr = serum creatinine in mg/dl

min(Scr/κ, 1) means use whichever value is least between Scr/κ or 1

max(Scr/κ, 1) means use whichever value is greater between Scr/κ or 1

Example: Scr = 0.9 and patient is female therefore:
Scr/κ = 0.9/0.7 = 1.28
for min(Scr/κ) would use 1
for max(Scr/κ) would use 1.28

CLINICAL MANIFESTATIONS AND COMPLICATIONS

SODIUM AND WATER RETENTION

Extracellular fluid volume is maintained till the very late stages of CKD. Absolute sodium excretion is preserved until late stages by increasing the fractional excretion of sodium.

Any derangement in sodium balance causes volume overload or volume depletion as total body sodium is the major determinant of extracellular fluid volume. Volume depletion is commonly seen with tubulointerstitial diseases (salt losing nephropathies) due to abrupt salt restriction. Volume overload is due to sodium retention leading to peripheral oedema, arterial hypertension and cardiac failure.

Higher doses of loop diuretics are recommended in CKD to force natriuresis. Though thiazide diuretics have very little role in CKD, loop diuretics can be combined with metolazone (thiazide) to promote natriuresis as it acts by blocking sodium chloride co transporter in the distal convoluted tubule thereby favouring increased sodium excretion. Metolazone is typically advised to be taken about half an hour to 45 minutes before the dose of loop diuretics such as furosemide/ torsemide.

HYPERKALEMIA

In CKD, as GFR decreases there is proportional reduction in the potassium excreting capacity of the kidney which in turn is compensated by increasing extra renal loss of potassium (i.e GIT) and by stimulating aldosterone secretion. These adaptive mechanisms fail when the GFR reduces to <10 ml/min/1.73 m^2.

The major causes of hyperkalemia in CKD is consuming diet rich in potassium, hemolysis, metabolic acidosis, protein breakdown and drugs such as ACE-I, ARBs, aldosterone antagonists and NSAIDs.
Treatment is based on severity of hyperkalemia.

Mild hyperkalemia (serum K^+ <6 mmol/L) is treated with loop diuretics, potassium binders such as Kayexalate.

Moderate hyperkalemia (serum K^+ 6-7 mmol/L) is treated with glucose with insulin, sodium bicarbonate and nebulized salbutamol

Severe hyperkalemia (serum K^+ >7mmol/L) is treated with calcium chloride or calcium gluconate, sodium bicarbonate, glucose with insulin, nebulized salbutamol, loop diuretics, kayexalate enema and hemodialysis.

METABOLIC ACIDOSIS

In the initial stages a normal anion gap metabolic acidosis is seen. But with advanced stages with reduced GFR and urinary acid excretion, a high anion gap metabolic acidosis sets in which in turn causes metabolic derangements by aggravating hyperkalemia and cellular dysfunction at all levels. Treatment is either by IV sodium bicarbonate or oral bicarbonate supplements based on severity. Hemodialysis is preferred in patients with refractory metabolic acidosis.

HEMATOLOGICAL CHANGES IN CKD

ANAEMIA

Anaemia is the most important hematological derangement in CKD. The major causes of anaemia in CKD are:

- Anaemia of Chronic disease
- Iron deficiency
- Erythropoietin deficiency
- Serum Vitamin B_{12} and folate deficiency
- Gastrointestinal blood loss
- Pure red cell aplasia due to ESA
- Shortened lifespan of RBCs
- ESA resistance
- Aluminium toxicity

- Bone marrow failure due to fibrosis

Peripheral smear of blood shows normocytic, normochromic or hypochromic RBCs depending on presence of coexistent iron deficiency. Iron profile study shows normal or increased ferritin, reduced serum iron, normal or increased total iron binding capacity (TIBC)

Patient is evaluated for establishing cause of anaemia before proceeding with therapy and the investigations needed for evaluation are

- Complete blood count (CBC)
- Serum ferritin levels
- Serum vitamin B_{12} and folate levels
- Absolute reticulocyte count
- Serum transferrin saturation (TSAT)

TREATMENT OF ANAEMIA

Treatment of anaemia depends upon the underlying cause and involves iron supplementation, blood transfusions, ESA initiation etc.,

Treatment should always be based on target haemoglobin to be achieved, urgency for treatment with careful consideration of benefits and risks involving each treatment and appropriate tailoring of the treatment according to the patient's tolerance, adverse effect profile while ensuring adequate compliance to treatment.

IRON THERAPY

A trial of IV iron agent may be tried in adult CKD patients not on ESA/iron therapy or on ESA but not on iron therapy if TSAT<30% and ferritin <500ng/ml.

The route of iron administration should be based on severity of iron deficiency, response to prior oral iron therapy, compliance of the patient, availability of venous access, side effects to prior oral or IV iron therapy and cost.

Oral iron therapy is recommended in pediatric CKD patients with anaemia not on ESA/ iron therapy if TSAT<20% and ferritin <100ng/ml. IV Iron is avoided in the presence of active infections.

IRON SELECTION AND DOSING

ORAL IRON	Daily dose of 200 mg of elemental iron
Ferrous gluconate	• 325 mg PO TID (35 mg of elemental iron/tablet, requires 2 tablets)
Ferrous sulfate tablets	• 325 mg PO TID (65 mg of elemental iron/tablet, requires 3 tablets)
Ferrous sulfate elixir	• 220 mg/5 mL elixir PO TID
Ferrous fumarate	• 325 mg PO TID (108 mg of elemental iron/tablet, requires 6 tablets)
Iron Polysaccharide (assess mg of elemental iron in each form, dose to 200 mg of elemental iron)	• Tablet: 50 to 100 mg PO BID • Capsule: 105 to 300 mg PO QD • Elixir:100 to 200 mg of elixir PO QD
IV IRON	
Iron sucrose	Pre-dialysis 200 mg IV over 2 hours, monthly
Iron dextran	500 mg/day IV is individualized based on weight and Hb to a maximum of 1,000 mg in 250-1,000 mL infused over 1-6 hrs
Ferumoxytol	510 mg IV over 1 mL/sec (30 mg/sec), followed by a second 510 mg IV 3 to 8 days later.

ESA AGENTS

Before initiating therapy with ESA agents all correctable causes of anaemia should be treated.

ESA should be used with caution in patients with active malignancy if cure is expected.

Benefits and risks of using ESA agents as therapy should be weighed before initiation of therapy.

Risks of ESA agents include hypertension and increased chances of stroke.

In CKD 5D patients ESA therapy is initiated to maintain Hb>9g/dl. Hb correction should not exceed 11.5g/dl in patients on ESA therapy; If it increases beyond 11.5g/dl then ESA dose should be reduced by 25%.

In pediatric CKD patients target Hb is between 11-12g/dl.

The following are the types of ESAs available:

- Erythropoietin (Epo)
- Epoetin alfa (Procrit/Epogen)
- Epoetin beta (NeoRecormon)
- Darbepoetin alfa (Aranesp)
- CERA (Mircera)

ESA DOSING

- Epoetin alpha and beta – 20 - 50 IU/kg / 3 weeks
- Darbopoietin alpha- 0.45 µg/ kg /week SC or IV administration or 0.75 µg/kg / 2 weeks by SC administration
- CERA- 0.6 µg/ kg /2 weeksSC or IV for CKD ND and CKD 5D patients respectively.
- ESA agents to be started at a lower dose in patients with previous history of stroke, thrombo-embolism, seizures, hypertension and CAD.

BLOOD TRANSFUSION

Red blood cell transfusions are avoided to the maximum possibility

- To minimize general risks of transfusion
- When planned for renal transplantation to minimize allosensitization

Red blood cell transfusion is indicated:

- When ESA therapy is not effective in cases with hemoglobinopathies, bone marrow failure and ESA resistance
- When rapid correction is needed pre-operatively
- To stabilize the patient’s clinical condition in cases of acute haemorrhage and unstable coronary artery disease

Bleeding diathesis due to uremia induced platelet dysfunction

Immune dysfunction due to reduced chemotactic activity of neutrophils, reduced phagocytic activity of macrophages, reduced complement activity, non-selective proteinuria leading to loss of immunoglobulins which in turn leads to increased susceptibility to common infections and opportunistic infections in advanced stages.

CKD AND BONE

Disorders of mineral metabolism in CKD results in both skeletal and extra-skeletal manifestations.

Mineral and bone metabolism disorder in CKD manifests as:

- Abnormalities of calcium, phosphorous, parathormone and vitamin D metabolism
- Abnormalities of bone turnover
- Vascular and soft tissue calcification

RENAL OSTEODYSTROPHY

PATHOGENESIS

High turnover bone disease

Secondary hyperparathyroidism in CKD is the cause for high turnover bone disease. In the early stages of CKD, there will be parathyroid gland hyperplasia and increased levels of parathormone in blood. These changes are caused by hypocalcemia, hyperphosphatemia, reduced synthesis of calcitriol, parathormone resistance, and intrinsic alterations in parathyroid gland.

Low turnover bone disease

Low turnover bone disease is characterised by depressed bone formation which is mainly seen in patients on dialysis. Osteomalacia can also occur mainly due to accumulation of aluminium at bone surfaces. Aplastic bone disease can be seen even before dialysis.

Mixed osteodystrophy

It includes features of both high turnover bone disease and low turnover bone disease.

HYPERTENSION

Hypertension though commonly occurs in CKD patients is not always treated. The most common change in blood pressure in dialysis patients is isolated systolic hypertension with increased pulse pressure which is due to arterial medial sclerosis and stiffening of vessel wall. Vessel stiffness leads to increased pulse wave velocity leading to increased systolic peak pressure. The relationship between BP and mortality is U shaped; isolated increased systolic BP and increased pulse pressure indicates high long term risk in dialysis patients, while low mean and diastolic BP predict early mortality.

DYSLIPIDEMIA

As CKD progresses there is increase in apo B containing lipids and decrease in apo A containing in lipids.

HDL cholesterol levels decrease and LDL, IDL, VLDL cholesterol, lipoprotein (a) levels and triglyceride levels increase as CKD progression occurs.

Dialysis patients are associated with increased oxidized LDL and decreased HDL irrespective of the type of dialysis.

PD patients have both hypercholesterolemia and hypertriglyceridemia in contrast to HD patients.

Elevated lipoprotein (a) levels are associated with increased CVD mortality

CKD AND NERVOUS SYSTEM

Uraemic encephalopathy

It may present as acute or subacute organic brain syndrome when GFR declined to less than 10% of normal. The clinical presentation of uraemic encephalopathy includes altered consciousness, psychomotor disturbances and disorders of thinking, memory, speech, perception and emotion**.**

Peripheral neuropathy

The classical features of peripheral neuropathy are seen in advanced stages (stage IV and V) of CKD. Sensory neuropathy is more common than motor neuropathy. Lower extremities are involved more than upper extremities and there is a predilection to involve distal than proximal parts of limbs.

Restless leg syndrome

The restless leg syndrome is one of the treatable causes of sleep disruption in end stage renal disease. It is a neurological movement disorder of the limbs associated with sleep disturbances. It is characterised by unpleasant sensations in legs and feet requiring frequent

limb movement. The urge to move limbs is more during rest and gets relieved with movements.

CKD and GIT

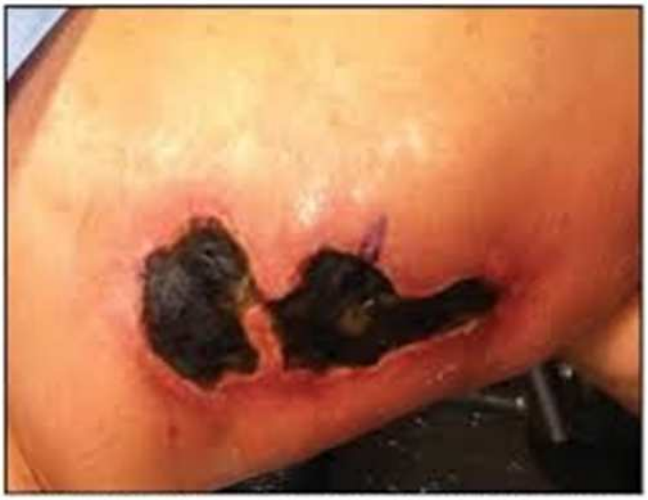
Uraemic gastritis, peptic ulcer disease and mucosal ulcerations can be seen anywhere in gastrointestinal tract in patients with chronic kidney disease.

METABOLIC DISTURBANCES

Fasting hyperinsulinemia and tendency for recurrent hypoglycaemia are seen in patients with end stage renal disease . Insulin requirement gets reduced in late stages of CKD. The other abnormalities seen are impaired glucose tolerance and reduced insulin sensitivity.

DERMATOLOGICAL ABNORMALITIES

The most common dermatological abnormalities seen in CKD include pruritus and skin excoriation. Abnormal calcium and phosphorus metabolism can lead to vascular and soft tissue calcification which results in skin and soft tissue necrosis. It is known as calciphylaxis seen mainly due to secondary hyperparathyroidism.



CKD AND HEART

CKD is an important and significant predictor of cardiovascular mortality. The incidence of cardiovascular events in patients with CKD is markedly increased when compared to the age matched counterparts in the general population.

RISK FACTORS

Traditional CVD Risk Factors	"Nontraditional" CVD Risk Factors
Older age	Type (diagnosis) of CKD
Male gender	Decreased GFR
White race	Proteinuria
Hypertension	Renin-angiotensin system activity
Elevated LDL cholesterol	Extra-cellular fluid volume overload
Decreased HDL cholesterol	Abnormal calcium and phosphorus
Diabetes mellitus	metabolism
Tobacco use	Dyslipidemia
Physical inactivity	Anemia
Menopause	Malnutrition
Psychosocial stress	Inflammation
Family history of CVD	Infection
	Thrombogenic factors
	Oxidative stress
	Elevated homocysteine
	Advanced glycation end-products (AGEs)
	Uremic toxins

- Age, Gender and Smoking:

  Increasing age is associated with increased prevalence of CVD in CKD patients.

  Gender distribution shows that females are associated with increased risk of mortality due to CVD.

  Smoking acts as one of the independent risk factors of mortality due to CVD in CKD

- Diabetes mellitus :

  It is the most common cause of ESRD. DM associated CKD patients have a greater chance for being initiated on RRT earlier. Multiple factors along with DM are involved in occurrence of CVD in CKD such as dyslipidemia, hypertension, oxidative stress and protein energy wasting.

- Hypertension :

  Hypertension though commonly occurs in CKD patients is not always treated. The most common change in blood pressure in dialysis patients is isolated systolic hypertension with increased pulse pressure which is due to arterial medial sclerosis and stiffening of vessel wall. Vessel stiffness leads to increased pulse wave velocity leading to increased systolic peak pressure.

This in turn leads to progressive left ventricular dysfunction and subsequently CHF which results in reduced mean arterial and diastolic BP and increased risk of cardiovascular death.

- Dyslipidemia :

As CKD progresses there is increase in apo B containing lipids and decrease in apo A containing in lipids.

HDL cholesterol levels decrease and LDL, IDL, VLDL cholesterol, lipoprotein (a) levels and triglyceride levels increase as CKD progression occurs.

Dialysis patients are associated with increased oxidized LDL and decreased HDL irrespective of the type of dialysis.

PD patients have both hypercholesterolemia and hypertriglyceridemia in contrast to HD patients.

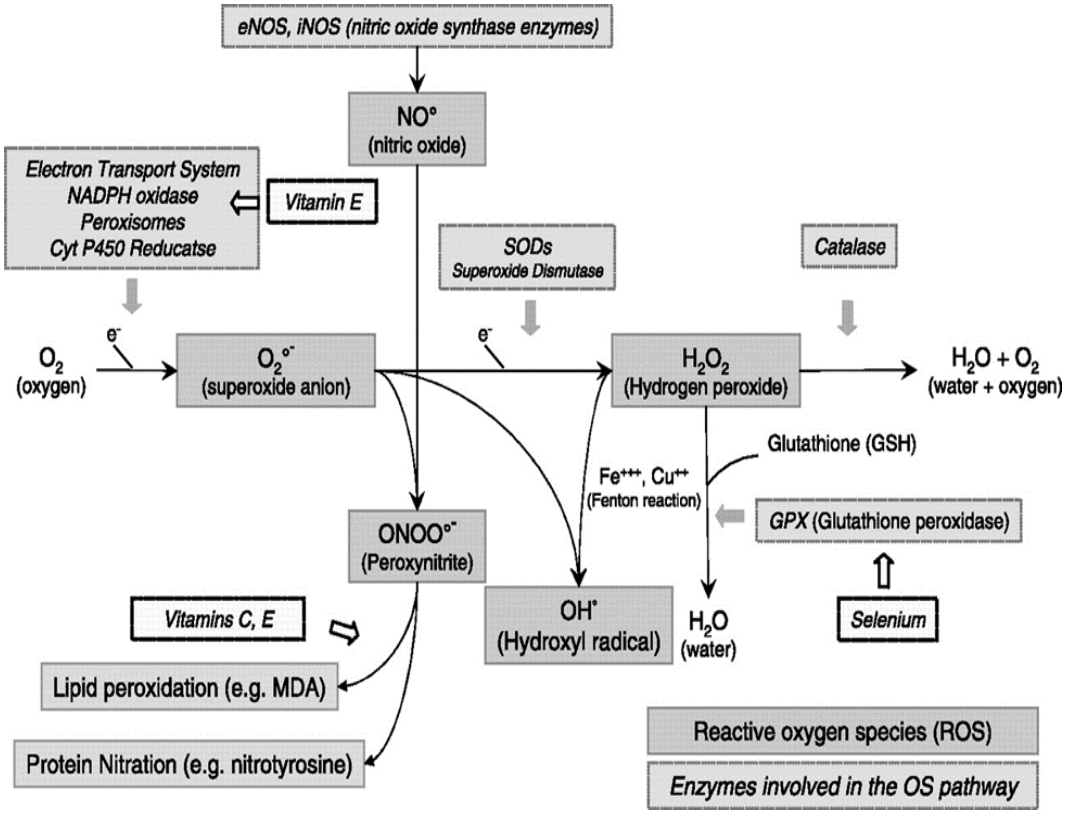
There is a weak correlation between CVD, hypercholesterolemia in CKD patients as in the case of cardiomyopathy and arteriosclerosis which may be less dependent on lipid abnormalities than on other factors.

In fact, low cholesterol level is associated with poor survival in HD patients than high cholesterol due to confounding PEW and inflammation which is a paradoxical occurrence.

Elevated lipoprotein (a) levels are associated with increased CVD mortality.

- Oxidative stress :

It is an important factor involved in pathogenesis of atherosclerosis and resulting atherosclerotic cardiac events. There are four oxidative stress pathways which can be hypothesized in CKD which are : carbonyl stress, nitrosative stress, chlorinated stress and classical oxidative stress.



- Inflammation :

Inflammatory biomarkers such as IL-6, CRP, WBC Count, fibrinogen are strong predictors of mortality in CKD patients.

- Hypoalbuminemia :

  In association with systemic inflammation, it acts as a strong predictor in CKD outcome.

- Endothelial dysfunction :

  Markers of endothelial dysfunction - pentraxin3, adhesion molecules and ADMA are independent predictors of mortality in CKD patients.

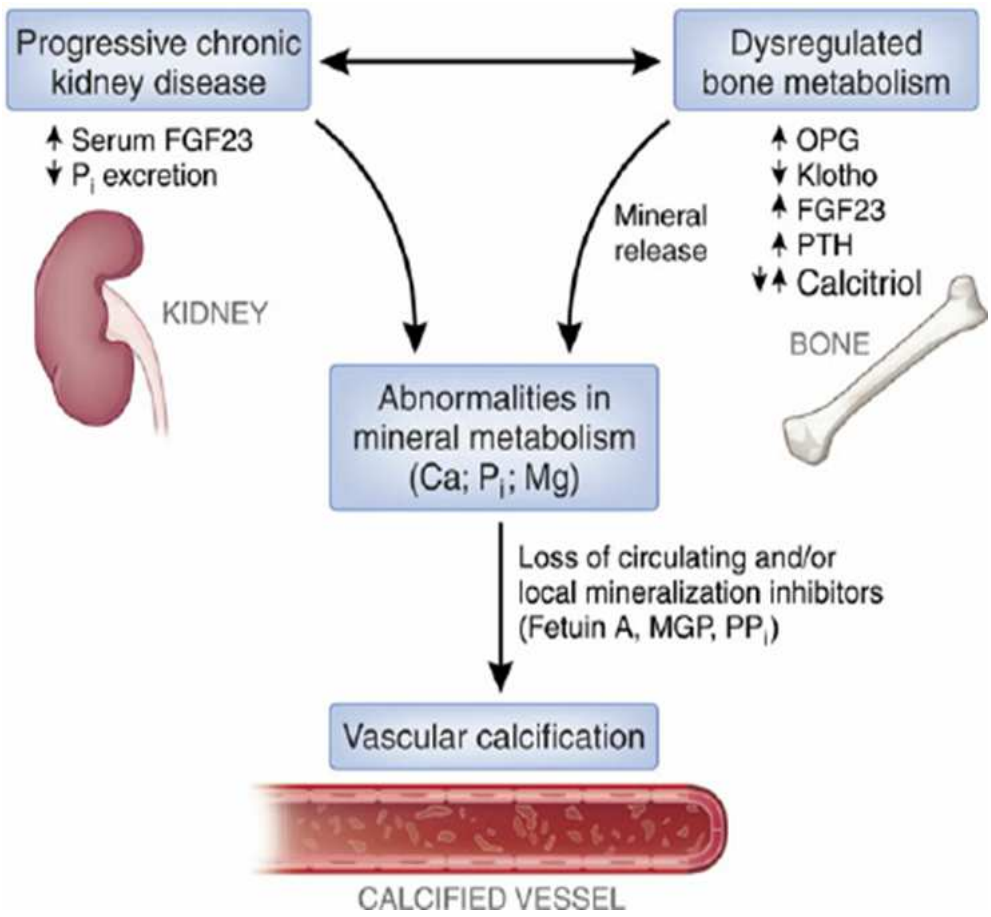
- Anaemia :

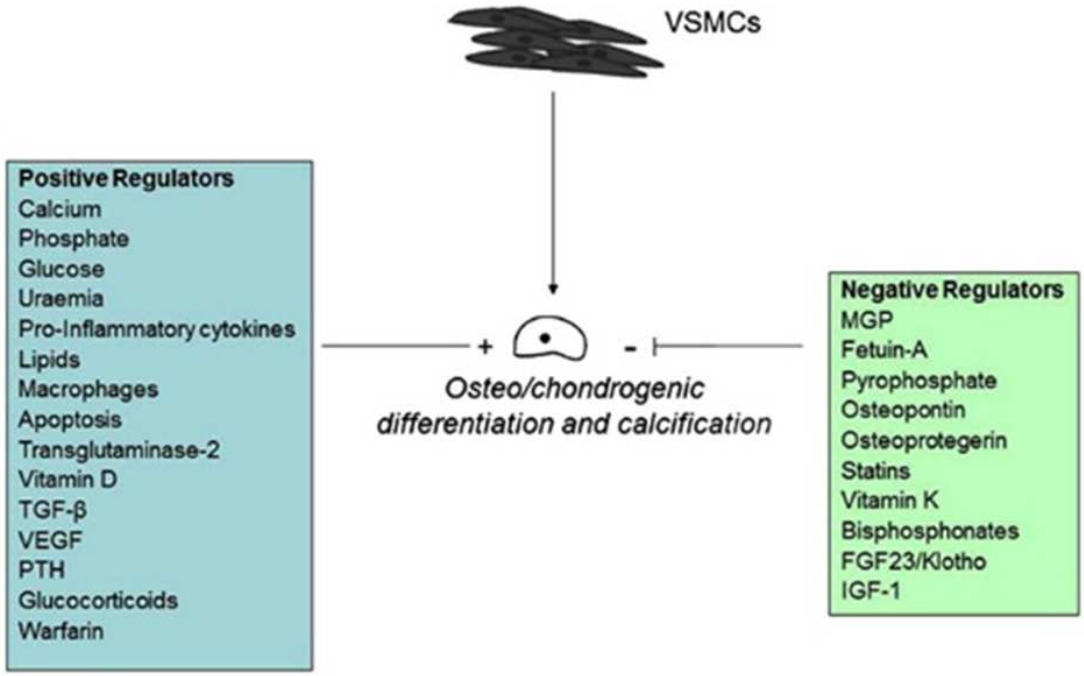
  It is one of the major causes of left ventricular hypertrophy and dysfunction in CKD.

- Cardiovascular Calcification :

  Cardiovascular calcification usually occur in the tunica media of arteries, myocardium, heart valves and atherosclerotic plaques.

  Medial calcification leads to arterial stiffness causing increase in pulse pressure. Atherosclerotic calcification is a potent cardiovascular risk event.


Progressive chronic kidney disease
Dysregulated bone metabolism
Serum FGF23
P_i excretion
KIDNEY
Mineral release
OPG
Klotho
FGF23
PTH
Calcitriol
BONE
Abnormalities in mineral metabolism (Ca; P_i; Mg)
Loss of circulating and/or local mineralization inhibitors (Fetuin A, MGP, PP_i)
Vascular calcification
CALCIFIED VESSEL

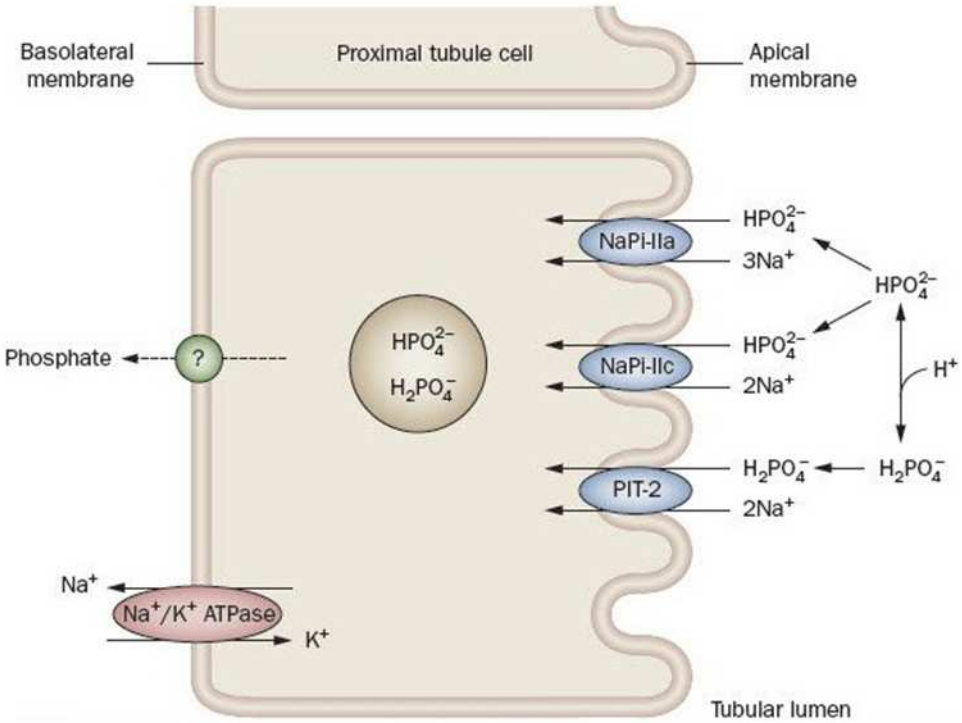

VSMCs
Positive Regulators
Calcium
Phosphate
Glucose
Uraemia
Pro-Inflammatory cytokines
Lipids
Macrophages
Apoptosis
Transglutaminase-2
Vitamin D
TGF-β
VEGF
PTH
Glucocorticoids
Warfarin
+
-
Osteo/chondrogenic differentiation and calcification
Negative Regulators
MGP
Fetuin-A
Pyrophosphate
Osteopontin
Osteoprotegerin
Statins
Vitamin K
Bisphosphonates
FGF23/Klotho
IGF-1

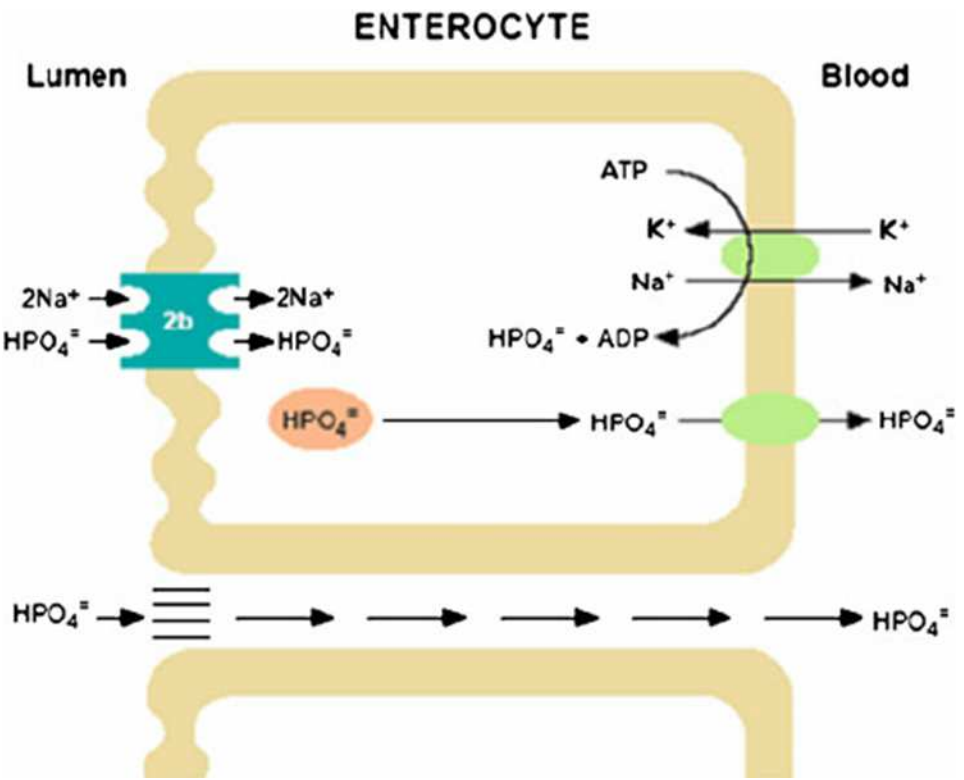
- Hyperhomocysteinemia :

  Homocysteine is a non protein sulfur-containing amino acid that may be freely oxidized (20% to 30%), protein bound (70% to 80%), or freely reduced (~1%) forms. Hyperhomocysteinemia is present in CKD patients is more than 90%. There is strong associations between total homocysteine and hypoalbuminemia, protein-energy wasting and inflammation. Hyperhomocysteinemia acts as a significant risk factor for cardiovascular events.

PHOSPHORUS METABOLISM

- Phosphorus plays an important role in bone formation, metabolism, nucleic acid synthesis and maintenance of acid-base balance
- Phosphorus is usually associated with oxygen in the form of phosphate.
- Extracellularly, phosphorus is present in bone and teeth in the form of hydroxyapatite and the serum levels account for <1%
- Phosphate balance is maintained by different mechanisms involving kidneys, parathyroid glands, bone and small intestine.
- Phosphate entry into renal tubular epithelial cell involves secondary active sodium-phosphate (Na-Pi) cotransport through three types of transporters- Na-Pi 1 in renal tubule, Na-Pi 2a and Na-Pi 2c in proximal tubule, Na-Pi 2b in gut and Na-Pi 3 (pit 1 and pit 2).
- Phosphate enters vascular smooth muscle cells through Pit1 which is thought to be the first step for start of pathologic smooth muscle calcification.
- PTH and FGF 23 are the two major phosphate excretion promoting hormones.
- Other factors which regulate serum phosphate are growth hormone, insulin.





Phosphate absorption in intestine

EFFECTS OF PTH ON PHOSPHATE

Parathyroid hormone is a major and potent regulator of phosphate metabolism.

It regulates serum phosphate by three mechanisms.

- By stimulating osteoclastic activity which in turn mobilises phosphate from bone into the blood thereby increasing serum phosphate.
- By suppressing reabsorption of phosphate in the proximal renal tubules by promoting internalization of NaPi-2a and 2c transport proteins from the luminal side thereby increasing phosphate excretion.
- By increasing production of calcitriol by inducing renal expression of 1-alpha hydroxylase thereby increasing intestinal phosphate absorption through indirect effects.

Intestinal phosphate absorption also acts as an important factor for maintaining serum phosphate.

In CKD patients, phosphate increases PTH production by post transcriptional stabilization of PTH messenger RNA.

EFFECTS OF FGF 23 ON PHOSPHATE

FGF 23 is a protein fragment produced by osteocytes which plays an important role in phosphate metabolism.

Its role in phosphate metabolism occurs by the following mechanisms :

- By suppressing expression of Na-Pi-2a and 2c cotransporters in renal tubules either directly or indirectly through parathormone thereby increasing phosphate excretion
- By decreasing production of calcitriol through suppression of renal expression of 1 alpha hydroxylase activity thereby decreasing intestinal phosphate reabsorption indirectly.
- By also increasing degradation of calcitriol by increasing synthesis of catabolic enzyme 24-hydroxylase.

In CKD patients, with declining renal function there is progressive increase in FGF 23 level and is maximum in the advanced stages of kidney disease.

FGF 23 acts at both proximal tubules and distal tubules, the former being klotho independent action. Non specific effects of FGF 23 which are klotho independent are activated if FGF 23 levels are very high as occurring in CKD. These are induction of cardiac hypertrophy and fibrosis, increased expression of cytokines in liver, reduced leukocyte

recruitment resulting in impaired immune response and increased TGF beta production promoting fibrosis.

KLOTHO AND FGF 23

Klotho, a type 1 membrane protein acts as a cofactor for FGF 23 without which FGF 23 cannot execute many of its functions.

It has a single transmembrane stretch of amino acids with N-terminus on the extra-cellular side and C-terminus on the cytoplasmic side.

It is commonly expressed in the distal tubules of kidney, parathyroid gland and choroid plexus of brain

FGF 23 exerts its functions by binding to FGF receptors (FGFR) of which FGFR1 is the most important receptor.

Klotho can bind to all types of FGF receptors (FGFR) and the Klotho-FGFR complex has high affinity for FGF 23 when compared with binding to either Klotho or FGFR alone. This explains the necessity of klotho as a cofactor for FGF 23 binding to FGFR1 to exert its various functions.

FGF 23 action in the distal tubules is klotho dependent which is the major mechanism by which FGF 23 mediates phosphate homeostasis, whereas its action in the proximal tubules is klotho independent.

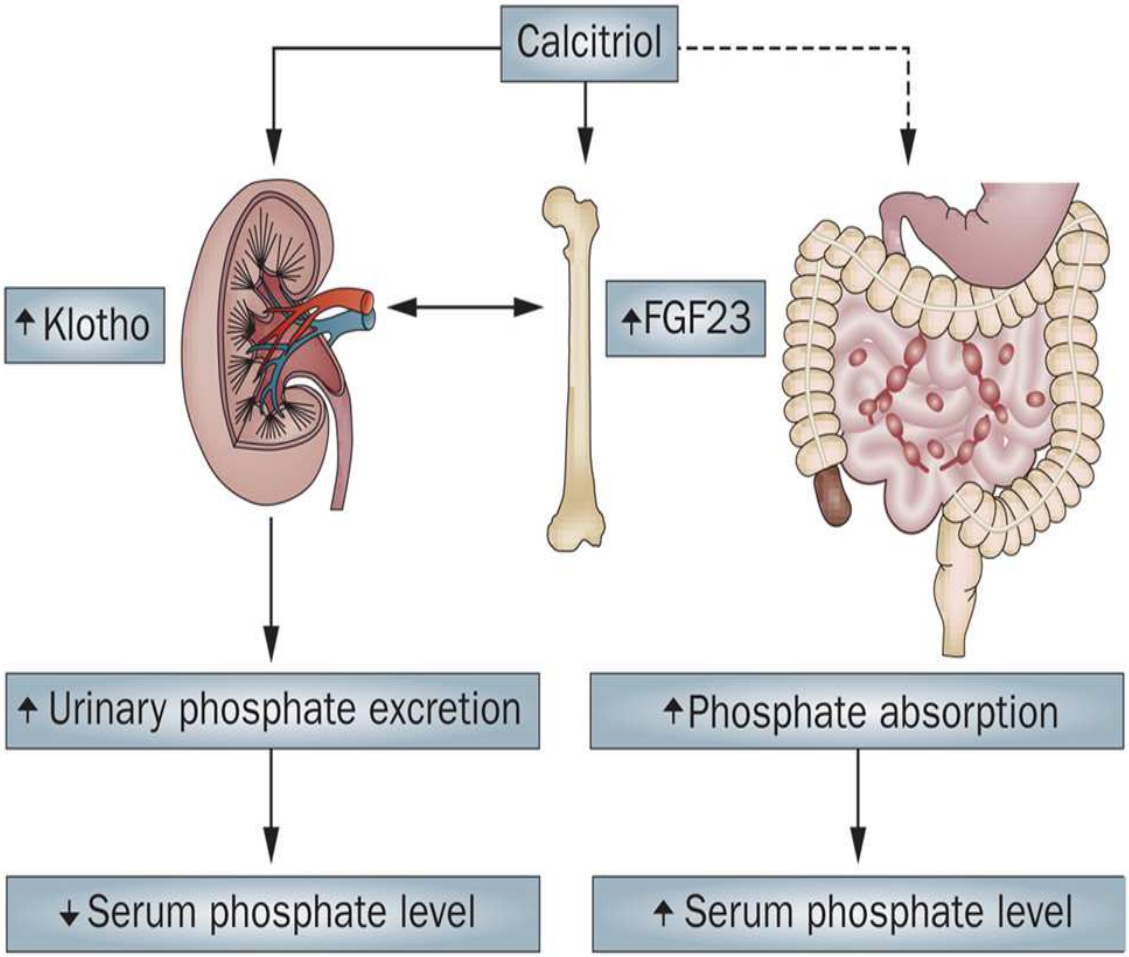
EFFECTS OF VITAMIN D ON PHOSPHATE

The mechanisms by which calcitriol (1,25 dihydroxy cholecalciferol), the active form of vitamin D modulates phosphate metabolism are :

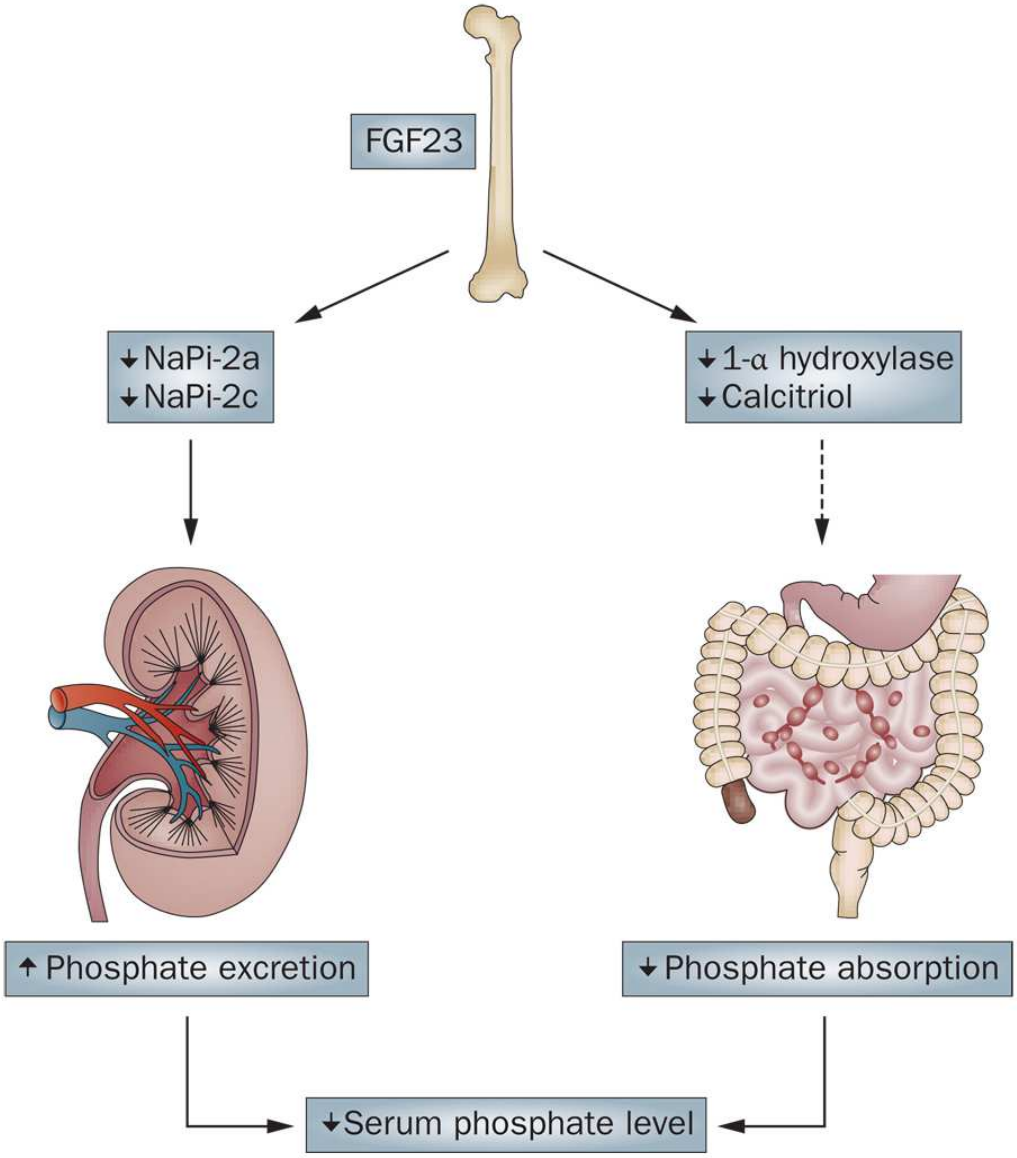
- By increasing expression of transporter Na-Pi-2b in intestine, thereby increasing intestinal transcellular phosphate absorption- direct effect
- By suppressing production of PTH thereby decreases renal reabsorption of phosphate though proximal tubules.
- By increasing FGF 23 production thereby decreases renal reabsorption of phosphate.

Vitamin D levels are in turn regulated by various factors such as:

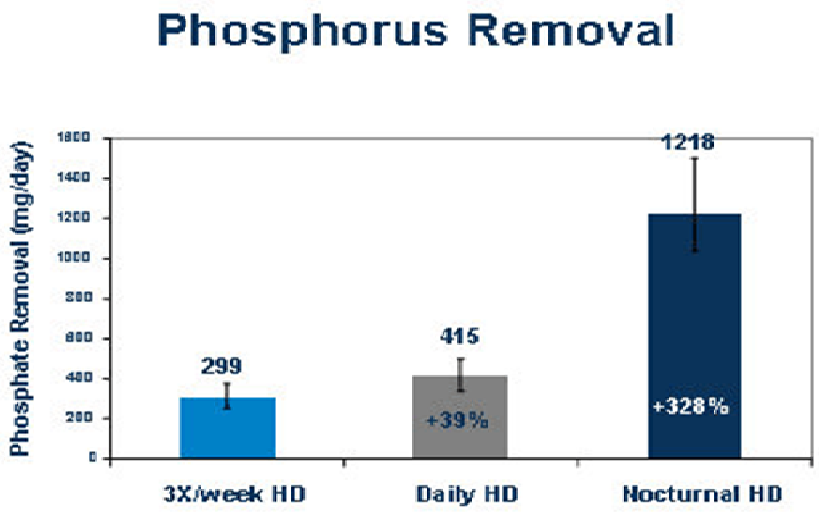
- Increased serum phosphate reduces calcitriol levels.
- Increased FGF 23 reduces calcitriol levels.
- PTH increases production of calcitriol by stimulating renal 1 alpha hydroxylase enzyme.
- Hypercalcemia and Calcitriol itself reduces production of calcitriol.



Effects of Vitamin D on serum phosphate



Effects of FGF 23 on serum phosphate



DIALYSIS PHOSPHATE REMOVAL 3 TIMES A WEEK		
DIET	1000 mg/day 7 x 1000 per week	7000 mg
ABSORPTION	60 % 7000 x 60 %	4200 mg
DIALYSIS	800 mg per HD 3 x 800 mg per week	2400 mg
BALANCE	4200-2400	1800 mg per week

CAROTID INTIMAL MEDIAL THICKNESS (CIMT)

Intimal medial thickness is the thickness of the intimal and medial layers of vessel wall.

Normal vessel wall has three layers from inner to outer, namely tunica intima, tunica media and tunica adventitia.

It is a direct marker of atherosclerosis and predicts cardiovascular mortality.

It is non-invasive, economic and cheap when compared to invasive methods to detect atherosclerosis such as angiogram.

IMT can be measured using external high resolution ultrasound or magnetic resonance imaging (MRI).

Ultrasound using B mode with 5-15 Hz frequency can be done in large accessible vessels such as carotid, radial, brachial and femoral arteries.

Of these carotid artery is the preferred vessel for measuring IMT.

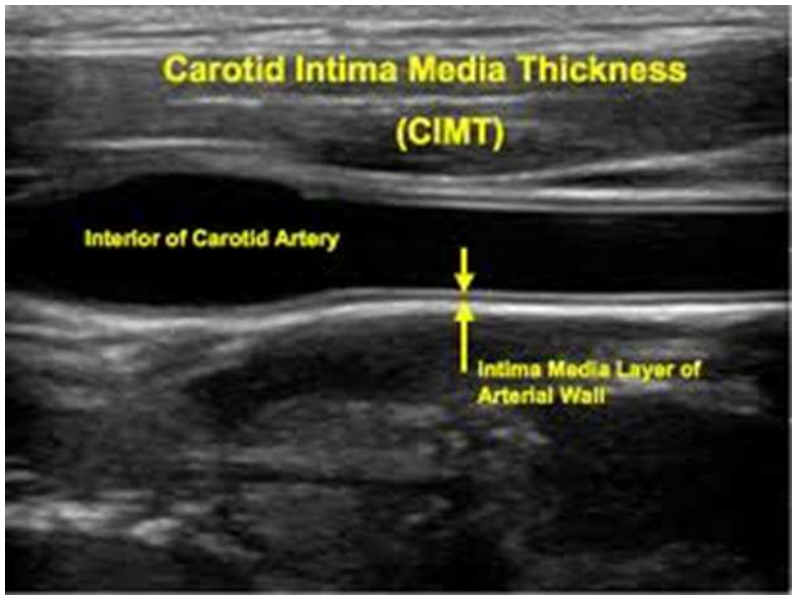
It is usually measured at three locations namely, distal common carotid artery, carotid bifurcation and proximal internal carotid artery on both sides.

Usually images are obtained from the near and far walls of both sides carotid arteries of which the measurements made from the far walls are considered more reliable.

Measurements made in plaque associated areas are better excluded as it gives a grossly elevated value and it is better interpreted as presence of plaques separately.

CIMT measurement is mainly used as a tool in screening atherosclerosis, calculating risk of future cardiovascular events and assessment of drug efficacy.

With patient lying in supine position, initially transverse view is used to locate best site for measuring CIMT. Then either anterolateral or posterolateral approach is used and CIMT measured by using calipers in ultrasound from start of first white line to end of second white line. 3 readings are taken on each side and average of them is used. CIMT of more than 1 mm is considered significant.



MATERIALS AND METHODS

SOURCE OF DATA:

Patients admitted in Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 diagnosed to have non-diabetic CKD, fulfilling the inclusion and exclusion criteria were included in the study group. 100 such patients were taken up for this study.

STUDY DESIGN:

Hospital based Observational study

STUDY DURATION:

6 months : Jan 2018 – June 2018

INCLUSION CRITERIA:

Patients with chronic kidney disease of stages 3,4 and 5

EXCLUSION CRITERIA:

- Patients with prior history of diabetes, coronary artery disease and stroke.
- Patients with fundoscopic evidence of diabetic retinopathy

DATA COLLECTION AND METHODS:

All non-diabetic chronic kidney disease patients had their clinical history taken and subjected to detailed clinical examination and the following investigations :

- Hemoglobin
- Erythrocyte sedimentation rate (ESR)
- Serum creatinine
- Serum Calcium
- Serum Phosphorus
- Fasting lipid profile
- Urine spot protein creatinine ratio
- Carotid artery Doppler
- Fundus examination
- Echocardiogram

The outcomes were documented using proforma.

STASTICAL METHODS APPLIED:

Statistics was analyzed using Epi Info and SPSS 20. The variables with $p < 0.05$ were considered significant.

CONSENT

Written consent from patients and attenders were obtained.

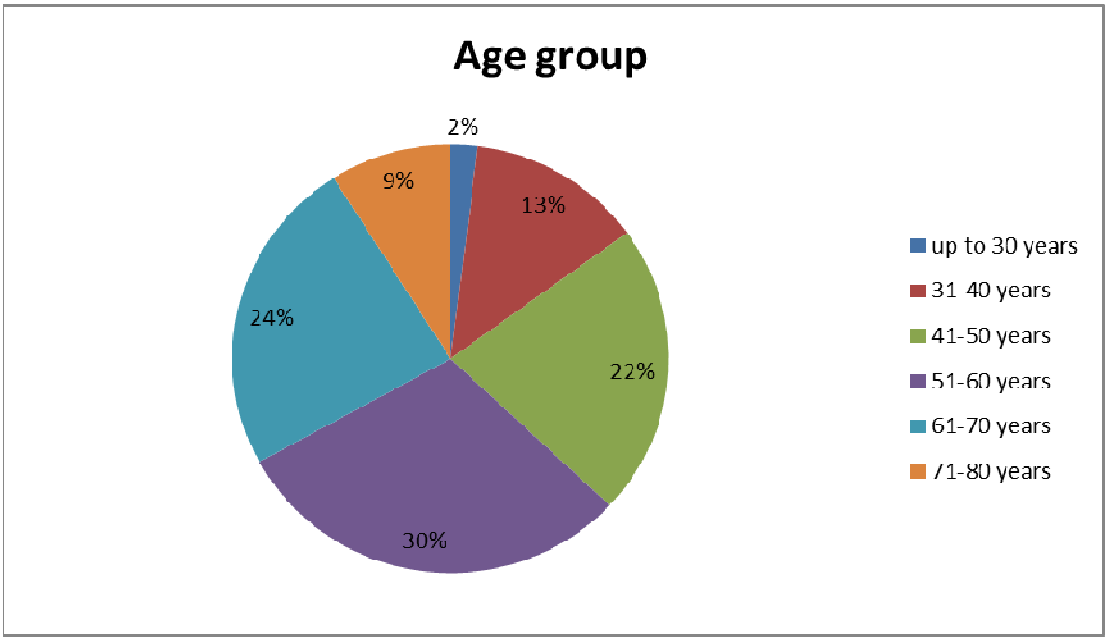
ETHICAL COMMITTEE APPROVAL

Institutional ethical committee of Madras Medical College approved the study.

OBSERVATION AND RESULTS

AGE DISTRIBUTION

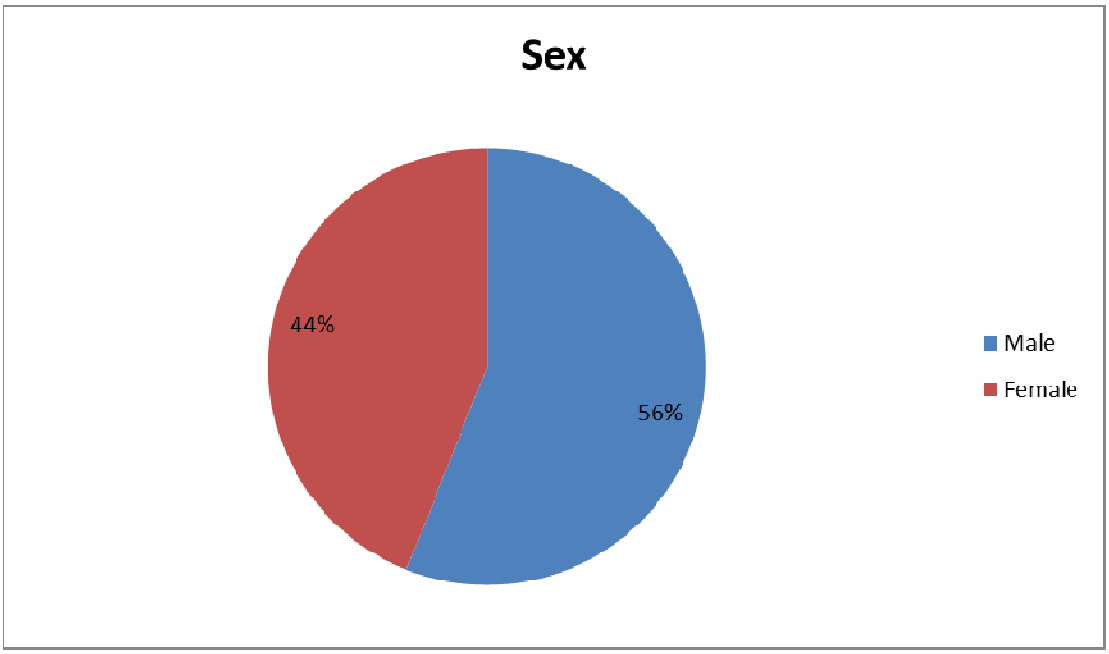
Age group	Frequency	Percent
up to 30 years	2	2.0
31-40 years	13	13.0
41-50 years	22	22.0
51-60 years	30	30.0
61-70 years	24	24.0
71-80 years	9	9.0
Total	100	100.0



In this study conducted in 100 patients, 30% belonged to 51-60 years, 24% to 61-70 years, 22% to 41-50 years, 13% to 31-40 years, 9% to 71-80 years and 2% to less than 30 years of age.

GENDER DISTRIBUTION

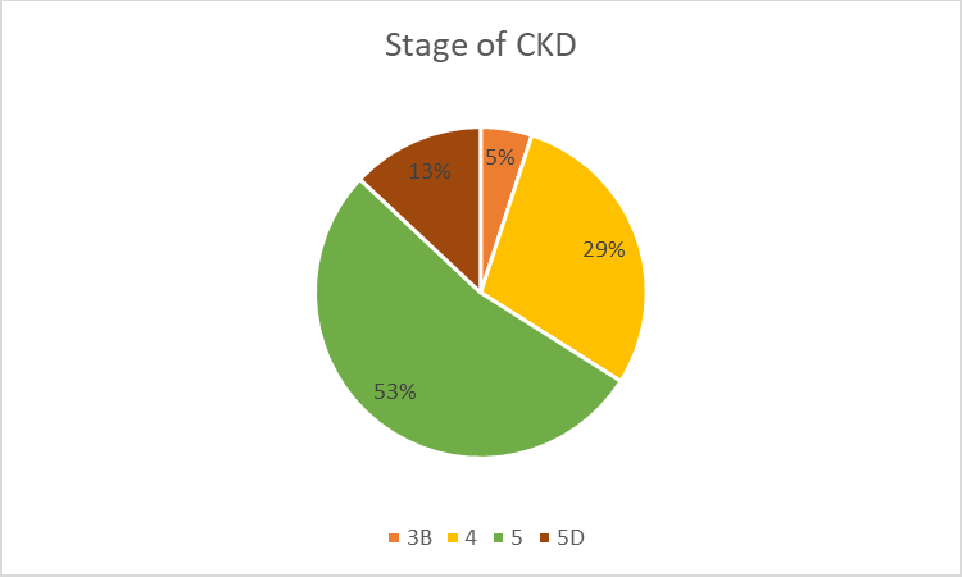
Sex	Frequency	Percent
Male	56	56.0
Female	44	44.0
Total	100	100.0



Of the 100 patients, 56 were males and 44 were females.

STAGE OF CKD DISTRIBUTION

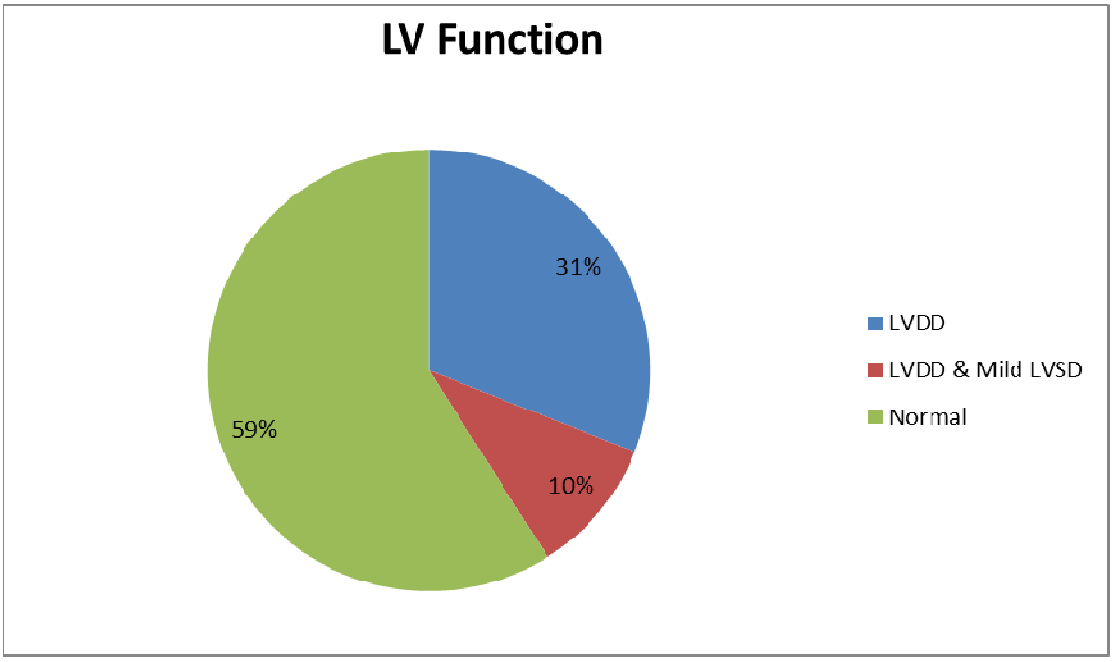
Stage of CKD	Frequency	Percent
3B	5	5.0
4.00	29	29.0
5.00	53	53.0
5 D	13	13.0
Total	100	100.0



In the study, 53 patients belonged to stage V, 29 patients to stage IV, 13 patients to stage VD and 5 patients to stage IIIB.

LEFT VENTRICULAR FUNCTION DISTRIBUTION

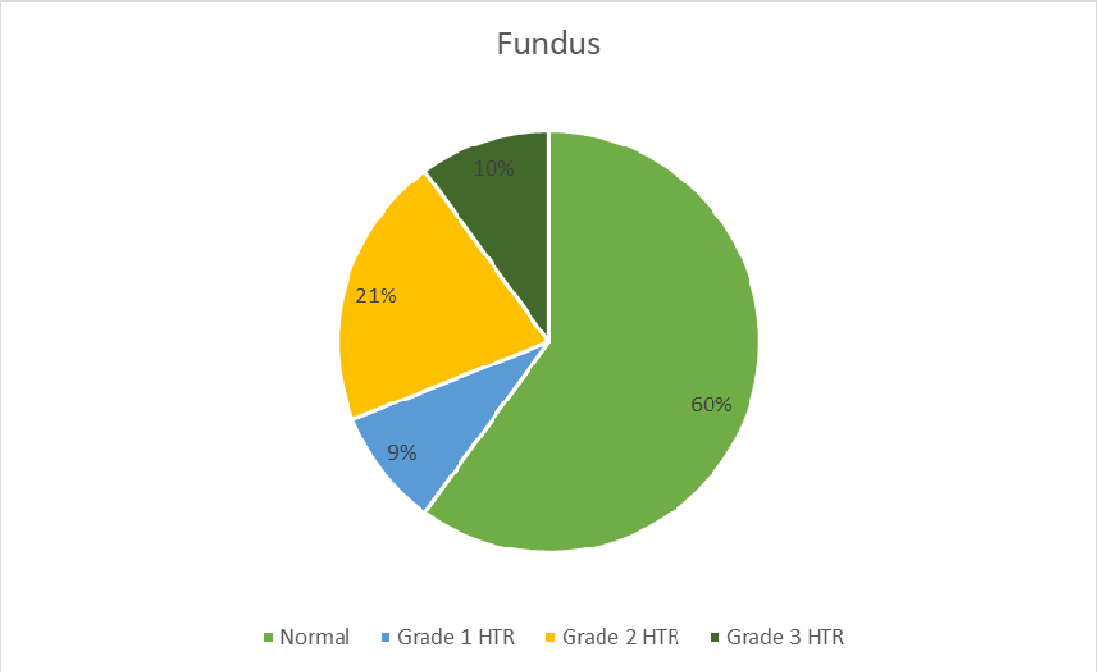
LV Function	Frequency	Percent
LVDD	31	31.0
Mild LVSD & LVDD	10	10.0
N	59	59.0
Total	100	100.0



In this study, 31 patients had LV diastolic dysfunction, 10 patients had both LVDD & Mild LV systolic dysfunction and 59 patients had normal LV function.

FUNDUS FINDINGS DISTRIBUTION

Fundus	Frequency	Percent
Normal	60	60.0
Grade 1 HTR	9	9.0
Grade 2 HTR	21	21.0
Grade 3 HTR	10	10.0
Total	100	100.0

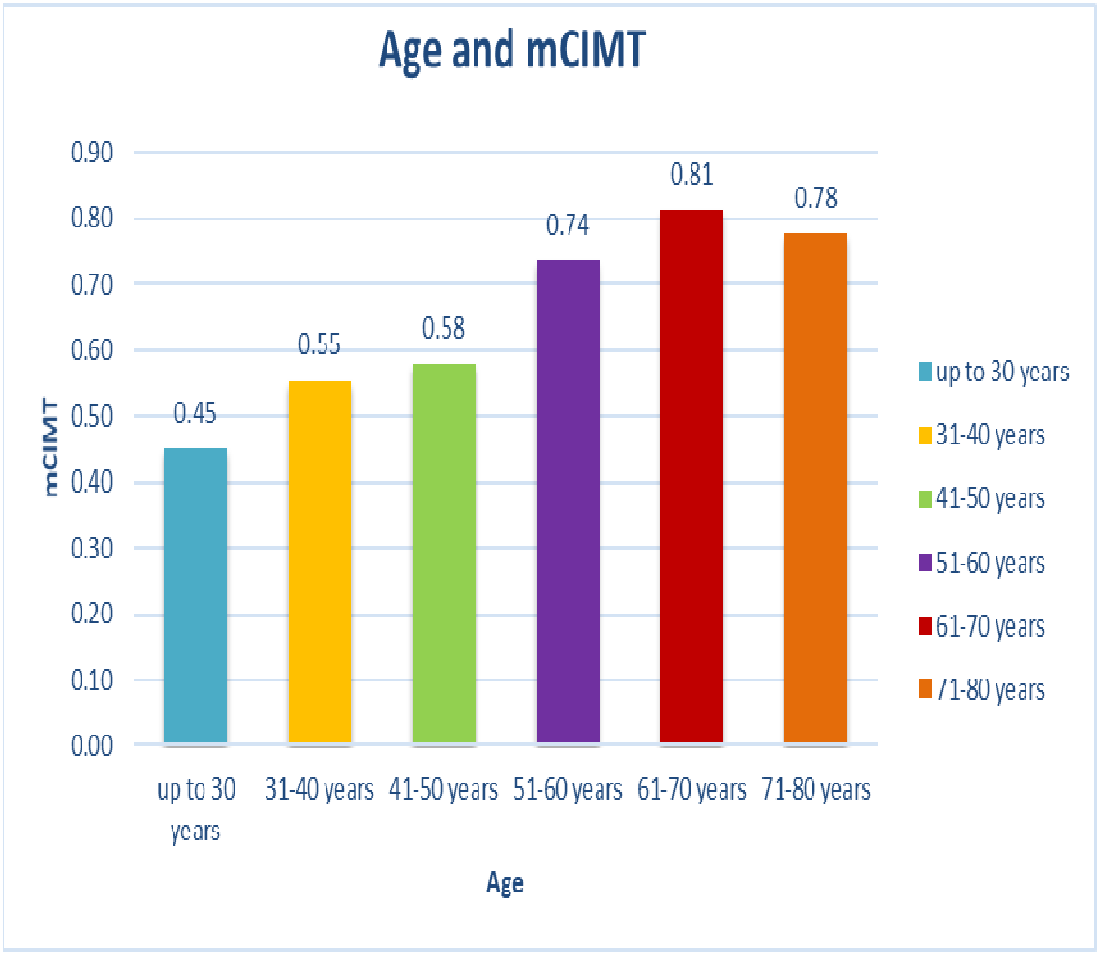


In this study, 10 patients had grade 3 hypertensive retinopathy, 21 patients had grade 2 hypertensive retinopathy, 9 patients had grade 1 hypertensive retinopathy and 60 patients had normal fundi.

AGE AND CIMT

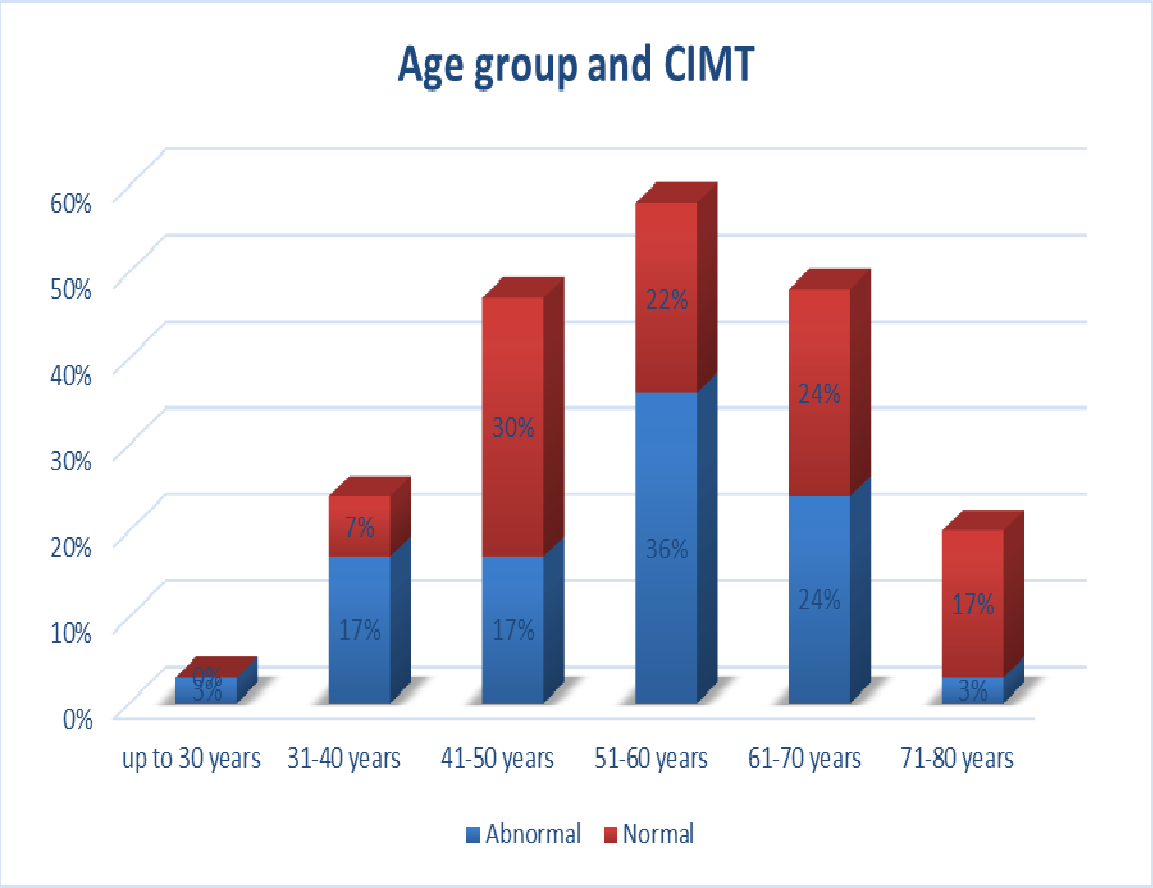
Mean CIMT

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	f value
					Lower Bound	Upper Bound			
up to 30 years	2	.4500	.07071	.05000	-.1853	1.0853	.40	.50	
31-40 years	13	.5538	.11808	.03275	.4825	.6252	.40	.80	
41-50 years	22	.5795	.08261	.01761	.5429	.6162	.45	.75	15.589**
51-60 years	30	.7353	.14294	.02610	.6820	.7887	.50	1.10	
61-70 years	24	.8133	.12903	.02634	.7588	.8678	.60	1.07	
71-80 years	9	.7767	.08382	.02794	.7122	.8411	.70	.95	
Total	100	.6942	.15778	.01578	.6629	.7255	.40	1.10	


Age and mCIMT
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
mCIMT
0.45
0.55
0.58
0.74
0.81
0.78
up to 30 years
31-40 years
41-50 years
51-60 years
61-70 years
71-80 years
Age
up to 30 years
31-40 years
41-50 years
51-60 years
61-70 years
/1-80 years

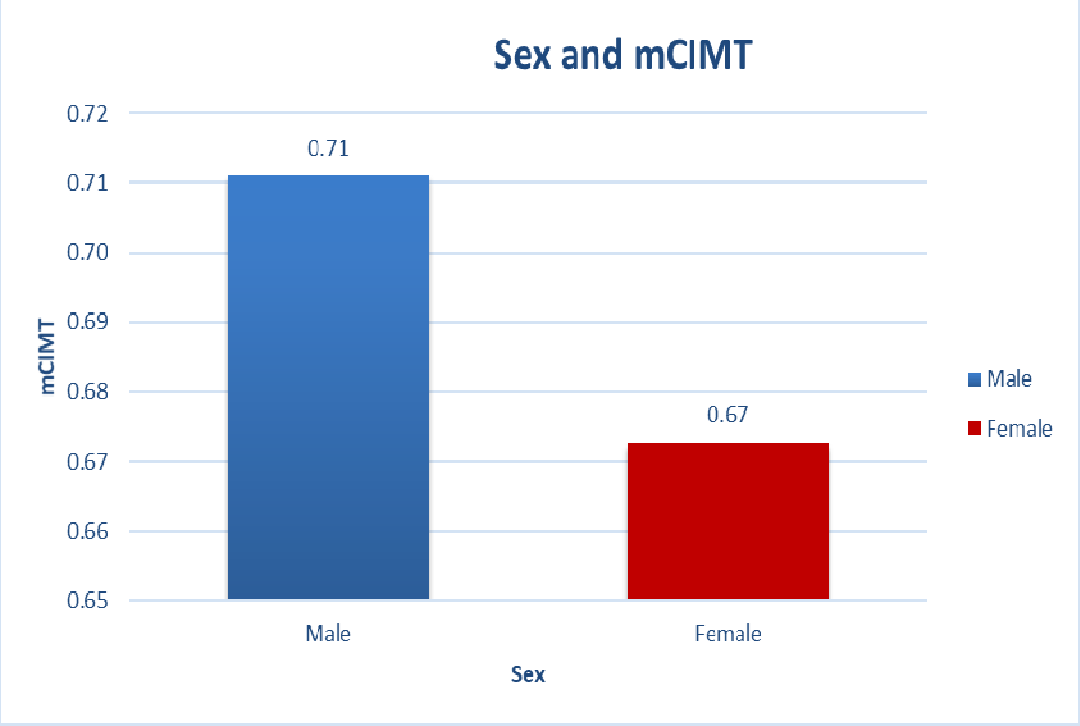
			CIMT		Total
			Abnormal	Normal	
Age group	up to 30 years	Count	2	0	2
		% within cimt_group	3.4%	.0%	2.0%
	31-40 years	Count	10	3	13
		% within cimt_group	16.9%	7.3%	13.0%
	41-50 years	Count	10	12	22
		% within cimt_group	16.9%	29.3%	22.0%
	51-60 years	Count	21	9	30
		% within cimt_group	35.6%	22.0%	30.0%
	61-70 years	Count	14	10	24
		% within cimt_group	23.7%	24.4%	24.0%
	71-80 years	Count	2	7	9
		% within cimt_group	3.4%	17.1%	9.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

Pearson Chi-Square=11.322* p=0.045


Age group and CIMT
60%
50%
40%
30%
20%
10%
0%
7%
30%
22%
24%
17%
17%
36%
24%
17%
3%
up to 30 years
31-40 years
41-50 years
51-60 years
61-70 years
71-80 years
Abnormal
Normal

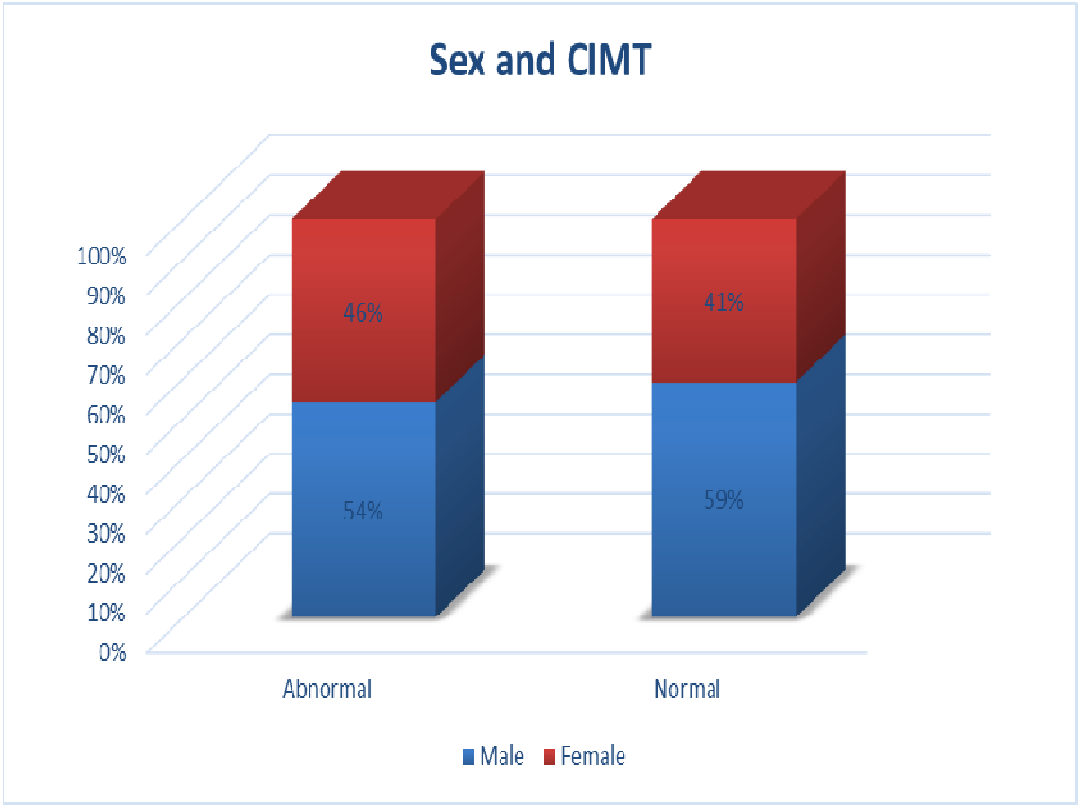
GENDER AND CIMT

	Gender	N	Mean	Std. Deviation	Std. Error Mean		
CIMT	Male	56	.7111	.15835	.02116		
	Female	44	.6727	.15620	.02355	**1.209**	0.230



			CIMT		Total
			Abnormal	Normal	
Gender	Male	Count	32	24	56
		% within cimt_group	54.2%	58.5%	56.0%
	Female	Count	27	17	44
		% within cimt_group	45.8%	41.5%	44.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

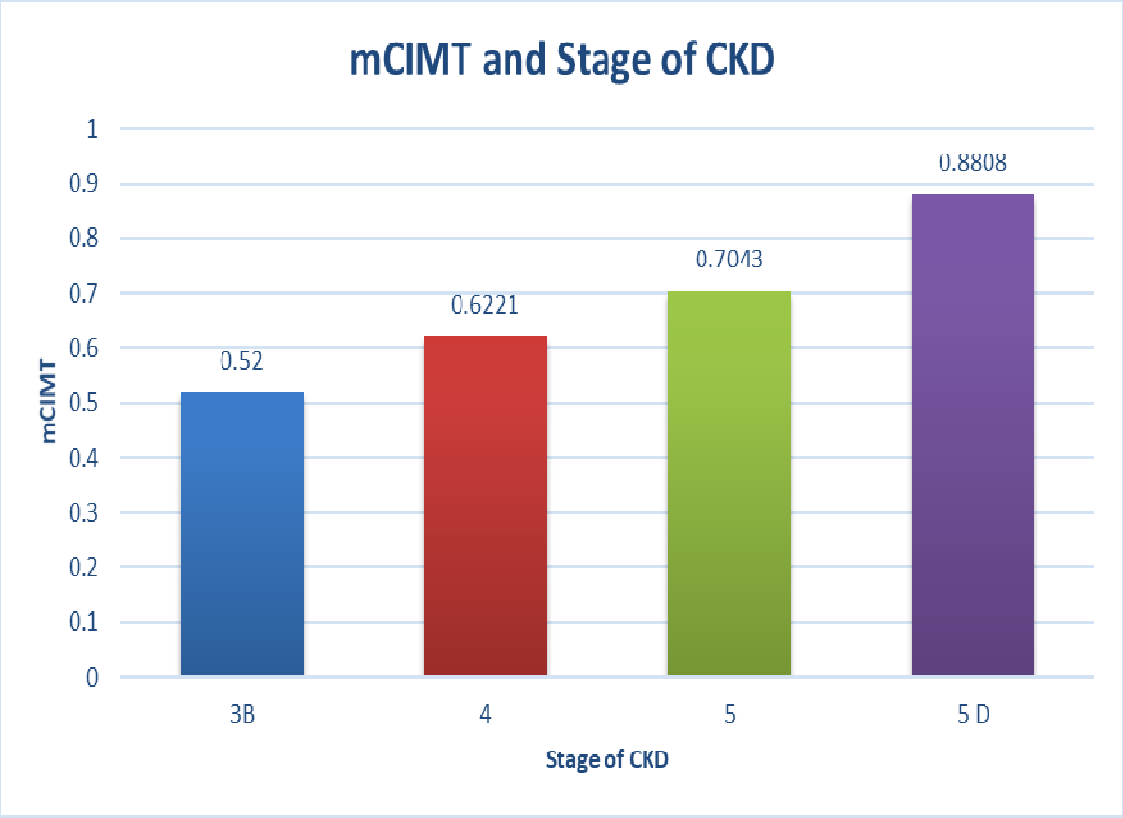
Pearson Chi-Square=0.181 p=0.670


Sex and CIMT
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
46%
54%
41%
59%
Abnormal
Normal
Male
Female

STAGE OF CKD AND CIMT

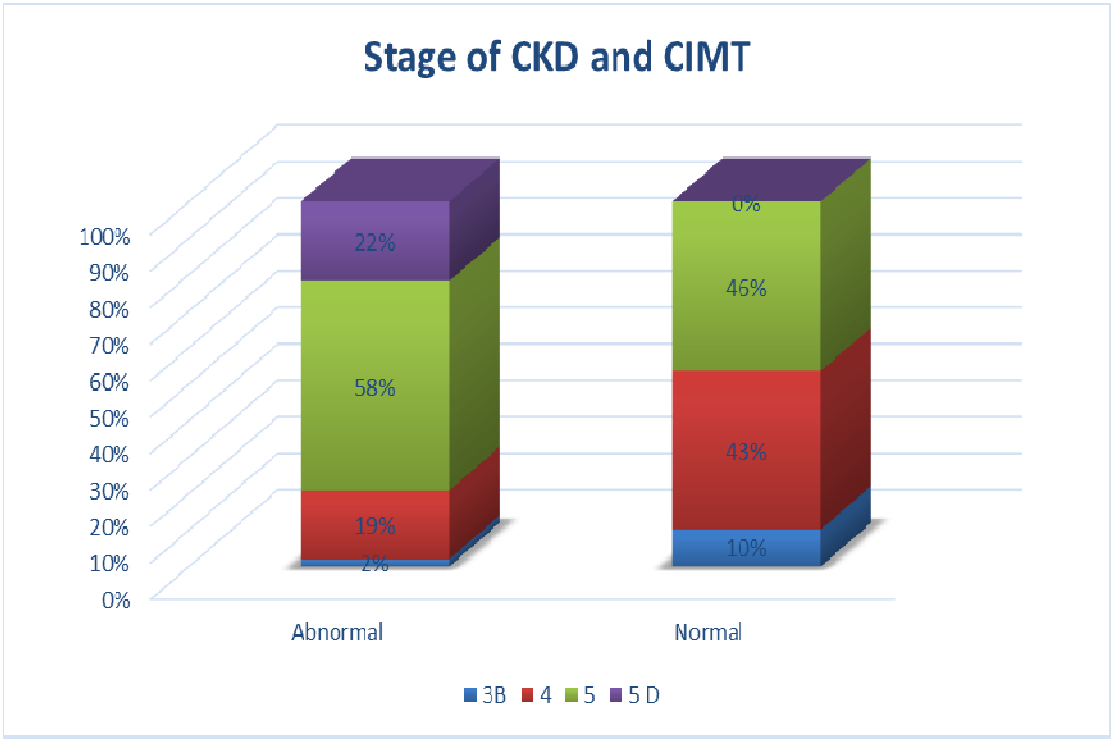
Mean CIMT

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	
					Lower Bound	Upper Bound			f value
3B	5	.5200	.10368	.04637	.3913	.6487	.40	.65	
4.00	29	.6221	.13634	.02532	.5702	.6739	.40	.95	**14.284****
5.00	53	.7043	.14024	.01926	.6657	.7430	.45	1.10	
5 D	13	.8808	.09903	.02747	.8209	.9406	.70	1.05	
Total	100	.6942	.15778	.01578	.6629	.7255	.40	1.10	


mCIMT and Stage of CKD
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
mCIMT
0.52
0.6221
0.7043
0.8808
3B
4
5
5 D
Stage of CKD

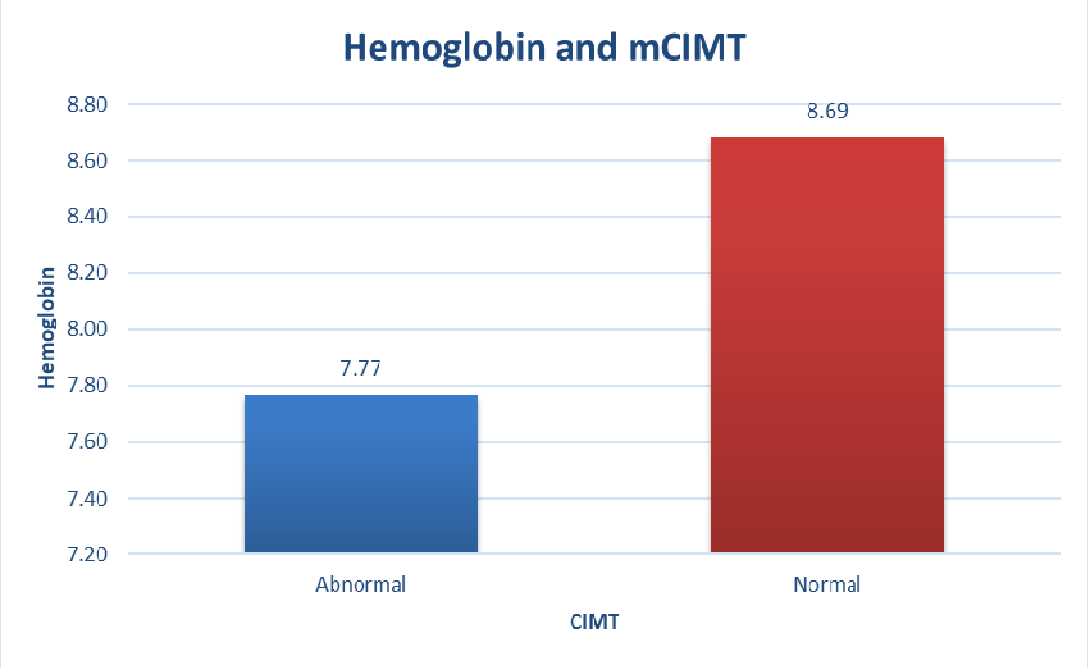
			CIMT		Total
			Abnormal	Normal	
Stage of CKD	3B	Count	1	4	5
		% within cimt_group	1.7%	9.8%	5.0%
	4.00	Count	11	18	29
		% within cimt_group	18.6%	43.9%	29.0%
	5.00	Count	34	19	53
		% within cimt_group	57.6%	46.3%	53.0%
	5 D	Count	13	0	13
		% within cimt_group	22.0%	.0%	13.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

Pearson Chi-Square=18.081* p=0.0001


Stage of CKD and CIMT
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
22%
58%
19%
2%
0%
46%
43%
10%
Abnormal
Normal
3B
4
5
5 D

HEMOGLOBIN AND CIMT

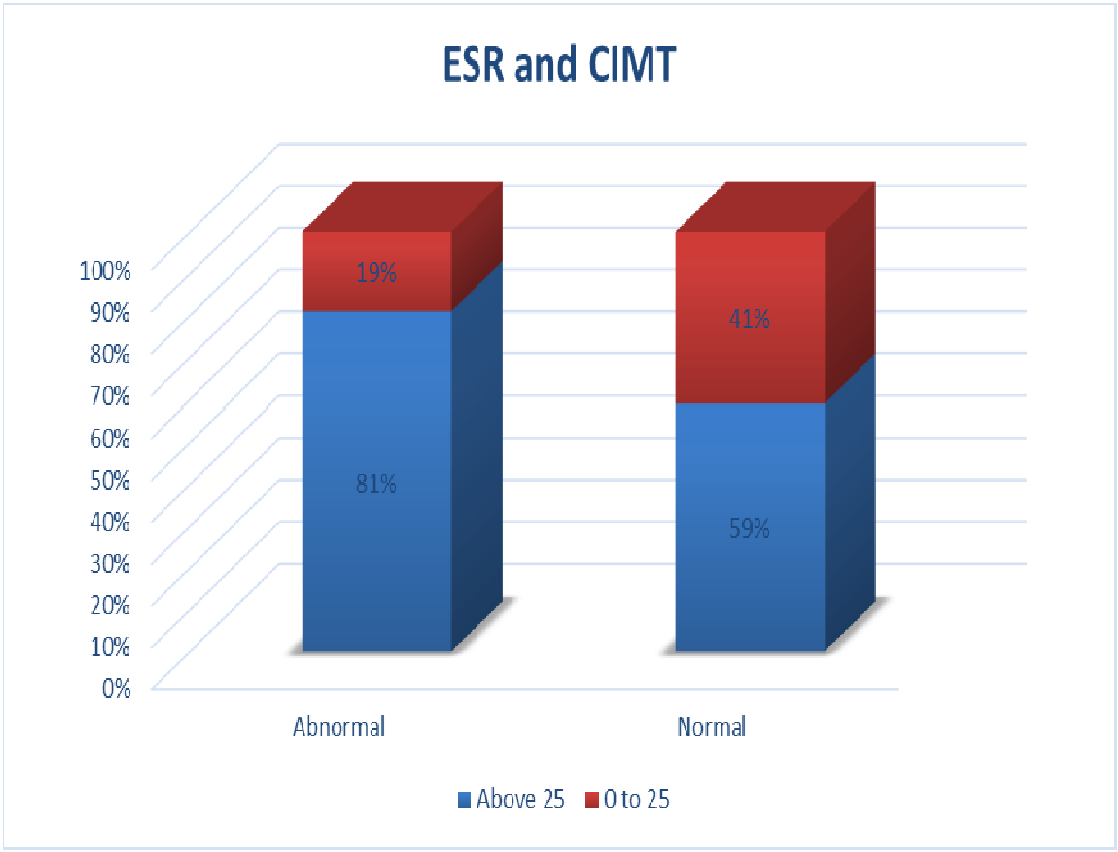
Independent t test						
	CIMT	N	Mean	Std. Deviation	Std. Error Mean	t value
Hemoglobin	Abnormal	59	7.7695	1.27810	.16639	3.598**
	Normal	41	8.6854	1.21338	.18950	



ESR AND CIMT

			CIMT		Total
			Abnormal	Normal	
ESR	Above 25	Count	48	24	72
		% within cimt_group	81.4%	58.5%	72.0%
	0-25	Count	11	17	28
		% within cimt_group	18.6%	41.5%	28.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

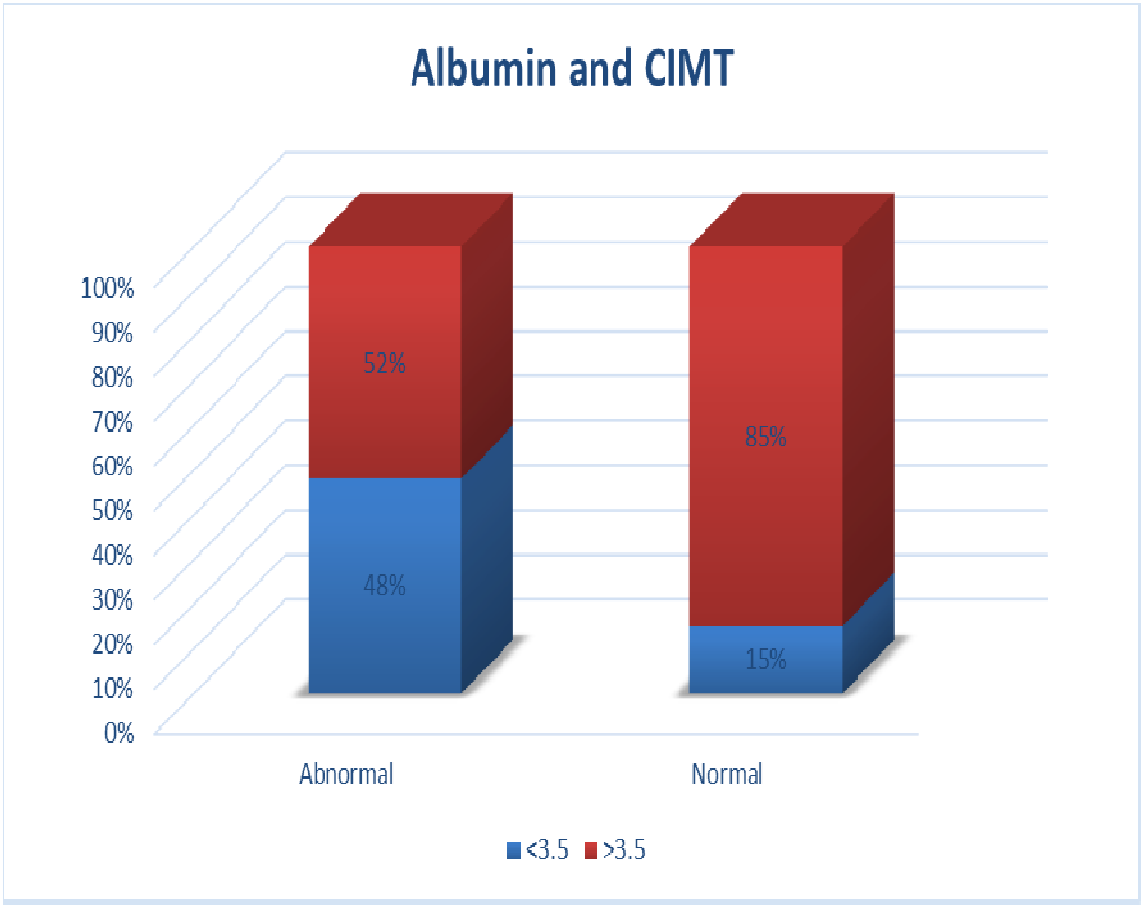
Pearson Chi-Square=6.248 * p=0.012


ESR and CIMT
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
19%
81%
41%
59%
Abnormal
Normal
Above 25
0 to 25

SERUM ALBUMIN AND CIMT

			CIMT		Total
			Abnormal	Normal	
Albumin	<3.5	Count	28	6	34
		% within cimt_group	47.5%	14.6%	34.0%
	Normal	Count	31	35	66
		% within cimt_group	52.5%	85.4%	66.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

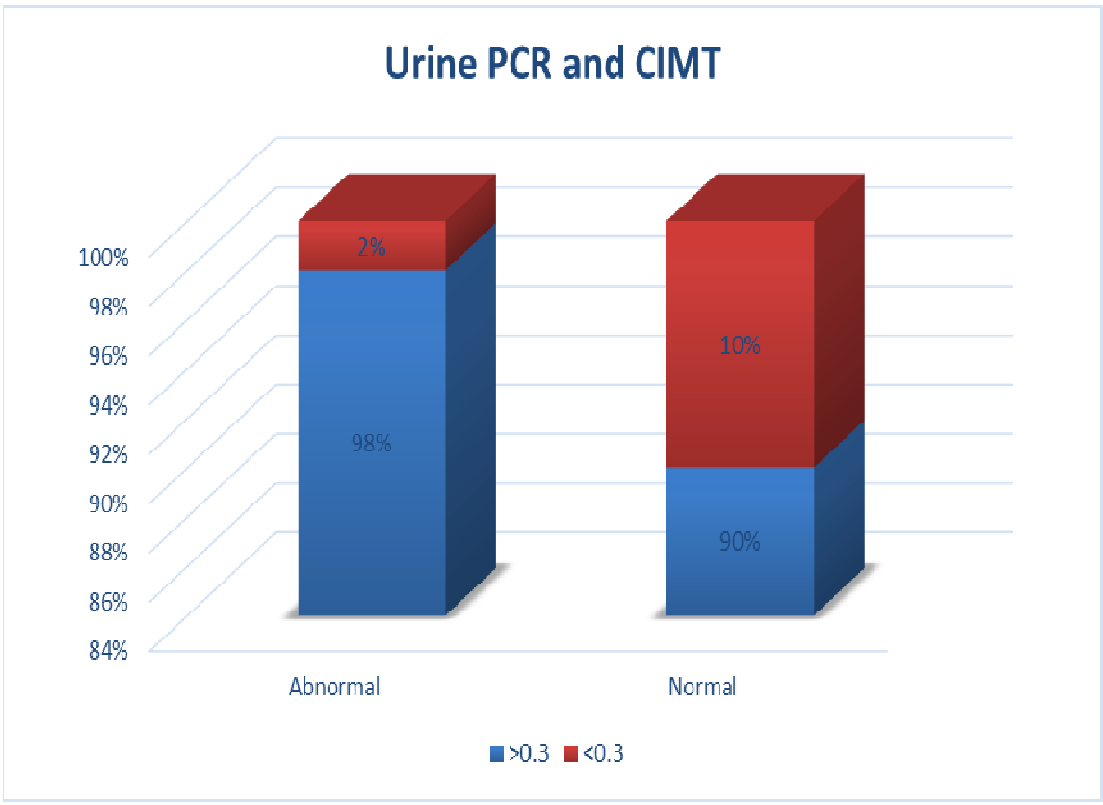
Pearson Chi-Square=11.614* p=0.001


Albumin and CIMT
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
52%
48%
85%
15%
Abnormal
Normal
<3.5
>3.5

URINE PCR AND CIMT

			CIMT		
			Abnormal	Normal	Total
Urine PCR	>0.3	Count	58	37	95
		% within cimt_group	98.3%	90.2%	95.0%
	<0.3	Count	1	4	5
		% within cimt_group	1.7%	9.8%	5.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

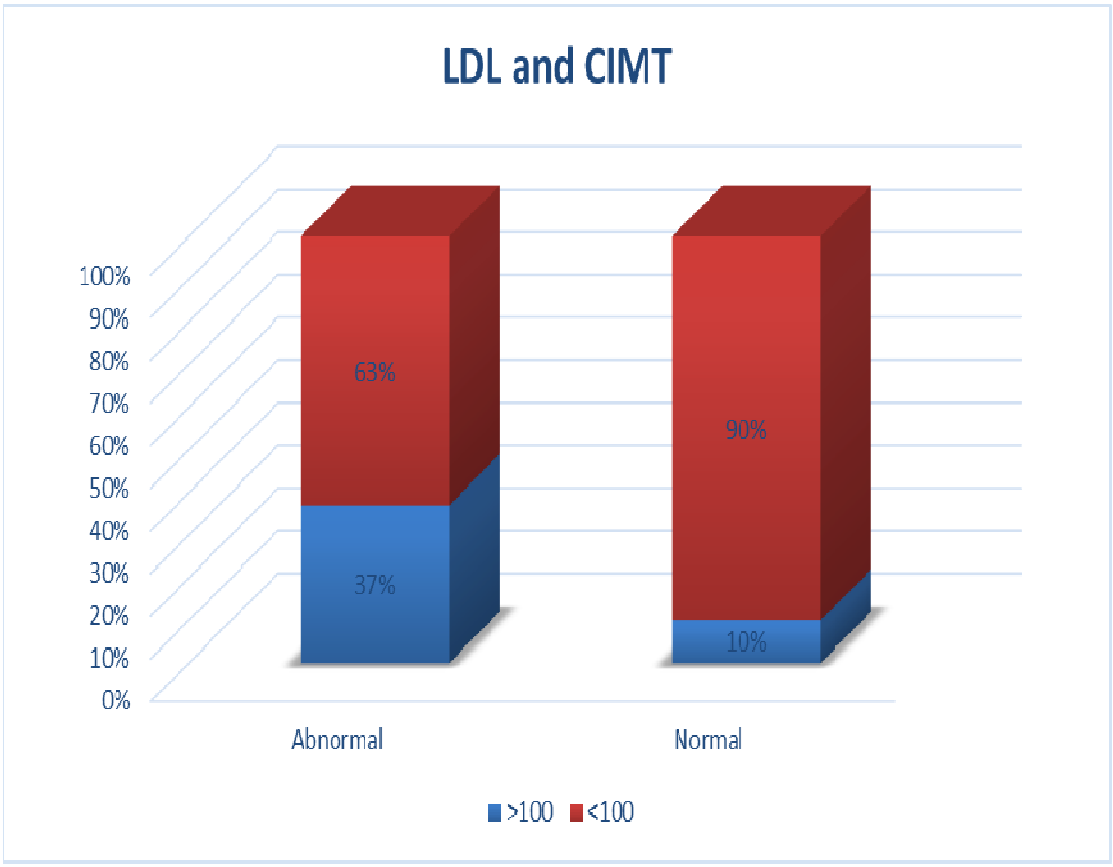
Pearson Chi-Square=3.39 p=0.0469


Urine PCR and CIMT
100%
98%
96%
94%
92%
90%
88%
86%
84%
2%
98%
10%
90%
Abnormal
Normal
>0.3
<0.3

LDL CHOLESTEROL AND CIMT

			CIMT		
			Abnormal	Normal	Total
LDL	>100	Count	22	4	26
		% within cimt_group	37.3%	9.8%	26.0%
	<100	Count	37	37	74
		% within cimt_group	62.7%	90.2%	74.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

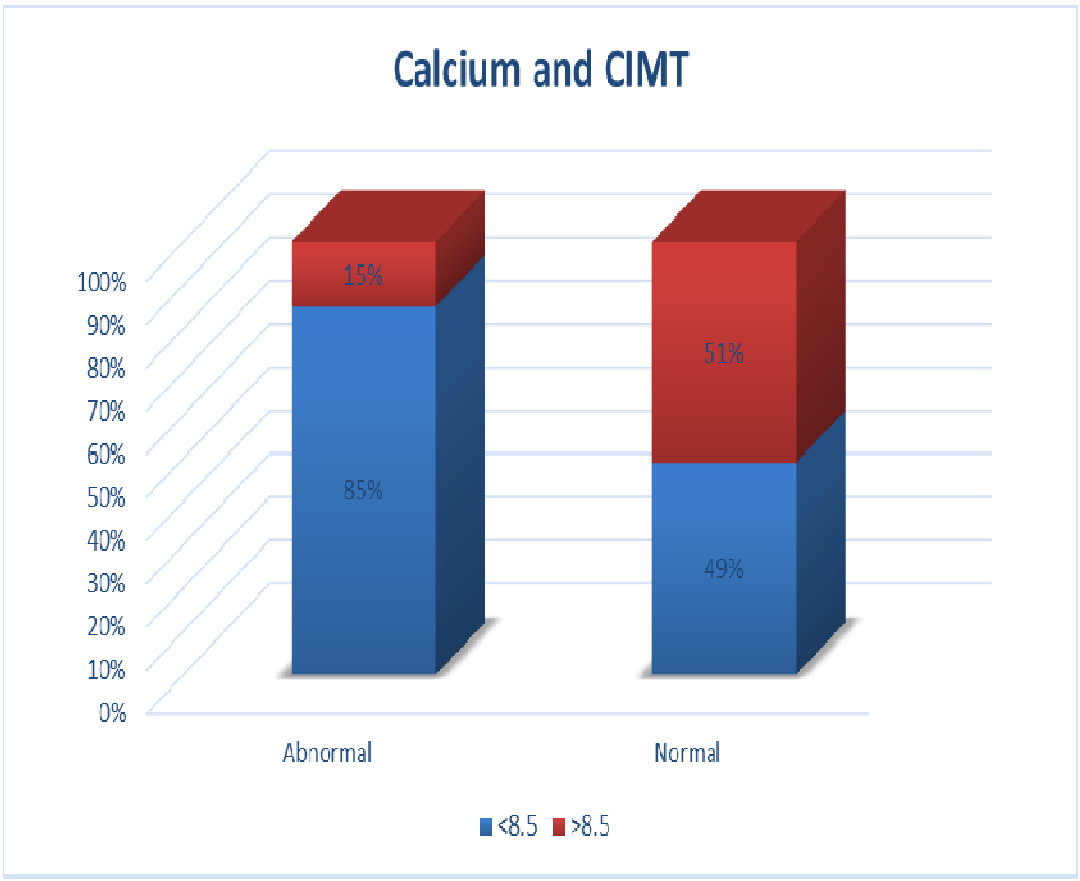
Pearson Chi-Square=9.530* p=0.002


LDL and CIMT
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
63%
37%
90%
10%
Abnormal
Normal
>100
<100

CALCIUM AND CIMT

			CIMT		
			Abnormal	Normal	Total
Calcium	<8.5	Count	50	20	70
		% within cimt_group	84.7%	48.8%	70.0%
	>8.5	Count	9	21	30
		% within cimt_group	15.3%	51.2%	30.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

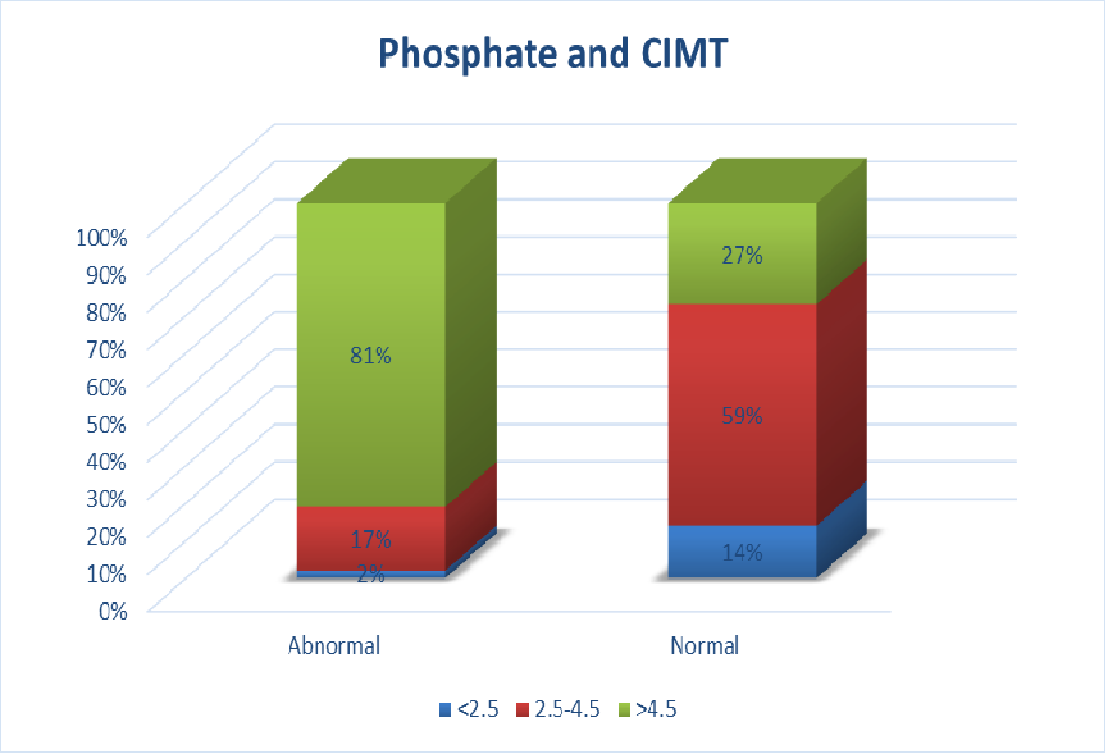
Pearson Chi-Square=14.900* p=0.001


Calcium and CIMT
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
15%
85%
51%
49%
Abnormal
Normal
<8.5
>8.5

PHOSPHATE AND CIMT

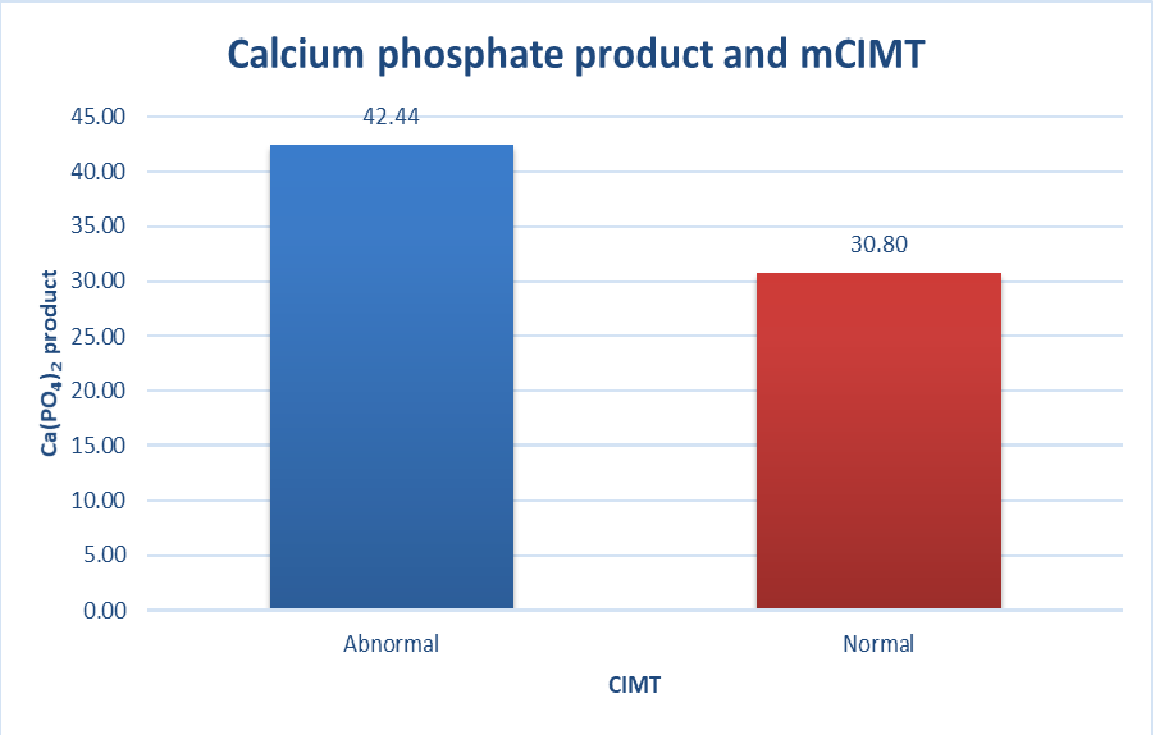
			CIMT		Total
			Abnormal	Normal	
Phosphate	<2.5	Count	1	6	7
		% within cimt_group	1.7%	14.6%	7.0%
	2.5-4.5	Count	10	24	34
		% within cimt_group	16.9%	58.5%	34.0%
	>4.5	Count	48	11	59
		% within cimt_group	81.4%	26.8%	59.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

Pearson Chi-Square=30.281** p=0.0001


Phosphate and CIMT
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
81%
17%
2%
27%
59%
14%
Abnormal
Normal
<2.5
2.5-4.5
>4.5

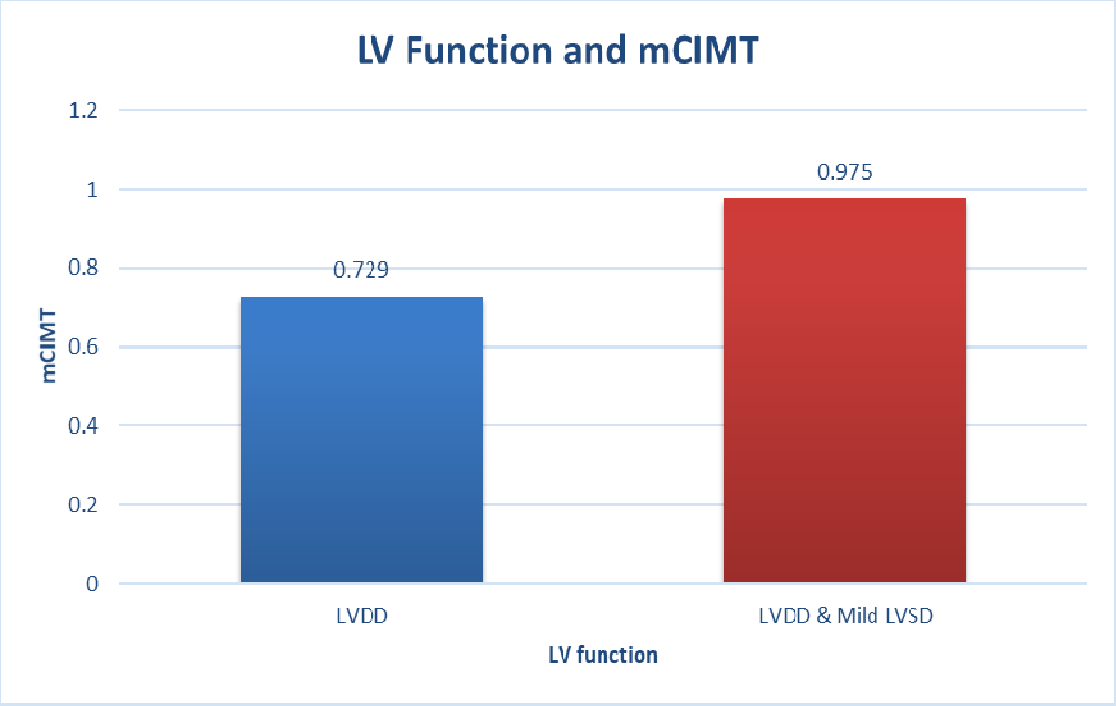
CALCIUM PHOSPHATE PRODUCT AND CIMT

Independent t test						
	CIMT	N	Mean	Std. Deviation	Std. Error Mean	t value
$Ca_3(PO_4)_2$ product	Abnormal	59	42.4427	6.83953	.89043	8.590**
	Normal	41	30.7990	6.40725	1.00064	



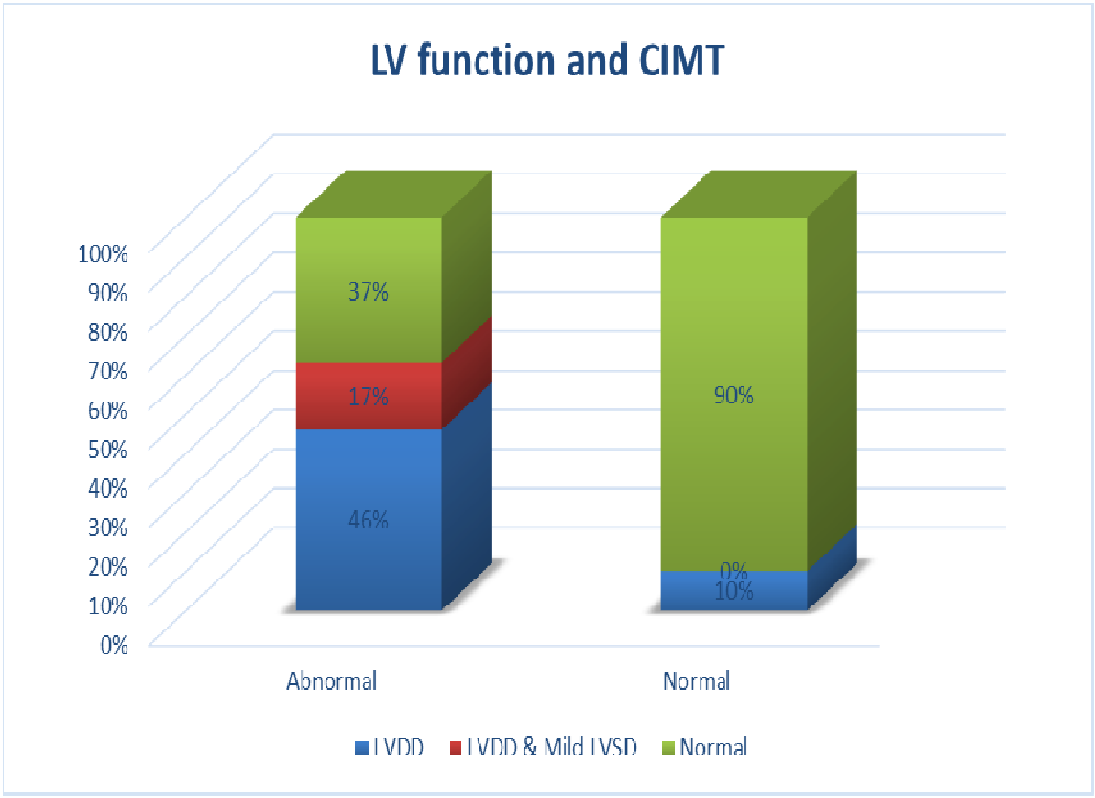
LV FUNCTION AND CIMT

	LV Function	N	Mean	Std. Deviation	Std. Error Mean	t value
CIMT	LVDD	31	.7290	.11956	.02147	5.998**
	Mild LVSD & LVDD	10	.9750	.08631	.02729	



			CIMT		Total
			Abnormal	Normal	
LV Function	LVDD	Count	27	4	31
		% within cimt_group	45.8%	9.8%	31.0%
	Mild LVSD	Count	10	0	10
		% within cimt_group	16.9%	.0%	10.0%
	Normal	Count	22	37	59
		% within cimt_group	37.3%	90.2%	59.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

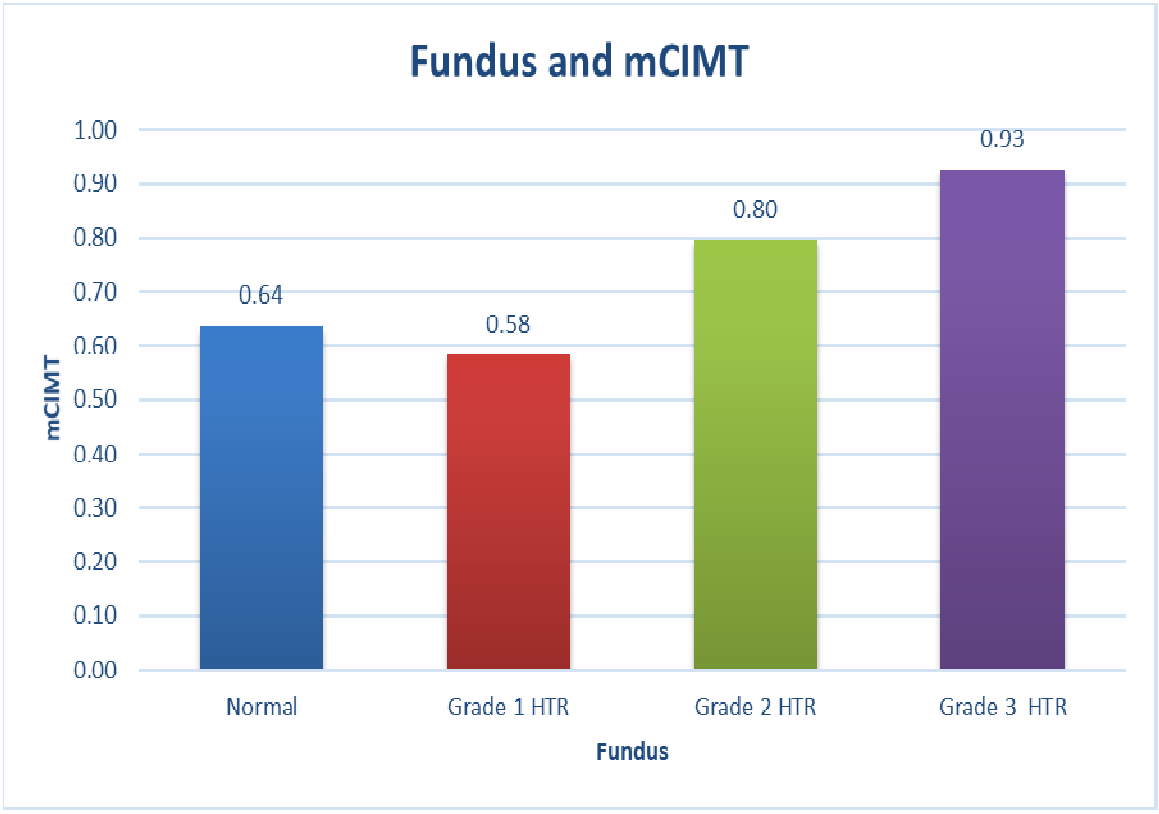
Pearson Chi-Square=28.564** p<0.0001


LV function and CIMT
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
37%
17%
46%
90%
0%
10%
Abnormal
Normal
LVDD
LVDD & Mild LVSD
Normal

FUNDUS AND CIMT

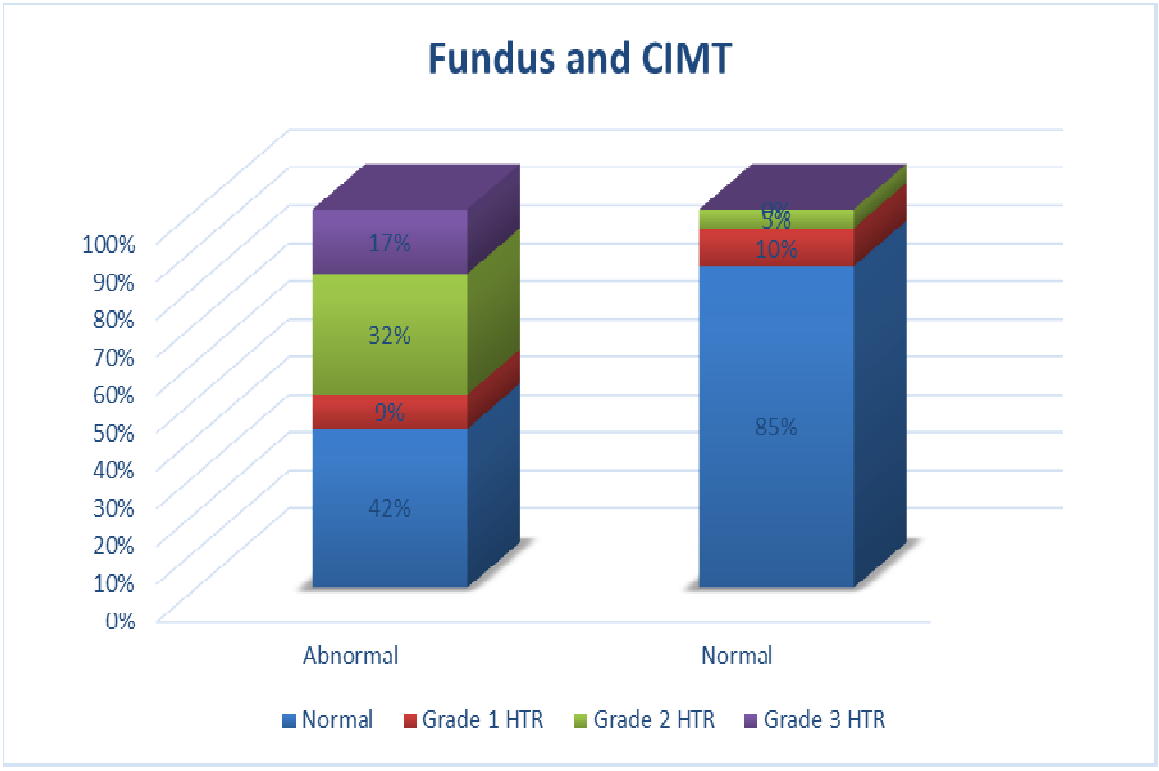
Mean CIMT

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	
					Lower Bound	Upper Bound			f value
Normal	60	.6362	.11608	.01499	.6062	.6662	.40	.95	
Grade 1 HTR	9	.5833	.12990	.04330	.4835	.6832	.40	.80	24.871**
Grade 2 HTR	21	.7962	.13231	.02887	.7360	.8564	.55	1.07	
Grade 3 HTR	10	.9280	.10881	.03441	.8502	1.0058	.75	1.10	
Total	100	.6942	.15778	.01578	.6629	.7255	.40	1.10	


Fundus and mCIMT
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
mCIMT
0.64
0.58
0.80
0.93
Normal
Grade 1 HTR
Grade 2 HTR
Grade 3 HTR
Fundus

			CIMT		Total
			Abnormal	Normal	
Fundus	Normal	Count	25	35	60
		% within cimt_group	42.4%	85.4%	60.0%
	Grade 1 HTR	Count	5	4	9
		% within cimt_group	8.5%	9.8%	9.0%
	Grade 2 HTR	Count	19	2	21
		% within cimt_group	32.2%	4.9%	21.0%
	Grade 3 HTR	Count	10	0	10
		% within cimt_group	16.9%	.0%	10.0%
Total		Count	59	41	100
		% within cimt_group	100.0%	100.0%	100.0%

Pearson Chi-Square=23.046* p<0.0001


Fundus and CIMT
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
17%
32%
9%
42%
3%
10%
85%
Abnormal
Normal
Normal
Grade 1 HTR
Grade 2 HTR
Grade 3 HTR

DISCUSSION

CIMT is a surrogate marker and predictor of coronary artery disease risk. This study was conducted in 100 non-diabetic CKD patients of stages 3,4,5 and 5 D to analyse the various factors affecting CIMT. Patients were stratified based on age, stage of CKD, sex, presence / absence of LV dysfunction, presence / absence of abnormal fundoscopic findings.

Based on age in years, 30 patients belonged to 51-60 years, 24 patients belonged to 61-70 years, 22 patients belonged to 41-50 years, 13 patients belonged to 31-40 years, 9 patients belonged to 71-80 years and 2 patients belonged to <30 years. The mean age as calculated was 54.57 years.

Based on sex, 56 patients were male and 44 patients were female.

Based on stage of CKD, 53 patients belonged to stage V, 29 patients belonged to stage IV, 13 patients belonged to stage V D and 5 patients belonged to stage III B.

Based on LV function, 31 patients had LV diastolic dysfunction, 10 patients had mild LV systolic dysfunction and diastolic dysfunction 59 patients had normal LV function.

Based on fundus examination, 10 patients had grade 3 HTR, 21 patients had grade 2 HTR, 9 patients had grade 1 HTR and 60 patients had normal fundi.

The mean values of different parameters were calculated and they were:

- Mean Blood urea was 155 mg/dl
- Mean Creatinine was 7 mg/dl
- Mean Haemoglobin was 8.14 g/dl
- Mean Albumin was 3.64 g/dl
- Mean ESR was 34
- Mean urine PCR was 3.9
- Mean Calcium was 7.9 mg/dl
- Mean Phosphate was 4.94 mg/dl
- Mean Calcium phosphate product was42.44
- Mean Total cholesterol was 134
- Mean LDL cholesterol was 93
- Mean eGFR was 11.5 ml/min/1.73 m^2

Mean CIMT compared between normal mean values for age and observed mean values in the patients included in the study showed the following differences :

Normal mean values	Age group	Observed mean values
0.34	21-30	0.45
0.43	31-40	0.55
0.52	41-50	0.58
0.61	51-60	0.74
0.70	61-70	0.81
0.79	71-80	0.78

The above findings indicate that the mean CIMT values were comparatively higher in the study group except for the age group 71-80 years when compared to normal mean values

COMPARISON OF CIMT WITH VARIOUS FACTORS

AGE

Comparison of CIMT with age showed that there was progressive increase in CIMT with increasing age in CKD patients with a significant p value of **0.045** thus showing a positive correlation between age and CIMT.

SEX

Comparison of CIMT with sex showed that mean CIMT was comparatively higher in males than females but there was no significant correlation with a p value of 0.670.

STAGE OF CKD

Comparison of CIMT with stage of CKD showed that there was an increase in mean CIMT with CKD progression. The percentage of patients with abnormal CIMT progressively increased with CKD progression with a significant p value of **0.001**, thus showing positive correlation.

HEMOGLOBIN

Comparison of CIMT with haemoglobin showed that patients with abnormal CIMT had a comparatively low mean haemoglobin than that of those with normal CIMT, thus showing negative correlation with significant t value of **3.598**.

LV FUNCTION

Comparison of CIMT with LV function showed that mean CIMT was comparatively higher in patients with both LV systolic and diastolic dysfunction than in patients with diastolic dysfunction. Also a significantly higher percentage of patients with abnormal CIMT had co-existent LV dysfunction, thus showing positive correlation with significant p value of **<0.0001**.

FUNDUS

Comparison of CIMT with fundus examination showed that there was progressive increase in mean CIMT in patients with higher grades of hypertensive retinopathy. Also significantly higher percentage of patients with abnormal CIMT had co-existent hypertensive retinopathy of various grades, thus showing positive correlation with significant p value of **<0.0001**.

SERUM ALBUMIN

Comparison of serum albumin with CIMT showed that presence of abnormal CIMT was comparatively more in patients with low serum albumin than in those with normal albumin, thus showing negative correlation with significant p value of **0.001**.

ESR

Comparison of ESR with CIMT showed that presence of abnormal CIMT was comparatively more in patients with ESR>25 than in those with normal ESR, thus showing positive correlation with significant p value of **0.012**.

URINE PCR

Comparison of urine PCR with CIMT showed that presence of abnormal CIMT was comparatively more in patients with elevated PCR than in those with normal PCR, thus showing fairly positive correlation with p value of **0.0469**.

LDL CHOLESTEROL

Comparison of urine LDL cholesterol with CIMT showed that presence of abnormal CIMT was a little bit higher in patients with LDL-C>100 mg/dl when compared with those with normal LDL-C, thus showing a fairly positive correlation with a p value of **0.002**.

SERUM CALCIUM

Comparison of serum calcium with CIMT showed that presence of abnormal CIMT was comparatively more in patients with serum calcium < 8.5 mg/dl than in those with normal calcium levels, thus showing a negative correlation with a significant p value of **0.001**.

SERUM PHOSPHATE

Comparison of serum phosphate with CIMT showed that presence of abnormal CIMT was comparatively more in patients with serum phosphate> 4.5 mg/dl than in those with levels <4.5 mg/dl, thus showing a positive correlation with a significant p value of **0.0001**.

CALCIUM PHOSPHATE PRODUCT

Comparison of calcium phosphate product with CIMT showed that patients with abnormal CIMT had a comparatively higher mean calcium phosphate product than in those with normal CIMT, thus showing a positive correlation with a significant t value of **8.590**.

CONCLUSION

- The mean CIMT in CKD patients was higher than age matched mean CIMT values of population.
- Mean phosphate, calcium phosphate product, LV dysfunction and grades of hypertensive retinopathy increase with progression of CKD.
- Mean haemoglobin, mean calcium, mean serum albumin decrease with progression of CKD.
- Stage of CKD, ESR, Severity of LV dysfunction and grades of retinopathy correlated positively with CIMT.
- Serum phosphate and calcium phosphate product strongly correlated positively and independently with CIMT.
- Urine PCR, age, LDL cholesterol fairly correlated positively with CIMT.
- Haemoglobin, serum albumin and serum calcium correlated negatively with CIMT.
- Gender did not correlate with CIMT independently.

SUMMARY

Chronic Kidney disease (CKD) is a significant predecessor of coronary artery disease and mortality. CKD patients are particularly more prone for coronary artery disease due to accelerated atherosclerosis. As coronary artery disease and stroke are the most common causes of mortality in end stage renal disease patients, prompt detection of atherosclerosis and treatment in the early stages of CKD may prevent or reduce the rate of progression of atherosclerosis thereby preventing mortality. Various risk factors have been attributed to cause atherosclerosis and hyperphosphatemia in advanced kidney disease is one among them. Studies have revealed the probable pathology behind hyperphosphatemia being a significant risk factor for accelerated atherosclerosis which is as follows:

- Augmentation of vascular calcification
- Induction of osteoblast phenotypic changes in vascular smooth muscle cells

These changes can cause vascular smooth muscle cell proliferation thereby leading to increased intimal medial thickness and thereby increased arterial wall thickness. This can be assessed non-invasively by means of B mode ultrasonogram of carotid artery thereby serving as an

early and direct marker of atherosclerosis and a predictor of future vascular events.

This study revealed a significant and strong positive correlation between serum phosphate and CIMT. So therapy aimed at reduction of serum phosphate levels in CKD patients by means of phosphate binders along with treatment of other risk factors can attenuate vascular calcification thereby reducing progression of atherosclerosis and incidence of vascular events.

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PROFORMA

A STUDY OF SERUM PHOSPHATE AS A MARKER OF CAROTID INTIMAL MEDIAL THICKNESS IN NON-DIABETIC CHRONIC KIDNEY DISEASE PATIENTS

Name :

Age/Sex :

OP/IP No :

Occupation :

Address :

Contact No. :

SYMPTOMS

- Dyspnea
- Chest pain
- Swelling of legs
- Facial puffiness
- Reduced urine output
- Abdominal distension
- Fatigue

- Loss of appetite
- Vomiting

PATIENT CHARACTERISTICS

- Smoker
- Alcoholic
- Hypertensive
- Bronchial Asthma/COPD
- Others

EXAMINATION

- Blood Pressure
- Pulse Rate
- JVP
- Heart sounds/ added sounds/murmurs
- Breath sounds/ added sounds
- Fundus examination

INVESTIGATIONS

Serum Creatinine

Hemoglobin

Erythrocyte Sedimentation Rate

Serum Calcium

Serum Phosphate

Serum Albumin

Fasting lipid profile

Urine Spot Protein Creatinine Ratio

Carotid Intimal Medial Thickness Right Left Mean

Echocardiogram

CALCULATIONS

Estimated Glomerular Filtration Rate

Calcium Phosphate Product

INFORMATION SHEET

We are conducting a study on **"SERUM PHOSPHATE AS A MARKER OF CAROTID INTIMAL MEDIAL THICKNESS IN NON-DIABETIC CHRONIC KIDNEY DISEASE PATIENTS"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to identify the relation between serumphosphate and carotid intimal medial thickness.

We are selecting certain cases and if you are found eligible, we may perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time. Your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant
Date :
Place :

PATIENT CONSENT FORM

Study Detail : **SERUM PHOSPHATE AS A MARKER OF CAROTID INTIMAL MEDIAL THICKNESS IN NON-DIABETIC CHRONIC KIDNEY DISEASE PATIENTS**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai

Patient's Name :

Patient's Age :

ID Number :

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that

arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical and radiological tests. ☐

Signature/thumb impression Signature of Investigator

Patient's name and address **DR.BADRI SRINIVASAN K**

ஆராய்ச்சியில் பங்கேற்பவர்கான தகவல் அறிக்கை

ஆராய்ச்சியின் தலைப்பு – நீரிழிவு நோய் இல்லாத நாள்பட்ட சிறுநீரக நோய்கள் சீரம் பாஸ்பேட் அளவுகள் மற்றும் கரோட்டிட் இரத்த நாளதடிமன் இடையே தொடர்பு

பங்குகொள்பவரின் பெயர் :

ஆராய்ச்சி செய்பவரின் பெயர் : மரு. பத்ரி சீனிவாசன்.க
இடம் : ராஜீவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை – 600003

இந்த ஆராய்ச்சி / ஆய்வு / செய்முறை / சோதனையில் தாங்கள் பங்கேற்க அழைக்கிறோம். இந்த தகவல் அறிக்கையில் கூறப்பட்டிருக்கும் தகவல்கள் தாங்கள் இந்த ஆராய்ச்சியில் பங்கேற்கலமா வேண்டாமா என்பதை முடிவு செய்ய உதவியாக இருக்கும். இந்த படிவத்தில் உள்ள தகவல்கள் பற்றி உள்ள சந்தேகங்களை நீங்கள் தயங்காமல் கேட்கலாம்

இந்த ஆய்வின் நோக்கம் என்ன?

நீரிழிவு நோய் இல்லாத நாள்பட்ட சிறுநீரக நோய்கள் சீரம் பாஸ்பேட் அளவுகள் மற்றும் கரோட்டிட் இரத்த நாளதடிமன் பெருந்தமனி தடிப்பு தொடர்புடையதாக உள்ளது. நீரிழிவு நோய் இல்லாத நாள்பட்ட சிறுநீரக நோய் சீரம் பாஸ்பேட் மற்றும் பெருந்தமனி தடிப்பு இடையே தொடர்பு ஆய்வு

ஆய்வு முறைகள் :

நீரிழிவு நோய் இல்லாத நாள்பட்ட சிறுநீரக நோய் நோயாளிகளின் இரத்த மாதிரிகள் எடுத்து கரோட்டிட் இரத்த நாள டாப்ளர் செய்யப்படுகின்றன

ஆய்வினால் மக்களுக்கு ஏற்படும் நன்மைகள் :

இந்த ஆய்வின் முடிவில் கிடைக்கும் தகவல்கள் சமுதாயதிற்கு பயனுள்ளதாகவும், எதிர்காலத்தில் நோயாளிகளுக்கு மருத்துவ தீர்வாகவும் அமையும்.

தங்களிடமிருந்து பெறப்படும் தகவல்களின் நம்பிகத்தன்மை :

தங்களிடமிருந்து பெறப்படும் தகவல்கள் பாதுகாக்கப்படுவதற்கான முழு உரிமையும் தங்களுக்கு உண்டு.

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு - **நீரிழிவு நோய் இல்லாத நாள்பட்ட சிறுநீரக நோய்கள் சீரம் பாஸ்பேட் அளவுகள் மற்றும் கரோட்டிட் இரத்த நாளதடிமன் இடையே தொடர்பு**

ஆராய்ச்சி செய்பவரின் பெயர் : **மரு. பத்ரி சீனிவாசன்.க**

இடம் : **ராஜீவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை** – 600003

_____ **எனும் நான், எனக்கு கொடுத்துள்ள தகவல் தாளை படித்து புரிந்து கொண்டேன். நான் பதினெட்டு வயதை கடந்துள்ளதால், என்னுடைய சுயநினைவுடனும், முழுசுதந்திரத்துடனும், இந்த ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.**

1. **நான் எனக்கு அளிக்கப்பட்ட ஒப்புதல் படிவத்தையும், தகவல்களையும் படித்து புரிந்து கொண்டேன்.**
2. **ஒப்புதல் படிவத்தில் உள்ள தகவல்கள் எனக்கு விளக்கிக் கூறப்பட்டன**
3. **ஆய்வின் தன்மை பற்றி எனக்கு விளக்கப்பட்டது**
4. **என்னுடைய உரிமைகளையும், பொறுப்புகளையும் ஆராய்ச்சியாளர் விளக்கிக் கூறினார்.**
5. **நான் இதுவரை எடுத்துள்ள / எடுத்து கொண்டிருக்கும் அணைத்து விதமான சிகிச்சை முறைகளையும் ஆராய்ச்சியாளரிடம் கூறியுள்ளேன்.**
6. **இந்த ஆராய்ச்சியினால் ஏற்படும் தீமைகள் பற்றி விளக்கப்பட்டன.**

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PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled "**SERUM PHOSPHATE AS A MARKER OF CAROTID INTIMAL MEDIAL THICKNESS IN NON-DIABETIC CHRONIC KIDNEY DISEASE PATIENTS**" of the candidate **Dr.K.BADRI SRINIVASAN** with registration Number **201611004** for the award of **M.D** in the branch of **GENERAL MEDICINE** was personally verified in urkund.com website for the purpose of plagiarism check. It is found that the uploaded dissertation file from introduction to conclusion and summary shows 3 percentage of plagiarism.

Guide & Supervisor sign with Seal.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.K.Badri Srinivasan
I Year PG in MD General Medicine
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.K.Badri Srinivasan,

The Institutional Ethics Committee has considered your request and approved your study titled **"SERUM PHOSPHATE AS A MARKER OF CAROTID INTIMAL MEDIAL THICKNESS IN NON-DIABETIC CHRONIC KIDNEY DISEASE PATIENTS " - NO.19062017(A)**

The following members of Ethics Committee were present in the meeting hold on **20.06.2017** conducted at Madras Medical College, Chennai 3

1. Prof.Dr.C.Rajendran, MD.,	:Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., Dean, MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	:Member Secretary
4. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3	: Member
5. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
6. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
7. Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
8.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
9.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
10.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

S.No	Sex	Age	Urea	Creatinine	Hb	Albumin	ESR	Calcium	Phosphorus	PCR	Cholesterol	LDL	eGFR	Stage of CKD	Calcium*Phosphate product	CIMT	Fundus	LVSD/LVDD
1	F	37	135	8.1	7.2	3.3	49	5.8	7.1	4.7	109	83	5.7	5D	41.18	0.8	Grade 3 HTR	LVDD
2	F	50	208	8.1	5.6	3.4	66	4.9	6.2	19.8	135	97	5.2	5	30.38	0.6	Grade 2 HTR	N
3	M	59	186	8.6	9.3	4	60	7.6	5.6	1.1	149	89	6.1	5D	42.56	0.8	Grade 2 HTR	LVDD
4	M	60	104	2.1	10.7	4.5	34	9	4.4	1.7	139	90	33.2	3B	39.6	0.65	N	N
5	M	70	106	5.9	10.1	3.3	57	8.6	5.1	2.1	155	108	8.9	5	43.86	0.85	N	N
6	F	60	89	10.9	6.8	3.3	34	7.1	6.7	2.5	199	133	3.4	5D	47.57	0.9	Grade 3 HTR	LVDD
7	F	56	49	1.7	9	3.5	35	8.9	2.4	2.8	132	90	33.1	3B	21.36	0.6	N	N
8	M	51	146	8.6	11	3.2	24	7.4	6.2	7.8	141	94	6.4	5	45.88	0.75	Grade 2 HTR	N
9	M	72	143	8.3	8.7	3.8	55	7.8	4.8	8.2	147	89	5.8	5	37.44	0.8	N	N
10	F	84	53	2.2	7.8	4.9	49	8.8	4.5	2.9	169	94	19.9	4	39.6	0.95	N	N
11	F	40	102	2.2	8.2	2.4	25	8.8	2.9	0.4	124	76	27.1	4	25.52	0.5	N	N
12	M	57	162	8.5	8.3	3	37	7.5	5.4	4.5	137	87	6.3	5	40.5	0.74	N	N
13	M	80	73	2.5	9.3	2.9	20	9.3	2.1	2.3	119	100	23.4	4	19.53	0.85	N	N
14	M	48	77	3.2	9.3	3.4	24	9.2	2.3	0.3	117	90	21.7	4	21.16	0.55	N	N
15	M	58	96	5.7	6.9	2.7	34	8.4	4.3	0.5	138	112	10.1	5	36.12	0.67	N	N
16	M	38	350	22	4.7	3.3	56	5.7	7.5	7.4	121	100	2.3	5	42.75	0.75	Grade 2 HTR	LVDD
17	M	49	137	7.9	8.6	3.6	24	8.4	5.1	3.4	142	102	7.2	5	42.84	0.75	N	N
18	M	67	124	7	9.4	4	28	8.5	3.9	0.9	124	98	7.4	5	33.15	0.7	N	N

19	F	54	194	9.2	7.3	3.7	32	8	5.6	2.1	176	135	4.4	5	44.8	0.85	Grade 2 HTR	LVDD
20	F	61	208	10.7	6.9	3	44	7.1	6.4	2.5	157	120	3.5	5D	45.44	0.9	Grade 3 HTR	LVDD
21	F	57	174	8.3	7.5	3.4	32	7.9	5.3	8.4	156	96	4.8	5	41.87	0.8	N	N
22	M	36	120	6.7	8.6	3.3	65	8	4.7	12.4	194	128	9.7	5	37.6	0.45	N	N
23	M	44	141	6.7	7.7	4.1	44	9	3.8	2.1	112	96	9.1	5	34.2	0.5	N	N
24	F	58	155	7.4	8	3.9	32	9	4.6	0.3	101	80	5.5	5	41.4	0.75	N	N
25	M	72	101	3.1	10.4	3.3	20	8.7	3.9	5.4	132	84	19.1	4	33.93	0.7	N	N
26	F	63	139	3	9.6	3.5	25	8.1	4.3	1.3	126	88	16.5	4	34.83	0.6	N	N
27	M	42	186	7.8	8.7	3.6	34	7.9	5.7	1.9	111	78	7.7	5	45.03	0.7	Grade 2 HTR	LVDD
28	F	39	97	1.7	11.4	4.1	15	9	3.3	0.3	96	75	37.3	3B	29.7	0.45	N	N
29	F	32	94	2.1	10.5	4	10	9	2.5	0.7	147	100	30.4	3B	22.5	0.4	Grade 1 HTR	N
30	F	49	141	7.4	8.8	3.6	24	8.3	5.1	1.7	152	104	5.9	5	42.33	0.65	N	LVDD
31	M	64	188	8.4	8.4	3.5	22	8.1	5.7	3.4	143	96	6	5D	46.17	0.9	Grade 2 HTR	Mild LVSD & LVDD
32	M	61	176	8.2	7.4	3.3	24	8.5	4.7	11.7	176	124	6.4	5	39.95	0.7	N	N
33	F	45	167	7.9	6.4	4	35	8.2	4.9	1.1	123	95	9.3	5	40.18	0.55	N	N
34	M	59	235	10.4	7.5	3	36	6.9	6.7	16.7	164	108	4.8	5D	46.23	0.95	Grade 2 HTR	LVDD
35	F	44	154	8.6	8.3	3.4	30	8	5.2	7.3	125	99	5.1	5	41.6	0.65	N	N
36	M	27	190	7.2	7.2	3.4	34	7.4	5.7	5.6	98	77	7.1	5	42.18	0.5	N	N
37	F	56	157	9	7	3.5	36	8	5.4	2.3	149	100	5.8	5	43.2	0.75	Grade 1 HTR	LVDD
38	F	38	187	7.4	7	3.5	36	7.9	5.2	0.4	162	104	6.4	5	41.08	0.6	N	LVDD
39	M	64	143	7.8	6.9	3.7	38	7.5	4.7	0.2	89	94	6.6	5	35.25	0.7	N	LVDD

40	M	68	132	7	8	4.1	30	8.2	3.8	0.3	94	82	7.3	5	31.16	0.7	N	N
41	M	71	109	2.2	9.5	4.5	24	8.9	3.6	0.2	108	90	29.1	4	32.04	0.7	N	N
42	F	65	154	5.2	8.4	3.6	28	8	4.6	3.2	128	92	8	5	36.8	0.72	N	N
43	F	50	112	2.2	8.1	3.4	30	8	3.8	6.5	154	99	25.3	4	30.4	0.55	N	N
44	F	56	132	3	10.4	4	20	8.7	3.1	0.2	99	74	16.7	4	26.97	0.6	N	N
45	M	43	163	3.9	8	4.1	30	8.2	3.7	0.3	105	78	17.7	4	30.34	0.5	N	N
46	M	55	156	6.4	8	3.8	30	8.2	3.2	2.1	103	84	8.9	5	26.24	0.6	N	N
47	M	40	149	4	8	3.7	32	8.2	3.5	1.7	175	98	17.5	4	28.7	0.5	N	N
48	F	64	184	9.1	7.5	3.4	34	6.7	6.4	8.4	152	88	4.1	5D	42.88	0.9	Grade 3 HTR	Mild LVSD & LVDD
49	M	60	139	5.6	9	3.7	26	8	3.2	4.4	139	96	10.1	5	25.6	0.6	N	N
50	F	51	98	2.2	7.6	3.9	34	9.3	3.4	1	134	76	18	4	31.62	0.5	N	N
51	M	29	137	3.4	8.6	3.3	26	9	3.4	12.4	178	120	23.1	4	30.6	0.4	N	N
52	F	40	102	2.1	8	3.4	30	8.4	4.7	9.3	162	82	28.7	4	39.48	0.5	Grade 1 HTR	LVDD
53	M	41	134	3.4	9	4.1	24	9	2.4	0.2	96	74	21.2	4	21.6	0.45	N	N
54	M	69	156	3	9	4	24	8.3	3.1	0.3	104	84	20.3	4	25.73	0.7	N	N
55	F	41	124	3.2	10.7	4.2	15	9.2	2.2	0.4	106	84	17.1	4	20.24	0.45	N	N
56	M	65	148	5.9	9.8	4	22	8.7	3.1	3.2	121	88	9.2	5	26.97	0.7	N	N
57	M	74	90	2.2	11.2	4	10	8.9	2.1	4.3	145	104	21.4	4	18.69	0.75	N	N
58	M	79	89	3	9.7	4.5	22	9	2.4	0.3	116	92	18.9	4	21.6	0.8	N	N
59	M	52	112	3.2	9	4	24	9.1	2.8	1.7	112	92	21.1	4	25.48	0.6	N	N
60	M	52	140	3.5	8	3.5	32	8.6	3.3	4.6	143	96	18.9	4	28.38	0.6	Grade 1 HTR	LVDD

61	M	49	135	5.8	9.4	3.8	21	8.8	3.1	3.2	123	88	10.5	5	27.28	0.5	N	N
62	M	63	149	8	7.4	3.4	35	7.6	4.8	6.9	153	98	6.5	5	36.48	0.7	Grade 2 HTR	LVDD
63	F	41	156	9.2	7	3.5	38	7.1	5.7	5.4	147	96	4.8	5	40.47	0.55	Grade 2 HTR	LVDD
64	F	71	98	2.1	8	4	28	8.5	3.2	1.3	119	78	23.1	4	27.2	0.7	N	N
65	F	59	168	8.4	6.7	3.4	36	7.9	4.9	5.7	120	80	4.7	5	38.71	0.7	Grade 2 HTR	LVDD
66	F	49	194	9.4	7	3.5	36	7.6	5.4	3.6	142	97	4.4	5	41.04	0.65	N	LVDD
67	M	62	208	10.1	6.5	3.7	38	5.9	7.4	2.2	156	94	4.9	5	43.66	0.9	Grade 3 HTR	Mild LVSD & LVDD
68	M	67	247	13.6	6.7	3.4	40	6.2	8.9	6.7	187	108	3.3	5D	55.18	1.05	Grade 3 HTR	Mild LVSD & LVDD
69	F	63	298	16	6.4	3.5	38	5.7	9.1	2.7	105	78	2.1	5	51.87	1.03	Grade 3 HTR	Mild LVSD & LVDD
70	M	59	224	12.4	6.9	3.7	48	6.1	8.7	1.9	100	84	3.9	5D	53.07	1	Grade 2 HTR	Mild LVSD & LVDD
71	F	52	186	10.3	7.4	3.3	32	7.1	7.4	11.2	165	112	3.9	5	52.54	0.95	Grade 3 HTR	Mild LVSD & LVDD
72	F	64	235	13.5	6.9	3.3	64	5.7	8.4	13.5	189	124	2.6	5D	47.88	0.95	Grade 2 HTR	LVDD
73	M	47	146	8.9	7.4	3.7	32	7.6	5.4	2.7	124	88	6.3	5	41.04	0.6	N	LVDD
74	M	69	239	13.8	6.4	3.4	56	6.7	7.9	9.3	139	94	3.2	5	52.93	1.07	Grade 2 HTR	Mild LVSD & LVDD
75	F	41	169	9	8	3.6	30	7.8	5.4	1.7	114	68	4.9	5	42.12	0.6	N	LVDD
76	M	55	199	10.7	7.6	3.4	46	7.2	5.9	4.3	143	100	4.8	5	42.48	0.7	N	LVDD

77	M	60	148	5.2	8	3.8	30	8.3	4.5	1.4	98	76	11.1	5	37.35	0.7	N	N
78	M	56	256	13.9	9.4	3.5	48	7.2	8.3	5.9	137	84	3.5	5	59.76	1.1	Grade 3 HTR	Mild LVSD & LVDD
79	F	63	174	8.8	8	3.7	28	7.9	4.9	2.4	112	75	4.3	5	40.29	0.7	N	N
80	M	37	187	9.4	9	3.5	24	7.4	5.7	2.5	120	74	6.4	5	42.18	0.55	N	LVDD
81	F	42	169	9.4	7	3.5	26	7.5	5.6	2.1	124	78	4.6	5	42	0.55	N	N
82	F	39	112	3	6.5	3.9	36	8.2	4.5	1.4	96	74	18.8	4	36.9	0.55	N	N
83	F	60	111	3	8.9	4	25	8.9	4.2	0.5	88	77	16.2	4	37.38	0.7	N	N
84	M	49	154	8.7	9	3.7	22	7.8	5.9	1.8	109	76	6.4	5D	46.02	0.7	Grade 2 HTR	LVDD
85	F	54	169	9.5	10	3.6	20	7.4	6	1.1	123	84	4.2	5	44.4	0.75	Grade 2 HTR	LVDD
86	M	67	183	10.7	7.2	3.4	36	7.2	6.1	4.4	143	98	4.4	5	43.92	0.8	Grade 1 HTR	LVDD
87	M	61	210	11.3	8.6	3.4	46	6.8	7.2	7.3	165	106	4.3	5D	48.96	0.85	Grade 2 HTR	Mild LVSD & LVDD
88	F	70	124	2.2	10.1	4.4	24	9.1	3.7	0.2	98	72	22	4	33.67	0.75	N	N
89	M	71	138	3.4	8	4.2	28	8.6	3.9	0.4	108	76	17.2	4	33.54	0.74	N	N
90	F	56	188	9.5	9	3.7	36	7.3	5.9	1.9	121	84	4.1	5D	43.07	0.75	Grade 3 HTR	LVDD
91	M	43	144	2.5	7.1	4	34	8.4	3.4	0.9	117	76	30.3	3B	28.56	0.5	Grade 1 HTR	N
92	F	51	108	2.4	8.1	3.8	30	8.1	3.9	2.1	129	78	22.6	4	31.59	0.55	Grade 1 HTR	N
93	M	54	231	11.6	7.1	3.4	46	7	6.9	13.7	186	129	4.4	5	48.3	0.85	Grade 2 HTR	LVDD
94	M	63	212	12.4	5.4	3.4	54	6.4	7.6	10.4	178	118	3.8	5	48.64	0.85	Grade 2 HTR	LVDD
95	M	42	176	8.8	6.2	3.6	38	7.6	5.7	4.3	136	86	6.7	5	43.32	0.65	Grade 1 HTR	N
96	M	37	193	9	7	3.5	34	7.6	6	3.6	166	120	6.7	5	45.6	0.65	Grade 2 HTR	LVDD

97	**F**	**39**	**121**	**3.4**	**6.9**	**3.7**	**32**	**7.4**	**5**	**2.4**	**158**	**104**	**16.1**	**4**	**37**	**0.5**	**Grade 1 HTR**	**N**
98	**F**	**57**	**210**	**9.7**	**8.4**	**3.5**	**34**	**7.2**	**5.3**	**3.7**	**133**	**87**	**4**	**5**	**38.16**	**0.6**	**N**	**N**
99	**F**	**45**	**169**	**7.9**	**9**	**3.5**	**24**	**8.2**	**4.4**	**3.9**	**140**	**96**	**5.6**	**5**	**36.08**	**0.55**	**N**	**N**
100	**M**	**64**	**114**	**3.4**	**7**	**3.9**	**32**	**7.5**	**5.9**	**0.6**	**110**	**86**	**18**	**4**	**44.25**	**0.8**	**Grade 2 HTR**	**LVDD**