DISSERTATION

on

ASSESSMENT OF VASCULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE PATIENTS

submitted in partial fulfillment of
requirements for

MD DEGREE EXAMINATION

BRANCH-I GENERAL MEDICINE

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI

INSTITUTE OF INTERNAL MEDICINE
MADRAS MEDICAL COLLEGE
CHENNAI – 600003
APRIL 2013

CERTIFICATE

This is to certify that the dissertation titled **"ASSESSMENT OF VASCULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE PATIENTS"** is a bona fide work done by **Dr. R. SENTHIL MURUGAN**, Post Graduate Student, Institute of Internal Medicine, Madras Medical College, Chennai – 600003, in partial fulfillment of the university rules and regulations for the award of MD DEGREE in GENERAL MEDICINE BRANCH-I, under our guidance and supervision, during the academic period from April 2010 to April 2013.

Prof. N. RAGHU, MD,

Director and Professor,
Institute of Internal Medicine,
MMC and RGGGH,
Chennai – 600003.

Prof. V. KANAGASABAI, MD,

Dean,
MMC and RGGGH,
Chennai – 600003.

DECLARATION

I solemnly declare that the dissertation titled **"ASSESSMENT OF VASCULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE PATIENTS"** was done by me at Madras Medical College, Chennai – 600003, during the period May 2012 to October 2012 under the guidance and supervision of **Prof. N. RAGHU, MD**, to be submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of MD DEGREE in GENERAL MEDICINE BRANCH-I.

Place : Chennai

Date : 24/12/2012

Dr. R. SENTHIL MURUGAN,

MD GENERAL MEDICINE,
Post Graduate Student,
Institute of Internal Medicine,
Madras Medical College,
Chennai – 600003.

ACKNOWLEDGEMENT

I thank **Prof. V. KANAGASABAI, MD**, Dean, Madras Medical College, for having permitted me to conduct the study and use the hospital resources in the study.

I express my heartfelt gratitude to **Prof. N. RAGHU, MD**, Director and Professor, Institute of Internal Medicine, for his inspiration, advice and guidance in making this work complete.

I express my deep gratitude to **Prof. N. GOPALAKRISHNAN, DM**, Professor and Head, Department of Nephrology, for his comments and guidance to complete the study.

I am extremely thankful to **Dr. M. ANUSUYA, MD**, Assistant Professor, Institute of Internal Medicine and **Dr. D.K. SIVAKUMAR, MD**, Assistant Professor, Institute of Internal Medicine, for guiding me academically and professionally during the period of study.

I also thank all the postgraduate students and paramedical staff for their cooperation which enormously helped me in the study. I am also indebted to thank all the patients and their caring relatives. Without their humble cooperation, this study would not have been possible.

ABBREVIATIONS

$1,25(OH)_2D$	1,25-Dihydroxyvitamin D
AD	Adynamic disease
CAC	Coronary artery calcium
CaSR	Calcium sensing receptor
CKD	Chronic kidney disease
MBD	Mineral and bone disorder
ECF	Extracellular fluid
ESRD	End stage renal disease
FGF23	Fibroblast growth factor 23
GFR	Glomerular filtration rate
GPCR	G protein coupled receptor
K/DOQI	Kidney disease outcomes quality initiative
KDIGO	Kidney Disease: Improving Global Outcomes
KEEP	Kidney Early Evaluation Program
NHANES	National Health and Nutrition Examination Survey
OF	Osteitis fibrosa
OM	Osteomalacia
Pi	Inorganic phosphate
PTH	Parathormone

PTHrP	PTH related peptide
PWV	Pulse wave velocity
RANK	Receptor activator of nuclear factor kappa-B
SD	Standard deviation
SEEK	Study to evaluate early kidney disease
TRPV	Transient receptor potential vanilloid
VDR	Vitamin D receptor

TABLE OF CONTENTS

INTRODUCTION

Chronic kidney disease (CKD) is a common health problem and about 5 to 10% of the population of the world suffers from the disease [1]. The morbidity and mortality is contributed by co-morbid medical conditions such as cardiovascular disease, diabetes and lipid disorders and complications secondary to progression of kidney disease which include hypertension, anemia, secondary hyperparathyroidism and malnutrition.

Although bone disease associated with secondary hyperparathyroidism is well established, vascular and valvular calcification and its relation to cardiovascular morbidity and mortality has gained importance in recent times.

Though coronary artery calcification as assessed in terms of CAC score using CT based imaging is a strong predictor of cardiovascular events, more readily available and less expensive techniques such as

- pulse wave velocity (PWV)
- lateral lumbar radiography of aorta and
- echocardiography

have been demonstrated to have good correlation with vascular calcification that occurs in CKD [2].

In this study, lateral abdominal X-ray is used to assess vascular calcification based on standardized scoring system which correlates with coronary artery calcification scores and hence predicts cardiovascular morbidity and mortality.

AIMS AND OBJECTIVES

- To assess the vascular calcification status of CKD patients in different stages using lateral lumbar radiography
- To study the biochemical parameters of mineral metabolism in different stages of CKD

REVIEW OF LITERATURE

Chronic kidney disease is a global health threat with increasing incidence and prevalence. It is a major health problem in India with an estimated prevalence of 0.8%, which if projected to the 1 billion population of India will mean that currently 8 million people are suffering from the disease [3].

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies [4].

CKD is classified into various stages based on the presence of kidney damage and decline in GFR [4].

Stage 1:	Kidney damage with normal or elevated GFR of ≥90 mL/min/1.73 m^2
Stage 2:	Kidney damage with mild reduction in GFR in the range of 60-89 mL/min/1.73 m^2
Stage 3:	Moderate reduction in GFR in the range of 30-59 mL/min/1.73 m^2
Stage 4:	Severe reduction in GFR in the range of 15-29 mL/min/1.73 m^2
Stage 5:	Kidney failure with GFR below 15 mL/min/1.73 m^2 or on dialysis

Creatinine clearance calculated using Cockcroft-Gault equation is taken as estimated GFR (eGFR) [5]. Other formulas used to calculate eGFR include

MDRD formula and CKD-EPI formula both of which consider race as a parameter. Recently methods to calculate eGFR based on both serum creatinine and serum cystatin C have been developed which are claimed to be more accurate than the previous methods but are not widely used [6].

$$eGFR = \frac{(140 - age) \times weight}{72 \times creatinine} \times (0.85\ if\ female)$$

Note:

- age in years
- weight in kg
- creatinine in mg/dL

CAUSES OF CKD:

Exact contribution from each cause varies depending on population characteristics. Common causes include the following:

- Diabetes
- Glomerulonephritis
- Hypertension
- Autosomal Dominant Polycystic Kidney Disease

COMPLICATIONS OF CKD:

CKD is a systemic disorder with manifestations involving almost every system of the body. Complications of CKD include the following:

- Electrolyte disturbances: hyperkalemia, hyponatremia
- Acid-base disorders
- Cardiovascular complications: hypertension, congestive cardiac failure, pericarditis
- Hematologic complications: anemia, coagulopathy
- Neurologic complications: uremic encephalopathy, peripheral neuropathy
- Endocrine disorders: hypoglycemia as well as insulin resistance, sexual disturbances
- Disorders of mineral metabolism

MINERAL METABOLISM

CALCIUM

Normal adult human body contains 1-2 kg of calcium on average. Out of the total body store, ~99% is present in the bone. Approximately 250-500 mg of calcium moves in and out of bones due to the action of osteoblasts and osteoclasts. Apart from this, 0.5-1% of the calcium present in the skeleton is in equilibrium with extracellular fluid calcium [Figure **1**].

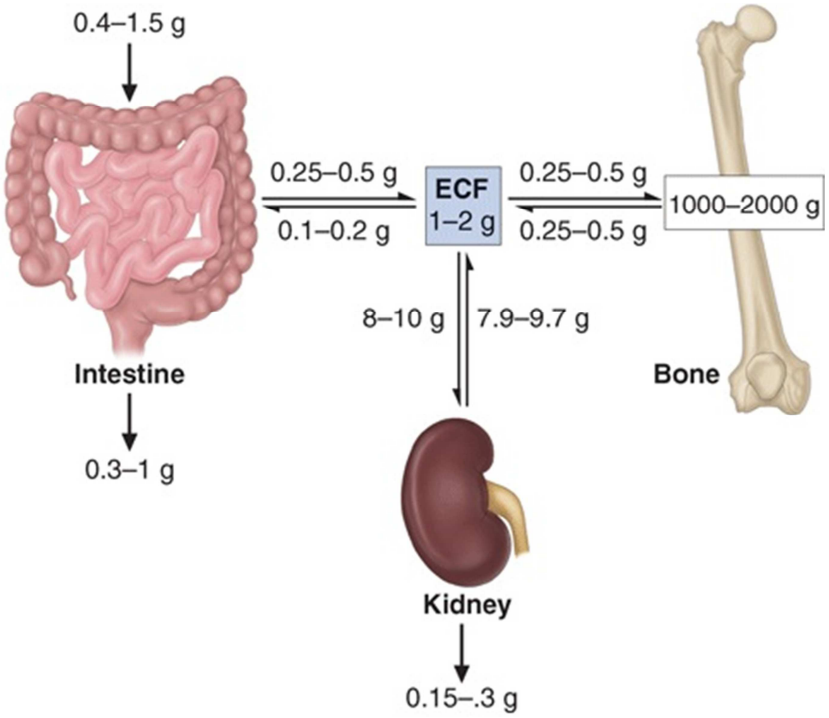


Figure 1: Calcium homeostasis

The concentration of ionized calcium in the ECF is maintained within a narrow range because it plays critical role in neuromuscular activity, secretion and signal transduction. Intracellular cytosolic free calcium level is ~100 nmol/L and is 10,000-fold lower than ionized calcium concentration in the blood and ECF. Cytosolic calcium serves a signaling function. In blood, total calcium concentration is normally 8.5–10.5 mg/dL, of which ~50% is ionized. The remainder is bound ionically to negatively charged proteins, predominantly albumin and immunoglobulins. Hence, alterations in serum protein concentrations directly affect the total blood calcium concentration even if the ionized calcium concentration remains normal. Albumin-corrected calcium [7,8] is calculated as follows:

$$Corrected\ calcium[mg/dL] = Measured\ total\ calcium[mg/dL] + 0.0704\ (3.4 - serum\ albumin[g/dL])$$

Ionized calcium concentration in the ECF is controlled by regulatory mechanisms acting at intestine and kidneys mediated by PTH and $1,25(OH)_2D$. Ionized calcium has negative feedback control over PTH secretion by following mechanisms:

- Activating calcium-sensing receptors (CaSRs) present in the parathyroid gland
- Promoting the production of $1,25(OH)_2D$ which in turn inhibits PTH production

Intestinal calcium handling

Ingested calcium is absorbed in two different ways:

- Active (transcellular) transport: involves apical calcium entry via specific ion channels (TRPV5 and TRPV6), normally ranges from 20 to 70% and occurs in proximal small bowel
- Passive (paracellular) transport: nonsaturable and approximates 5% of daily calcium intake

Dietary intake of calcium regulates synthesis of $1,25(OH)_2D$ which modulates active transport of calcium across the intestinal epithelium. Due to

this feedback control, net calcium absorption is maintained around ~200–400 mg/d. About 100–200 mg/d of calcium is excreted as an obligate component of intestinal secretions and is not regulated by hormones.

Renal calcium handling

The daily load of absorbed calcium is excreted by the kidneys, which is tightly regulated by the concentration of ionized calcium in the blood. Out of 8-10 g/d of calcium that is filtered by the kidneys, ~97-98% is reabsorbed.

- Proximal tubule: 65% is reabsorbed through paracellular route coupled to sodium chloride reabsorption and is not under hormonal regulation
- Cortical thick ascending limb of Henle's loop: 20% is reabsorbed through paracellular route and it requires paracellin-1 which is inhibited by elevated levels of calcium or magnesium acting via CaSR
- Distal convoluted tubules: 10% is reabsorbed through transcellular pathway in which calcium enters the cell via apical calcium channels (TRPV5) across the gradient maintained by Ca^{2+}-ATPases and Na^{+}/Ca^{2+} exchangers present in the basolateral membrane under the control of PTH

Abnormal situations

The homeostatic mechanisms that normally maintain a constant serum ionized calcium concentration may fail at extremes of calcium intake or when the hormonal systems or organs involved are compromised.

- Low dietary calcium intake: increased PTH and 1,25$(OH)_2$D levels mobilize calcium from bone and cause negative calcium balance
- High dietary calcium intake: renal reabsorption is downregulated and leads to hypercalciuria and nephrocalcinosis
- Deficiency or excess of PTH
- Deficiency of excess of vitamin D
- Intestinal disease
- Renal failure

PHOSPHORUS

Total body phosphorus store is ~600 g, of which 85% is present in the bone. Phosphorus differs from calcium in that the intracellular and extracellular concentrations do not have much difference. In cells and in the ECF, phosphorus exists predominantly as $H_2PO_4^-$ or $NaHPO_4^-$ and the remaining as HPO_4^{2-}. In serum, about 12% of phosphorus is bound to proteins and the normal range of elemental phosphorus in adults is 2.5–4.5 mg/dL.

Intestinal phosphorus handling

Phosphate is widely available in foods. Net intestinal absorption of phosphorus is ~500–1000 mg/d and is absorbed efficiently by two ways:

- Passive transport: up to 65% of ingested phosphorus can be absorbed
- Active transport: involving Na^+/PO_4^{2-} co-transporters activated by $1,25(OH)_2D$

Phosphate absorption can be inhibited by phosphate binders like calcium salts, sevelamer acetate and lanthanum carbonate. Low serum phosphate stimulates renal proximal tubular synthesis of $1,25(OH)_2D$ by suppressing blood levels of FGF23.

Factors influencing serum phosphorus levels:

- Circadian rhythm that produces a nadir between 7 and 10 a.m.
- IV dextrose solutions in fasting subjects can decrease serum phosphate by 2 mg/dL due to rapid uptake into and utilization by cells

Renal phosphorus handling

Urinary excretion varies directly with dietary intake. Phosphorus is mainly reabsorbed in the proximal tubule through the apical membrane Na^+/PO_4^{2-} co-transporters (NaPi-2 and NaPi-2c) which are down regulated by PTH [9,10].

FGF23 can also impair phosphate reabsorption. The following factors affect renal phosphorus reabsorption:

- Impair: Hypocalcemia, hypomagnesemia, and severe hypophosphatemia
- Enhance: dehydration

Hyperphosphatemia

Serum phosphorus levels are controlled by altering the reabsorption by the NaPi-2 co-transporters in the proximal tubule for the given filtered load of phosphorus and GFR. The principal hormonal regulators of NaPi-2 activity are PTH and FGF23 [9,11].

In chronic kidney disease, reduction of GFR leads to retention of phosphorus. Hyperphosphatemia inhibits the synthesis of $1,25(OH)_2D$ by the kidneys as well as stimulates the synthesis of PTH by the parathyroids both directly and indirectly (by lowering blood ionized calcium levels). Thus, hyperphosphatemia is a major cause of secondary hyperparathyroidism in renal failure and must be addressed in the early stages of the disease.

Causes of hyperphosphatemia:

I. Impaired renal phosphate excretion
   A. Renal insufficiency
   B. Hypoparathyroidism

1. Developmental
2. Autoimmune
3. After neck surgery or radiation
4. Activating mutations of the calcium-sensing receptor

C. Parathyroid suppression
1. Parathyroid-independent hypercalcemia
a. Vitamin D or vitamin Aintoxication
b. Sarcoidosis, other granulomatous diseases
c. Immobilization, osteolytic metastases
d. Milk-alkali syndrome
2. Severe hypermagnesemia or hypomagnesemia

D. Pseudohypoparathyroidism

E. Acromegaly

F. Tumoral calcinosis

G. Heparin therapy

II. Massive extracellular fluid phosphate loads

A. Rapid administration of exogenous phosphate (intravenous, oral, rectal)

B. Extensive cellular injury or necrosis
1. Crush injuries
2. Rhabdomyolysis

3. Hyperthermia
4. Fulminant hepatitis
5. Cytotoxic therapy
6. Severe hemolytic anemia

C. Transcellular phosphate shifts
1. Metabolic acidosis
2. Respiratory acidosis

The clinical consequences of hyperphosphatemia are due to the formation of widespread calcium phosphate precipitates and resulting hypocalcemia:

- Tetany
- Seizures
- Accelerated nephrocalcinosis
- Pulmonary or cardiac calcifications

VITAMIN D

Synthesis and Metabolism

1,25-dihydroxyvitamin D [1,25$(OH)_2$D] is a steroid hormone which is involved in the homeostatis of calcium and phosphorus.

Sources of vitamin D include:

- Endogenous: vitamin D is produced from 7- dehydrocholesterol on exposure to ultraviolet radiation in the skin and this process is impaired by melanin and high solar protection sunscreens
- Exogenous: vitamin D_2 is the form present in plant sources whereas vitamin D_3 is present in animal sources like fish oil, dairy products and egg yolk, both of which have equivalent biologic activity

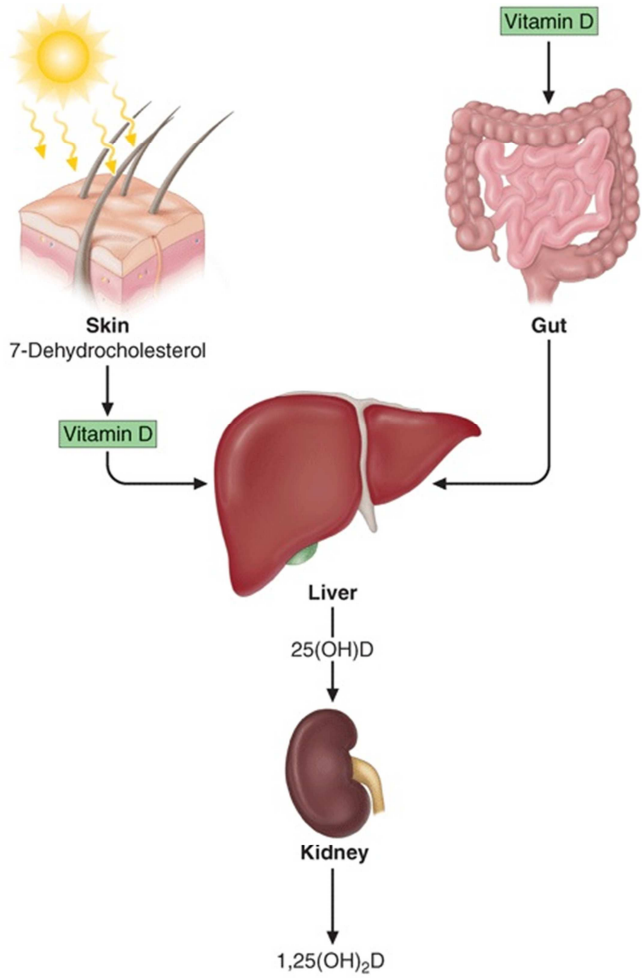


Figure 2: Synthesis of $1,25(OH)_2D$

In the circulation vitamin D is present in association with vitamin D–binding protein, an α-globulin synthesized in the liver. Vitamin D is

subsequently 25-hydroxylated in the liver. 25(OH)D is the major circulating and storage form of vitamin D. Further conversion to $1,25(OH)_2D$ occurs in the proximal convoluted tubule cells of the kidney [Figure **2**]. Factors regulating 1- α hydroxylase are:

- Inducers: PTH and hypophosphatemia
- Inhibitors: calcium, FGF23 and $1,25(OH)_2D$

Polar metabolites of $1,25(OH)_2D$ are secreted into the bile and reabsorbed via the enterohepatic circulation. Impairment of this recirculation leads to accelerated losses of vitamin D metabolites.

Actions of $1,25(OH)_2D$

$1,25(OH)_2D$ mediates its biologic effects by binding to a member of the nuclear receptor superfamily, the vitamin D receptor (VDR), which has only one isoform, in contrast to the other members of its family. The VDR binds to target DNA sequences as a heterodimer with the retinoid X receptor, recruiting a series of co-activators that modify chromatin and approximate the VDR to the basal transcriptional apparatus, resulting in the induction of target gene expression.

VDR has high affinity for $1,25(OH)_2D$ compared to other vitamin D metabolites. Hence, in vitamin D toxicity, elevated levels of 25(OH)D can cause hypercalcemia by itself

- by directly interacting with the VDR
- by displacing $1,25(OH)_2D$ from vitamin D-binding protein

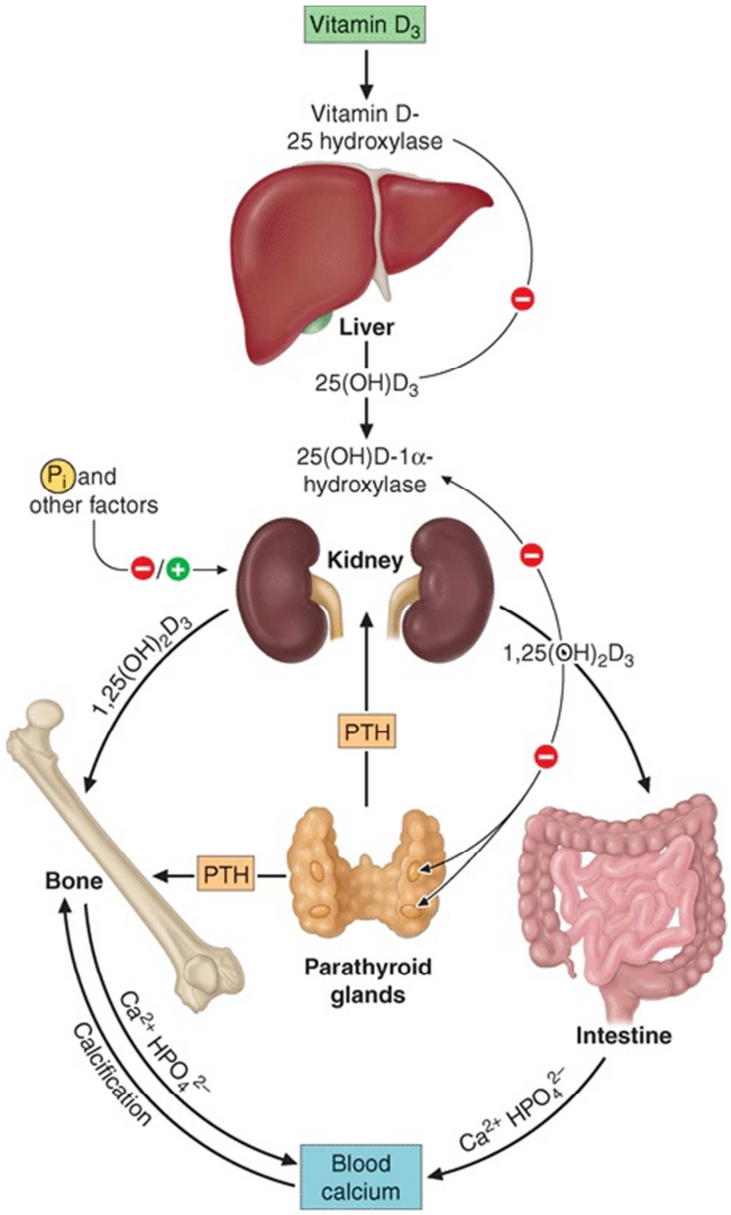


Figure 3: Vitamin D metabolism

Intestine:

Vitamin D promotes intestinal calcium absorption by the following mechanisms:

- $1,25(OH)_2D$ induces a calcium binding protein, calbindin 9K in the intestine which is involved in the active transport of calcium through the enterocyte
- Vitamin D also induces the calcium transporters TRPV5 and TRPV6 (transient receptor potential vanilloid) that are expressed in the apical membrane

Bone:

The VDR is expressed in osteoblasts. Genes regulated by VDR include the following bone matrix proteins:

- Osteocalcin
- Osteopontin

Both $1,25(OH)_2D$ and PTH induce the expression of RANK ligand, which promotes osteoclast differentiation and increases osteoclast activity, by binding to RANK on osteoclast progenitors and mature osteoclasts. This is the mechanism by which $1,25(OH)_2D$ induces bone resorption.

Parathyroid gland:

Vitamin D has inhibitory effects on the parathyroid gland [Figure **3**]:

- Antiproliferative effects on parathyroid cells
- Suppress the transcription of the parathyroid hormone gene

The effects of $1,25(OH)_2D$ on the parathyroid gland are an important part of the rationale for current therapies directed at preventing and treating hyperparathyroidism associated with renal insufficiency.

PARATHYROID HORMONE

Physiology

Calcium homeostasis is predominantly controlled directly as well as indirectly by PTH [Figure **4**]. Hypocalcemia due to any cause is sensed by parathyroid and PTH synthesis is increased proportionately. The effector organs of PTH are bone and kidneys. PTH can mobilize calcium from bone and it can increase renal reabsorption of calcium. Apart from that PTH can also activate renal 1-α hydroxylase and promote the synthesis of $1,25(OH)_2D$. PTH increases intestinal absorption of calcium indirectly through vitamin D.

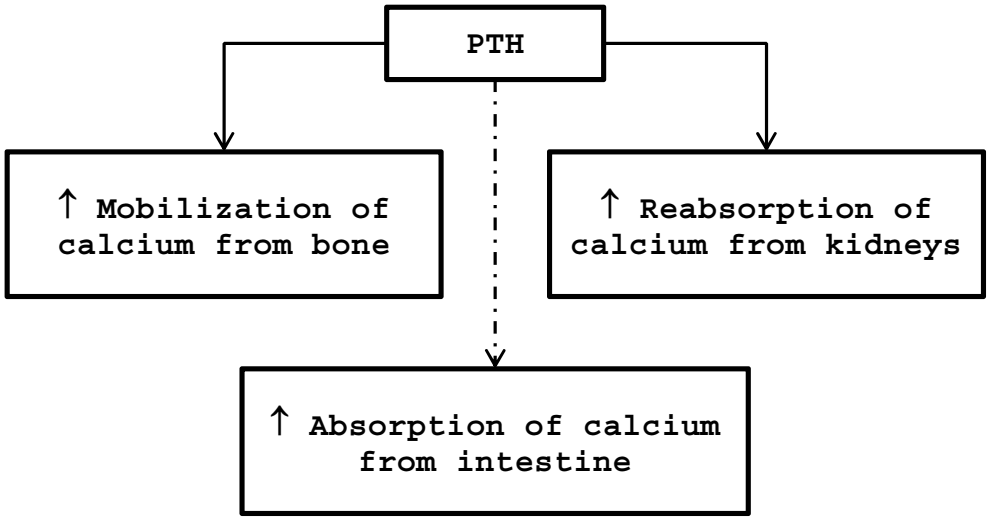


Figure 4: Functions of PTH

Transient rise and fall in serum calcium levels are controlled by PTH primarily by its effects on the bone and less on the renal clearance. Steady-state calcium levels are primarily affected by the actions of $1,25(OH)_2D$ on intestinal absorption of calcium.

Kidney:

PTH acts at multiple sites in the kidneys:

- Inhibits phosphorus transport (proximal tubule)
- Augments calcium reabsorption (distal tubule)
- Stimulates the renal 25(OH)D-1α-hydroxylase

Bone:

As much as 500 mg of calcium is transferred between the ECF and bone each day (a large amount in relation to the total ECF calcium pool), and PTH has a major effect on this transfer. The homeostatic role of the hormone can maintain calcium concentration in blood at the expense of bone demineralization. PTH has both direct and indirect actions on bone. Within minutes PTH can mobilize calcium from the bone. When chronically elevated, PTH increases the number of both osteoblasts and osteoclasts and increases the remodeling of bone; these effects manifest within hours after the hormone is given and persist for hours after PTH is withdrawn.

- Continuous exposure to elevated PTH: leads to increased bone resorption mediated by osteoclasts
- Intermittent administration of PTH: elevated hormone levels for 1–2 hours per day leads to a net stimulation of bone formation rather than bone breakdown

Even though the primary action of PTH is activating the osteoclasts to promote bone demineralization, osteoclasts do not have PTH/PTHrP receptors. These receptors are present in the osteoblasts. Hence, activation of osteoclasts by PTH is indirect through osteoblasts. Cytokines are released by osteoblasts on stimulation by PTH and they in turn activate the osteoclasts. Presence of PTH/PTHrP receptor in the osteoblasts explains the bone-forming effects of PTH.

Structure

PTH is a peptide consisting of 84 amino acids. The 34 amino acids present in the amino-terminal portion are critical for the biologic actions of the hormone. Synthetic PTH fragments containing only the 11 amino-terminal amino acids are sufficient to activate the PTH/PTHrP receptor. The carboxyl-terminal regions of the full-length PTH(1–84) molecule also can bind to a separate binding protein/receptor (cPTH-R), but this receptor has been incompletely characterized. Fragments shortened at the amino terminus

possibly by binding to cPTH-R can inhibit some of the biologic actions of full-length PTH(1–84) and of PTH(1–34).

Synthesis

Parathyroid cells have multiple methods of adapting to increased needs for PTH production:

- Secretion of preformed hormone in response to hypocalcemia (within minutes)
- PTH mRNA expression is induced by sustained hypocalcemia (within hours)
- Cellular replication to increase gland mass (within days)

Parathyroid gland synthesizes preproparathyroid hormone containing 115 amino acids which is further metabolized to release mature PTH. After a first cleavage step to remove the "pre" sequence of 25 amino acid residues, a second cleavage step removes the "pro" sequence of 6 amino acid residues before secretion of the mature peptide comprising 84 residues.

Regulation of PTH Secretion

Calcium present in the extracellular fluid interacts with a G protein-coupled receptor which is a calcium sensor and through that it controls the secretion of PTH. This receptor is a member of a distinctive subgroup of the GPCR

superfamily that is characterized by a large extracellular domain suitable for "clamping" the small-molecule ligand.

- When the calcium level falls below the normal range (measured as total calcium), PTH secretion increases steeply; the ionized fraction of serum calcium being the one determining the hormone secretion
- Severe intracellular magnesium deficiency impairs PTH secretion

Metabolism

The secreted form of PTH contains 84 amino acids. It is denoted as PTH(1–84). Metabolism of PTH occurs in the liver and kidney and fragments containing less amino acid are produced. These fragments lack the critical amino-terminal sequence and hence they are biologically inactive.

The rate of clearance of the secreted 84-amino-acid peptide from blood is more rapid than the rate of clearance of the biologically inactive fragments corresponding to the middle and carboxyl-terminal regions of PTH.

Consequently, the interpretation of results obtained with earlier PTH radioimmunoassays is influenced by the nature of the peptide fragments detected by the antibodies. PTH assays fall into three categories [12]:

- First generation assays: detect both PTH(1-84) as well as the fragments lacking amino-terminal sequence

- Second generation assays: did not detect fragments lacking amino-terminal sequence but a truncated form of PTH denoted as PTH(7-84) which is elevated primarily in patients with chronic renal insufficiency lead to misdiagnosis of secondary HPT and treatment causing adynamic bone disease
- Third generation assays: detect only the full-length PTH(1-84) form but not readily available commercially at present

Actions of PTH

Both PTH and PTHrP bind to and activate the PTH/PTHrP receptor. The PTH/PTHrP receptor is G-protein coupled receptor and it is called as PTH1R. Although both ligands activate the PTH1R, the two peptides induce distinct responses in the receptor.

PTH1R is characterized by the fact that it can bind to more than one G-protein and activate different second messenger pathways. Hence, PTH can activate multiple pathways having different effects. PTH acts by activating protein kinases A and C and calcium channels with tissue specific responses:

- Inhibition of phosphate and bicarbonate transport
- Stimulation of calcium transport
- Activation of renal 1α-hydroxylase
- Increased bone turnover

CHRONIC KIDNEY DISEASE – MINERAL AND BONE DISORDER AND RENAL OSTEODYSTROPHY:

Vitamin D deficiency that occurs in CKD leads on to hypocalcemia and secondary hyperparathyroidism. Pathologic changes that occur in bones are described as renal osteodystrophy. Abnormalities in mineral metabolism also manifest in soft tissues including blood vessels and heart valves. Hence, a new term 'Mineral and Bone Disorder' was coined to describe this spectrum of complications that occur in CKD.

KDIGO defines CKD-MBD as a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth or strength
- Vascular or other soft-tissue calcification

Renal osteodystrophy is an alteration of bone morphology in patients with CKD. It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy [1].

Abnormalities of mineral metabolism

In a cross sectional study, named 'SEEK' study, Levin et al studied around 1,800 patients with CKD belonging to stages 3 to 5 who are not on dialysis [13]. They measured the levels of calcium, phosphorus, vitamin D and PTH in the serum. The levels of PTH started to rise early in the disease course starting from stage 3. The levels of calcium and phosphorus on the other hand were relatively stable until stage 5 [Figure **5**].

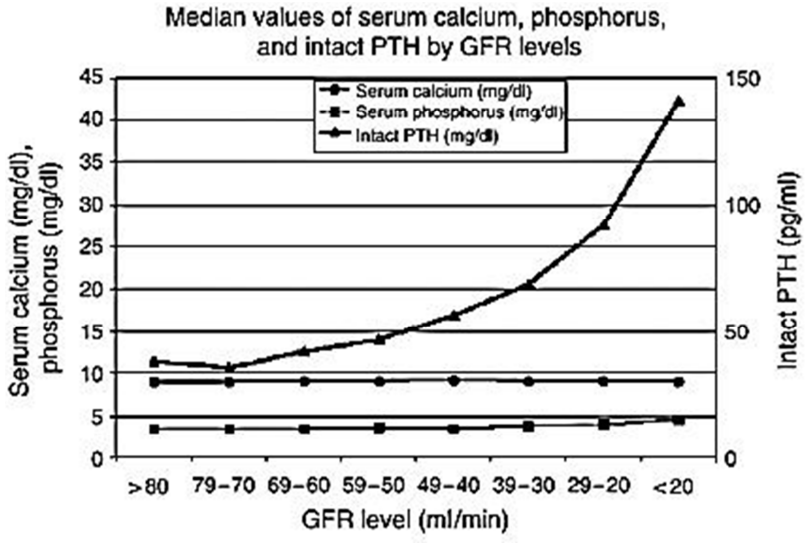


Figure 5: Results of the SEEK study

Vassalotti et al studied around 2,600 patients at increased risk of CKD from 2005 to 2006 in KEEP, a program conducted by the National Kidney Foundation [14]. They also analyzed NHANES 1999 to 2004 data. This study also confirmed the results of the SEEK study that increased PTH level occurs

early in patients with stage 3, typically with normal calcium and phosphorus levels.

Abnormalities in mineralization of bone

Skeletal changes in MBD can take various forms and it also varies based on whether the patient is on dialysis or not [15]. Common abnormalities involving bones include the following:

- Adynamic bone: a state of reduced bone turnover characterized by relatively low PTH, reduced osteoclasts and osteoblasts, reduced mineralization of bone but not associated with excess osteoid formation and it is common in patients on dialysis
- Osteitis fibrosa: occurs secondary to hyperparathyroidism characterized by increased osteoclastic activity that leads on to increased bone resorption and formation of fibrosis and cysts
- Osteomalacia: inadequate mineralization of the bone whereas osteoid formation is not affected and it is usually due to vitamin D deficiency
- Mixed forms

Prevalence of various types of skeletal changes [Figure **6**] varies in CKD patients not on dialysis and patients on dialysis [1].

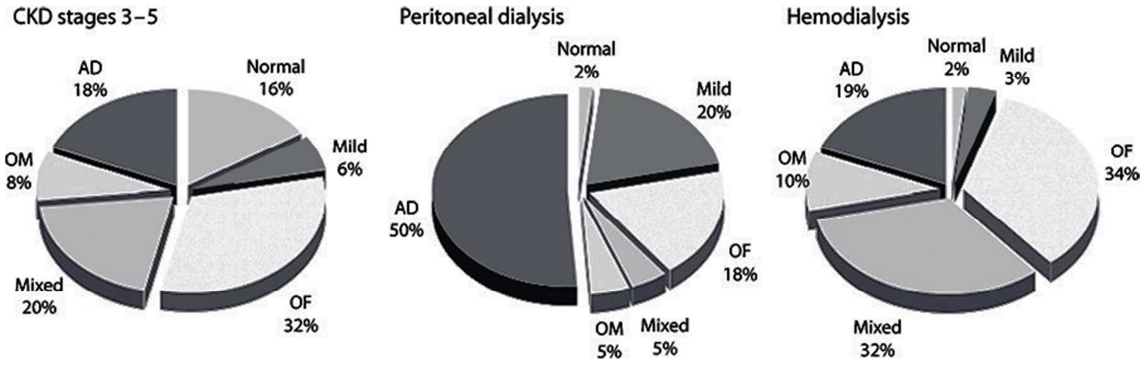


Figure 6: Prevalence of various types of skeletal changes

Whatever be the pathologic change in the bone, these skeletal changes reduce the tensile strength of the bone and make the bones more fragile and increase the risk of fracture.

Vascular or other soft-tissue calcification

CKD is associated with increased cardiovascular morbidity and mortality. Increased cardiovascular risk in CKD patients is due to the following factors:

- Traditional risk factors like diabetes, hypertension and old age
- Risk factors specific to CKD like albuminuria, anemia and electrolyte disturbances
- Uremia by itself may promote atherosclerosis by various mechanisms including oxidative stress and inflammation. A hallmark of atherosclerosis in CKD is vascular calcification [16]

Since cardiovascular risk in CKD patients is due to multiple factors apart from traditional risk factors, prediction of cardiovascular risk in this population requires measurement of non-traditional risk factors like vascular calcification.

MECHANISMS OF VASCULAR CALCIFICATION:

Vascular calcification may occur either in tunica intima or tunica media of the vessel wall [Figure 7]. In atherosclerosis, calcification commonly occurs in intima. Medial calcification is common in CKD patients [17]. It may be independent of atherosclerosis and probably has a different pathogenesis from intimal calcification. Current evidence suggests that vascular calcification in CKD is a dynamically regulated process.

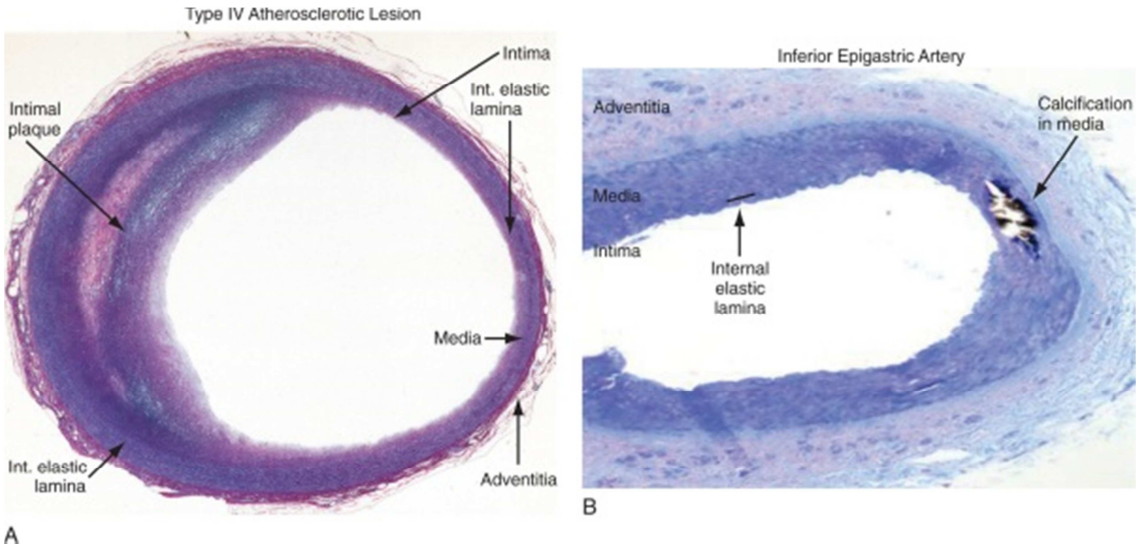


Figure 7: Intimal calcification (A) and medial calcification (B)

Vascular smooth muscle cells and osteoblasts arise from a mesenchymal precursor cell. A transcription factor, known as core-binding factor alpha 1 (Cbfa1) possibly switches vascular smooth muscle cells to the osteoblast phenotype. The expression of bone related proteins like PTH, PTHrP, osteonection and BMP7 at the sites of medial arterial calcification also suggests the presence of osteoblastic activity in the vessel wall. Hyperphosphatemia has

been shown to induce osteoblastic changes in vascular smooth muscle cells and it is dependent on a sodium-dependent phosphate cotransporter, known as Pit-1. Osteoprotegerin is a soluble marker belonging to tumor necrosis factor (TNF)-α receptor superfamily, the levels of which are elevated in ESRD patients. Osteoprotegerin has been demonstrated in vasculature and it inhibits osteoclastogenesis and leads to vascular calcification [Figure **8**].

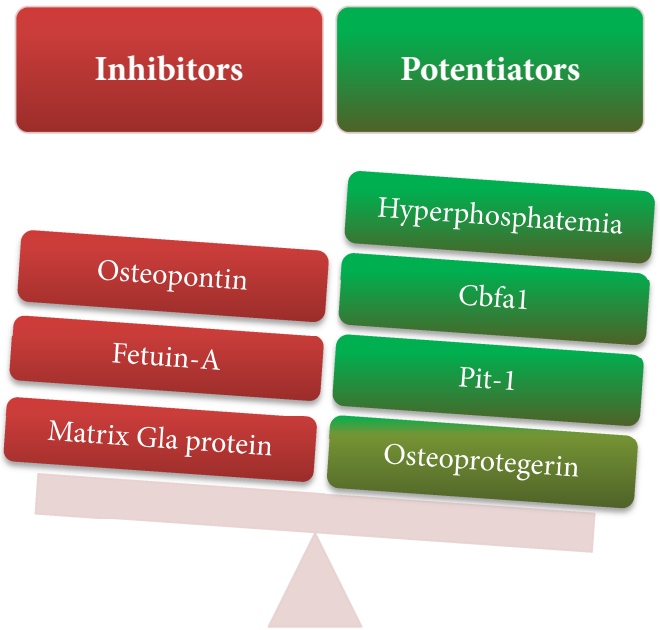


Figure 8: Imbalance between inhibitors and potentiators of vascular calcification in CKD

Inhibitors of ectopic calcification include fetuin-A, matrix Gla protein and osteopontin. Fetuin-A is reduced in renal failure, especially in association with increasing inflammation in dialysis patients. Matrix Gla protein is found in normal arterial wall and inhibits mesenchymal cell differentiation into

osteogenic phenotype. Osteopontin is also a negative regulator of calcification [16,18].

CONSEQUENCES OF VASCULAR CALCIFICATION:

Medial calcification leads to increased vascular stiffness and reduced vascular compliance. It results in increased pulse wave velocity, systolic blood pressure and fall in diastolic blood pressure. Pulse pressure is widened as a result [Figure **9**]. Medial calcification also has an impact on plaque vulnerability. These factors result in adverse cardiovascular consequences [18].

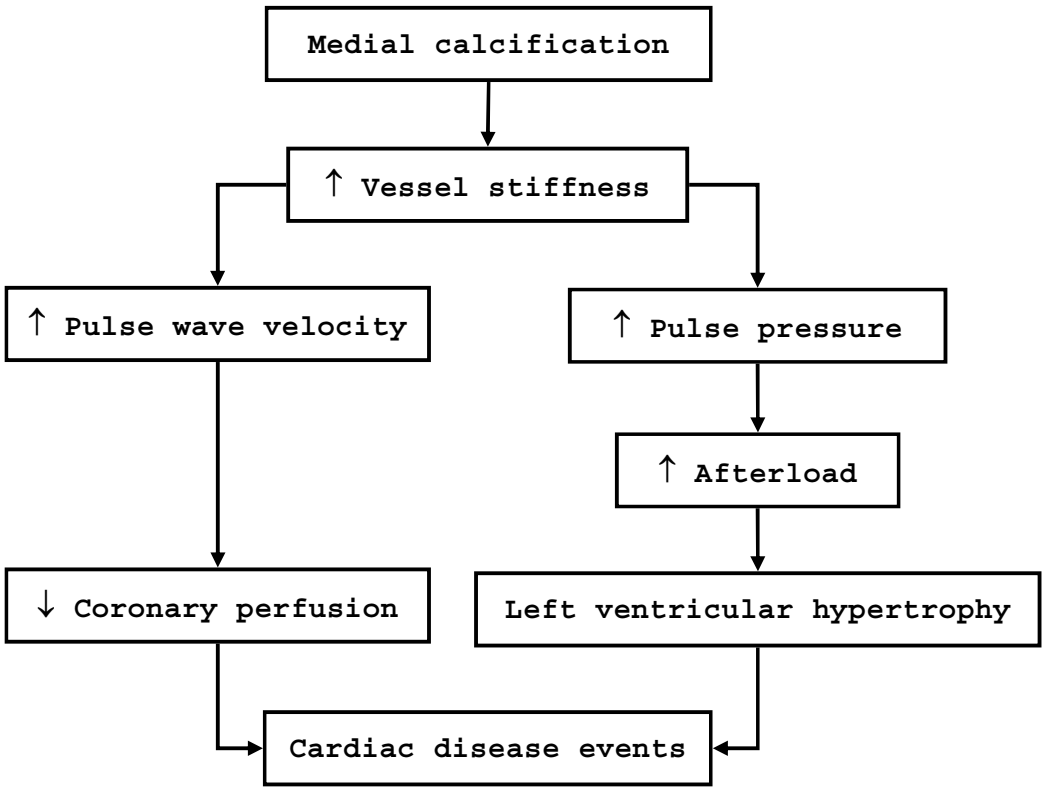


Figure 9: Consequences of medial calcification

METHODS TO ASSESS VASCULAR CALCIFICATION:

Electron Beam CT (EBCT) or Multi-Slice CT (MSCT) of coronary arteries

The cardiovascular risk associated with CKD has a strong correlation with coronary artery calcification. It is measured by CT-based techniques such as EBCT and MSCT. Coronary artery calcium score is calculated based on the following characteristics:

- Number of calcific lesions
- Areas of calcific lesions
- Peak Hounsfield computed tomographic numbers of the calcific lesions

CAC score [2,19] is the most sensitive way of assessing vascular calcification in CKD.

Pulse pressure

Vascular calcification causes arterial stiffness that leads to increased systolic blood pressure and decreased diastolic blood pressure ultimately widening the pulse pressure. But studies comparing CAC score and pulse pressure have shown poor correlation between the two [20].

Pulse wave velocity

Pulse wave velocity is a reproducible measure of arterial stiffness [19]. It is usually measured non-invasively using sonographic principles. Carotid and

femoral artery waveforms are recorded consecutively, analyzed with software and then pulse wave velocity is calculated. It has a strong correlation with cardiovascular events.

Intima-media thickness (IMT)

IMT is a measure of the thickness of tunica intima and tunica media of the vessel wall [21]. The measurement is usually done by external ultrasonography. IMT is used to detect the presence of atherosclerosis as well as to track the regression, arrest or progression of atherosclerosis. But the usefulness of measuring IMT over time is disputed.

Multi-Slice CT of abdominal aorta

Hanada et al utilized CT scan of the abdominal aorta to measure abdominal aortic calcification index (ACI) [22]. 10 slices of 10 mm thickness above the bifurcation of the aorta were analyzed. An area >1 mm^2 having a density of ≥130 Hounsfield units was taken as evidence for calcification. Each slice was divided into 12 segments radially and analyzed for the presence of calcification. ACI was calculated using the following formula:

$$ACI = \frac{Total\ score\ for\ calcification\ in\ all\ slices}{Number\ of\ segments\ in\ each\ slice \times Number\ of\ slices} \times 100$$

Echocardiography

Echocardiography is used to assess valvular calcification in both mitral and aortic valves [Figure **10**]. Compared to mitral valve, aortic valve calcification has stronger association with CAC score. But overall valvular calcification does not correlate well. Since echocardiography is a non-invasive method and assessment of valvular calcification is relatively easy, the recent KDIGO guidelines recommend echocardiography in the routine evaluation of patients with CKD.

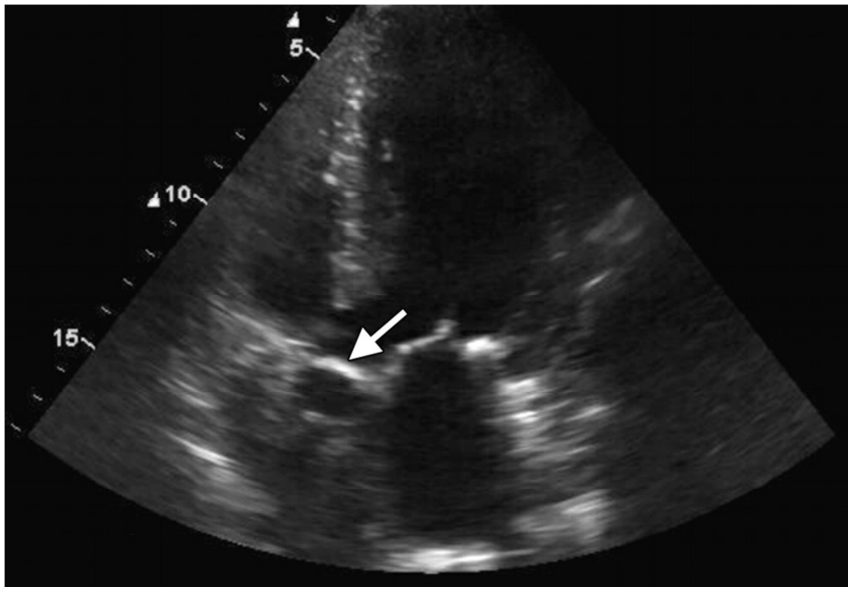


Figure 10: Aortic valve calcification visualized on echocardiography

Lateral lumbar radiography

Calcification of abdominal aorta can be assessed using lateral lumbar radiography. Aorta lies lateral to the vertebral column in the upper abdomen and it becomes anterior before its bifurcation. So the calcification of the lower

portion of abdominal aorta can be visualized on a lateral film. Calcification usually starts in the lower portion of abdominal aorta and extends cranially in advanced cases.

The utility of lateral lumbar radiography in the evaluation of abdominal aortic calcification was developed by Kauppila et al in 1997 [23]. Grading of the calcific lesions was performed and a scoring system was developed.

Abdominal aorta will be visualized in front of the vertebral column as two vertical lines corresponding to the anterior and posterior walls of the aorta [Figure **11**]. They are divided into four segments corresponding to L1 to L4 vertebrae. Calcification is then assessed separately in each segment both in the anterior wall and posterior wall. Each portion is graded on a numerical scale from 0 to 3. Grade 0 indicates no calcification. Grade 1 indicates calcification extending less than 1/3 of the vessel wall vertically. Grade 2 corresponds to calcific lesions involving 1/3 to 2/3 of the wall. Grade 3 indicates more than 2/3 of the vessel wall is calcified [Table **1**].

The *composite score* for anterior–posterior severity is the sum of scores of individual aortic segments both for the anterior and posterior walls (maximum score 24). The *affected segments score* is the total number of aortic segments showing any level of calcification (maximum score 4) [Table **2**].

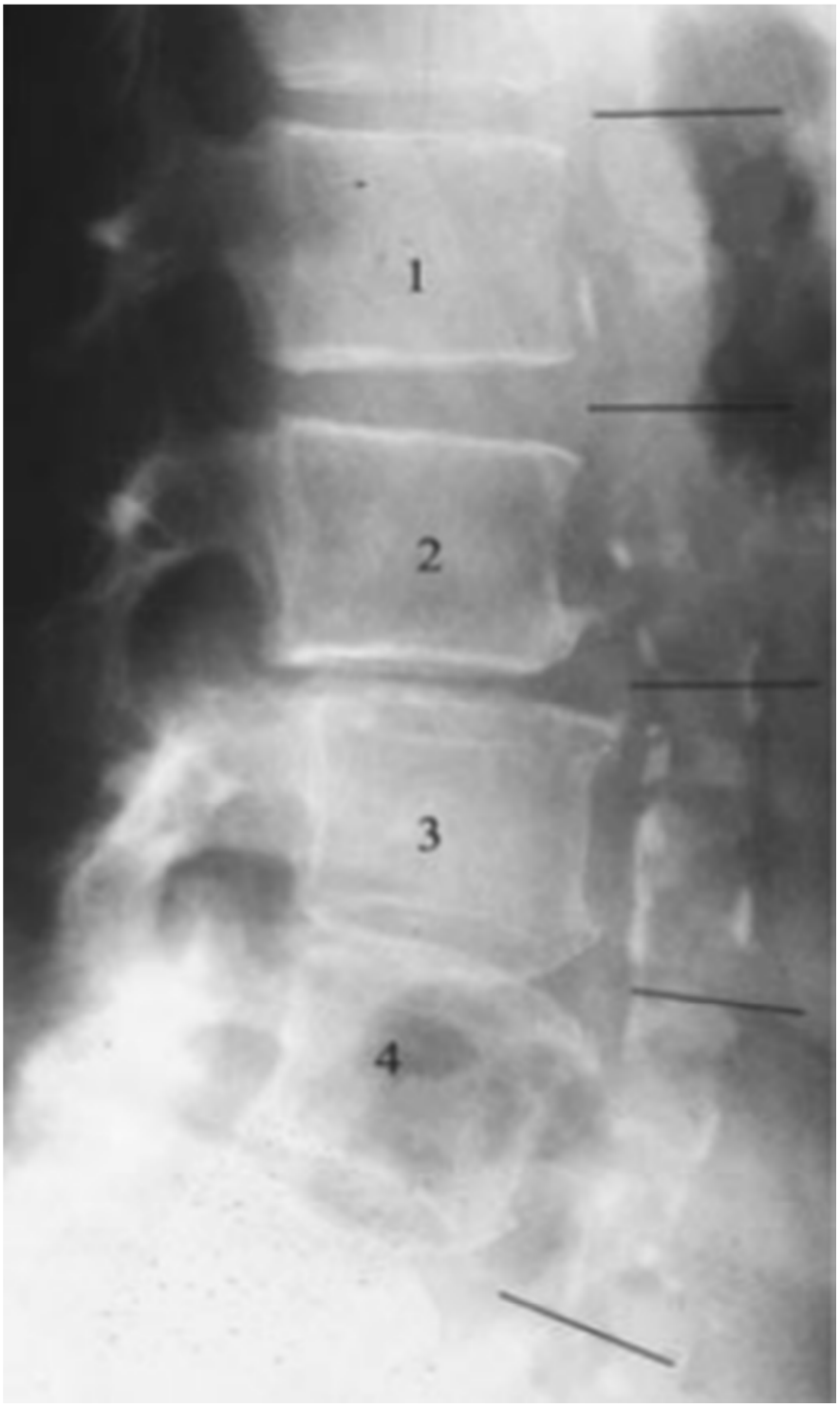


Figure 11: Lateral lumbar radiography of aorta

Table 1: Grading system

Grading	Description
0	No calcific deposits in front of the vertebra
1	Small scattered calcific deposits filling less than 1/3 of the longitudinal wall of the aorta
2	1/3 to 2/3 of the wall calcified
3	2/3 or more of the wall calcified

Table 2: Scoring system

Level	Affected segment	Anterior wall range	Posterior wall range	Anterior-posterior severity range
L1	0 - 1	0 - 3	0 - 3	0 - 6
L2	0 - 1	0 - 3	0 - 3	0 - 6
L3	0 - 1	0 - 3	0 - 3	0 - 6
L4	0 - 1	0 - 3	0 - 3	0 - 6
Affected segments score	**0 - 4**	*Composite score*		**0 - 24**

THERAPIES FOR MINERAL AND BONE DISORDER

Management options currently available for CKD-MBD fall under three categories:

1. Vitamin D analogs: Calcitriol, doxercalciferol, paricalcitol
2. Calcimimetics: Cinacalcet HCl
3. Phosphate binders: Calcium carbonate, calcium gluconate, sevelamer, lanthanum

Vitamin D analogs

Naturally occurring forms of vitamin D like cholecalciferol and ergocalciferol need renal activation which is deficient in patients with chronic renal insufficiency. Synthetic analogs which do not require in vivo activation are used in the treatment of secondary hyperparathyroidism [24]. Hypercalcemia and hyperphosphatemia are the common side effects of vitamin D therapy.

Calcimimetics

Cinacalcet acts on the CaSR in the parathyroid gland and inhibits the secretion of PTH [25,26]. Hypocalcemia remains a significant problem with calcimimetic therapy. Currently they are not recommended for the treatment of secondary hyperparathyroidism.

Phosphate binders

Aluminium containing phosphate binders were used previously. Association of adynamic bone disease with aluminium toxicity lead to withdrawal of aluminium compounds in the CKD population.

Calcium containing phosphate binders like calcium carbonate and calcium gluconate are now increasingly being used. But increased risk of vascular calcification associated with these agents precludes their use in patients at risk of calcification. Use of non-calcium containing phosphate binders is being investigated.

Sevelamer is a non-calcium containing phosphate binder and it is recommended for patients who are at risk of vascular calcification [27,28,29]. Sevelamer has favorable effects on lipid profile and decreases the rate of progression of atherosclerosis [30].

Lanthanum carbonate is also a non-calcium containing phosphate binder, but it does not have additional benefits as sevelamer [31].

MATERIALS AND METHODS

Study Centre:

Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai

Duration of the Study:

6 months

Study Design:

Cross sectional study

Sample Size:

60 patients

Study Population:

Chronic kidney disease (as defined by K/DOQI [4]) patients attending the outpatient clinic of nephrology department at Rajiv Gandhi Government General Hospital, Chennai meeting the inclusion criteria were included in the study after screening for exclusion criteria.

Inclusion Criteria:

- CKD stage III-V patients
- Aged ≥18 years
- Duration since diagnosis ≥6 months

Exclusion Criteria:

- Structural diseases of aorta
- Patients on dialysis
- CKD stage I and II

Methodology:

Patients have their history taken according to a questionnaire and subjected to clinical examination.

Patients were subjected to the following investigations:

- Blood urea
- Serum creatinine
- Hemoglobin
- Serum albumin
- Lipid profile
- Serum calcium
- Serum phosphorus
- Serum PTH
- USG KUB

Lateral lumbar radiography of aorta was taken for all patients and abdominal aorta calcification was documented in terms of composite score and affected segment score.

Ethical Committee Clearance:

Obtained

Informed Consent:

Obtained from all patients included in the study

Statistical Analysis:

Statistical analysis was done using SPSS software version 21.0

Chi-square test, unpaired t-test and ANOVA were used in appropriate cases

P value <0.05 was taken as statistically significant (95% confidence interval)

Conflicts of Interest:

None

OBSERVATIONS AND RESULTS

STUDY POPULATION

In our study, totally 60 patients were enrolled based on the inclusion and exclusion criteria. The study population consisted of patients who aged from 43 years to 69 years. More than 50% of patients were between 61 and 65 years of age. Among 60 patients, 39 patients were males (65%) and 21 were females (35%) [Table **3**, Figure **12**, Figure **13**, Figure **14**].

Table 3: Age and sex distribution

Age group [years]	Sex		Total	P value
	Male	Female		
≤50	0	3	3	0.11
	0%	14.3%	5%	
51-55	5	1	6	
	12.8%	4.8%	10%	
56-60	9	4	13	
	23.1%	19.0%	21.7%	
61-65	20	12	32	
	51.3%	57.1%	53.3%	
>65	5	1	6	
	12.8%	4.8%	10%	
Total	39	21	60	
	65%	35%	100%	

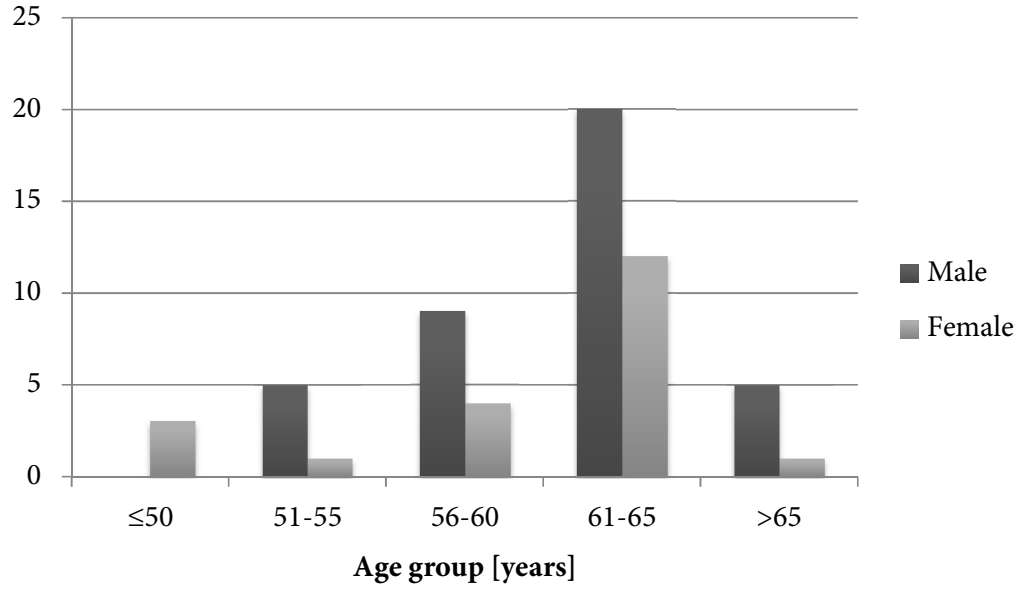


Figure 12: Age and sex distribution

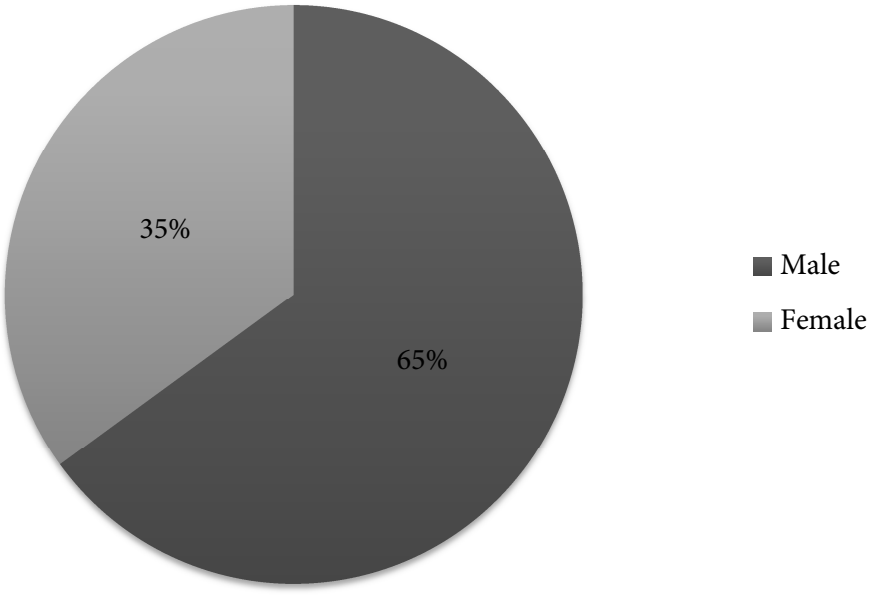


Figure 13: Sex distribution

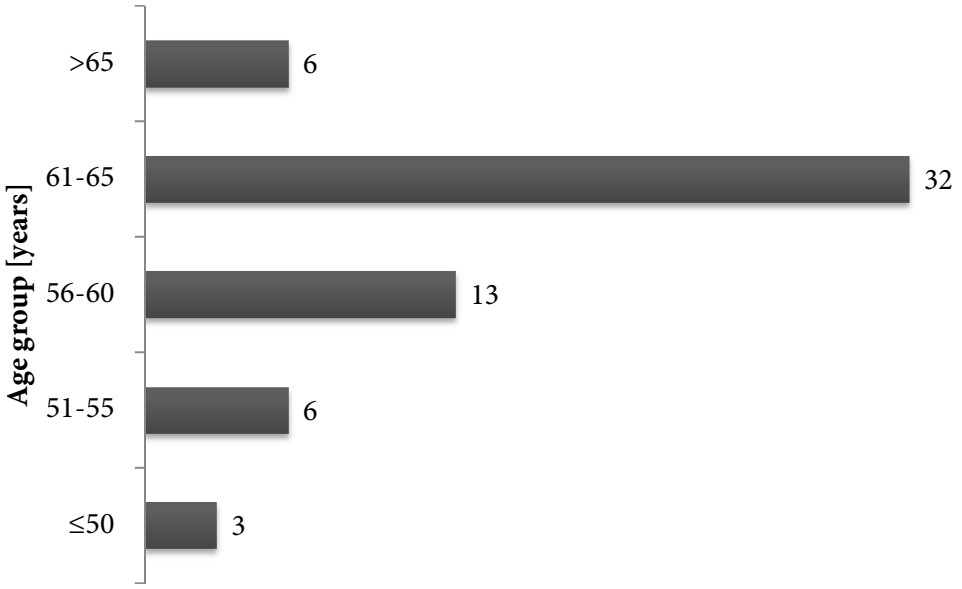


Figure 14: Age distribution

METHOD OF ANALYSIS

Patients were studied for their abdominal aortic calcification status in terms of composite score derived from lateral lumbar radiography. Analysis was performed in the following ways:

1. **Calcification** is present (composite score >0) or absent (composite score = 0)
2. **Degree of calcification** represented by the absolute value of composite score itself

Parameters like sex, stage of CKD, serum calcium level and diabetic status were analyzed both for presence as well as degree of calcification.

AGE versus CALCIFICATION

Calcification was noted in one third of the study population. Patients aged between 61 and 65 years represented the majority as 14 out of 20 patients (70%) who had calcification fell in that age group. None of the patients below 50 years of age had calcification (n = 3). No significant association was noted between age and presence of calcification (p = 0.293) [Table **4**, Figure **15**].

Table 4: Age *versus* calcification

Age group [years]	**Calcification**		**Total**	**P value**
	Present	**Absent**		
≤50	0	3	3	0.293
	0%	7.5%	5.0%	
51-55	2	4	6	
	10.0%	10.0%	10.0%	
56-60	2	11	13	
	10.0%	27.5%	21.7%	
61-65	14	18	32	
	70.0%	45.0%	53.3%	
>65	2	4	6	
	10.0%	10.0%	10.0%	
Total	20	40	60	
	33.3%	66.7%	100.0%	

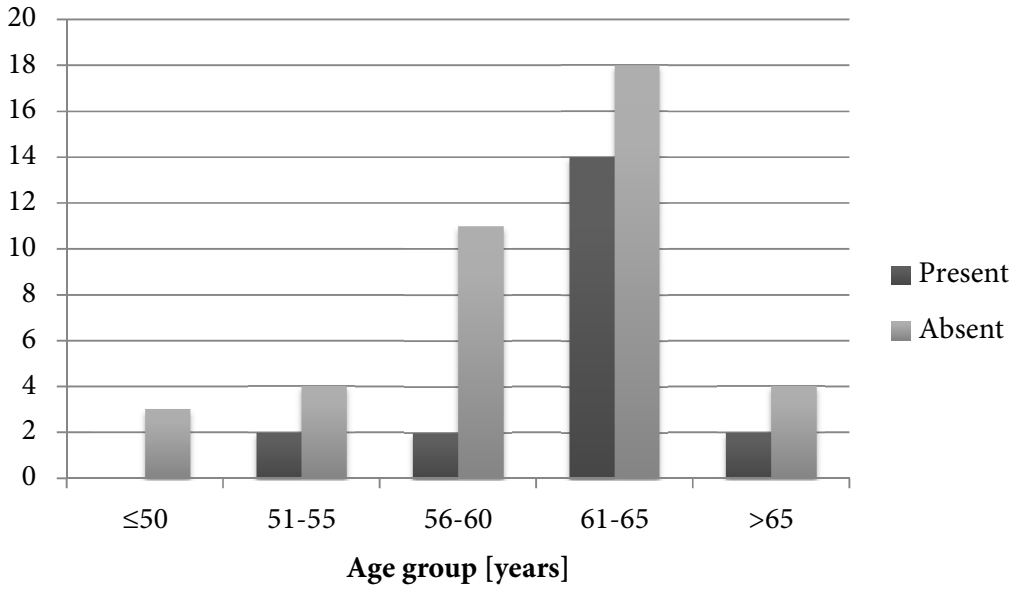


Figure 15: Age *versus* calcification

Age was not associated with the degree of calcification also (p = 0.062)

[Table **5**, Figure **16**].

Table 5: Age *versus* degree of calcification

Age group [years]	n	Mean	Standard deviation	P value
≤50	0	0.00	0.000	0.062
51-55	2	1.50	0.707	
56-60	2	10.50	6.364	
61-65	14	8.00	3.464	
> 65	2	11.00	2.828	
Total	20	7.90	4.103	

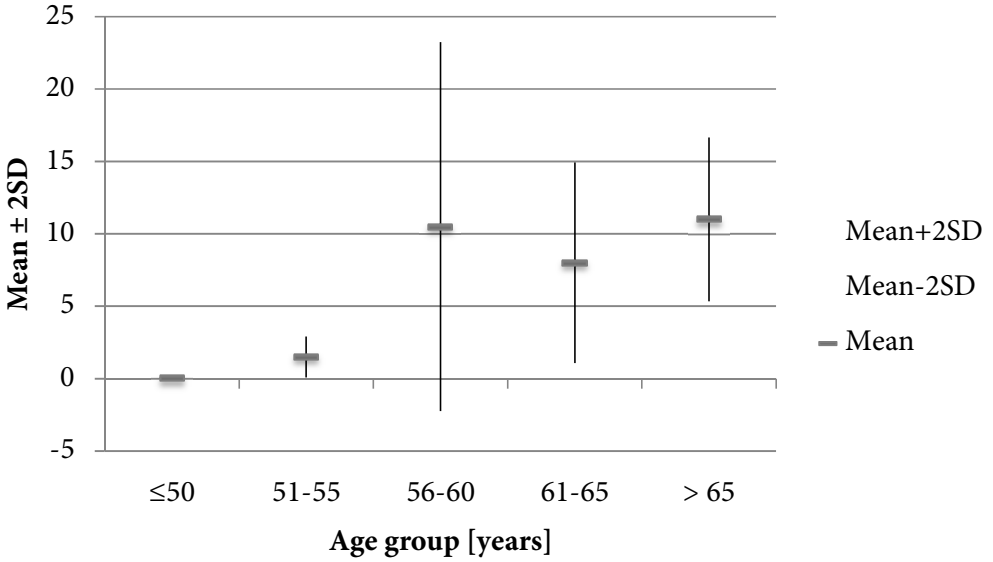


Figure 16: Age *versus* degree of calcification

SEX versus CALCIFICATION

Out of 20 patients who showed evidence of calcification, 14 patients were males (n = 39) representing 70% and the remaining 6 patients were females (n = 21) accounting for 30%. Males outnumbered females in having calcification probably because they represent roughly two third of the study population. Statistical analysis did not reveal any association between sex and presence of calcification (p = 0.566) [Table **6**, Figure **17**]. Mean composite score among males was 7.64 (SD = 4.465) and among females was 8.50 (SD = 3.391). Degree of calcification also did not have any association with sex (p = 0.680) [Table **7**, Figure **18**].

Table 6: Sex *versus* calcification

Sex	Calcification		Total	P value
	Present	Absent		
Male	14	25	39	0.566
	70.0%	62.5%	65.0%	
Female	6	15	21	
	30.0%	37.5%	35.0%	
Total	20	40	60	
	33.3%	66.7%	100%	

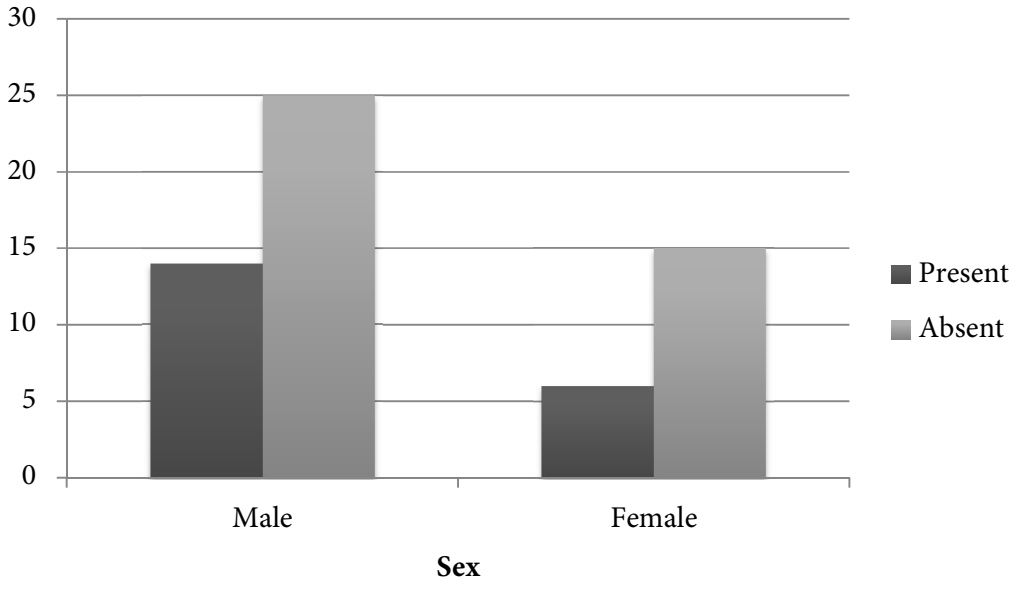


Figure 17: Sex *versus* calcification

Table 7: Sex *versus* degree of calcification

Sex	n	Mean	Standard deviation	P value
Male	14	7.64	4.465	0. 680
Female	6	8.50	3.391	

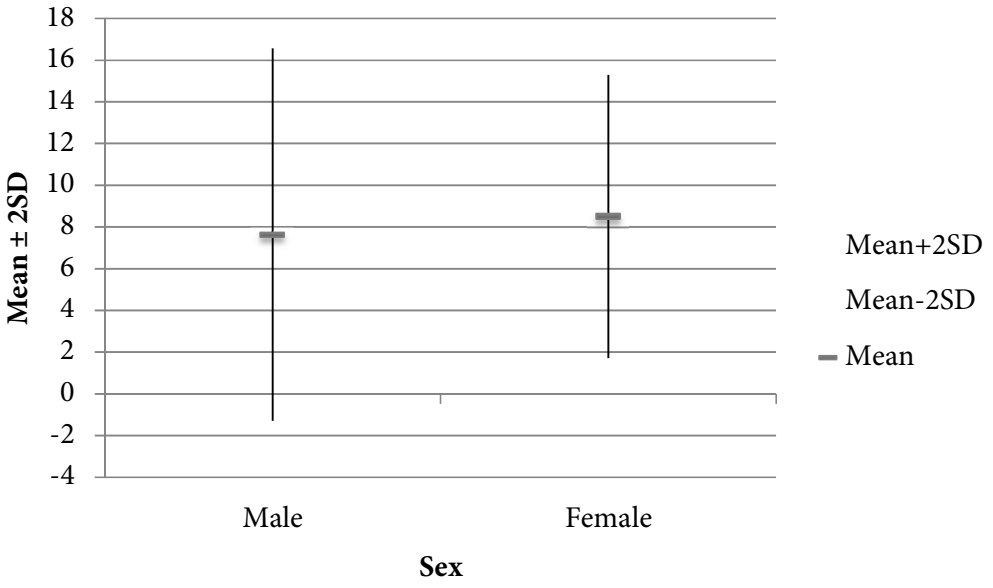


Figure 18: Sex *versus* degree of calcification

DURATION OF CKD versus CALCIFICATION

None of the patients with duration of disease ≤2 years showed evidence of calcification. Twelve out of 23 patients (52.2%) with 4-6 years of disease and 3 out of 4 patients (75%) with >6 years of disease had calcification. Duration of disease has got direct correlation with presence of calcification (p = 0.006) [Table **8**, Figure **19**].

Table 8: Duration of CKD *versus* calcification

Duration [years]	Calcification		Total	P value
	Present	Absent		
≤2	0	6	6	0.006
	0%	15.0%	10.0%	
2-4	5	22	27	
	25.0%	55.0%	45.0%	
4-6	12	11	23	
	60.0%	27.5%	38.3%	
>6	3	1	4	
	15.0%	2.5%	6.7%	
Total	20	40	60	
	33.3%	66.7%	100%	

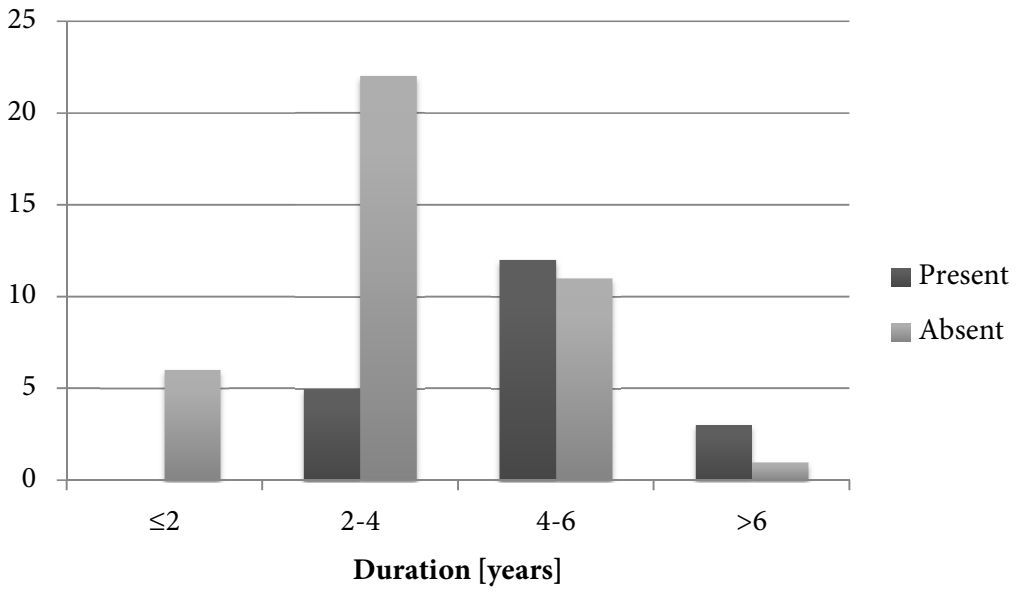


Figure 19: Duration of CKD *versus* calcification

Mean composite score for patients with disease duration 2-4 years was 9.80 (SD = 4.604); 7.92 for 4-6 years duration (SD = 3.370); and 4.67 for >6 years (SD = 5.508). Degree of calcification was not associated with duration of disease (p = 0.240) [Table **9**, Figure **20**].

Table 9: Duration of CKD *versus* degree of calcification

Duration [years]	n	Mean	Standard deviation	P value
≤2	0	0.00	0.000	0.240
2-4	5	9.80	4.604	
4-6	12	7.92	3.370	
>6	3	4.67	5.508	
Total	20	7.90	4.103	

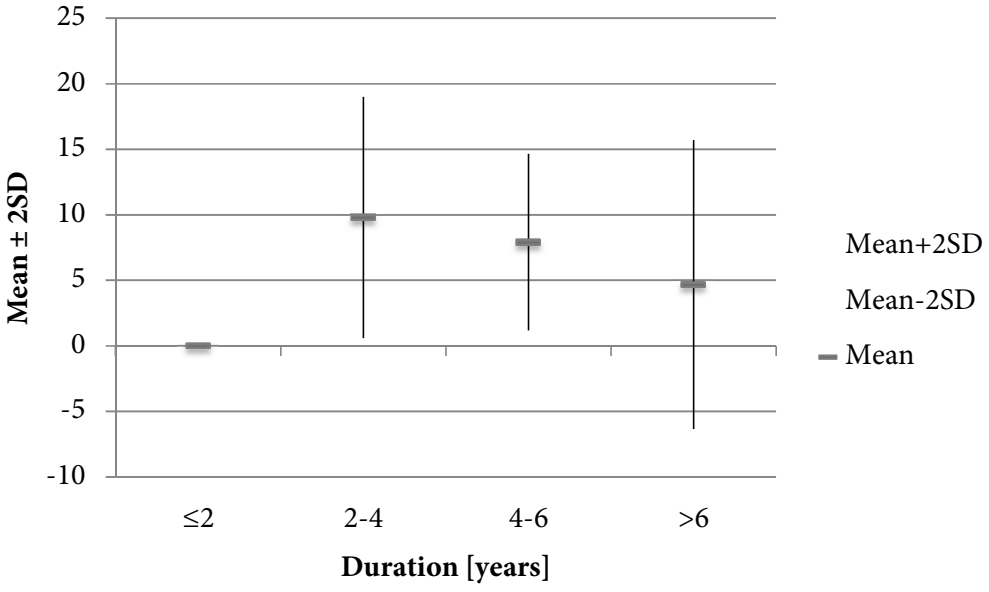


Figure 20: Duration of CKD *versus* degree of calcification

SERUM CALCIUM LEVEL versus CALCIFICATION

Mean serum calcium level was 9.12 mg/dL in stage 3 (n = 15), 8.74 mg/dL in stage 4 (n = 17) and 8.49 mg/dL in stage 5 (n = 28) CKD patients. Twelve out of 20 patients (60%) with serum calcium level ≤8.5 mg/dL had evidence of calcification. On the contrary, only one patient out of 8 patients with serum calcium level >9.0 mg/dL showed evidence of calcification. Hypocalcemia was associated with an increased risk of vascular calcification (p = 0.018) [Table **10**, Figure **21**].

Table 10: Serum calcium level *versus* calcification

Calcium [mg/dL]	**Calcification**		**Total**	**P value**
	Present	**Absent**		
≤8.5	12	8	20	0.018
	60.0%	20.0%	33.3%	
8.6-9.0	7	25	32	
	35.0%	62.5%	53.3%	
9.1-9.5	1	5	6	
	5.0%	12.5%	10.0%	
>9.5	0	2	2	
	0%	5.0%	3.3%	
Total	20	40	60	
	33.3%	66.7%	100%	

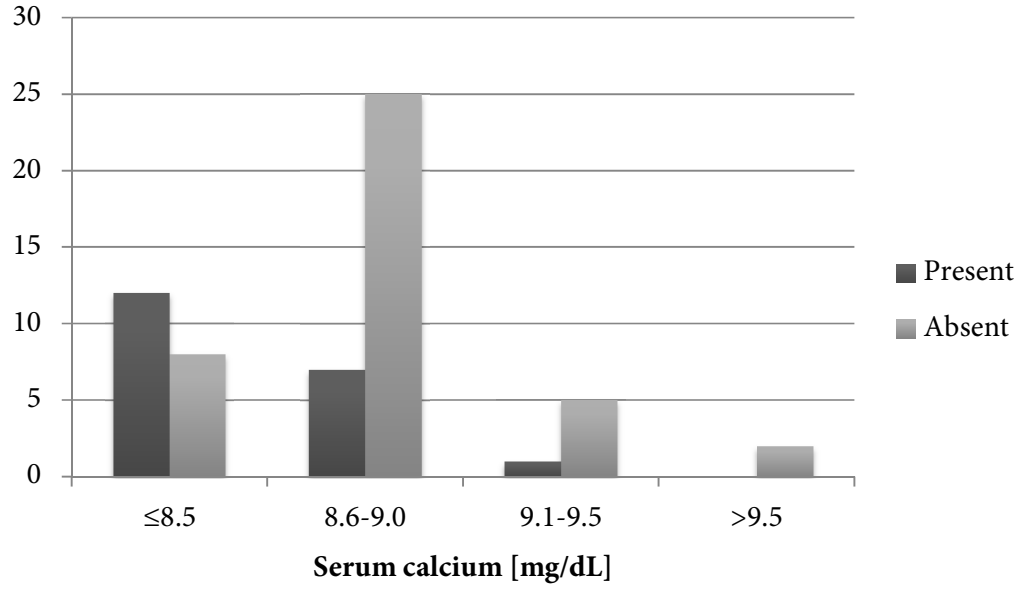


Figure 21: Serum calcium level *versus* calcification

Mean composite score was 9.58 (SD = 3.450) in patients with serum calcium level ≤8.5 mg/dL. The mean score showed a decreasing trend with higher calcium levels (p = 0.045). The mean score was 2.00 (SD = 0.000) in patients with calcium levels 9.1-9.5 mg/dL [Table **11**, Figure **22**].

Table 11: Serum calcium level *versus* degree of calcification

Calcium [mg/dL]	**n**	**Mean**	**Standard deviation**	**P value**
≤8.5	12	9.58	3.450	0.045
8.6-9.0	7	5.86	3.891	
9.1-9.5	1	2.00	0.000	
>9.5	0	0.00	0.000	
Total	20	7.90	4.103	

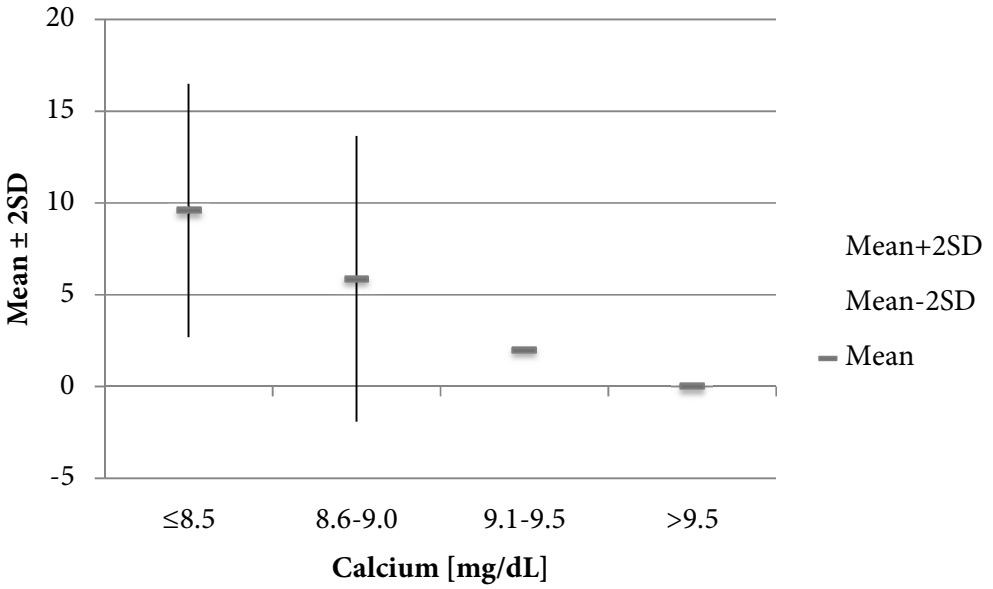


Figure 22: Serum calcium level *versus* degree of calcification

SERUM PHOSPHORUS LEVEL versus CALCIFICATION

About 50% of patients with calcification had serum phosphorus levels in the range of 4.6-5.0 mg/dL. Patients with serum phosphorus levels in the range of 4.1-4.5 mg/dL and 3.6-4.0 mg/dL contributed 15% (n = 3) and 20% (n = 4) respectively. All patients with serum phosphorus levels >5.0 mg/dL showed evidence of calcification (n = 3). Two patients with serum phosphorus levels ≤3.5 mg/dL did not have calcification. Higher serum phosphorus levels of phosphorus are associated with increased incidence of calcification (p = 0.002) [Table **12**, Figure **23**].

Table 12: Serum phosphorus level *versus* calcification

Phosphorus [mg/dL]	Calcification		Total	P value
	Present	Absent		
≤3.5	0	2	2	0.002
	0%	5.0%	3.3%	
3.6-4.0	4	11	15	
	20.0%	27.5%	25.0%	
4.1-4.5	3	20	23	
	15.0%	50.0%	38.3%	
4.6-5.0	10	7	17	
	50.0%	17.5%	28.3%	
>5.0	3	0	3	
	15.0%	0%	5.0%	
Total	20	40	60	
	33.3%	66.7%	100%	

Table 13: Serum phosphorus level *versus* degree of calcification

Phosphorus [mg/dL]	n	Mean	Standard deviation	P value
≤3.5	0	0.00	0.000	<0.001
3.6-4.0	4	2.75	1.708	
4.1-4.5	3	4.33	.577	
4.6-5.0	10	9.80	2.936	
>5.0	3	12.00	1.000	
Total	20	7.90	4.103	

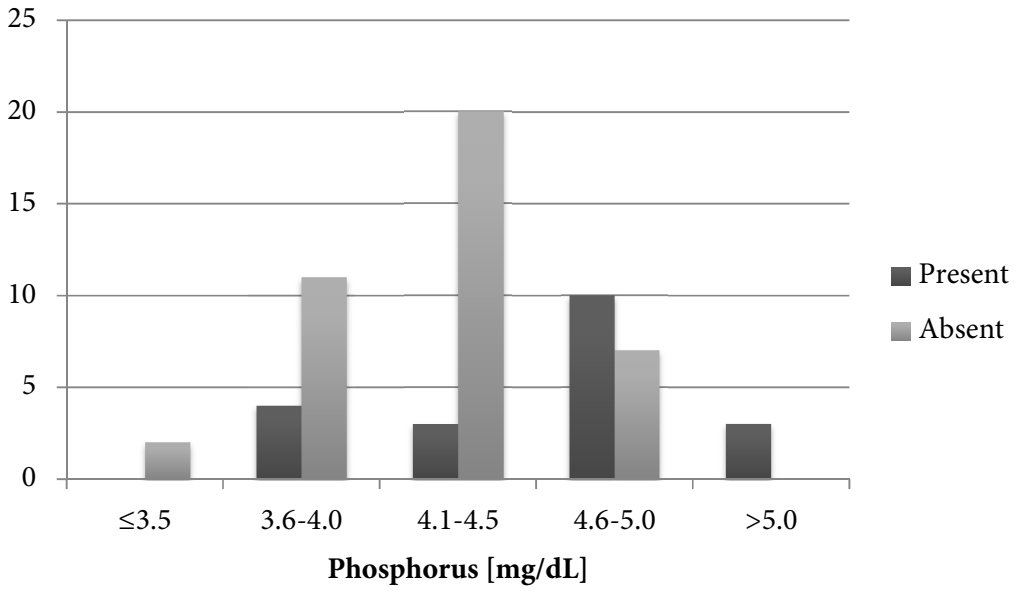


Figure 23: Serum phosphorus level *versus* calcification

Serum phosphorus levels showed statistically significant correlation with degree of calcification ($p < 0.001$) [Table **13**, Figure **24**].

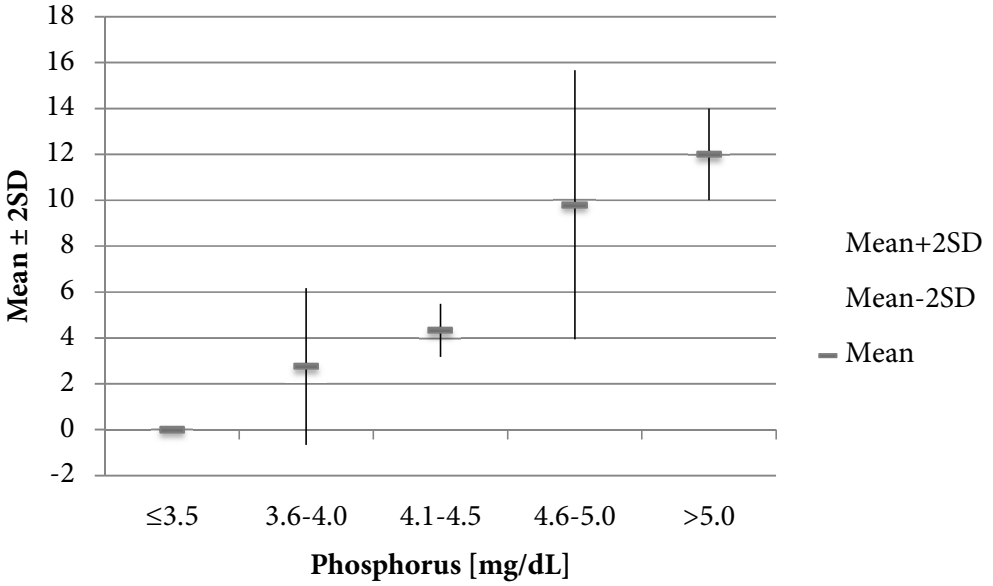


Figure 24: Serum phosphorus level *versus* degree of calcification

SERUM PTH LEVEL versus CALCIFICATION

Patients with PTH levels ≤50 pg/mL did not have calcification. Beyond that level presence of aortic calcification was noted in all the ranges of serum PTH level (p = 0.098) [Table **14**, Figure **25**].

Table 14: Serum PTH level *versus* calcification

PTH [pg/mL]	**Calcification**		**Total**	**P value**
	Present	**Absent**		
≤50	0	3	3	0.098
	0%	7.5%	5.0%	
51-100	5	15	20	
	25.0%	37.5%	33.3%	
101-150	2	5	7	
	10.0%	12.5%	11.7%	
151-200	4	10	14	
	20.0%	25.0%	23.3%	
201-250	4	6	10	
	20.0%	15.0%	16.7%	
>250	5	1	6	
	25.0%	2.5%	10.0%	
Total	20	40	60	
	33.3%	66.7%	100%	

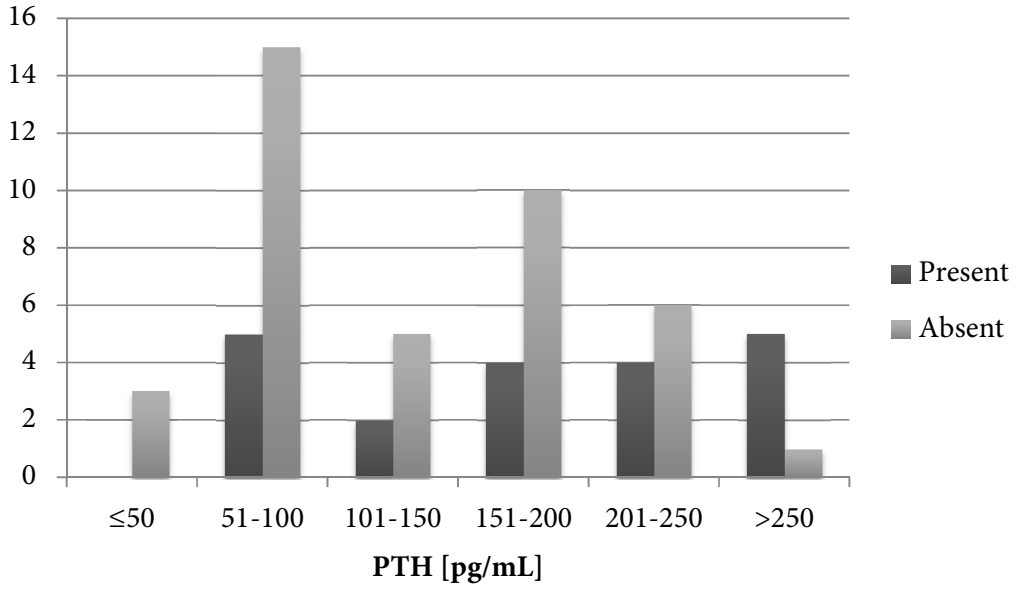


Figure 25: Serum PTH level *versus* calcification

Serum PTH levels did not show any correlation with degree of calcification (p = 0.061) [Table **15**, Figure **26**].

Table 15: Serum PTH level *versus* degree of calcification

PTH [pg/mL]	n	Mean	Standard deviation	P value
≤50	0	0.00	0.000	0.061
51-100	5	6.40	5.367	
101-150	2	7.00	4.243	
151-200	4	4.50	1.291	
201-250	4	8.75	2.363	
>250	5	11.80	2.588	
Total	20	7.90	4.103	

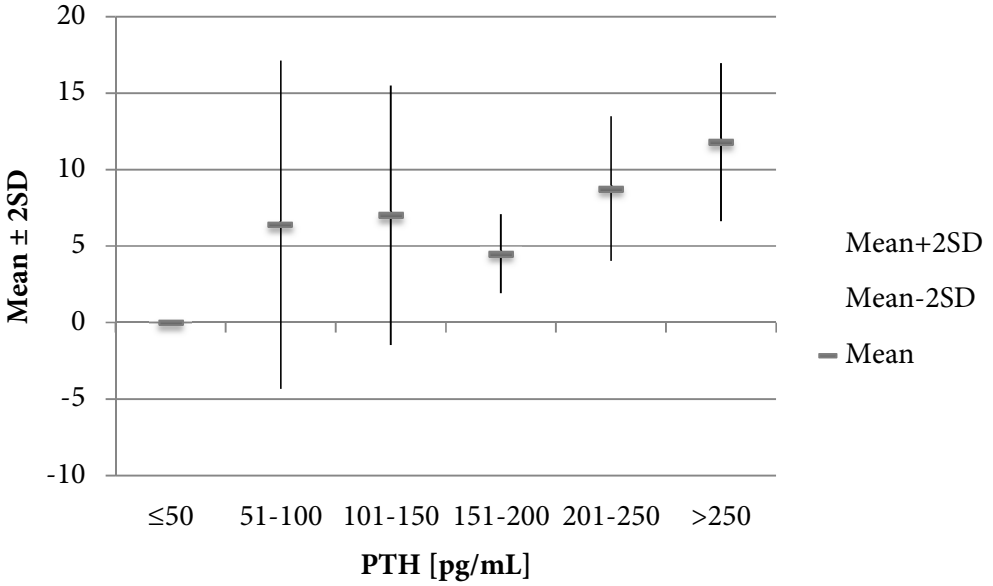


Figure 26: Serum PTH level *versus* degree of calcification

SERUM CREATININE LEVEL versus CALCIFICATION

Patients with serum creatinine level >5 mg/dL represented 40% of patients with calcification. Only 10% of patients with calcification had serum creatinine in the range below 2 mg/dL. Patients with higher levels of serum creatinine showed more incidence of calcification (p = 0.001) [Table **16**, Figure **27**]. Patients with serum creatinine level ≤2 mg/dL had a mean composite score of 1.50 (SD = 0.707), whereas those with serum creatinine level >5 mg/dL a mean score of 11.13 (SD =2.696). Degree of calcification was also strongly associated with serum creatinine level (p <0.001) [Table **17**, Figure **28**].

Table 16: Serum creatinine level *versus* calcification

Creatinine [mg/dL]	Calcification		Total	P value
	Present	Absent		
≤2	2	11	13	0.001
	10.0%	27.5%	21.7%	
2-3	1	10	11	
	5.0%	25.0%	18.3%	
3-4	5	3	8	
	25.0%	7.5%	13.3%	
4-5	4	14	18	
	20.0%	35.0%	30.0%	
>5	8	2	10	
	40.0%	5.0%	16.7%	
Total	20	40	60	
	33.3%	66.7%	100%	

Table 17: Serum creatinine level *versus* degree of calcification

Creatinine [mg/dL]	n	Mean	Standard deviation	P value
≤2	2	1.50	0.707	<0.001
2-3	1	4.00	0.000	
3-4	5	4.60	1.140	
4-5	4	9.75	2.217	
>5	8	11.13	2.696	
Total	20	7.90	4.103	

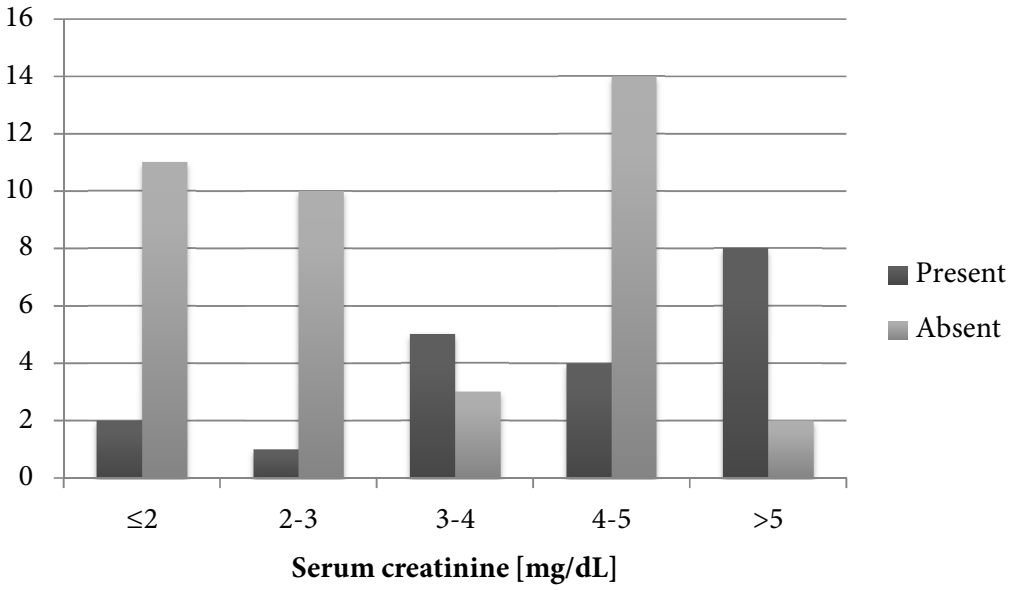


Figure 27: Serum creatinine level *versus* calcification

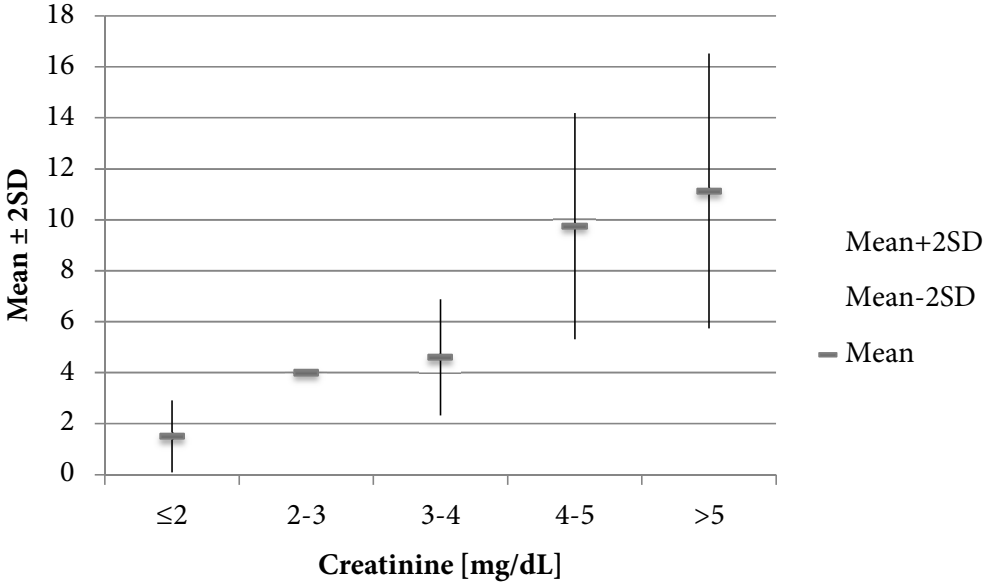


Figure 28: Serum creatinine level *versus* degree of calcification

STAGE OF CKD versus CALCIFICATION

Two out of 15 patients in stage 3 (13.3%), 6 out of 17 patients in stage 4 (35.3%) and 12 out of 28 patients in stage 5 (42.9%) showed evidence of calcification. Among patients with calcification, 10% were in stage 3, 30% were in stage 4 and 60% were in stage 5 (n = 20).

Even though it appears that progression of the disease is associated with increased incidence of calcification, no statistically significant correlation was noted between the stage of the disease and presence of calcification (p = 0.144) [Table **18**, Figure **29**].

Table 18: Stage of CKD *versus* calcification

Stage	Calcification		Total	P value
	Present	Absent		
3	2	13	15	0.144
	10.0%	32.5%	25.0%	
4	6	11	17	
	30.0%	27.5%	28.3%	
5	12	16	28	
	60.0%	40.0%	46.7%	
Total	20	40	60	
	33.3%	66.7%	100%	

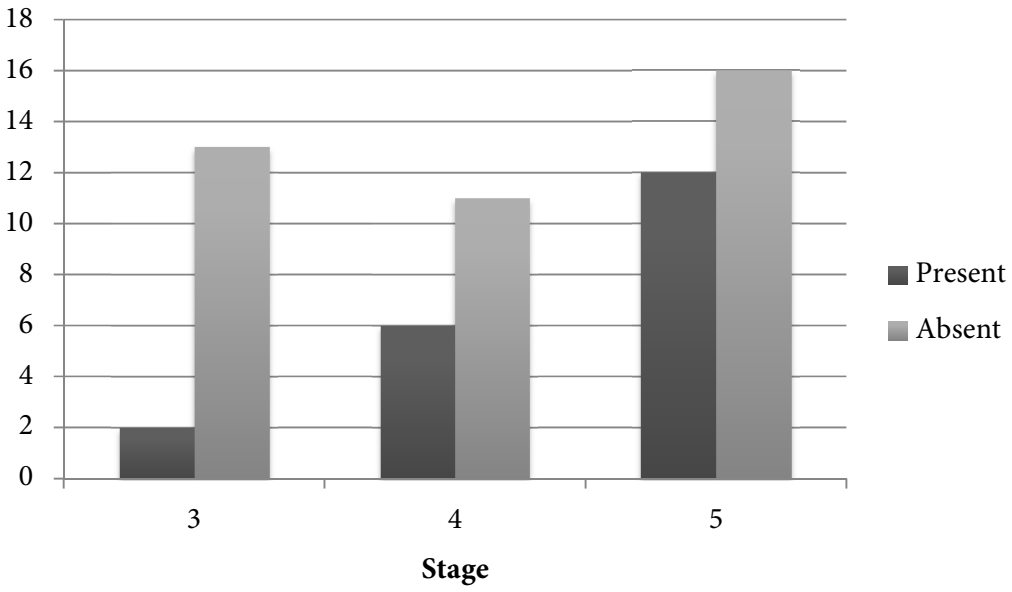


Figure 29: Stage of CKD *versus* calcification

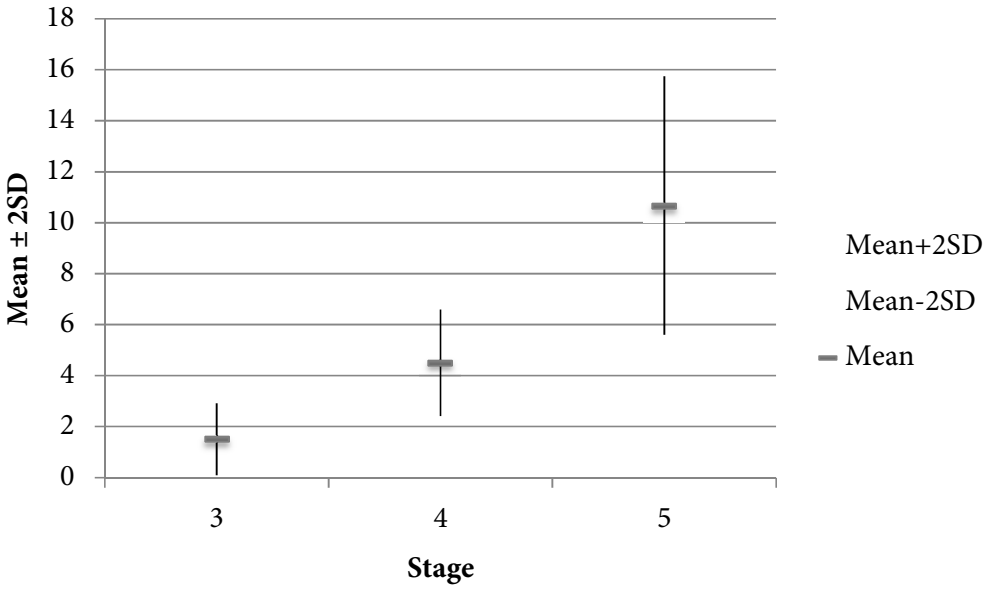


Figure 30: Stage of CKD *versus* degree of calcification

Mean composite score was 1.50 (SD = 0.707) in stage 3, 4.50 (SD = 1.049) in stage 4 and 10.67 (SD = 2.535) in stage 5. While stage of CKD was not associated with incidence of calcification, it had a significant correlation with the severity of calcification (p <0.001) [Table **19**, Figure **30**].

Table 19: Stage of CKD *versus* degree of calcification

Stage	n	Mean	Standard deviation	P value
3	2	1.50	0.707	<0.001
4	6	4.50	1.049	
5	12	10.67	2.535	
Total	20	7.90	4.103	

DIABETES versus CALCIFICATION

Table 20: Diabetes *versus* calcification

Diabetes	Calcification		Total	P value
	Present	Absent		
Diabetics	9	8	17	0.043
	45.0%	20.0%	28.3%	
Non-diabetics	11	32	43	
	55.0%	80.0%	71.1%	
Total	20	40	60	
	33.3%	66.7%	100%	

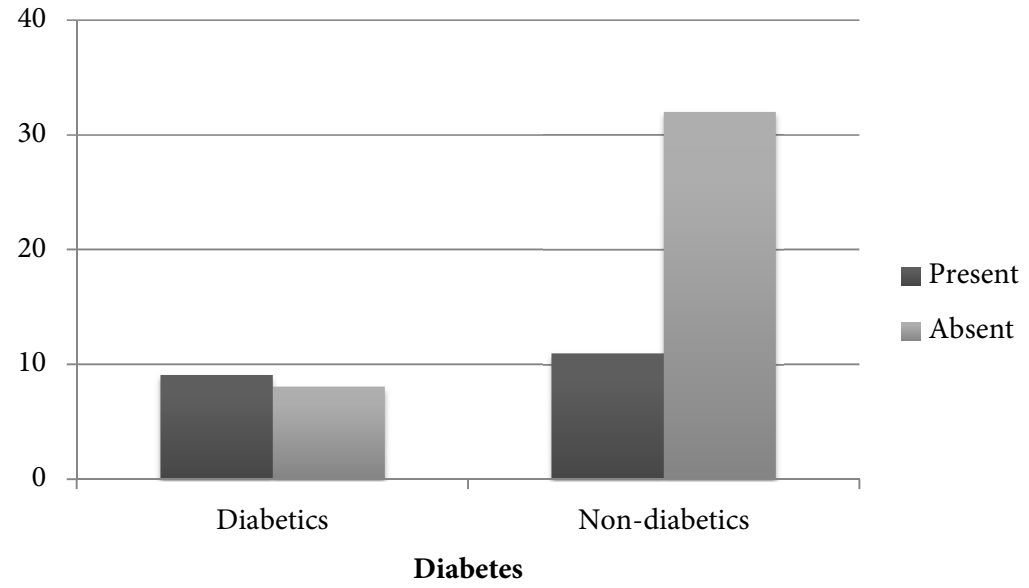


Figure 31: Diabetes *versus* calcification

Out of 17 diabetic patients, 9 patients (52.9%) had calcification while 11 patients (25.6%) among 43 non-diabetics showed evidence of calcification. Mean composite score was 8.56 (SD = 3.321) among diabetic patients and 7.36 (SD = 4.739) among non-diabetic patients. Diabetes was associated with presence (p = 0.043) but not with degree (p = 0.533) of calcification [Table **20**, Table **21**, Figure **31**, Figure **32**].

Table 21: Diabetes *versus* degree of calcification

Diabetes	n	Mean	Standard deviation	P value
Diabetics	9	8.56	3.321	0.533
Non-diabetics	11	7.36	4.739	

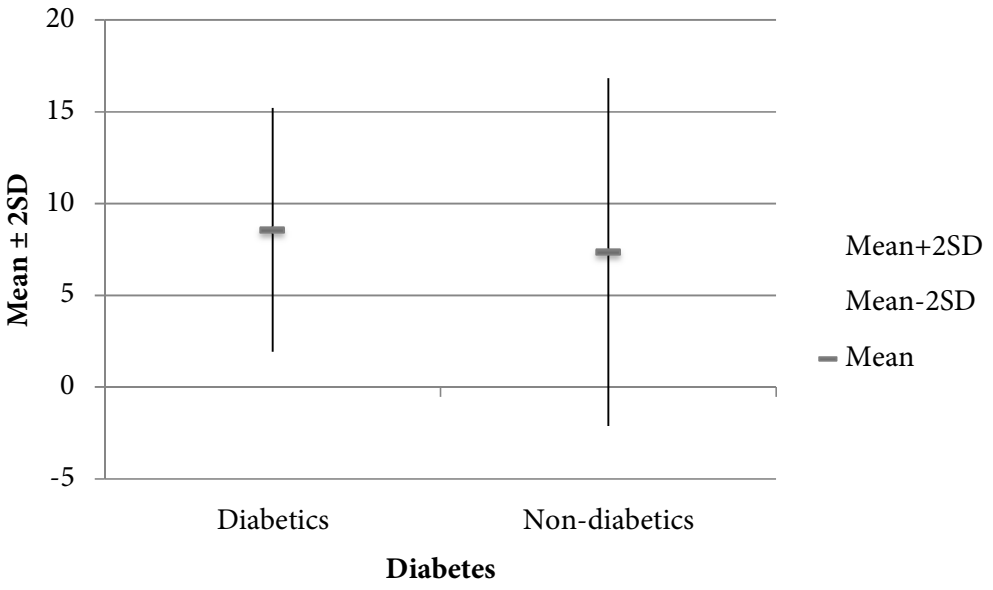


Figure 32: Diabetes *versus* degree of calcification

HYPERTENSION versus CALCIFICATION

Fourteen out of 31 hypertensives (45.2%) and 6 out of 29 non-hypertensives (20.7%) had calcification.

Table 22: Hypertension *versus* calcification

Hypertension	Calcification		Total	P value
	Present	Absent		
Hypertensives	14	17	31	0.044
	70.0%	42.5%	51.7%	
Non-hypertensives	6	23	29	
	30.0%	57.5%	48.3%	
Total	20	40	60	
	33.3%	66.7%	100%	

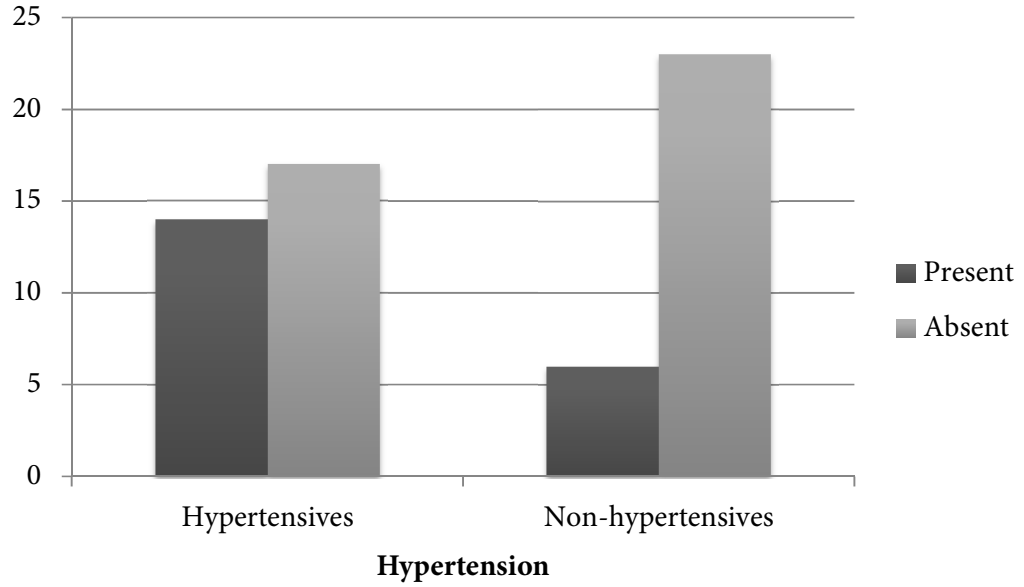


Figure 33: Hypertension *versus* calcification

Mean composite score was 8.50 (SD = 4.653) among hypertensives and 6.50 (SD = 2.074) among non-hypertensives.

Hypertension was associated with an increased incidence (p = 0.044) of calcification but not with the severity (p = 0.331) of calcification [Table **22**, Table **23**, Figure **33**, Figure **34**].

Table 23: Hypertension *versus* degree of calcification

Hypertension	n	Mean	Standard deviation	P value
Hypertensives	14	8.50	4.653	0.331
Non-hypertensives	6	6.50	2.074	

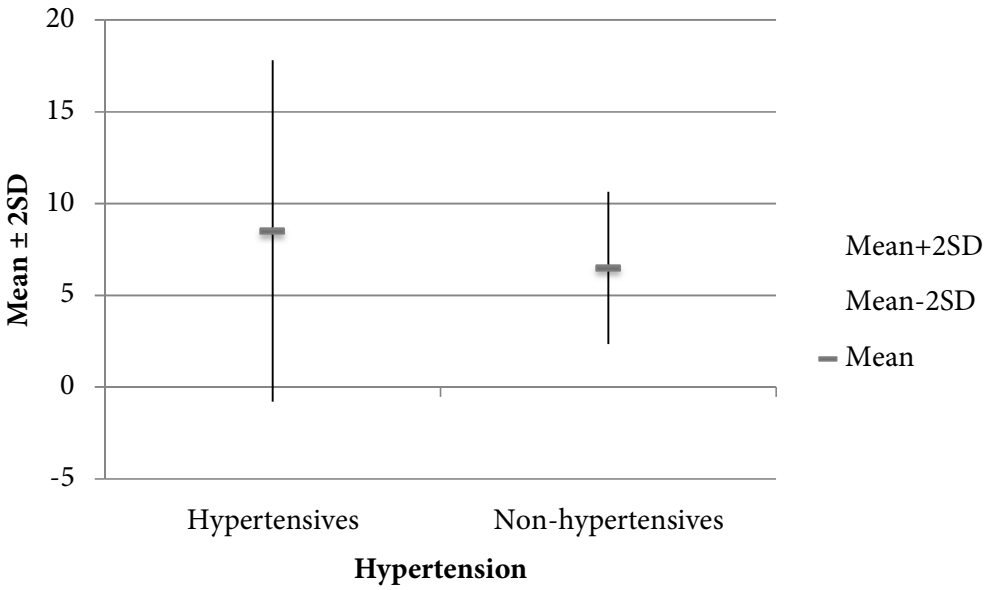


Figure 34: Hypertension *versus* degree of calcification

SMOKING versus CALCIFICATION

38.1% of smokers (n = 21) and 30.8% of non-smokers (n = 39) demonstrated vascular calcification.

Table 24: Smoking *versus* calcification

Smoking	Calcification		Total	P value
	Present	Absent		
Smokers	8	13	21	0.566
	40.0%	32.5%	35.0%	
Non-smokers	12	27	39	
	60.0%	67.5%	65.0%	
Total	20	40	60	
	33.3%	66.7%	100%	

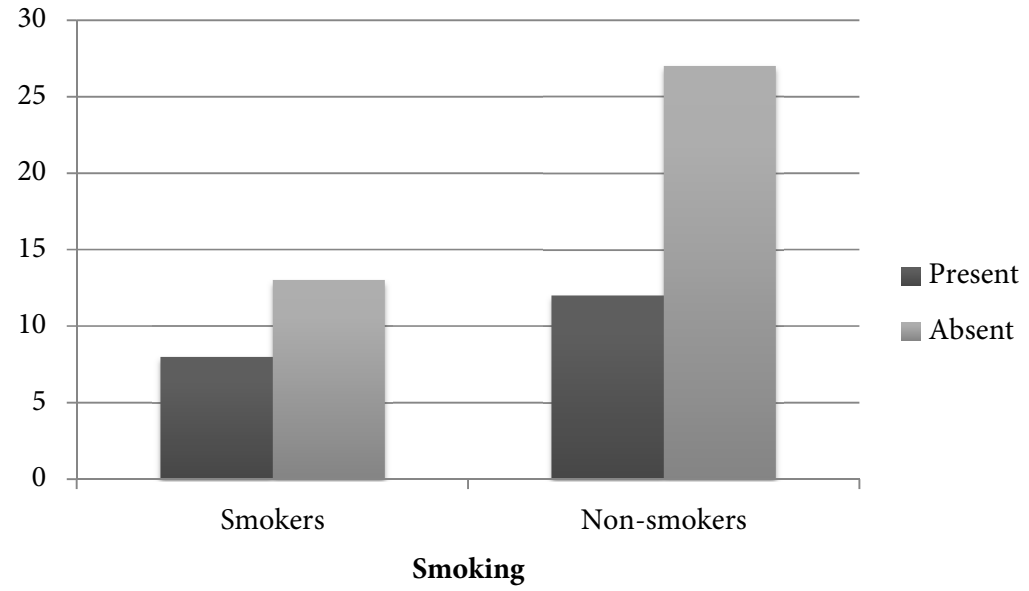


Figure 35: Smoking *versus* calcification

Mean composite score was 8.75 (SD = 4.713) among smokers and it was 7.33 (SD = 3.750) among non-smokers.

Smoking was neither associated with the presence (p = 0.566) nor the degree (p = 0.464) of vascular calcification [Table **24**, Table **25**, Figure **35**, Figure **36**].

Table 25: Smoking *versus* degree of calcification

Smoking	n	Mean	Standard deviation	P value
Smokers	8	8.75	4.713	0.464
Non-smokers	12	7.33	3.750	

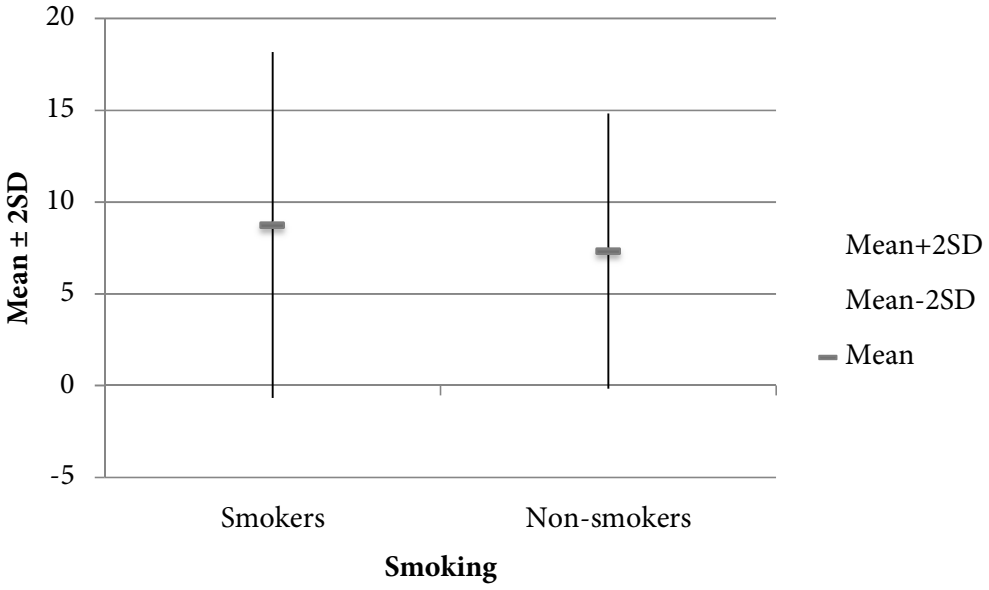


Figure 36: Smoking *versus* degree of calcification

DISCUSSION

The role of vascular calcification in augmenting the cardiovascular risk in CKD patients has been well established. Current knowledge about the factors and mechanisms involved in the development of vascular calcification indicates that the biology of vascular calcification differs significantly between CKD patients who are on dialysis and pre-dialysis CKD patients.

In our study, we analyzed the patient characteristics and biochemical parameters of 60 CKD patients who were in stages 3 to 5. Patients who were on any form of dialysis were excluded from the study.

Univariate analysis was performed between abdominal aortic calcification score and the following factors: age, sex, duration of CKD, serum creatinine, stage of CKD, serum calcium, serum phosphorus, serum PTH, diabetes, hypertension and smoking.

Age was not associated with presence or severity of calcification in our study. Calcification was noted in most of the age groups. No correlation was seen between sex and calcification also. Both males and females had similar prevalence of calcification.

Duration of CKD has got a positive correlation with calcification but it did not influence on the severity of calcification. Serum creatinine level showed significant association both for the presence as well as degree of calcification.

Stage of CKD did not appear to predict the presence of calcification, whereas patients in advanced stage of CKD had more severe calcification than patients in early stage of the disease.

Hypocalcemia is associated with more prevalence of calcification and degree of hypocalcemia was correlated with degree of calcification. Hence, treatment with vitamin D analogs seems reasonable to prevent hypocalcemia apart from controlling secondary hyperparathyroidism.

Hyperphosphatemia is also an important risk factor for vascular calcification. It has also been proposed as one of the causative factors involved in vascular calcification. Most of the treatment options are targeted against hyperphosphatemia. Non-calcium containing phosphate binders are preferred in the management of hyperphosphatemia in the presence of vascular calcification.

Serum PTH levels were not associated with vascular calcification probably because both high turnover states as well as low turnover states are associated with vascular calcification and we did not do bone biopsy to differentiate between these entitites.

Both diabetes and hypertension were associated with presence of calcification but not with the degree of calcification. No association was noted between smoking and vascular calcification.

Comparison of pulse pressure between patients with calcification and without calcification revealed a statistically significant difference between the groups but the difference between the means was less.

The results obtained in our study correlates with the study done by Hanada et al [22] using CT based imaging techniques. The prevalence of vascular calcification was more in their study because the use of CT scan improved the sensitivity.

The CORD study group [32] applied the same technique of assessing abdominal aortic calcification in the hemodialysis population.

LIMITATIONS OF THE STUDY

1. Abdominal aortic radiography does not differentiate between intimal calcification and medial calcification which is peculiar of CKD
2. Association of degree of vascular calcification with cardiovascular outcome requires prospective long term follow up study design
3. Most of the patients were diagnosed in the stage of established CKD and hence no association could be made between the etiology of the disease and vascular calcification
4. Small size of the study population limits our ability to extrapolate the results to the community level

CONCLUSION

Because of various factors like westernization, the incidence and prevalence of diabetes which is one the most common risk factor for the development of CKD is expected to rise in the near future. CKD significantly increases the burden on the health care expenditure. CKD is not just a disease of the kidneys as evidenced by its various manifestations and complications in almost any system of the body. Improvement in the outcome of patients with CKD requires addressing all the aspects of the disease. Mineral and Bone Disorders in CKD pose significant health problems. Vascular calcification is one of the important components of CKD-MBD and it is associated with increased cardio-vascular mortality and morbidity. Risk factors for the development of vascular calcification like hypocalcemia and hyperphosphatemia require proper therapy and monitoring to minimize vascular calcification which in turn could lead to better patient outcomes.

BIBLIOGRAPHY

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009 Aug;(113): S1-130.
2. Bellasi A, Ferramosca E, Muntner P, Ratti C, Wildman RP, Block GA, et al. Correlation of simple imaging tests and coronary artery calcium measured by computed tomography in hemodialysis patients. Kidney Int. 2006; 70(9): 1623-8.
3. Dash SC, Agarwal SK. Incidence of chronic kidney disease in India. Nephrol Dial Transplant. 2006; 21: 232-233.
4. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39(2 Suppl 1): S1-266.
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16(1): 31-41.
6. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012; 367(1): 20-9.
7. Clase CM, Norman GL, Beecroft ML, Churchill DN. Albumin-corrected calcium and ionized calcium in stable haemodialysis patients. Nephrol Dial Transplant. 2000; 15(11): 1841-6.
8. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003; 42: S1–201.

9. Tenenhouse HS. Regulation of phosphorus homeostasis by the type IIa na/phosphate cotransporter. Annu Rev Nutr. 2005; 25: 197-214.
10. Lau WL, Festing MH, Giachelli CM. Phosphate and Vascular Calcification - Emerging Role of the Sodium-Dependent Phosphate Cotransporter PiT-1. Thromb Haemost. 2010; 104(3): 464-70.
11. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res. 2004; 19: 429-435.
12. Gao P, D'Amour P. Evolution of the parathyroid hormone (PTH) assay - importance of circulating PTH immunoheterogeneity and of its regulation. Clin Lab. 2005; 51(1-2): 21-9.
13. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease - Results of the study to evaluate early kidney disease. Kidney Int. 2007; 71(1): 31-8.
14. Vassalotti JA, Uribarri J, Chen SC, Li S, Wang C, Collins AJ, et al. Trends in Mineral Metabolism - Kidney Early Evaluation Program (KEEP) and the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis. 2008; 51(4 Suppl 2): S56-68.
15. Spasovski GB, Bervoets AR, Behets GJ, Ivanovski N, Sikole A, Dams G, et al. Spectrum of renal bone disease in end-stage renal failure patients not yet on dialysis. Nephrol Dial Transplant. 2003; 18(6): 1159-66.
16. Dellegrottaglie S, Sanz J, Rajagopalan S. Vascular calcification in patients with chronic kidney disease. Blood Purif. 2006; 24: 56–62.
17. Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB, et al.

Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. Kidney Int. 2002; 61: 638–647.

18. Giachelli CM. Vascular Calcification Mechanisms. J Am Soc Nephrol. 2004; 15(12): 2959–2964.
19. Haydar AA, Covic A, Colhoun H, Rubens M, Goldsmith DJ. Coronary artery calcification and aortic pulse wave velocity in chronic kidney disease patients. Kidney Int. 2004; 65(5): 1790-4.
20. Sigrist M, Bungay P, Taal MW, McIntyre CW. Vascular calcification and cardiovascular function in chronic kidney disease. Nephrol Dial Transplant. 2006; 21: 707–714.
21. Stompor T, Rajzer M, Pasowicz M, Krasniak A, Sulowicz W, Kawecka-Jaszcz K, et al. Coronary artery calcification, common carotid artery intima-media thickness and aortic pulse wave velocity in patients on peritoneal dialysis. Int J Artif Organs. 2006; 29: 736–744.
22. Hanada S, Ando R, Naito S, Kobayashi N, Wakabayashi M, Hata T, et al. Assessment and significance of abdominal aortic calcification in chronic kidney disease. Nephrol Dial Transplant. 2010; 25(6): 1888-1895.
23. Kauppila LI, Polak JF, Cupples LA, Hannan MT, Kiel DP, Wilson PW. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. Atherosclerosis. 1997; 132(2): 245-50.
24. Slatopolsky E, Finch J, Brown A. New vitamin D analogs. Kidney Int. 2003; 63: S83–S87.
25. Chonchol M, Locatelli F, Abboud H, Charytan C, de Francisco A, Jolly S, et al. A randomized, double-blind, placebo-controlled study to assess the

efficacy and safety of cinacalcet HCl in participants with CKD not receiving dialysis. Am J Kidney Dis. 2009; 53(2): 197-207.

26. Strippoli GF, Palmer S, Tong A, Elder G, Messa P, Craig JC. Meta-analysis of biochemical and patient-level effects of calcimimetic therapy. Am J Kidney Dis. 2006; 47(5): 715-26.

27. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int. 2005; 68: 1815–1824.

28. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int. 2002; 62: 245–252.

29. Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney Int. 2007; 72: 1255–1261.

30. Mathew S, Lund RJ, Strebeck F, Tustison KS, Geurs T, Hruska KA. Reversal of the adynamic bone disorder and decreased vascular calcification in chronic kidney disease by sevelamer carbonate therapy. J Am Soc Nephrol. 2007; 18(1): 122-30.

31. Sprague SM, Abboud H, Qiu P, Dauphin M, Zhang P, Finn W. Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: a randomized trial. Clin J Am Soc Nephrol. 2009; 4: 178–185.

32. Honkanen E, Kauppila L, Wikström B, Rensma P, Krzesinski J, Aasarod K, et al. Abdominal aortic calcification in dialysis patients: results of the CORD study. Nephrol Dial Transplant. 2008; 23(12): 4009-15.

ASSESSMENT OF VASCULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE PATIENTS

Name :

Age/Sex : Weight :

IP No : Diagnosis :

Patient ID No : Duration :

Patient characteristics	**Medications**	
❑ Smoking	❑ Calcium containing phosphate binders	
❑ Alcoholism	❑ Statins	
❑ Diabetes	❑ ACE inhibitors	
❑ Systemic hypertension	❑ Others	

Vascular complications	
❑ Coronary events	❑ Cerebrovascular events
❑ Peripheral vascular diseases	

Clinical examination			
❑ Vessel wall thickening	❑ Skeletal abnormalities		
❑ Carotid bruit	Upper limb BP		
❑ Renal bruit	Lower limb BP		

INVESTIGATIONS					
RFT			**LFT**		
Glucose (Fasting)		mg/dL	Total bilirubin		mg/dL
Urea		mg/dL	Direct bilirubin		mg/dL
Creatinine		mg/dL	SGOT		U/L
Electrolytes			SGPT		U/L
Na^+		mEq/l	ALP		U/L
K^+		mEq/l	Total protein		g/dL
Ca^{2+}		mg/dL	Albumin		g/dL
$PO4^{2-}$		mg/dL	**eGFR**		mL/min
				STAGE	

Fasting lipid profile			Others		
Total cholesterol		mg/dL	Hemoglobin		g/dL
LDL		mg/dL	PTH		pg/mL
HDL		mg/dL	Chest X-ray		
Triglycerides		mg/dL	USG KUB		

Lateral lumbar radiography

Level	Affected segment	Anterior wall range	Posterior wall range	Anterior-posterior severity range
L1				
L2				
L3				
L4				
Affected segments score		*Composite score*		

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜிவ் காந்தி அரசு பொது மருத்துவமனையில் அனுமதிக்கப்படும் நாள்பட்ட சிறுநீரக நோயினைப் பற்றிய ஒரு ஆராய்ச்சி நடைபெற்று வருகிறது.

நாள்பட்ட சிறுநீரக நோயினால் இரத்த நாளங்களில் கால்சியம் படிவதை எக்ஸ்ரே மூலம் அறிவதே இந்த ஆராய்ச்சியின் நோக்கமாகும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருத்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு:

நாள்பட்ட சிறுநீரக நோயினால் இரத்த நாளங்களில் கால்சியம் படிமானமாவதைப் பற்றிய ஆராய்ச்சி.

பெயர்: தேதி:

வயது: உள்நோயாளி எண்:

பால்: ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

நாள்பட்ட சிறுநீரக நோயினால் இரத்த நாளங்களில் கால்சியம் படிமானமாவதைப் பற்றியும் அதனைக் கண்டறிய மேற்கொள்ளப்படும் பரிசோதனைகளைப் பற்றியும் ஆராய்ச்சியாளர் கூற முழுவதும் விளங்கப்பெற்றேன்.

மேற்கொண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின்விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமார சம்மதிக்கிறேன்.

கையொப்பம்

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. R. Senthil Murugan
PG in MD General Medicine
Madras Medical College, Chennai -3

Dear Dr. R. Senthil Murugan

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Assessment of Vascular calcification in Chronic kidney disease patients" No.24042012.

The following members of Ethics Committee were present in the meeting held on 19.04.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member Secretary
3.	Prof. B. Kalaiselvi MD Prof. of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. Md. Ali. MD.DM Prof & HOD, Dept. of MGE, MMC, Ch-3	-- Member
6.	Prof.P.Karkuzhali MD Director i/c, Prof., Inst. of Pathology, MMC, Ch-3	-- Member
7.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
8.	Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member
9.	Thiru. S. Govindsamy. BABL	-- Lawyer
10.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

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

Sd/ Chairman & Other Members

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

turnitin

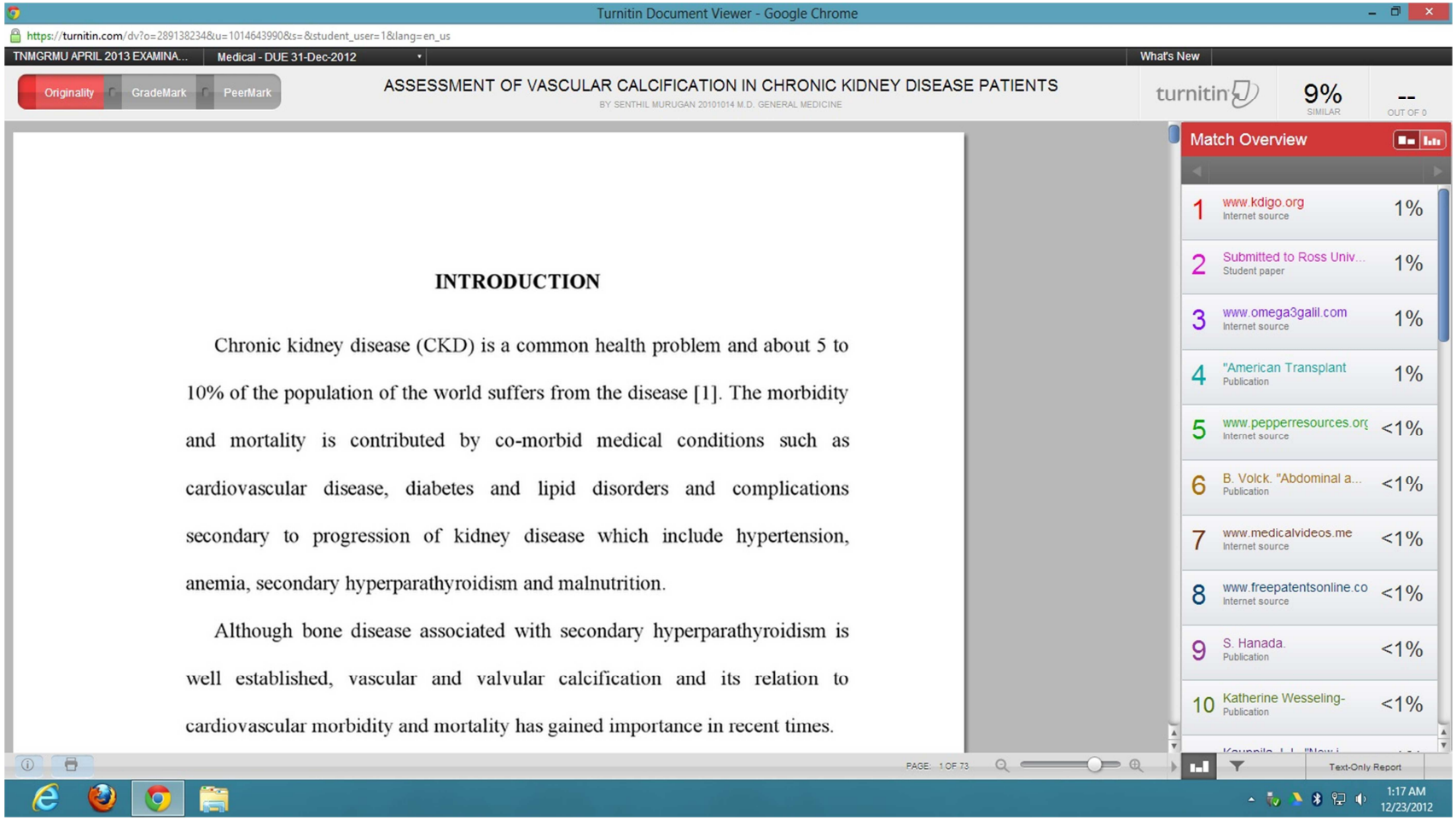
Your digital receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

Paper ID	289138234
Paper title	ASSESSMENT OF VASCULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE PATIENTS
Assignment title	Medical
Author	Senthil Murugan 20101014 M.D. General Medicine
E-mail	doctorsenthilmurugan@yahoo.com
Submission time	22-Dec-2012 02:18PM
Total words	8183

First 100 words of your submission

INTRODUCTION Chronic kidney disease (CKD) is a common health problem and about 5 to 10% of the population of the world suffers from the disease [1]. The morbidity and mortality is contributed by co-morbid medical conditions such as cardiovascular disease, diabetes and lipid disorders and complications secondary to progression of kidney disease which include hypertension, anemia, secondary hyperparathyroidism and malnutrition. Although bone disease associated with secondary hyperparathyroidism is well established, vascular and valvular calcification and its relation to cardiovascular morbidity and mortality has gained importance in recent times. Though coronary artery calcification as...


Turnitin Document Viewer - Google Chrome
https://turnitin.com/dv?o=289138234&u=1014643990&s=&student_user=1&lang=en_us
TNMGRMU APRIL 2013 EXAMINA...
Medical - DUE 31-Dec-2012
What's New
Originality
GradeMark
PeerMark
ASSESSMENT OF VASCULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE PATIENTS
BY SENTHIL MURUGAN 20101014 M.D. GENERAL MEDICINE
turnitin
9%
SIMILAR
--
OUT OF 0
INTRODUCTION
Chronic kidney disease (CKD) is a common health problem and about 5 to 10% of the population of the world suffers from the disease [1]. The morbidity and mortality is contributed by co-morbid medical conditions such as cardiovascular disease, diabetes and lipid disorders and complications secondary to progression of kidney disease which include hypertension, anemia, secondary hyperparathyroidism and malnutrition.
Although bone disease associated with secondary hyperparathyroidism is well established, vascular and valvular calcification and its relation to cardiovascular morbidity and mortality has gained importance in recent times.
PAGE: 1 OF 73
Match Overview
1 www.kdigo.org Internet source 1%
2 Submitted to Ross Univ... Student paper 1%
3 www.omega3galil.com Internet source 1%
4 "American Transplant Publication 1%
5 www.pepperresources.org Internet source <1%
6 B. Volck. "Abdominal a... Publication <1%
7 www.medicalvideos.me Internet source <1%
8 www.freepatentsonline.co Internet source <1%
9 S. Hanada. Publication <1%
10 Katherine Wesseling- Publication <1%
Text-Only Report
1:17 AM
12/23/2012

MASTER CHART

ID	Age	Sex	Weight	Duration	Smoking	Alcoholism	Diabetes	Hypertension	Systolic BP	Diastolic BP	Pulse Pressure	Hemoglobin	Glucose	Urea	Creatinine	Sodium	Potassium	Calcium	Phosphorus	PTH	eGFR	Stage	ASS	CS
1	62	F	66	4.5	N	N	N	Y	140	80	60	7.4	64	76	5.2	129	4.6	8.5	5.1	284	11.69	5	3	11
2	63	M	65	6	Y	Y	N	Y	144	84	60	10.3	112	57	1.7	134	4	9.3	3.4	56	40.89	3	0	0
3	56	M	65	4.5	N	N	N	N	130	80	50	11.3	104	48	1.5	142	3.8	9.6	4.1	45	50.56	3	0	0
4	66	M	63	2	N	N	N	N	130	70	60	8.8	92	69	3.1	130	4.6	8.6	4.4	134	20.89	4	0	0
5	64	F	72	2	N	N	N	N	112	72	40	9.4	95	68	2.9	129	3.4	8.6	4.2	98	22.28	4	0	0
6	67	M	53	5	Y	Y	N	Y	130	70	60	8.1	84	79	5.4	132	437	8.3	4.9	259	9.95	5	3	13
7	58	F	72	3.25	N	N	Y	N	120	80	40	11.2	112	48	1.8	139	3.8	8.9	4.1	98	38.72	3	0	0
8	62	M	63	2.5	Y	N	Y	Y	124	90	34	9.7	120	59	3.2	131	4	8.9	3.9	96	21.33	4	0	0
9	58	M	68	4	N	N	N	Y	136	86	50	11.2	98	68	1.9	132	3.8	9.3	3.8	72	40.76	3	0	0
10	58	F	67	3	N	N	Y	Y	130	80	50	7.6	84	71	4.9	139	4.1	8.6	4.1	243	13.24	5	0	0
11	64	F	68	5.5	N	N	Y	N	128	78	50	8.4	96	70	5.1	136	4.8	8.7	4.9	112	11.96	5	2	10

ID	Age	Sex	Weight	Duration	Smoking	Alcoholism	Diabetes	Hypertension	Systolic BP	Diastolic BP	Pulse Pressure	Hemoglobin	Glucose	Urea	Creatinine	Sodium	Potassium	Calcium	Phosphorus	PTH	eGFR	Stage	ASS	CS
12	62	M	61	3.5	Y	Y	N	Y	140	90	50	7.6	78	67	5.2	128	5.1	8.3	4.8	210	12.71	5	0	0
13	63	M	58	3	Y	Y	N	Y	136	84	52	7.6	96	84	4.8	134	4.2	8.4	4.2	225	12.92	5	0	0
14	52	M	65	6.5	Y	N	N	Y	132	84	48	9.8	86	67	1.8	140	3.7	9.2	3.8	89	44.14	3	1	2
15	58	F	65	2	N	N	N	Y	130	90	40	7.6	76	73	4.8	134	4	8.7	4.3	223	13.11	5	0	0
16	63	M	61	4.5	N	N	Y	Y	130	80	50	9.3	128	63	3.4	128	4.2	8.5	4.3	62	19.19	4	2	5
17	63	F	61	3	N	N	Y	N	130	80	50	7.9	136	82	4.7	131	4.1	8.4	4.3	213	11.8	5	0	0
18	60	F	68	3	N	N	Y	N	120	70	50	9.2	148	61	3.3	135	4.2	8.6	4.6	152	19.46	4	2	6
19	62	F	68	1.5	N	N	N	N	130	70	60	9.6	70	67	3	129	4.2	8.7	4.1	112	20.87	4	0	0
20	61	F	68	3.5	N	N	N	N	130	80	50	9.6	113	49	2.9	134	3.9	8.7	4.5	92	21.87	4	0	0
21	67	M	63	3	N	N	N	N	120	70	50	8.4	78	78	4.6	134	4.9	8.6	4.3	196	13.89	5	0	0
22	62	M	60	5	N	N	N	N	120	80	40	7.9	64	84	5.2	132	5	8.4	4.9	230	12.5	5	2	7
23	54	M	64	4.5	Y	Y	N	N	124	76	48	9.8	84	64	1.6	136	3.9	9.1	4	84	47.78	3	0	0
24	69	M	56	5	Y	Y	Y	Y	150	90	60	8.6	116	67	4.2	130	4.7	8.5	4.5	196	13.15	5	0	0

ID	Age	Sex	Weight	Duration	Smoking	Alcoholism	Diabetes	Hypertension	Systolic BP	Diastolic BP	Pulse Pressure	Hemoglobin	Glucose	Urea	Creatinine	Sodium	Potassium	Calcium	Phosphorus	PTH	eGFR	Stage	ASS	CS
25	65	F	61	5.5	N	N	Y	N	120	70	50	7.6	128	68	4.9	132	4.3	8.4	4.9	238	11.02	5	2	7
26	52	M	69	9	N	N	N	Y	130	90	40	10.4	92	49	1.8	137	3.8	9	3.7	89	46.85	3	1	1
27	66	F	60	3.5	N	N	N	N	124	80	44	8.4	66	76	4.5	136	4.3	8.6	4.3	190	11.65	5	0	0
28	56	M	62	5	N	N	Y	N	124	84	40	10.3	126	58	2.1	134	3.8	8.9	3.6	68	34.44	3	0	0
29	65	M	58	6	Y	N	Y	Y	140	70	70	7.8	146	76	5.1	129	4.8	8.5	4.9	276	11.85	5	2	8
30	56	M	56	3.5	N	N	N	Y	130	84	46	9.6	100	59	2.5	132	3.9	8.8	4.3	110	26.13	4	0	0
31	53	M	66	4.5	Y	N	N	N	110	80	30	9.8	98	43	2.2	128	3.8	9.1	4.1	38	36.25	3	0	0
32	65	F	62	5	N	N	Y	Y	136	90	46	7.3	110	84	5.1	134	4.7	8.3	5.3	84	10.76	5	3	13
33	60	M	58	3.5	N	N	N	N	130	80	50	8.4	75	68	4.8	132	4.8	8.6	4.6	168	13.43	5	0	0
34	63	M	58	3	Y	N	N	N	120	70	50	9.5	96	68	2.8	136	4.1	8.9	4.1	132	22.15	4	0	0
35	64	M	59	5.5	Y	N	N	N	120	70	50	9.1	84	67	3.1	134	4.1	8.9	3.9	158	20.09	4	2	5
36	63	M	57	3.5	N	N	Y	Y	140	90	50	7.8	112	67	4.9	129	4.9	8.4	5.1	246	12.44	5	3	12
37	64	M	57	7	N	N	Y	N	128	76	52	8.3	124	69	5.1	138	4.9	8.6	4.7	189	11.8	5	0	0

ID	Age	Sex	Weight	Duration	Smoking	Alcoholism	Diabetes	Hypertension	Systolic BP	Diastolic BP	Pulse Pressure	Hemoglobin	Glucose	Urea	Creatinine	Sodium	Potassium	Calcium	Phosphorus	PTH	eGFR	Stage	ASS	CS
38	63	M	58	9	Y	N	N	Y	136	70	66	8.2	68	68	4.9	130	4.2	8.5	4.8	84	12.66	5	3	11
39	65	M	59	4.5	N	Y	N	N	110	80	30	8.6	86	67	4.6	129	4.8	8.4	4.9	256	13.36	5	0	0
40	64	F	62	4	N	N	N	N	120	70	50	8.4	118	68	4.6	134	4.8	8.5	4.8	193	12.09	5	0	0
41	57	M	62	3	Y	Y	N	N	126	84	42	11.5	88	68	1.6	130	4.1	8.9	3.1	56	44.67	3	0	0
42	60	M	54	3	Y	Y	N	Y	130	70	60	8.1	72	84	5.3	134	4.3	8.4	5	278	11.32	5	3	15
43	58	M	57	4	Y	N	N	Y	136	86	50	8.3	86	67	4.8	129	4.6	8.5	4.7	231	13.52	5	0	0
44	67	M	59	4.5	N	N	N	Y	150	80	70	7.5	76	75	4.9	129	4.7	8.4	4.9	246	12.21	5	2	9
45	65	M	58	6	N	N	N	Y	120	80	40	8.9	104	50	3.4	132	4.7	8.6	3.9	156	17.77	4	1	3
46	64	M	60	4	N	N	N	Y	140	80	60	9.3	76	69	2.8	132	3.9	8.9	4.1	153	22.62	4	0	0
47	64	M	58	2.5	Y	Y	Y	Y	130	80	50	7.9	138	69	5.1	129	4.2	8.6	4.7	280	12	5	3	12
48	65	F	63	2.5	N	N	N	Y	120	76	44	9.1	101	58	2.8	135	3.8	8.8	3.9	86	19.92	4	0	0
49	49	F	70	5.5	N	N	N	N	120	70	50	10.6	68	58	1.4	134	3.7	8.9	3.8	98	53.72	3	0	0
50	53	F	68	4	N	N	N	Y	136	94	42	10.1	76	64	1.9	132	3.8	9.1	3.8	79	36.76	3	0	0

ID	Age	Sex	Weight	Duration	Smoking	Alcoholism	Diabetes	Hypertension	Systolic BP	Diastolic BP	Pulse Pressure	Hemoglobin	Glucose	Urea	Creatinine	Sodium	Potassium	Calcium	Phosphorus	PTH	eGFR	Stage	ASS	CS
51	65	F	63	4.5	N	N	N	N	120	80	40	8	92	67	4.6	129	3.8	8.7	4.5	184	12.13	5	0	0
52	60	M	62	2.5	Y	N	N	Y	140	70	70	9.3	85	64	3.2	129	4.2	9	4.2	84	21.53	4	0	0
53	43	F	65	4.5	N	N	Y	N	110	70	40	11.1	130	62	1.5	139	3.4	9.6	3.9	72	49.62	3	0	0
54	64	M	58	2.5	Y	N	N	Y	140	100	40	8.9	68	72	4.8	126	4.9	8.4	4.6	153	12.75	5	0	0
55	48	F	67	2	N	N	N	Y	130	80	50	10.5	98	68	1.8	128	3.5	9	3.7	59	40.43	3	0	0
56	63	F	62	4	N	N	N	Y	136	80	56	9.1	96	64	2.9	129	3.7	8.4	4.5	163	19.43	4	1	4
57	54	M	68	5.5	Y	N	N	Y	140	90	50	10.3	112	60	1.8	136	3.2	8.9	3.6	23	45.12	3	0	0
58	62	M	56	4.5	Y	Y	Y	N	110	60	50	8.9	136	64	3.2	132	4.6	8.8	4.2	148	18.96	4	2	4
59	62	M	58	2	N	N	N	N	124	86	38	8.3	84	78	4.8	129	4.5	8.6	4.5	198	13.09	5	0	0
60	64	M	62	4	N	N	N	N	110	80	30	9.6	84	61	2.8	134	4.2	8.8	4	124	23.37	4	0	0