INTRODUCTION

Globally, Chronic kidney disease (CKD) affects 5–10% of the world's population (1,2) This vast section of the population is at an increased risk of developing bone and mineral metabolism disturbances. These disturbances lead to a constellation of bone lesions which was previously referred to as renal osteodystrophy (ROD), with affected patients manifesting with symptoms such as muscle-tendon rupture, bone pain, pruritus and fractures. (3,4)

Evidence has now emerged that patients with ROD are also predisposed to cardiovascular calcification, which is associated with a high rate of morbidity and mortality. (5,6)

Anemia and metabolic bone disease are both typical consequences of chronic kidney disease, especially in the late stages. Anemia in CKD is predominantly normocytic and normochromic. (7)

The major causes of anaemia in CKD include relative erythropoietin insufficiency and resistance, as well as altered iron homeostasis, which is mostly related to hepcidin regulation. High levels of parathyroid hormone have also been related to reduced endogenous erythropoietin synthesis, which may be partially reversed by vitamin D suppression. Anemia becomes more frequent if GFR falls below 60ml/min/1.73m2, particularly in diabetics. (8)

As the estimated glomerular filtration rate (eGFR) decreases, anaemia becomes more common and severe. Anemia was twice as common in patients with CKD as in the general population, according to a study using cross-sectional data from the NationalHealth and Nutrition Examination Survey (NHANES) in 2007–2008 and 2009–2010 (7). (15.4 percent vs. 7.6). Anemia prevalence increased with CKD

development, from 8.4 percent at stage 1 to 53.4 percent at stage 5. A similar pattern was discovered in a more recent research published by the CKD Prognosis Consortium (8).

Hyperphosphatemia is a common complication of chronic kidney disease. Reduced filtered phosphate load leads to it early in renal illness and is intimately connected to the common occurrence of secondary hyperparathyroidism. Early in the illness, increased parathyroid hormone levels correct both calcium and phosphate levels. As a result, with an eGFR greater than 30ml/min/1.73m2, phosphate balance and serum phosphate levels are maintained. (4)

Renal osteodystrophy is a skeletal condition that affects nearly all individuals with end-stage renal failure, with secondary hyperparathyroidism and vitamin D deficiency being important contributors. Histologically, renal osteodystrophy may be divided into two types: high turnover and low turnover. (5) High turnover types are more prevalent and include osteitis fibrosis and mixed diseases, whereas low turnover forms include adynamic bone disease and osteomalacia. (5)

We propose this study to elucidate the link between anaemia and CKD-MBD markers in advanced cases of CKD who have not yet been started on dialysis in comparison to data immediately after the first session. This, in turn, may help us determine the extent of mineral and bone disorders in these individuals by looking at haemoglobin levels, and may potentially aid in screening for further investigations, and vice versa. We also get an understanding of how a single dialysis session can influence these indicators.

AIMS & OBJECTIVES

Aim:

The study is aimed to determine relationship of serum levels of albumin-corrected calcium and phosphorus with anemia in advanced stage 3 to 5 CKD patients, before initiating hemodialysis and 4 weeks after first session of hemodialysis.

Primary objective:

1. To determine relationship of anemia with serum albumin-corrected calcium and phosphorus levels in advanced CKD.

Secondary objective:

2. To evaluate whether the relationship is preserved after initiating dialysis and to assess the changes in these values before and after first session of hemodialysis.

3. To assess whether each of these bone metabolism biomarkers are independently related to anemia.

REVIEW OF LITERATURE

Chronic kidney disease (CKD):

Chronic kidney disease (CKD) has emerged as a major public health issue around the world. (13) It is widely acknowledged that low-income countries cannot afford the treatment required to manage individuals with end-stage renal disease. (14) Chronic renal failure refers to the process of continuous significant irreversible decrease in nephron number, which commonly correlates to CKD stages 3-5.

End-stage renal disease (ESRD) refers to a stage of CKD in which toxins, fluids, and electrolytes that are typically discharged by the kidneys accumulate, resulting in uremic syndrome. Unless the poisons are eliminated through renal replacement therapy, such as dialysis or kidney transplantation, this illness will result in mortality. (15)

Chronic kidney disease is divided in to five stages based on the estimated GFR. To be classified as stage 1 or stage 2, there must be an accompanying structural or functional defect (e.g. proteinuria, hematuria) as the GFR is normal or near normal in this stages. (14, 16)

DEFINITION OF CHRONIC KIDNEY DISEASE: (16)

National kidney foundation has defined CKD as,

CRITERIA:

1. Renal damage lasting more than three months, evidenced by pathologic abnormalities or signs of kidney damage in blood, urine, or imaging investigations, with or without decreased GFR.

2. GFR < 60 ml/min/1.73 sq m for more than 3 months, with or without renal damage.

CKD results in several extraskeletal manifestations. But these crucial extraskeletal manifestations are not included by the name ROD. As a result, the Kidney Disease - Improving Global Outcomes (KDIGO) Foundation convened a controversial conference with the goal of developing a universally recognised description and categorization system for renal osteodystrophy. (16)

The KDIGO panel suggested that the systemic disease of mineral and bone metabolism caused by CKD be referred to as CKD–mineral and bone disorder (CKD-MBD), and that the term renal osteodystrophy be reserved for problems in bone morphology associated with CKD. (6) Review of literature on recommended levels of corrected calcium, phosphorus and parathyroid hormone by different professional groups has been summarised in the following table.

Table 1 Recommended Guidelines by Different Professional Groups

Group	Year	Recommended Levels		
		Corrected Calcium (mg/dL)	Phosphorous (mg/dL)	PTH (pg/mL)
KDIGO[17]	2017	Near normal range	Near normal range	2–9× upper limit of normal
KDIGO[18]	2009	Within normal range	Within normal range	2–9× upper limit of normal
K/DOQI[15]	2003	8.4–9.5	3.5–5.5	150–300
Canadian Society of Nephrology[19]	2006	Within normal range	Within normal range	100–500
Japanese Society for Dialysis Therapy[20]	2008	8.4–10.0	3.5–6.0	60–240
UK Renal Association[21]	2002	8.8–10.4	<5.6	<4× upper normal range

Chronic renal failure refers to the process of a continual substantial irreversible decrease in nephron number, which generally correlates to CKD stages 3-5. Based on the estimated GFR, chronic renal disease is classified into five stages. In order to be classed as stage 1 or stage 2, there must be an accompanying structural or functional problem (e.g., proteinuria, hematuria) because the GFR is normal or near normal in these stages. 2 and 3.

A bone biopsy is less commonly used in clinical settings since it is an invasive and time-consuming process that requires highly skilled professionals to evaluate the tissue samples. As a result, doctors rely heavily on trends in parathyroid hormone levels, as well as serum phosphate, calcium, and alkaline phosphatase levels, as markers of bone turnover, to guide treatment of mineral bone disorders. (4)

The relationship between kidney disease and bone abnormalities has been known since 1883, when Lucas coined the term "renal rickets" to describe patients

with albuminuria and deformities. (17) Following an examination of 88 patients with endocrine bone problems, Bauer et al established a link between bone lesions (osteitis fibrosa cystica) and the parathyroid gland in 1930. (18) Albright et al. proposed seven years later that CKD patients with phosphate retention and low calcium levels are more likely to develop parathyroid gland hyperplasia and renal osteitis fibrosa. The term renal osteodystrophy was introduced in the 1940s and is now used interchangeably with renal rickets. (19)

Bricker and Slatopolsky developed the "trade-off hypothesis", which shed light on the pathophysiology of renal osteodystrophy. According to the theory, progressive nephron loss in CKD patients triggers a number of compensatory mechanisms, including an increase in PTH in response to retained phosphate. (20,21)

In the 1960s and 1970s, osteitis fibrosa and mixed uraemic osteodystrophy were the most common forms of renal osteodystrophy in patients with end-stage kidney disease (ESKD), with a subset of patients presenting with osteomalacia prior to dialysis. (22)

However, following the start of dialysis, osteomalacia developed as a result of aluminium poisoning in some centres; the two most afflicted dialysis facilities (Ottawa and Newcastle) had high levels of aluminium and fluoride in their tap water.

Microcytic anaemia and encephalopathy were symptoms of this kind of renal osteodystrophy (osteomalacia). (23)

Adynamic bone disease, on the other hand, was not only linked to aluminium contamination of dialysis water, but also to the use of high quantities of aluminum-containing phosphate binders and active vitamin D treatment. As a result of improved water filtration systems and lower prescriptions of aluminum-containing phosphate binders, the occurrence of this disease entity has decreased dramatically. (24)

PATHOPHYSIOLOGY OF CHRONIC KIDNEY DISEASE:

The pathophysiology of CKD is comprised of two large groups of damaging mechanisms:

1) Initiating mechanisms specific to the underlying aetiology (e.g., immune complexes and inflammatory mediators in certain types of glomerulonephritis, or toxin exposure in certain disorders of the renal tubules and interstitium).

2) A series of progressive mechanisms including hyperfiltration and hypertrophy of the remaining surviving nephrons that are a frequent consequence of long-term renal mass loss, regardless of the underlying aetiology.

Even in individuals with normal GFR, it is critical to identify risk factors for CKD. (15)

Risk factors:

1) High blood pressure

2) Diabetes mellitus

3) Autoimmune disorders

4) Advanced age

5) Urinary tract anomalies

6) Background of kidney illness in the family

7) History of acute renal failure.

8) Proteinuria

9) Excessive urinary sediment

Diabetic nephropathy, which is most commonly caused by type 2 diabetes mellitus, is the most common cause of CKD. In the elderly, hypertensive nephropathy is a prevalent cause of CKD. Glomerulonephritis is the third most common cause of chronic kidney disease. Early CKD, manifested as albuminuria and even moderate decreases in GFR, is increasingly recognised as a substantial risk factor for cardiovascular disease. Other causes, such as interstitial nephritis,

HIV nephropathy, and others, account for a sizable number of cases progressing to End Stage Renal Disease. (14, 15)

Historically, prior to the discovery of fibroblast growth factor 23 (FGF23), the main cause of secondary hyperparathyroidism was thought to be phosphate retention due to a loss in renal function. (26) The retained phosphate causes a triad of hyperphosphatemia, low 1,25(OH)2D3, and hypocalcemia, all of which are well-known triggers for PTH production, which in turn increases phosphate excretion and leads to the development of secondary hyperparathyroidism in advanced CKD. However, what mitigates this process in the early stages of CKD has remained a topic of debate. According to several writers, calcitriol shortage existed before hyperphosphatemia and hypocalcemia, implying that it is the primary initiator of secondary hyperparathyroidism. As a result, the pathophysiology of secondary hyperparathyroidism is a complex process involving the interplay of multiple variables. In the traditional hypnosis (20,27)

Phosphate's significance in the aetiology of secondary hyperparathyroidism was reinforced further by studies that found a link between high phosphate diets and parathyroid hyperplasia. (28,29) However, as new findings have been made, the pathophysiology of secondary hyperparathyroidism has developed. (4) For example, the emergence of FGF23 has revolutionized the understanding of the mechanisms underlying the development of secondary hyperparathyroidism, leading to an

updated trade-off hypothesis. Plasma FGF23 levels become elevated with progressively worsening renal function, likely to occur before observed changes in the levels of phosphate and PTH. (30)) For example, the discovery of FGF23 has transformed our understanding of the mechanisms driving secondary hyperparathyroidism development, leading to an updated trade-off theory. Plasma FGF23 levels rise when renal function deteriorates, and this is likely to happen before alterations in phosphate and PTH levels are noticed. (30) The following figure summarises the updated trade-off hypothesis versus the classic hypothesis. (31)

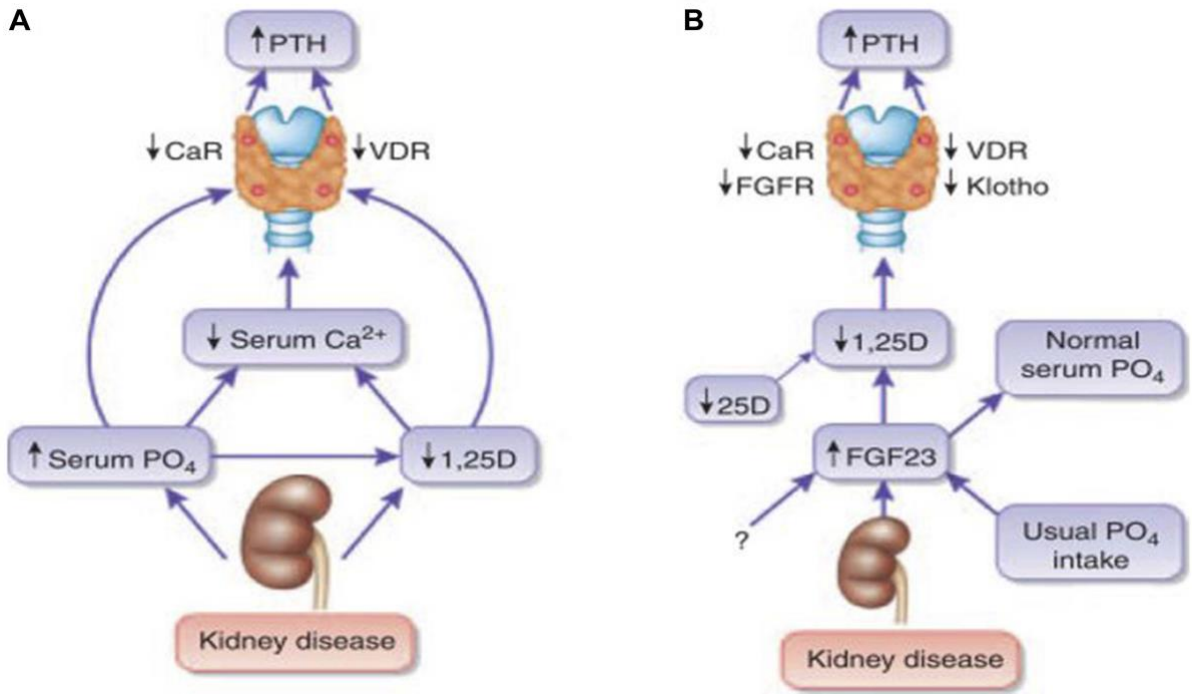


Figure: Pathogenesis of disordered mineral metabolism in CKD.

Notes: (A) Traditional view of the mechanisms that maintain secondary hyperparathyroidism in advanced chronic kidney disease. (B) Updated view of the

mechanisms that initiate secondary hyperparathyroidism in chronic kidney disease, emphasizing the central role of FGF23. Reprinted from Kidney International, 78(10). Isakova T, Wolf MS.

FGF23 or PTH: which comes first in CKD? Kidney Int. 2010;78(10):947–9. Abbreviations: CaR, calcium-sensing receptor; FGFR, fibroblast growth factor receptor; PTH, parathyroid hormone; VDR, vitamin D receptor.

Role of FGF23 in the Pathogenesis of Secondary Hyperparathyroidism:

Fibroblast growth factor 23 (FGF23) is produced by osteocytes and is essential for vitamin D and phosphate metabolism. It needs klotho (a transmembrane protein) to bind to the FGF receptor (FGFR) in typical target organs including the kidneys and parathyroid glands. (32)

Plasma FGF23 increases phosphate excretion in the proximal renal tubule by reducing the expression of luminal sodium-dependent phosphate transporters, and it may also reduce intestinal phosphate absorption by lowering NaPi cotransporter function. (33) Furthermore, it inhibits the production of 1,25-dihydroxyvitamin D [1,25(OH)2D3] by decreasing the activity of 1-hydroxylase while increasing the activity of 24-hydroxylase. (34, 35) High levels of FGF23 in the early stages of CKD reduce hyperphosphatemia at the price of 1,25(OH)2 vitamin D suppression, triggering the development of secondary hyperparathyroidism. (35)

Reduced serum 1,25(OH)2D3 results in reduced intestinal calcium absorption. The combination of low calcium, calcitriol, and hyperphosphatemia increases PTH production even more. Excess PTH causes calcium mobilisation from the bone and osteitis fibrosa. Other consequences of progressive kidney function decline include hyporesponsiveness of the vitamin D receptor (VDR) on the parathyroid gland, which leads to increased PTH production, and decreased expression of the calcium-sensing receptor on the parathyroid gland, which leads to parathyroid gland hyperplasia. The parathyroid gland hypertrophy and becomes autonomous in select subgroups of individuals. (36 - 39)

DIALYSIS:

Dialysis is classified into two types: hemodialysis and peritoneal dialysis. The best type will be determined by several variables. The most prevalent type of dialysis is hemodialysis. Blood is removed from the body via tubes and cleaned in a machine using dialysis fluid in this approach. (41) Dialysis is normally performed three times each week. Each session lasts between four and five hours.

The choice to begin chronic dialysis for individuals with chronic kidney disease (CKD) is made in partnership between the nephrologist and the patient. Although dialysis efficiently cures the signs and symptoms of uremia and fluid

overload (some of which can be life threatening), it is a lifelong therapy that causes discomfort, inconvenience, and some risk to the patient.

Thus, dialysis should begin when the benefit of reducing uremic signs and symptoms is deemed to outweigh the risk and associated effect on quality of life, but not earlier.

Dialysis preparation is integrated into the overall care of the patient with advanced CKD. Ideally, the choice to begin dialysis is made after the patient has been evaluated for kidney transplantation, determined their preferred dialysis modality, and has a working dialysis access. When the estimated glomerular filtration rate falls below 30 mL/min/1.73 m^2, patients should be referred for kidney transplant evaluation, with every effort made to seek living donors prior to the requirement for dialysis. (42)

SERUM CALCIUM:

Chronic kidney disease (CKD) disrupts bone metabolism and increases the risk of renal osteodystrophy, a kind of bone disease. These abnormalities can also induce calcium deposits in the blood arteries, which can lead to heart disease. It is important to evaluate calcium, phosphorus, and PTH levels to establish calcium status. Calcium supplements may be administered if calcium levels are low.

Calcium-based phosphorus binders are occasionally given to treat both low calcium and excessive phosphorus levels. (43)

To assist manage calcium levels, high calcium diets, calcium supplements, and calcium-based phosphorus binders may be limited or avoided. CKD patients need to keep their phosphorus levels between 3.0 to 5.5 mg/dL, or as close to the laboratory reference range as possible. The KDOQI calcium target range is 8.4 to 10.2 mg/dL. Calcium levels above 10.2 are considered high and may necessitate dietary changes, calcium-based binders, or a reduction in vitamin D therapy. (10)

SERUM ALBUMIN:

The most prevalent protein present in blood is albumin. It gives the body the protein it needs to maintain growth and repair tissues. During dialysis, the albumin in your blood also aids in fluid elimination. It aids in the "pulling" of surplus fluid from swollen tissues back into the bloodstream, where it may be removed by dialysis. (44) The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines indicate a blood albumin level of 4.0 g/dl or greater. (10)

CORRECTED CALCIUM:

Chronic kidney disease (CKD) is frequently worsened by Ca and phosphorus metabolism problems [2]. Endocrine problems, such as these metabolic diseases,

are linked to an elevated risk of cardiovascular events and mortality (45–49). Therefore, advice on goal values and treatment techniques for serum Ca correction,

Phosphate (P) and parathyroid hormone levels based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) and the Kidney Disease Clinical practice guidelines for Improving Global Outcomes (KDIGO) were issued to prevent Cardiovascular illness and death. (50,51)

Recently, it was found that adjusted Total Ca concentrations calculated using serum albumin cannot reliably predict corrected Calcium in patients with stage 3–5 CKD, and that low plasma pH is an independent cause for corrected Total Ca underestimation. (52)

SERUM PHOSPHATE:

The priority of CKD-MBD management is primarily to avoid the negative implications of secondary hyperparathyroidism. As a result, secondary hyperthyroidism treatment is dependent on well-established quantifiable surrogate signs of disturbed mineral bone metabolism. (53) Serum calcium, phosphate, intact parathyroid hormone, and 25-hydroxyvitamin D are the indicators. As a result, the latest KDIGO recommendation suggests treating patients based on the serial trends of these biochemical indicators. (54)

Although hyperphosphatemia has been associated to a number of negative clinical outcomes, there is no evidence that lowering phosphate levels improves patient outcomes. A recent randomised clinical trial, for example, found a substantial decrease in serum phosphate and a non-significant fall in serum FGF23 levels, as well as worsening of coronary calcification scores in patients given phosphate-lowering treatment. (55) As a result, the updated KDIGO recommendation that prevention of hyperphosphatemia in patients with CKD stages G3a to G5D may be more important than treatment or phosphate level normalisation. (54)

Phosphate restriction, the use of phosphate-lowering medications, and dialysis for individuals with CKD stage G5D are all methods of preventing hyperphosphatemia.

Phosphate Restriction

Attempts should be made to reduce daily phosphate intake to fewer than 800 mg; this can be accomplished by limiting the consumption of high phosphate meals and fizzy beverages containing phosphate additions. (56)

Moreover, since most phosphate-rich foods are also high in protein, the nutritional status of these patients should be continuously managed to avoid malnutrition. When developing dietary recommendations, the dietary supply of phosphate should be taken into account. This is required because the intestine

absorptive capacity varies depending on the source of the phosphate. The intestinal absorption rate of inorganic phosphate, such as that found in additives and beverages, is between 80% and 100%, while that of plant-based phosphate, such as nuts, ranges between 20% and 40%. (56)

Phosphate Binders

Phosphate binders are typically given with meals in order to inhibit phosphate absorption from the gut by generating a nonabsorbable combination with phosphate. Phosphate binders are classified into three types: aluminum-based phosphate binders, Ca-based phosphate binders, and non-Ca-based phosphate binders. (56) Long-term usage of aluminum-based phosphate binders has been hampered by related adverse effects such as osteomalacia and encephalopathy. (57) The administration of calcium-containing or noncalcium-containing phosphate binders should be directed by the patients' serum calcium and PTH levels. Overuse of calcium-based phosphate binders has been associated to negative effects, particularly in non-dialysis patients. (58) For example, a recent study comparing calcium-containing phosphate binders to a non-calcium-based phosphate binder (sevelamer) in patients on maintenance hemodialysis found that calcium-containing phosphate binders accelerated coronary artery calcification. Sevelamer, in addition to preventing calcium excess, has been linked to lower cholesterol and uric acid levels, as well as having an antiinflammatory effect. (55) In another trial, however,

the mortality outcome for patients on calcium-based phosphate binders and sevelamer was comparable. (58)

Phosphate Removal Through Dialysis

Dialysis removes phosphate, depending on the kind of dialysis, session time, and dialysate. An estimated 2.3–2.6 g of phosphate will be eliminated every week for a 4-hour dialysis session performed three times per week. When the session length is increased to 8 hours three times per week (as in nocturnal dialysis), phosphate elimination rises to 3.0–3.6 g per week. Peritoneal dialysis patients will have an estimated 2.0–2.2 g of phosphate removed per week for 4 times per day, 2 litres exchanges. (56,59)

SERUM ALKALINE PHOSPHATASE:

Mineral metabolism changes, particularly alkaline phosphatase (AP), are frequently reported in hemodialysis (HD) patients with end-stage renal disease (ESRD). In hemodialysis, Serum AP levels that are high in patients are linked to Secondary hyperparathyroidism (SHPT) (60, 61) renal osteodystrophy (62, 63) heart failure, diastolic dysfunction, (64) and cardiovascular disease are all examples of secondary hyperparathyroidism (CVD). (65) Serum total AP is frequently comprised of isoenzymes derived from bones and liver, as well as kidneys, intestines and leukocytes. (66, 67)

Although elevated AP isoenzyme levels have been linked to elevated parathyroid hormone (PTH), few research have looked into the dangers of elevated AP in HD patients. Notably, Kalantar-Zadeh et al. (68) found an increased risk of all-cause mortality in HD patients with higher baseline and time-varying AP levels, even after controlling for elevated serum phosphorus and calcium levels, which have been linked to an increased risk of mortality. (69)

ANEMIA IN CKD:

Anemia is a prevalent issue among CKD patients. The cause of CKD anaemia is complex. (However, the most essential etiologic factor is erythropoietin insufficiency.) Even though normochromic normocytic anaemia is usually thought to be caused by erythropoietin insufficiency, other factors such as iron shortage play a significant role, and this is exacerbated in dialysis patients. (70)

Anemia is a multifactorial risk factor for the progression of CKD to end stage renal disease (ESRD) and is associated with considerable morbidity and death. Anemia occurs earlier in CKD patients with diabetes mellitus, and the severity of anaemia is greater than in nondiabetic patients. (71) The degree of anaemia reflects the severity of the condition.

Anemia is defined by the World Health Organization as a haemoglobin level of less than 13 gm/dl in adult men and less than 12 gm/dl in adult women. The

National Renal Foundation's kidney disease outcome quality initiative anaemia recommendations define anaemia in CKD as a level of less than 13.5gm/dl for males and 12gm/dl for women. (51)

Anemia becomes increasingly common as renal function diminishes, becoming nearly universal in end-stage renal failure (ESRD). Hsu and colleagues evaluated 12,055 adult ambulatory individuals from Boston health clinics and discovered that when creatinine clearance was less than 60 mL/min in men and less than 40 mL/min in women, mean haematocrit values fell progressively. Only when GFR was substantially decreased, less than 30 mL/min in women and 20 mL/min in men, was moderately severe anaemia, Haematocrit less than 33%, prevalent (present in >20 percent of patients).

Nearly 90% of cases of anaemia are caused by erythropoietin insufficiency along with absolute or functional iron shortage. India leads the world in iron deficiency. (72)

Etiology of Anemia In CKD:

1) Deficiency of erythropoietin

2) Deficiency of iron (absolute/functional)

- Reduced RBC life-span,

- Reduced food / iron intake & absorption as a result of uremia

- Increased iron loss – GI bleeding, other bleeding tendencies

- Urinary transferrin loss as a result of proteinuria, resulting in poor iron transport.

Factors contributing to Anemia:

1) Toxic uremic poisons

2) Medications

3) Toxicity of aluminium

4) Hyperparathyroidism secondary to bone marrow fibrosis

5) A lack of folate/ Vitamin B12.

6) Infections with HIV/HCV

7) Cytokines and chronic inflammation

8) Hemoglobinopathy

9) Co-morbid conditions, such as auto-immune disorders

Consequences of Anemia: (14, 72)

1) Reduced quality of life

2) Reduced tolerance to exercise

3) Impairment of cognitive functions

4) Hypertrophy of the left ventricle

5) Heart failure with congestive edoema

6) Angina pectoris / myocardial infarction

7) Disrupted sleeping pattern

8) Reduced immunological response

Cardiac disease has a serious impact on individuals with kidney disease, lowering quality of life and increasing the risk of hospitalizations and death. The risk of death from cardiovascular disease is more than 15 times higher in hemodialysis patients than in the general population.

Approximately half of all CKD deaths are caused by cardiovascular disease, including congestive heart failure (CHF), acute myocardial infarction, and sudden cardiac death. (73). Indeed, CKD patients are considerably more likely to die from cardiac events than to advance to ESRD. (74). Anemia, a prevalent consequence of CKD, may have a significant role in increasing risk. Anemia in CKD causes long-term alterations in the cardiovascular system. A strong cardiac output and vasodilated state, which somewhat mitigates the effect of diminished oxygen

carriage by the bloodstream, are part of the body's adaptation for anaemia. Chronic increases in cardiac output may be maladaptive, increasing cardiac work and leading to left ventricular hypertrophy and an increased risk of cardiovascular events. (74, 75).

Anemia and left ventricular hypertrophy (LVH)

The most common cardiac problem associated with persistent anaemia is left ventricular hypertrophy. It is easily identified by specific echocardiography results. (75) with a left ventricular mass index more than 134 g/m2 in men and 110 g/m2 in women. (76) It is an especially significant result because it is a strong independent predictor of mortality risk. Each 1 gm/dL reduction in haemoglobin was related with a 6% increase in the risk of LVH. (77) Taken as a whole, the data suggests a very consistent link between anaemia and LVH. Smaller studies with severe anaemia correction have shown at least partial regression of LVH.

Other Effects of Anemia in Chronic Kidney Disease:

Anemia and its direct result, diminished oxygen carrying and delivery, may have additional negative effects in CKD patients. By depriving damaged kidneys of oxygen, worsening anaemia has the potential to hasten the progression of renal disease. Mohanram and colleagues recently published a post-hoc study of the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist

Losartan) experiment. Initial Hb was an important predictor of renal outcome in 1513 participants with type 2 diabetes mellitus, including time to ESRD or serum creatinine doubling. Every 1g/dL drop in Hb levels increased the risk by 11%. For every 1 g/dL decrease in Hb, there was a 30% increase in infection risk.

A lot of research have been conducted to investigate the impact of anaemia on brain and cognitive function. Anemia has continuously been associated to reduced function, and rHuEPO treatment has resulted in meaningful benefits. (78, 79)

Beneficial effects of correction of Anemia:

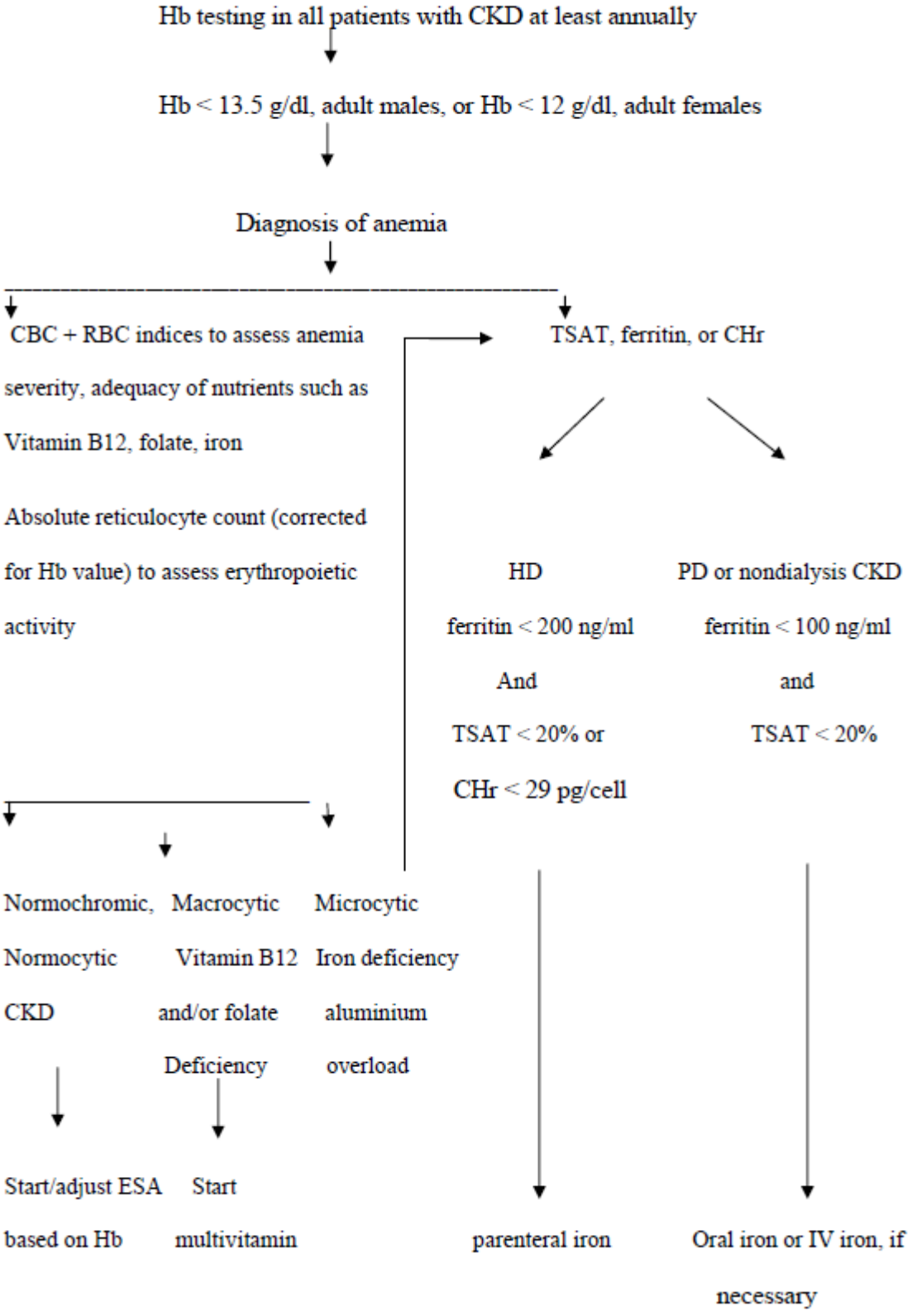
1) Less requirement for blood transfusions - Lower risk of Human Immunodeficiency Virus/Hepatitis C Virus - Lower risk of alloantibodies (transplant rejection) - Lower risk of iron overload

2) Increased life satisfaction and work tolerance

3) Left ventricular hypertrophy regression and rare congestive heart failure

4) Lower incidences of angina/myocardial infarction (72)

Anemia treatment algorithm



BLOOD UREA AND SERUM CREATININE:

Chronic renal disease (CRD) is a pathophysiologic process caused by a variety of etiologies that results in irreversible loss of nephron number and function and frequently leads to end stage renal disease (ESRD). (80). ESRD, on the other hand, denotes a clinical state or condition in which there is irreversible loss of endogenous renal function to the point where the patient is permanently dependent on renal replacement treatment. (Dialysis or transplantation) in order to avert potentially fatal uraemia. Uremia is a clinical and laboratory illness characterised by organ system dysfunction as a result of untreated or undertreated chronic renal failure. Significant chronic nephron damage has already occurred by the time plasma creatinine concentrations are even modestly raised.

The pathophysiology of the uremic syndrome can be separated into two groups of abnormalities:

1. Those resulting from the buildup of protein metabolism products.

2. Those caused by the loss of other renal functions, such as fluid and electrolyte homeostasis, as well as hormonal anomalies. (42)

Because the kidneys are so important in regulating body fluids, electrolytes, and acid-base balance. Multiple derangements are caused by CKD and ESRD, including hyperkalemia, metabolic acidosis, and hyperphosphatemia. (81) This, in

turn, causes major problems such as muscle atrophy, bone mineral disoders, vascular calcifications, and death. Unlike acute renal failure, which occurs suddenly and abruptly, chronic renal failure occurs gradually over a period of weeks, months, or years as the kidneys gradually stop performing, eventually leading to end-stage renal disease. (82) The widespread availability of dialysis has extended the lives of hundreds of thousands of patients with end-stage renal illness. The presence of uremia, hyperkalemia unresponsive to conservative methods, acidosis refractory to medical treatment, and a creatinine clearance of 10 ml/min/1.73 m^2 are all commonly accepted criteria for placing patients on dialysis. (83). The procedure of haemodialysis is conducted two to three times per week, with dialysis lasting two to four hours. The duration of dialysis is determined by a number of parameters, including kidney function, the amount of waste in the body, salt levels, and body weight.

When the kidneys are compromised, hemodialysis plays a critical role in the process of extracorporeal removal of waste products - creatinine, urea, and free water from blood. The diffusion of solutes over a semipermeable membrane is the underlying principle of hemodialysis. The movement of metabolic waste products from the circulation into the dialysate occurs along a concentration gradient. A tiny molecule, such as urea (60 Da), is eliminated efficiently, but a bigger molecule, such as creatinine (113 Da), is cleared less efficiently. (84)

eGFR:

As the testing for GFR can be a complicated and time-consuming operation, clinicians utilise a formula to predict GFR or eGFR. Accurate estimations of GFR are critical for detecting renal disease, which frequently has no symptoms until the kidneys fail. A simple blood test that evaluates your creatinine levels is the conventional method for estimating GFR. Creatinine is a by-product of protein digestion and the regular breakdown of muscle tissue. Aside from CKD, additional factors such as food, muscle mass, malnutrition, and other chronic conditions can also affect creatinine levels. (15, 16)

CLASSIFICATION OF CHRONIC KIDNEY DISEASE (16):

STAGE DESCRIPTION GLOMERULAR FILTRATION RATE (ml/min/1.73 m2)

0 - With a CKD risk factor of greater than 90

1 - Kidney injury caused by normal or increased GFR ≥ 90

2 - Mild decline in GFR between 60 and 89

3 - GFR reduction of 30 – 59 mL/min

4 - Severe reduction in GFR 15 – 29

5 - Renal failure is GFR < 15 or on dialysis

(Stage 0 – with chronic kidney disease risk factor)

CALCULATION OF GFR (14, 15)

GFR estimation equation based on blood creatinine, age, gender, race, and body weight.

To assess kidney function from serum creatinine, three formulas are typically used: (1) Cockcroft-Gault and (2) MDRD with four variables

(Modification of Diet in Renal Disease).

Cockcroft-Gault: CrCl (mL/min) = (140 – age (years) × weight (kg) ×

[0.85 if female])/ (72 × sCr (mg/dL)

MDRD: eGFR (mL/min per 1.73 m2) = 186.3 × PCr (e–1.154) × age (e–0.203)

× (0.742 if female) × (1.21 if black).

Another formula for calculating eGFR as given by Matsuo et al (85)

eGFR (ml/min/1.73 m^2) = 194 × S-Cr $^{-1.094}$ × age $^{-0.287}$; for women:

eGFR = 194 × S-Cr $^{-1.094}$ × age $^{-0.287}$ × 0.739,

where S-Cr is the serum creatinine concentration (mg/dl).

MATERIALS AND METHODS

Study Setting:

The study has been done at Department of General Medicine of the Government Kilpauk Medical College Hospital, Chennai.

Study population:

All the patients with chronic kidney disease of stage 3 to 5, admitted in the Department of General Medicine at the Government Kilpauk Medical College Hospital, Chennai.

Study Design:

Pre post analytical study

Sample Size calculation:

Sample size was calculated assuming the prevalence of Bone mineral Disease among individuals with chronic kidney disease to be 5% with a power of 80% and 95% confidence level. The following formula was used for sample size calculation, (86)

$$N = \frac{Z^2 P(1-P)}{d^2}$$

Where n = Sample size

Z= Z statistic for a level of confidence level

P = Expected prevalence/proportion of outcome

d = Precision

The required sample size as per the above-mentioned calculation was 73 individuals with stage 3 – 5 chronic kidney disease.

Study Period:

September 2019 – January 2021

INCLUSION CRITERIA:

1) Aged above 18years

2) Stage 3-5 CKD with eGFR of less than 60 ml/min/1.73m2, according to CKD-EPI equation based on serum creatinine

3) Informed consent

EXCLUSION CRITERIA:

1) Age below 18 years

2) On maintenance hemodialysis

3) Chronic kidney disease patients with eGFR more than 60ml/min/1.73m^2

4) Pregnancy

5) Recent transfusions

6) Use of erythropoietin stimulating agents

7) Malignancy

8) Known history of parathyroid illness

9) Documented rickets or osteomalacia

10) History of blood loss

11) Bleeding disorder or myeloproliferative disorders

12) Alcohol dependency

13) Long term infections

14) Inflammatory or autoimmune diseases

STUDY PROCEDURE:

After obtaining approval from the Institute Ethical Committee, a total of 73 adult patients with chronic kidney disease, with eGFR of less than 60 ml/min/1.73m2, according to CKD-EPI equation based on serum creatinine, were recruited consecutively after applying inclusion and exclusion criteria. A written informed consent was obtained from all the study participants, after explaining them about the study and its purpose in the local language. The written informed consent was obtained by the principal investigator who was trained and was also fluent in the local language. Serum levels of calcium, phoshate, albumin, Haemoglobin, creatinine and Blood urea were measured from venous blood sample collected from brachial vein at the cubital fossa. The obtained blood samples were immediately sent to biochemical laboratory in the department of Biochemistry at the Government Kilpauk Medical College Hospital to be processed immediately. Blood was collected under aseptic precautions for hematological (Haemoglobin) and biochemical (Blood Urea, Serum Creatinine, Serum calcium, albumin, serum alkaline phosphate, serum phosphate) investigations. Hematological profile was done on the standard automated analyzer. These laboratory parameters that was collected prior to hemodialysis session was regarded as Pre-dialysis parameters. Serum creatinine was measured using a kinetic rate Jaffe method. (87) eGFR was calculated by using the CKD-EPI equation, expressed as a single equation, is GFR = 141 × min(Scr/κ,

$1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] _ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. (88)

Correction for albumin levels done using the formula:

Corrected calcium = (0.8*(normal albumin-patient's albumin)) + serum calcium

Anemia as defined by KDIGO guidelines (51) has been adapted in the current study, with less than 13.0 g/dl and 12.0 g/dl being the cut-off Haemoglobin levels for an adult male and adult female respectively.

All the 73 patients who underwent their first session of hemodialysis were followed up for 4 weeks. At the end of 4^{th} week, Serum levels of calcium, phoshate, albumin, Haemoglobin, creatinine and Blood urea were again measured from venous blood collected from brachial vein at the cubital fossa. The obtained blood samples were immediately sent to biochemical laboratory in the department of Biochemistry at the Government Kilpauk Medical College Hospital to be processed immediately. These parameters which were obtained 4 weeks after their initial hemodialysis were considered as the post-dialysis parameters.

Variables:

1. Serial No
2. Name
3. Age

4. Gender

PRE-DIALYSIS

5. Serum Calcium (mg/dl)
6. Albumin (g/dl)
7. Corrected calcium (mg/dl)
8. Serum phosphate (mg/dl)
9. Serum alkaline phosphatase (U/l)
10. Haemoglobin (g/dl)
11. Blood Urea (mg/dl)
12. Serum creatinine (mg/dl)
13. eGFR (ml/min/1.73m2)

POST-DIALYSIS

14. Serum Calcium (mg/dl)
15. Albumin (g/dl)
16. Corrected calcium (mg/dl)
17. Serum phosphate (mg/dl)
18. Serum alkaline phosphatase (U/l)
19. Haemoglobin (g/dl)
20. Blood Urea (mg/dl)

21. Serum creatinine (mg/dl)
22. eGFR (ml/min/1.73m2)

Statistical analysis:

Data was collected from the study participants after obtaining written informed consent. Continuous variables such as age, Serum Calcium (mg/dl), Albumin (g/dl), corrected calcium (mg/dl), Serum phosphate (mg/dl), Serum alkaline phosphatase (U/l), Haemoglobin (g/dl), Blood Urea (mg/dl), Serum creatinine (mg/dl), eGFR (ml/min/1.73m2) were summarised as mean (SD) or Median (IQR) depending upon their distribution. Categorical variables such as gender were summarised as frequency (proportions).

Paired t test was used to assess the mean difference, while pearson's correlation was used to determine the correlation between the pre-dialysis and post-dialysis parameters. The sub group analysis was conducted to compare the pre dialysis biochemical parameters with that of post dialysis biochemical parameters among various age group categories. Data entry was done using Microsoft Excel 2016. Data analysis was done using SPSS Version 20.0. P value of less than 0.05 was considered to be statistically significant in the current study.

RESULTS

The current study was conducted in the department of General medicine at the Government Kilpauk Medical College Hospital, Chennai, Tamil Nadu. A total of 73 individuals with stage 3 to 5 chronic kidney disease, who presented to the department of general medicine department during the period September 2019 – January 2021, were recruited as participants for the current study. Table 1 depicts the age distribution characteristics of the study participants.

Table 1: Age distribution of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

Variable	Frequency (n)	Percentage (%)
Age categories (years) **{Mean age with SD = 57.67 (10.5) years}**		
< 40	6	8.2
40 - 49	12	16.4
50 - 59	20	27.4
60 - 69	29	39.7
≥ 70	6	8.2

The mean age of the participants in the current study was found to be **57.67** years with standard deviation of **10.5**. The range of age distribution varied between a minimum age 35 years to the maximum of 79 years.

The age distribution of the study of the study participants shows that 39.7% of the those who participated in the study belongs to 60 – 69 years age group as shown in table 1. While 20 (27.4%) of study participants belonged to the age group of 50 – 59 years of age, less than 40 years and more than 70 years age group contributed for 6 (8.2%) each as shown in figure 1.

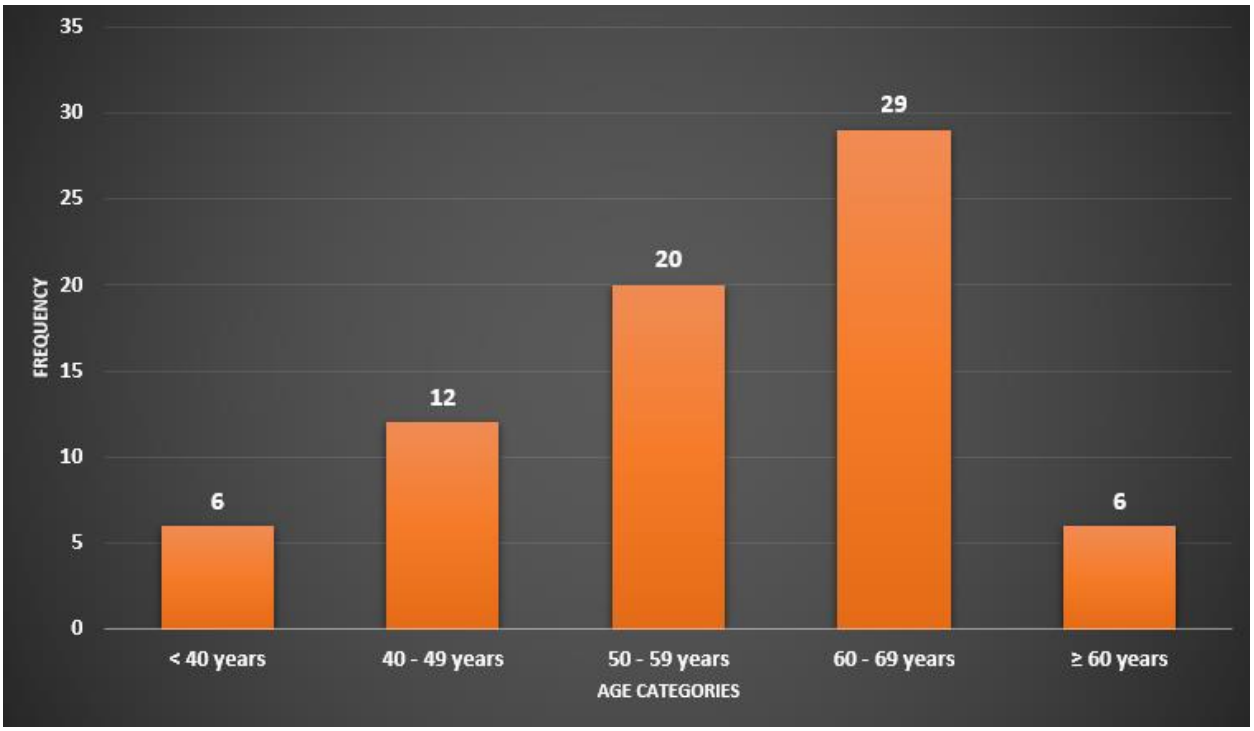


Figure 1: Age distribution of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

Table 2: Gender distribution of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

Variable	Frequency (n)	Percentage (%)
Gender		
Female	28	38.4
Male	45	61.6

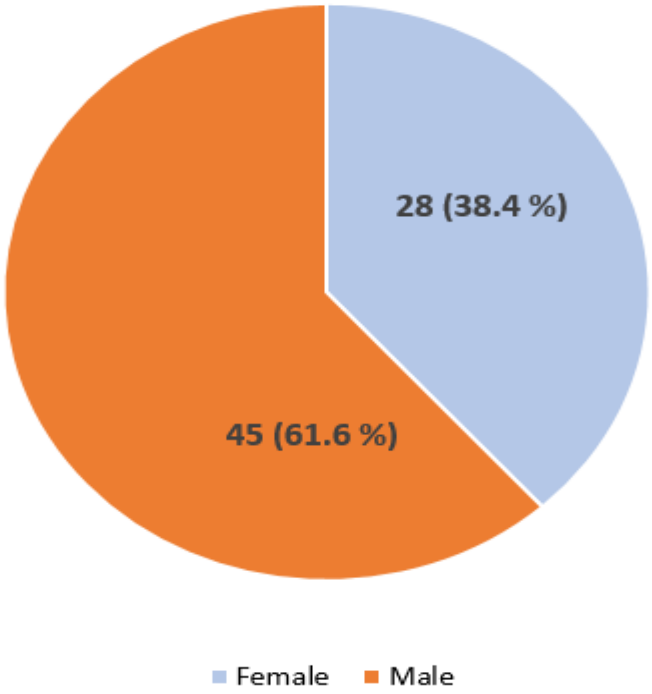


Figure 2: Gender distribution of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

Table 2 shows the distribution of study participants based on gender, wherein males contributed for 61.6% of study participants in the current study. Out of the 73 individuals with stage 3 to 5 chronic kidney disease, 28 (38.4%) study participants were females as shown in figure 2.

Table 3: Comparison of Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

Biochemical parameters	Pre dialysis		Post dialysis	
	Mean	SD	Mean	SD
Serum calcium (mg/dl)	8.6	0.85	8.69	0.71
Albumin (g/dl)	3.59	0.47	3.58	0.34
Corrected calcium (mg/dl)	8.92	0.82	9.02	0.76
Serum phosphate (mg/dl)	4.96	2.19	4.68	1.96

Serum alkaline phosphatase (U/l)	69.51	22.56	69.51	22.56
Haemoglobin (g/dl)	8.02	1.69	8.65	1.38
Blood Urea (mg/dl)	151.78	33.8	115.36	27.07
Serum creatinine (mg/dl)	9.61	2.15	8.41	1.78
eGFR (ml/min/1.73m2)	5.05	1.77	5.99	1.55

Table 4: Mean difference between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

Biochemical parameters	Paired difference (Pre and Post Dialysis)		t	P value
	Mean difference	SD		
Serum calcium (mg/dl)	-0.0904	0.6828	-1.131	0.262
Albumin (g/dl)	0.0082	0.3811	.184	0.854
Corrected calcium (mg/dl)	-0.0973	0.6656	-1.248	0.216
Serum phosphate (mg/dl)	0.2795	0.6216	3.841	<0.001
Serum alkaline phosphatase (U/l)	0	0	-	1.000
Haemoglobin (g/dl)	-0.6247	0.6839	-7.804	<0.001
Blood Urea (mg/dl)	36.425	21.736	14.318	<0.001
Serum creatinine (mg/dl)	1.2027	.7167	14.339	<0.001

eGFR (ml/min/1.73m2)	-0.932	0.788	-10.106	<0.001

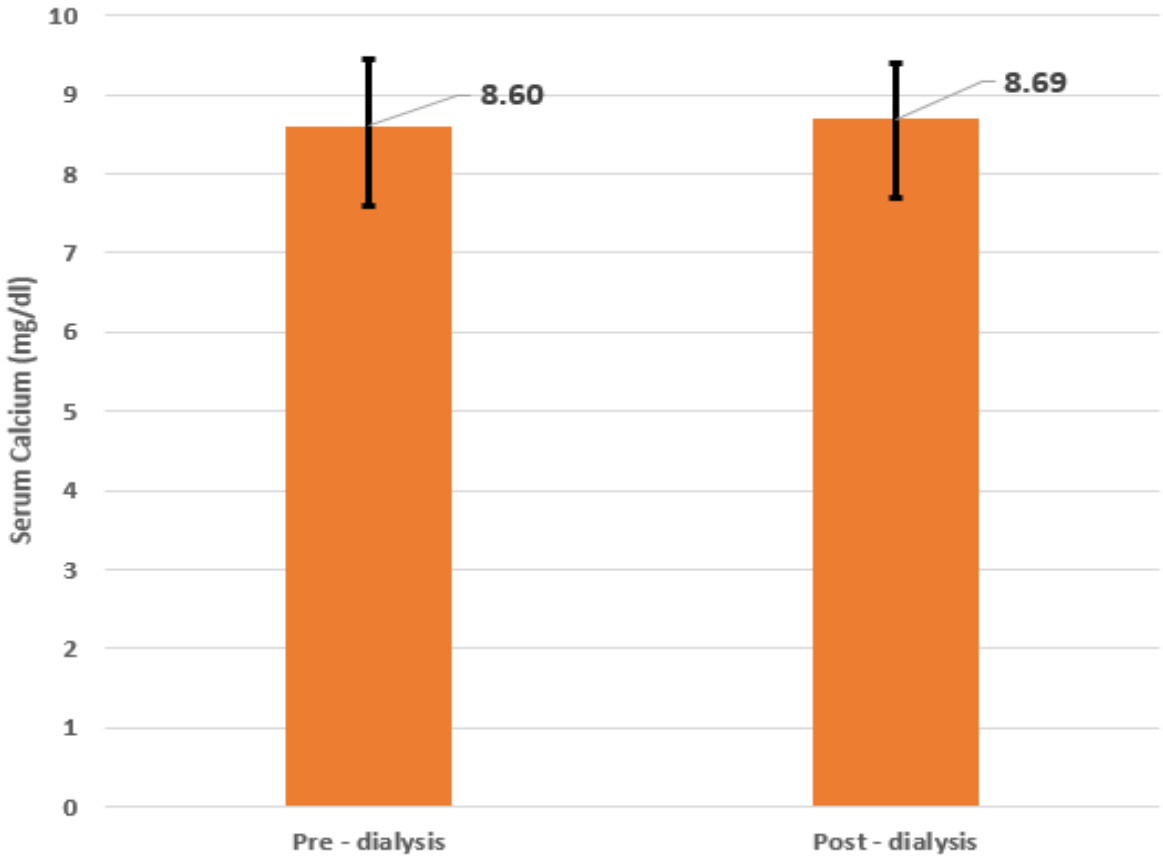


Figure 3: Comparison of Pre and Post dialysis Serum Calcium of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

The mean (SD) of Serum Calcium among the study participants in the Pre-dialysis stage was 8.6 (0.85) mg/dl as shown in table 3. The mean (SD) of Serum Calcium after dialysis (post-dialysis) was 8.6 (0.85) mg/dl as shown in figure 3. The mean difference of Pre and Post Dialysis Serum Calcium was found to be -0.0904 (0.6828) mg/dl and it was not found to be statistically significant as shown in table 4.

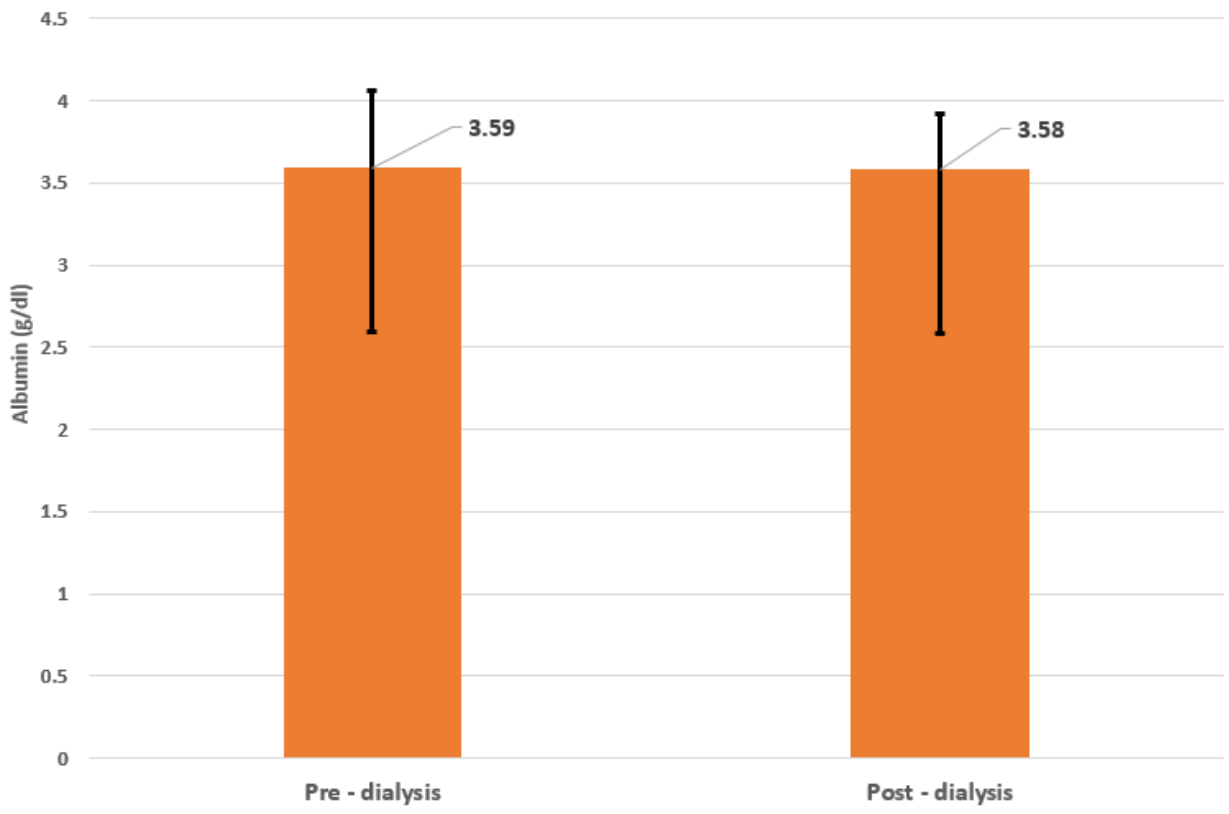


Figure 4: Comparison of Pre and Post dialysis Albumin of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

The mean (SD) of Albumin among the study participants in the Pre-dialysis stage was 3.59 (0.47) g/dl as shown in table 3. The mean (SD) of Albumin after dialysis (post-dialysis) was 3.58 (0.34) g/dl as shown in figure 4. The mean difference of Pre and Post Dialysis Albumin was found to be 0.0082 (0.3811) g/dl and it was not found to be statistically significant. (Table 4)

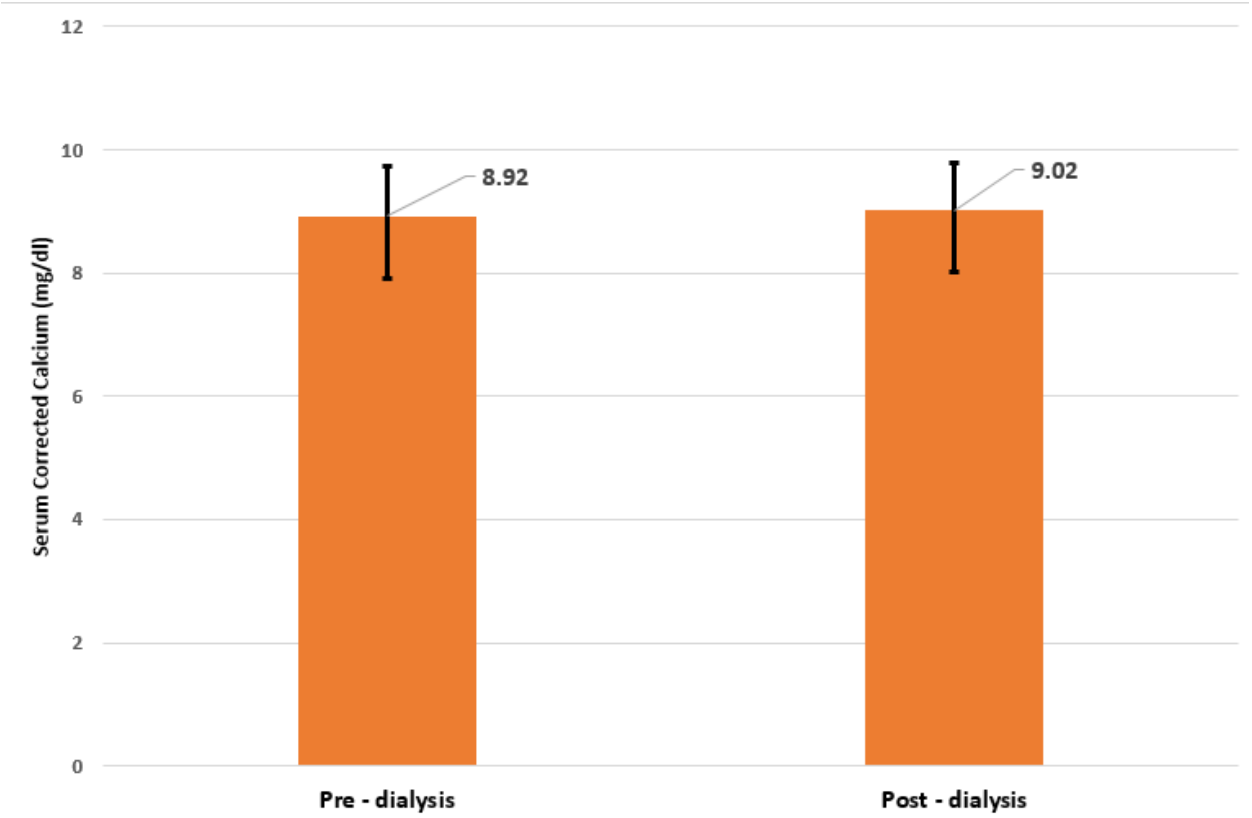


Figure 5: Comparison of Pre and Post dialysis Serum Corrected calcium of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

The mean (SD) of Serum Corrected calcium among the study participants in the Pre-dialysis stage was 8.92 (0.82) mg/dl as shown in table 3. The mean (SD) of Serum Corrected calcium after dialysis (post-dialysis) was 9.02 (0.76) mg/dl as shown in figure 5. Table 4 shows that the mean difference of Pre and Post Dialysis Serum Corrected calcium was found to be -0.0973 (0.6656) mg/dl and it was found to be statistically not significant.

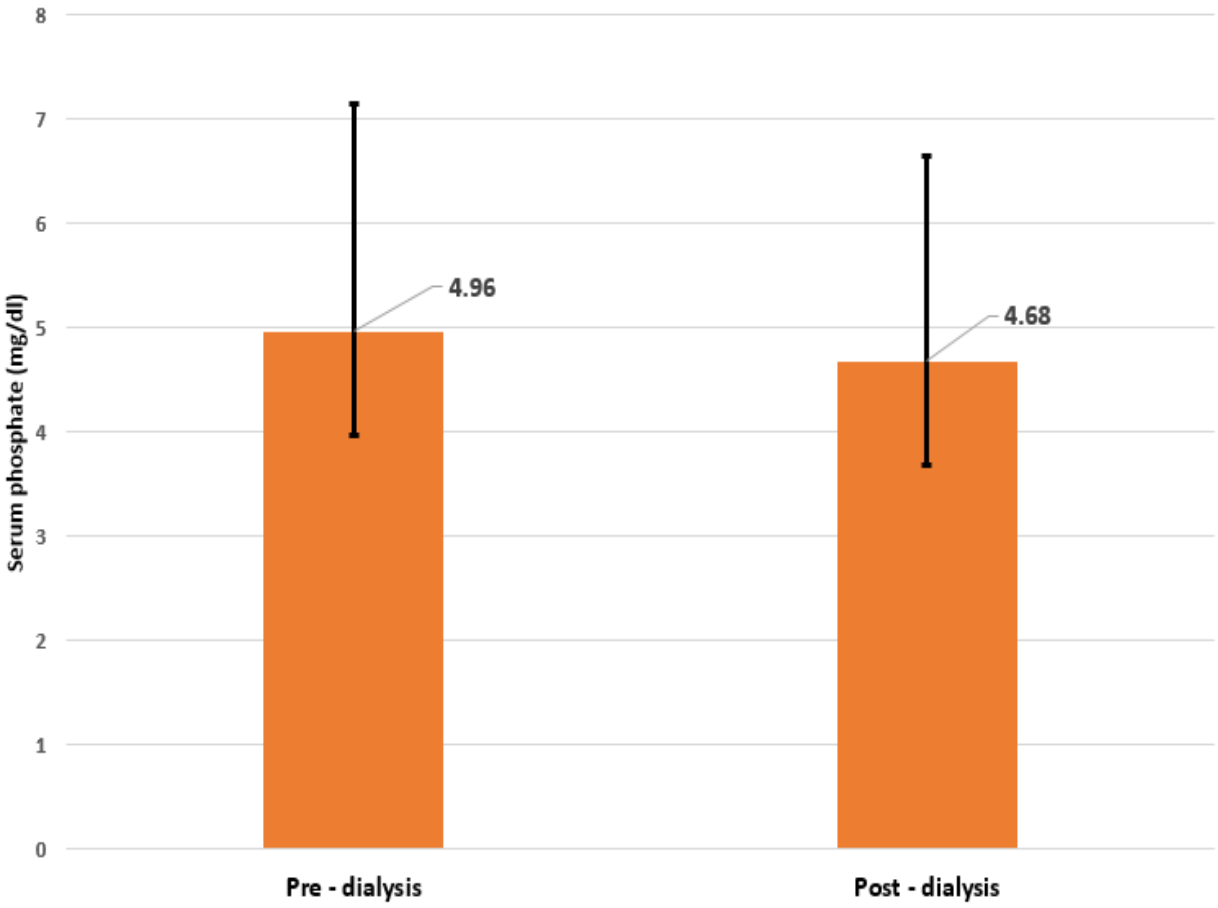


Figure 6: Comparison of Pre and Post dialysis Serum Phosphate of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

The mean (SD) of Serum Phosphate among the study participants in the Pre-dialysis stage was 4.96 (2.19) mg/dl as shown in table 3. The mean (SD) of Serum Phosphate after dialysis (post-dialysis) was 4.68 (1.96) mg/dl as shown in figure 6. Table 4 shows that the mean difference of Pre and Post Dialysis Serum Phosphate was found to be -0.2795 (0.6216) mg/dl and it was found to be statistically significant (P<0.001).

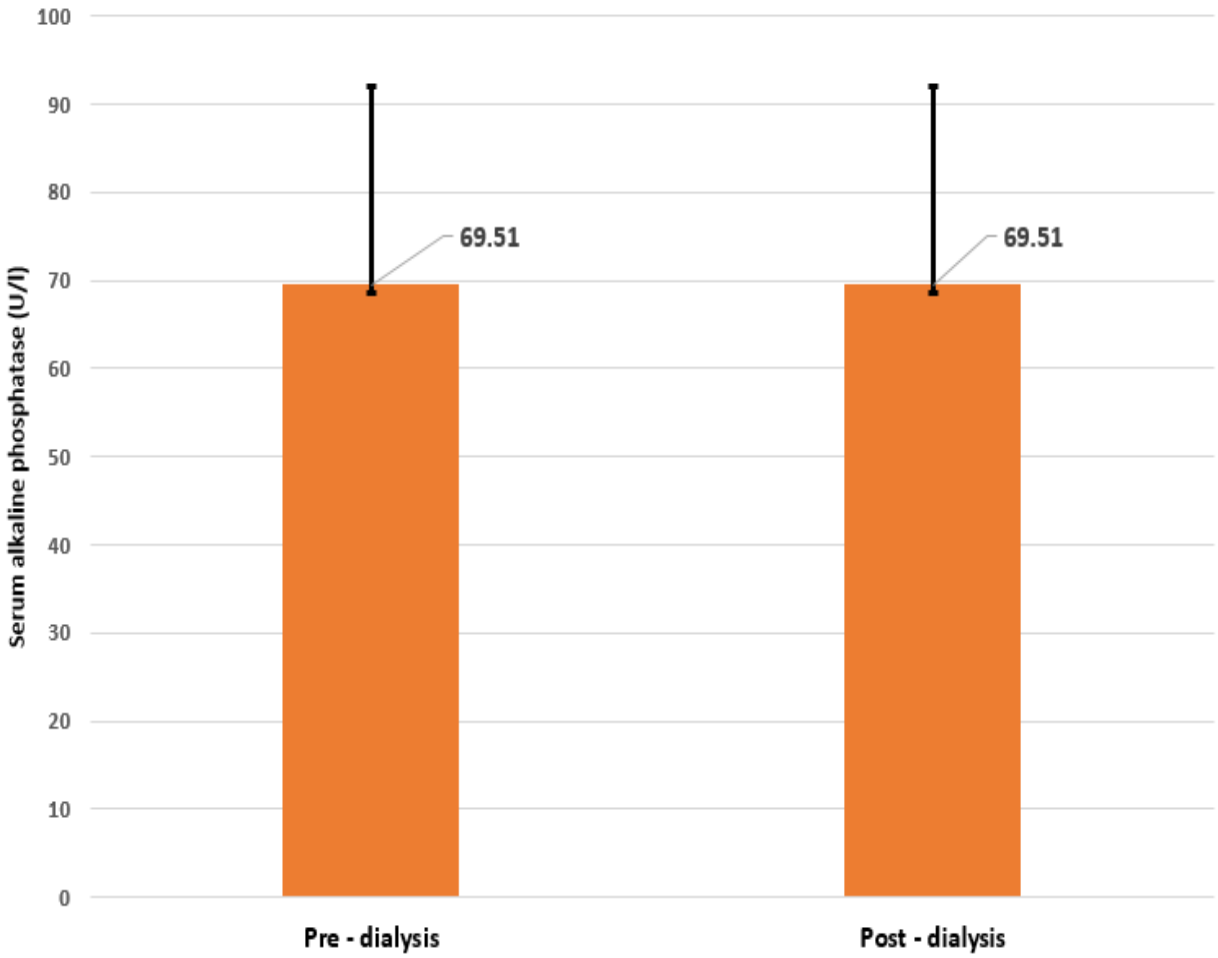


Figure 7: Comparison of Pre and Post dialysis Serum alkaline phosphatase of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

Table 3 shows that the mean (SD) of Serum Alkaline Phosphatase among the study participants was found to be 69.51 (22.56) U/I in both the Pre-dialysis as well as post-dialysis stages. (Figure 7) The mean difference of Pre and Post Dialysis Serum Phosphate was found to be zero mg/dl as shown in Table 4.

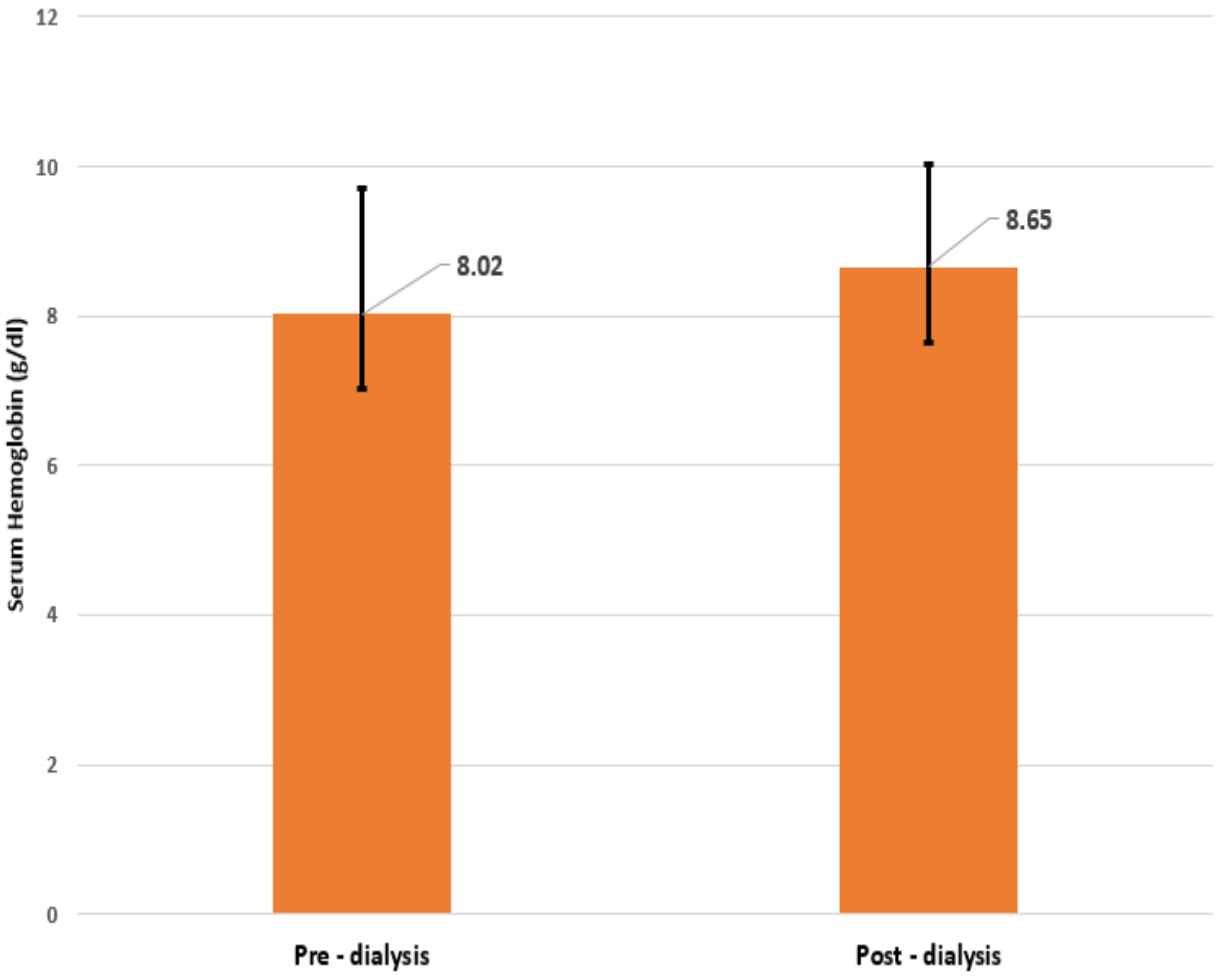


Figure 8: Comparison of Pre and Post dialysis Haemoglobin of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

The mean (SD) of Haemoglobin among the study participants in the Pre-dialysis stage was 8.02 (1.69) g/dl as shown in table 3. The mean (SD) of Haemoglobin after dialysis (post-dialysis) was 8.65 (1.38) g/dl as shown in figure 8. Table 4 shows that the mean difference of Pre and Post Dialysis Haemoglobin was found to be -0.6247 (0.6839) g/dl and it was found to be statistically significant (P<0.001).

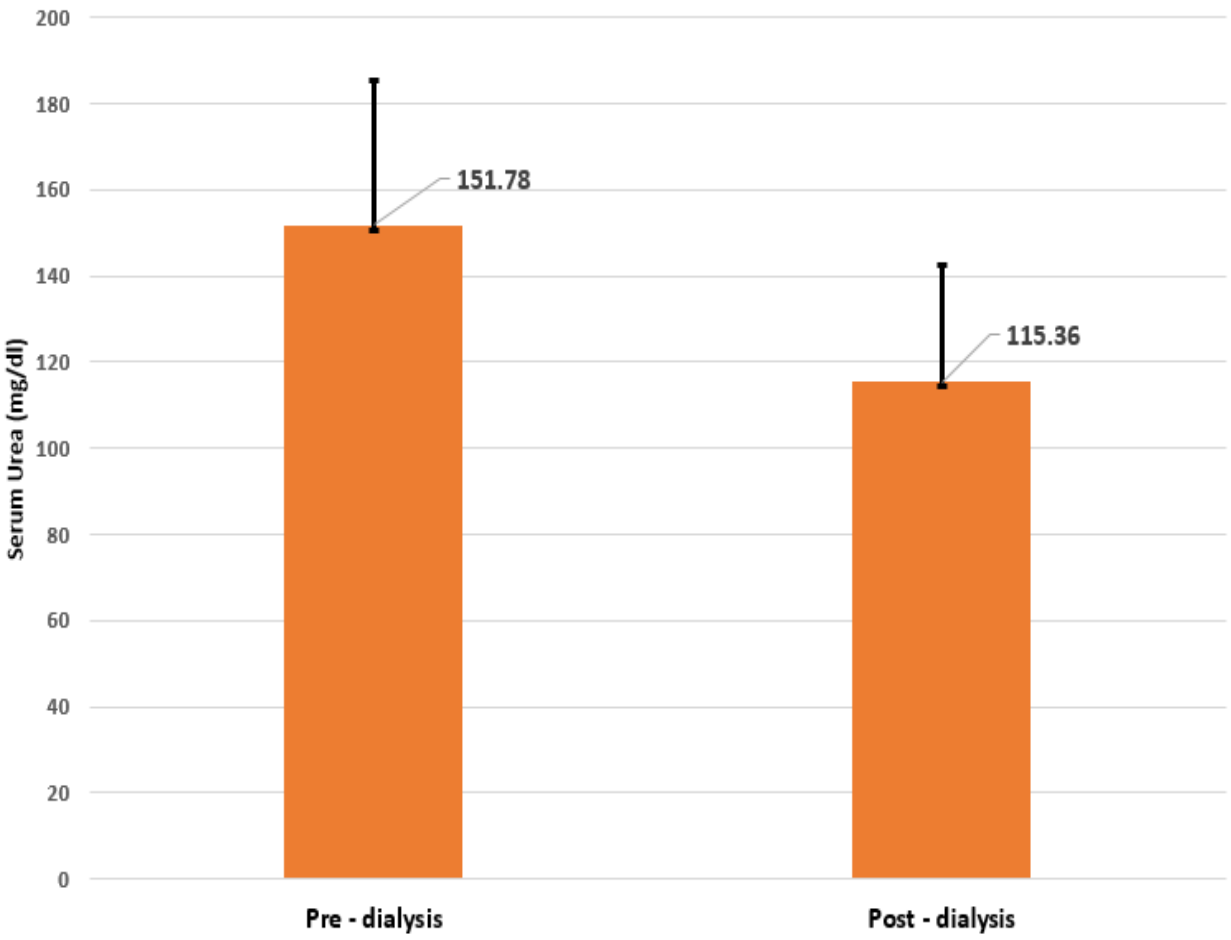


Figure 9: Comparison of Pre and Post dialysis Blood Urea of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

The mean (SD) of Blood Urea among the study participants in the Pre-dialysis stage was 115.36 (27.07) mg/dl as shown in table 3. The mean (SD) of Blood Urea after dialysis (post-dialysis) was 151.78 (33.8) mg/dl as shown in figure 9. The mean difference of Pre and Post Dialysis Blood Urea was found to be 36.425 (21.736) mg/dl and it was found to be statistically significant (P<0.001) as shown in table 4.

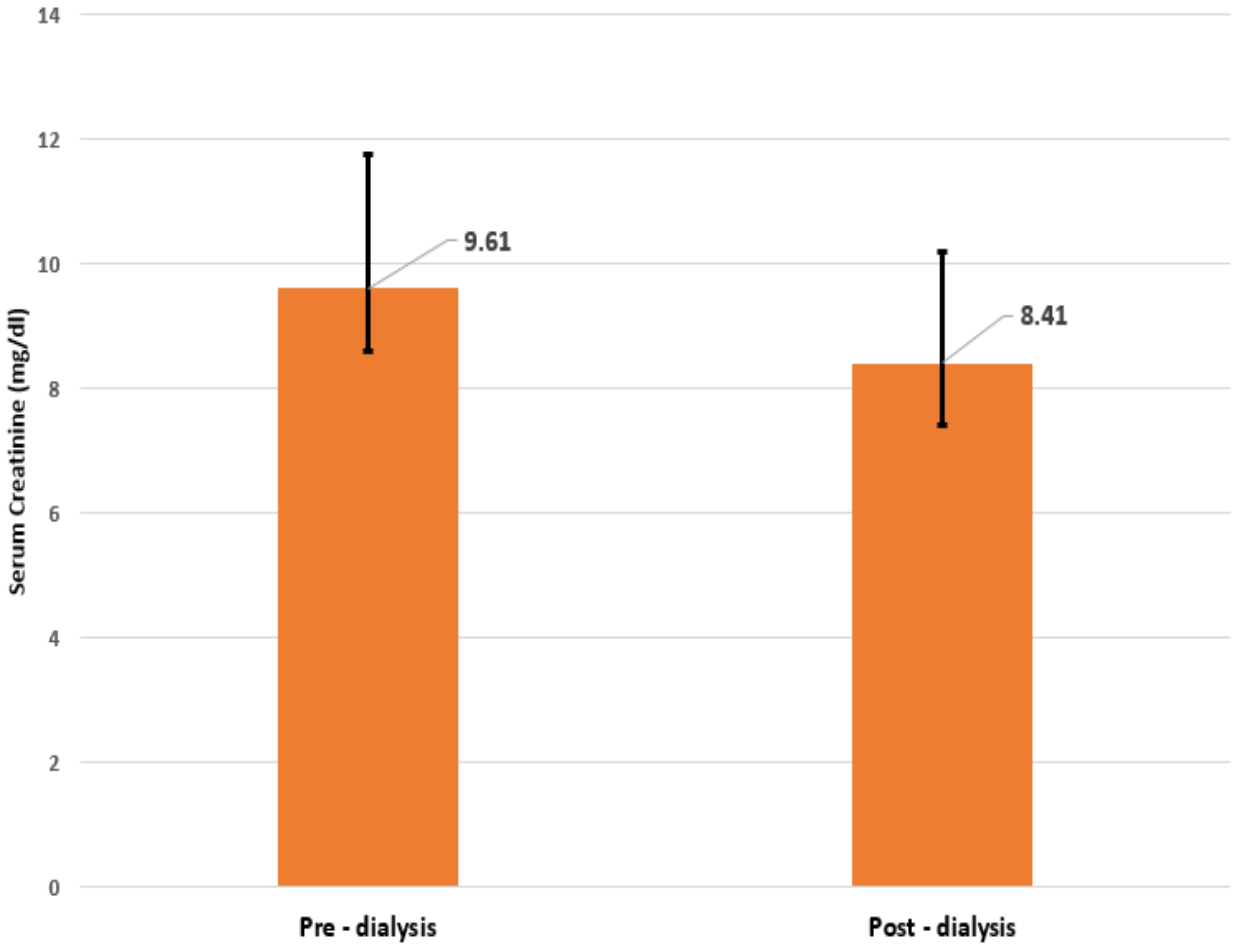


Figure 10: Comparison of Pre and Post dialysis Serum Creatinine of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

The mean (SD) of Serum Creatinine among the study participants in the Pre-dialysis stage was 9.61 (2.15) mg/dl as shown in table 3. The mean (SD) of Serum Creatinine after dialysis (post-dialysis) was 8.41 (1.78) mg/dl as shown in figure 10. Table 4 shows that the mean difference of Pre and Post Dialysis Serum Creatinine was found to be 1.2027 (0.7167) mg/dl and it was found to be statistically significant (P<0.001).

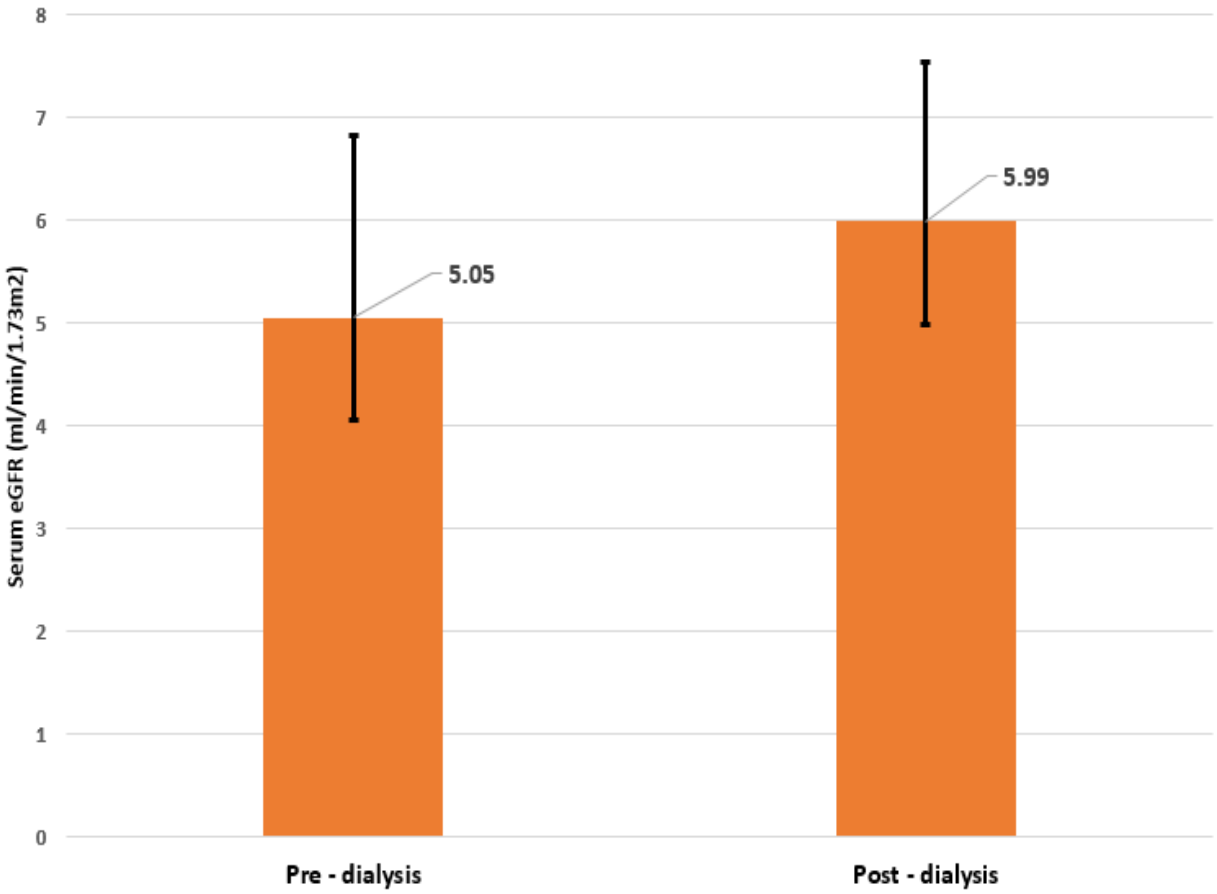


Figure 11: Comparison of Pre and Post dialysis eGFR of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

The mean (SD) of eGFR among the study participants in the Pre-dialysis stage was 5.05 (1.77) ml/min/1.73m^2 as shown in table 3. The mean (SD) of eGFR after dialysis (post-dialysis) was 5.99 (1.55) ml/min/1.73m^2 as shown in figure 11. The mean difference of Pre and Post Dialysis eGFR was found to be -0.932 (0.788) ml/min/1.73m^2 and it was found to be statistically significant (P<0.001) as shown in table 4

Table 5: Correlation between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

Biochemical parameters	Correlation (Pre and Post Dialysis)	P value
Pre and Post - Serum calcium (mg/dl)	0.627	< 0.001
Pre and Post - Albumin (g/dl)	0.601	0.854
Pre and Post - Corrected calcium (mg/dl)	0.647	0.216
Pre and Post - Serum phosphate (mg/dl)	0.961	<0.001
Pre and Post - Haemoglobin (g/dl)	0.920	<0.001
Pre and Post - Blood Urea (mg/dl)	0.767	<0.001

Pre and Post - Serum creatinine (mg/dl)	0.951	<0.001
Pre and Post - eGFR (ml/min/1.73m2)	0.868	<0.001

Table 5 shows that the biochemical parameters such as Serum Calcium, Serum phosphate, Haemoglobin, Blood Urea, Serum creatinine and eGFR had a correlation coefficient of 0.627, 0.961, 0.920, 0.767, 0.951, 0.868 between pre and post dialysis stages and they were found to be statistically significant ($P < 0.001$)

The biochemical parameters such as Albumin and Corrected calcium (mg/dl) had a correlation coefficient of 0.601 and 0.647 respectively and were not found to be statistically significant as shown in table 5.

SUB GROUP ANALYSIS:

The sub group analysis was performed to compare the pre dialysis biochemical parameters with that of post dialysis biochemical parameters among various age group categories as shown in table 1.

LESS THAN 40 YEARS AGE GROUP:

Out of 73 study participants, 6 (8.2%) participants belonged to age group of less than 40 years.

Table 6: Mean difference between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease belonging to less than 40 years age group who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 6)

Biochemical parameters	Paired difference (Pre and Post Dialysis)		t	P value
	Mean difference	SD		
Serum calcium (mg/dl)	1.0000	.8532	-1.131	0.262
Albumin (g/dl)	-.1333	.2733	.184	0.854
Corrected calcium (mg/dl)	1.1333	.8311	-1.248	0.216
Serum phosphate (mg/dl)	-.0333	.6772	3.841	<0.001
Serum alkaline phosphatase (U/l)	0	0	-	1.000

Haemoglobin (g/dl)	-.9667	.4412	-7.804	<0.001
Blood Urea (mg/dl)	20.333	16.256	14.318	<0.001
Serum creatinine (mg/dl)	0.9333	.4590	14.339	<0.001

* The t value of eGFR cannot be computed because the standard error of the difference is 0.

Table 6 shows that the biochemical parameters such as Serum phosphate, Haemoglobin, Blood Urea and Serum creatinine had statistically significant (P < 0.001) mean difference between the pre dialysis and post dialysis stages among the study participants belonging to less than 40 years age group.

The mean difference of biochemical parameters such as Serum Calcium, Albumin and Corrected calcium (mg/dl) were not found to be statistically significant between the pre dialysis and post dialysis stages among the study participants belonging to less than 40 years age group as shown in table 6.

Table 7: Correlation between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease belonging to less than 40 years age group who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 6)

Biochemical parameters	Correlation (Pre and Post Dialysis)	P value
Pre and Post - Serum calcium (mg/dl)	0.866	0.026
Pre and Post - Albumin (g/dl)	0.828	0.042
Pre and Post - Corrected calcium (mg/dl)	0.825	0.043
Pre and Post - Serum phosphate (mg/dl)	0.908	0.012
Pre and Post - Haemoglobin (g/dl)	0.988	<0.001
Pre and Post - Blood Urea (mg/dl)	0.999	<0.001
Pre and Post - Serum creatinine (mg/dl)	0.955	0.003

* The correlation of eGFR cannot be computed because the standard error of the difference is 0.

Table 7 shows that the biochemical parameters such as Serum Calcium, Albumin, Serum phosphate, Corrected calcium, Haemoglobin, Blood Urea and Serum creatinine had a correlation coefficient of 0.866, 0.828, 0.825, 0.908, 0.988, 0.999 and 0.955 respectively between pre and post dialysis stages and they were found to be statistically significant among the study participants belonging to less than 40 years age group.

40 - 49 YEARS AGE GROUP:

Out of 73 study participants, 12 (16.4%) participants belonged to 40 - 49 years age group.

Table 8: Mean difference between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease belonging to 40 - 49 years age group who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 12)

Biochemical parameters	Paired difference (Pre and Post Dialysis)		t	P value
	Mean difference	SD		

Serum calcium (mg/dl)	0.1333	0.7075	0.653	0.527
Albumin (g/dl)	0.1833	0.1267	5.011	<0.001
Corrected calcium (mg/dl)	-0.0333	0.7572	-.152	0.882
Serum phosphate (mg/dl)	-0.1167	0.3689	-1.096	0.297
Serum alkaline phosphatase (U/l)	0	0	-	1
Haemoglobin (g/dl)	-0.7833	0.7590	-3.575	0.004
Blood Urea (mg/dl)	27.833	19.904	4.844	0.001
Serum creatinine (mg/dl)	1.3167	0.4648	9.812	<0.001
eGFR (ml/min/1.73m2)	-1.667	0.778	-7.416	<0.001

Table 8 shows that the biochemical parameters such as Albumin, Haemoglobin, Blood Urea, Serum creatinine and eGFR had statistically significant mean difference between the pre dialysis and post dialysis stages among the study participants belonging to 40 – 49 years age group.

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The mean difference of biochemical parameters such as Serum Calcium, Corrected calcium (mg/dl), Serum phosphate and Serum alkaline phosphatase were not found to be statistically significant between the pre dialysis and post dialysis stages among the study participants belonging to 40 – 49 years age group as shown in table 8.

Table 9: Correlation between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease belonging to 40 - 49 years age group who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 12)

Biochemical parameters	Correlation (Pre and Post Dialysis)	P value
Pre and Post - Serum calcium (mg/dl)	-0.046	0.888
Pre and Post - Albumin (g/dl)	0.951	<0.001
Pre and Post - Corrected calcium (mg/dl)	-0.435	0.157

Pre and Post - Serum phosphate (mg/dl)	0.981	<0.001
Pre and Post - Haemoglobin (g/dl)	0.879	<0.001
Pre and Post - Blood Urea (mg/dl)	0.720	<0.001
Pre and Post - Serum creatinine (mg/dl)	0.913	<0.001
Pre and Post - eGFR (ml/min/1.73m2)	0.948	<0.001

Table 9 shows that the biochemical parameters such as Albumin, Serum phosphate, Haemoglobin, Blood Urea, Serum creatinine and eGFR had a correlation coefficient of 0.951, 0.981, 0.879, 0.720, 0.913 and 0.948 respectively between pre and post dialysis stages among the study participants belonging to 40 - 49 years age group and they were found to be statistically significant ($P < 0.001$)

The biochemical parameters such as Serum Calcium and Corrected calcium (mg/dl) had a correlation coefficient of -0.046 and -0.435 respectively among the study

participants belonging to 40 - 49 years age group and were not found to be statistically significant as shown in table 9.

50 - 59 YEARS AGE GROUP:

Out of 73 study participants, 20 (27.4%) participants belonged to 50 – 59 years age group.

Table 10: Mean difference between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease belonging to 50 - 59 years age group who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 20)

Biochemical parameters	Paired difference (Pre and Post Dialysis)		t	P value
	Mean difference	SD		
Serum calcium (mg/dl)	-0.2250	0.6439	-1.563	0.135
Albumin (g/dl)	-0.0200	0.3665	-0.244	0.810
Corrected calcium (mg/dl)	-0.2250	0.5129	-1.962	0.065

Serum phosphate (mg/dl)	0.1250	0.7362	0.759	0.457
Serum alkaline phosphatase (U/l)	0	0	-	1
Haemoglobin (g/dl)	-0.7850	0.8839	-3.972	0.001
Blood Urea (mg/dl)	38.100	14.345	11.878	<0.001
Serum creatinine (mg/dl)	1.2300	0.9404	5.849	<0.001
eGFR (ml/min/1.73m2)	-0.650	0.489	-5.940	<0.001

Table 10 shows that the biochemical parameters such as Haemoglobin, Blood Urea, Serum creatinine and eGFR had statistically significant mean difference between the pre dialysis and post dialysis stages among the study participants belonging to 50 – 59 years age group.

The mean difference of biochemical parameters such as Serum Calcium, Albumin, Corrected calcium (mg/dl), Serum phosphate and Serum alkaline phosphatase were not found to be statistically significant between the pre dialysis and post dialysis stages among the study participants belonging to 50 – 59 years age group as shown in table 10.

Table 11: Correlation between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease belonging to 50 - 59 years age group who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 20)

Biochemical parameters	Correlation (Pre and Post Dialysis)	P value
Pre and Post - Serum calcium (mg/dl)	0.672	<0.001
Pre and Post - Albumin (g/dl)	0.509	0.022
Pre and Post - Corrected calcium (mg/dl)	0.852	<0.001
Pre and Post - Serum phosphate (mg/dl)	0.936	<0.001

Pre and Post - Haemoglobin (g/dl)	0.924	<0.001
Pre and Post - Blood Urea (mg/dl)	0.869	<0.001
Pre and Post - Serum creatinine (mg/dl)	0.919	<0.001
Pre and Post - eGFR (ml/min/1.73m2)	0.887	<0.001

Table 11 shows that the biochemical parameters such as Serum Calcium, Albumin, Corrected calcium, Serum phosphate, Haemoglobin, Blood Urea, Serum creatinine and eGFR had a correlation coefficient of 0.672, 0.509, 0.852, 0.936, 0.924, 0.869, 0.919 and 0.887 respectively between pre and post dialysis stages among the study participants belonging to 50 - 59 years age group and they were found to be statistically significant.

60 - 69 YEARS AGE GROUP:

Out of 73 study participants, 29 (39.7%) participants belonged to 60 – 69 years age group.

Table 12: Mean difference between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease belonging to 60 - 69 years age group who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 29)

Biochemical parameters	Paired difference (Pre and Post Dialysis)		t	P value
	Mean difference	SD		
Serum calcium (mg/dl)	-0.2862	0.4518	-3.412	0.002
Albumin (g/dl)	-0.0414	0.4851	-0.459	0.650
Corrected calcium (mg/dl)	-0.2414	0.4110	-3.163	0.004
Serum phosphate (mg/dl)	0.4931	0.4697	5.653	<0.001

Serum alkaline phosphatase (U/l)	0	0	-	1
Haemoglobin (g/dl)	-0.4379	0.4255	-5.543	<0.001
Blood Urea (mg/dl)	37.759	24.789	8.203	<0.001
Serum creatinine (mg/dl)	1.2897	0.7218	9.622	<0.001
eGFR (ml/min/1.73m2)	-0.862	0.915	-5.073	<0.001

Table 12 shows that the biochemical parameters such as Serum Calcium, Corrected calcium (mg/dl), Serum phosphate, Haemoglobin, Blood Urea, Serum creatinine and eGFR had statistically significant mean difference between the pre dialysis and post dialysis stages among the study participants belonging to 60 – 69 years age group.

The mean difference of biochemical parameters such as Albumin and Serum alkaline phosphatase were not found to be statistically significant between the pre

dialysis and post dialysis stages among the study participants belonging to 60 – 69 years age group as shown in table 12.

Table 13: Correlation between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease belonging to 60 - 69 years age group who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 29)

Biochemical parameters	Correlation (Pre and Post Dialysis)	P value
Pre and Post - Serum calcium (mg/dl)	0.905	<0.001
Pre and Post - Albumin (g/dl)	0.593	0.001
Pre and Post - Corrected calcium (mg/dl)	0.863	<0.001

Pre and Post - Serum phosphate (mg/dl)	0.974	<0.001
Pre and Post - Haemoglobin (g/dl)	0.962	<0.001
Pre and Post - Blood Urea (mg/dl)	0.658	<0.001
Pre and Post - Serum creatinine (mg/dl)	0.970	<0.001
Pre and Post - eGFR (ml/min/1.73m2)	0.747	<0.001

Table 13 shows that the biochemical parameters such as Serum Calcium, Albumin, Corrected calcium, Serum phosphate, Haemoglobin, Blood Urea, Serum creatinine and eGFR had a correlation coefficient of 0.905, 0.593, 0.863, 0.974, 0.962, 0.658, 0.970 and 0.747 respectively between pre and post dialysis stages among the study participants belonging to 60 - 69 years age group and they were found to be statistically significant.

70 YEARS AND ABOVE AGE GROUP:

Out of 73 study participants, 6 (8.2%) participants belonged to 70 years and above age group.

Table 14: Mean difference between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease belonging to 70 years and above age group who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 6)

Biochemical parameters	Paired difference (Pre and Post Dialysis)		t	P value
	Mean difference	SD		
Serum calcium (mg/dl)	-0.2333	0.5465	-1.046	0.344
Albumin (g/dl)	0.1333	0.1366	2.390	0.062
Corrected calcium (mg/dl)	-0.3333	0.6346	-1.287	0.255

Serum phosphate (mg/dl)	0.8667	0.4926	4.309	0.008
Serum alkaline phosphatase (U/l)	0	0	-	1
Haemoglobin (g/dl)	-0.3333	0.8262	-0.988	0.368
Blood Urea (mg/dl)	57.667	19.846	7.117	0.001
Serum creatinine (mg/dl)	0.7333	0.0516	34.785	<0.001
eGFR (ml/min/1.73m2)	-0.667	0.516	-3.162	0.025

Table 14 shows that the biochemical parameters such as Serum phosphate, Blood Urea, Serum creatinine and eGFR had statistically significant mean difference

between the pre dialysis and post dialysis stages among the study participants belonging to 70 years and above age group.

The mean difference of biochemical parameters such as Serum Calcium, Albumin, Corrected calcium (mg/dl) Serum alkaline phosphatase and Haemoglobin were not found to be statistically significant between the pre dialysis and post dialysis stages among the study participants belonging to 70 years and above age group as shown in table 14.

Table 15: Correlation between Pre and Post dialysis biochemical parameters of the individuals with chronic kidney disease belonging to 70 years and above age group who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 6)

Biochemical parameters	Correlation (Pre and Post Dialysis)	P value
Pre and Post - Serum calcium (mg/dl)	0.212	0.687
Pre and Post - Albumin (g/dl)	0.929	0.007

Pre and Post - Corrected calcium (mg/dl)	-0.832	0.040
Pre and Post - Serum phosphate (mg/dl)	0.988	<0.001
Pre and Post - Haemoglobin (g/dl)	0.782	0.066
Pre and Post - Blood Urea (mg/dl)	0.784	0.065
Pre and Post - Serum creatinine (mg/dl)	0.996	<0.001
Pre and Post - eGFR (ml/min/1.73m2)	0.982	<0.001

Table 15 shows that the biochemical parameters such as Albumin, Corrected calcium, Serum phosphate, Serum creatinine and eGFR had a correlation coefficient of 0.929, -0.832, 0.988, 0.996 and 0.982 respectively between pre and post dialysis stages among the study participants belonging to 70 years and above age group and they were found to be statistically significant.

The biochemical parameters such as Serum Calcium, Haemoglobin and Blood Urea had a correlation coefficient of 0.212, 0.782 and 0.784 respectively among the study participants belonging to 70 years and above age group and were not found to be statistically significant as shown in table 9.

Table 16: Pearson's Correlation between Pre and Post dialysis haemoglobin with various biochemical parameters of the individuals with chronic kidney disease who presented to Department of General Medicine at Government Kilpauk Medical College Hospital, Chennai (N= 73)

	Pre – dialysis Haemoglobin	P value	Post dialysis Haemoglobin	P value
Serum calcium (mg/dl)	-0.144	0.223	-0.147	0.213
Albumin (g/dl)	0.154	0.192	-0.132	0.265
Corrected calcium (mg/dl)	-0.224	0.056	-0.092	0.438
Serum phosphate (mg/dl)	0.482	<0.001	0.353	0.002
Serum alkaline phosphatase (U/l)	0.041	0.730	0.064	0.589
Blood Urea (mg/dl)	-0.109	0.361	-0.069	0.564

Serum creatinine (mg/dl)	-0.091	0.445	0.008	0.946
eGFR (ml/min/1.73m2)	0.053	0.655	0.041	0.730

The person's correlation coefficient between Serum Calcium with that of Haemoglobin is found to be -0.144 and -0.147 for pre and post dialysis states and was not found to be statistically significant as shown in table 16. Serum Corrected Calcium and Haemoglobin had a pearson's correlation coefficient of -0.224 and -0.092 for pre and post dialysis states respectively and was not found to be statistically significant. The person's correlation coefficient between Albumin with that of Haemoglobin is found to be 0.154 and -0.132 for pre and post dialysis states respectively and was not found to be statistically significant. Serum Phosphate and Haemoglobin had a positive pearson's correlation coefficient of 0.482 and 0.353 for pre and post dialysis states respectively and was found to be statistically significant as shown in table 16.

DISCUSSION

The current study was carried out primarily to determine relationship of anemia with serum albumin-corrected calcium and phosphorus levels in advanced CKD. A total of was 73 individuals with stage 3 – 5 chronic kidney disease were assessed for various biochemical parameters pre and post dialysis. Though the correlation between corrected calcium and haemoglobin showed positive increase after dialysis, it was not found to be statistically significant. The correlation between serum albumin and haemoglobin decreased from 0.154 to -0.132 but it was also not found to be statistically significant. It is important to note that the Serum Phosphate and Haemoglobin reduced and had a positive pearson's correlation coefficient of 0.482 and 0.353 for pre and post dialysis states respectively and was found to be statistically significant.

The mean age of the study participants in the current study was 57.67 (10.5) years, which is relatively lower compared to the Japan study conducted by Kaku et al, which had a mean (SD) of 66.0 (12.2) years. (89) But the mean age of the study participants in Nigeria study conducted by Iyawe et al was lower (49.39 (4.84) years) when compared to the current study. (90)

Nearly 38.4% of the study participants were females in the current study, compared to 32.5% in the Japan study by Kaku et al. (89) But the Nigeria study conducted by Iyawe et al reported higher proportion of female study participants (46.3%), which may be due to incorporation of entire spectrum of CKD patients (Stage 1 - 5) in their study, whereas the current study has recruited only stage 3 – 5 CKD patients. (90)

The pre dialysis mean serum Calcium in the current study was found to 8.6 (0.85) mg/dl, which is relatively lower compared to the mean serum calcium levels reported in a study conducted by Blayney et al, which was found to be 9.1 (1.0) mg/dl. (91)

The mean serum albumin of the study participants at pre dialysis stage in the current study was 3.59 (0.47) g/dl, which is very much comparable to the mean serum albumin levels reported in a study conducted by Blayney et al, which was found to be 3.6 (0.5) g/dl. (91)

The mean corrected calcium among the study participants in the current study at their pre dialysis stage was found to be 8.92 (0.82), which is comparable with several studies conducted around the world. The studies conducted by Jain et al and Portale et al reported the corrected calcium among their study participants to be 8.10 (0.78) and 8.90 (0.78) respectively, whereas the research done by Payne et al, Ferrari et al and Kaku et al reported the corrected calcium among their study participants to be 8.99 (0.82), 9.24 (1.10) and 9.34 (0.81) respectively. (89, 92 - 95) This slight difference in the corrected calcium values may be attributed to the study setting, as they have been conducted among different groups of study participants around the world.

Study	**Corrected calcium, mean (SD)**
Jain et al (92)	8.10 (0.78)
Portale et al (93)	8.90 (0.78)
Current study	8.92 (0.82)

Payne et al (94)	8.99 (0.82)
Ferrari et al (95)	9.24 (1.10)
Kaku et al (89)	9.34 (0.81)

The Current study showed that the pre dialysis mean serum phosphate among the study participants was 4.96(2.19) mg/dl which is comparatively lower than that reported in the study by blayney et al, wherein the pre dialysis mean serum phosphate among the study participants was 5.6 (1.8) mg/dl. (91) It is also important to note that the mean difference between pre dialysis and post dialysis values of serum phosphate was 0.2795 (0.6216) mg/dl and was found to be statistically significant.

It was important to note that there was no difference in the serum alkaline phosphatase values among the study participants in the current study between their pre dialysis and post dialysis values as both stands at 69.51 (22.56) U/I.

Anemia is one of the most common complication of CKD. Our study showed that almost 100% of our study participants were anemic. This can be attributed to the fact that all the study participants in the current study belonged to stage 3 – 5 chronic kidney disease. Similar results were found in a Haryana study conducted by Sundhir et al in 2016, wherein all the study participants were found to be anemic. (96) It also reported that the mean (SD) haemoglobin in post dialysis of chronic kidney disease patients was 7.59 (1.43) g/dl which is slightly lower when compared to our study result of 8.65 (1.38). (96) A Nigerian study conducted in 2014 by Iyawe

et al reported mean haemoglobin of 8.71 (2.70) among the pre – dialysis study participants which is similar to the results of the current study (8.02 (1.69) g/dl). (90) It is also important to note that the mean difference between pre dialysis and post dialysis values of haemoglobin was 0.6247 (0.6839) g/dl and was found to be statistically significant.

The current study showed that the mean (SD) serum urea in pre dialysis and post dialysis groups of chronic kidney disease patients were 115.36 (27.07) mg/dl and 151.78 (33.8) mg/dl respectively. A study conducted by Gulavani et al in Pune showed that the mean (SD) serum urea in pre dialysis and post dialysis groups of chronic kidney disease patients were 130.45 (56) mg/dl and 30.81 (25.4) mg/dl respectively, which was statistically significant. (97) The difference in these values can be due to the fact that the post dialysis evaluation of bio-parameters among the study participants were done after a gap of 4 weeks post dialysis. A highly significant mean difference was found between pre and post dialysis serum urea values among the study participants in the current study as shown in table 4.

The current study showed that the mean (SD) serum creatinine in pre dialysis and post dialysis groups of chronic kidney disease patients were 9.61 (2.15) mg/dl and 8.41 (1.78) mg/dl respectively. A study conducted by Gulavani et al in Pune showed that the mean (SD) serum urea in pre dialysis and post dialysis groups of chronic kidney disease patients were 8.65 (2.6) mg/dl and 2.06 (1.31) mg/dl respectively, which was statistically significant. (97) Though the pre dialysis values are comparable, the difference in post dialysis values between the studies is because of the four-week period after which the post dialysis values were recorded

in the current study. A significant mean difference between the pre dialysis and post dialysis values of Serum creatinine was found in the current study. (Table 4)

The Nigerian study conducted by Iyawe et al in 2014 showed that the eGFR among the pre dialysis study participants was 35.74 (26.26) mL/min/1.73 m^2, which is largely greater when compared with the mean dialysis eGFR of the current study (5.05 (1.77) ml/min/1.73m^2). (90) This can be due to the fact that the Nigerian study incorporated study participants involving even stage 1 and 2 CKD along with stage 3 – 5 CKD. The mean difference of the eGFR between the pre dialysis and post dialysis state was found to be statistically significant in the current study. (Table 4)

The current study reports a comparison of the biochemical and haematological parameters between the pre dialysis and the post dialysis states, along with their mean differences. It is to be noted that the biochemical parameters such as serum calcium, albumin, corrected calcium and Serum alkaline phosphatase did not show much difference between the pre dialysis and post dialysis states and were also not found to be statistically significant.

Meanwhile, parameters such as Serum phosphate, Haemoglobin, Blood Urea, Serum creatinine and eGFR had been reported with a statistically significant mean difference between the pre dialysis and post dialysis states as shown in table 4.

Overall, all the biochemical parameters showed a positive correlation between the pre dialysis and post dialysis states among the study participants in the current study. (Table 5) Serum phosphate showed the highest correlation of 0.961 followed by serum creatinine and haemoglobin with correlation coefficients of 0.951

and 0.920 respectively between the pre dialysis and post dialysis states among the study participants in the current study as reported in table 5.

Note many studies in the literature have carried out a sub group analyses based on five age categories as carried out in the current study. The mean difference of Serum Calcium between the pre dialysis and post dialysis states among the study participants showed a drastic reduction over the age categories from less than 40 years age group to more than 70 years age group, but they were not found to be statistically significant. A significant positive correlation was elicited between the pre dialysis and post dialysis serum calcium among the study participants over the age categories except for age groups of 40 – 49 years and more than 70 years. (Table 6 – 15)

The albumin levels between the pre dialysis and post dialysis states among the study participants showed a significant mean difference only among 40 – 49 years age group, while other age groups were not found to be statistically significant. A significant positive correlation was elicited between the pre dialysis and post dialysis albumin among the study participants over all the age categories from age groups of less than 40 years to more than 70 years. (Table 6 – 15)

The mean difference of corrected Calcium between the pre dialysis and post dialysis states among the study participants was reported to be significant only among 40 – 49 years age group, while other age group were not found to be statistically significant. A significant positive correlation was elicited between the pre dialysis and post dialysis corrected calcium among the study participants over the age categories except for age groups of less than 40 years and more than 70 years. (Table 6 – 15)

The Serum phosphate levels between the pre dialysis and post dialysis states among the study participants showed a significant mean difference among all age groups except 40 – 49 years age group and 50 – 59 years age group. A significant positive correlation was elicited between the pre dialysis and post dialysis Serum phosphate among the study participants over all the age categories from age groups of less than 40 years to more than 70 years. (Table 6 – 15)

The haemoglobin levels between the pre dialysis and post dialysis states among the study participants showed a significant mean difference among all age groups except 70 years and above age group. A significant positive correlation was elicited between the pre dialysis and post dialysis haemoglobin among the study participants over all the age categories except 70 years and above age group. (Table 6 – 15)

The mean difference of serum urea between the pre dialysis and post dialysis states among the study participants showed across age groups from less than 40 years to above 70 years age group and was also found to be statistically significant across all age groups. A significant positive correlation was elicited between the pre dialysis and post dialysis serum urea among the study participants over the age categories except for age group of more than 70 years. (Table 6 – 15)

The serum creatinine levels between the pre dialysis and post dialysis states among the study participants showed a significant mean difference among all age groups. A significant positive correlation was elicited between the pre dialysis and post dialysis serum creatinine among the study participants over all the age categories. (Table 6 – 15)

The eGFR levels between the pre dialysis and post dialysis states among the study participants showed a significant mean difference among all age groups except less than 40 years age group. A significant positive correlation was elicited between the pre dialysis and post dialysis eGFR among the study participants over all the age categories except less than 40 years age group as depicted in tables 6 – 15.

It is important to note that in the current study, Corrected calcium showed a negative correlation with haemoglobin in both pre dialysis and post dialysis states as shown in table 16. But it is clear that there was relative increase in the correlation in positive direction on comparing pre dialysis with post dialysis correlation between corrected calcium and haemoglobin, though it was not statistically significant.

The serum phosphate values correlated positively with that of Haemoglobin. This positive correlation was seen in both pre dialysis and post dialysis states among the study participants in the current study. A correlation comparison between the pre dialysis parameters and the post dialysis biochemical parameters was carried out as depicted in the table 16. It is very evident that there is clear drop in the correlation levels between serum phosphate and haemoglobin on comparing the pre dialysis state with that of the post dialysis state. This reduction in correlation between these two biochemical parameters was found to be statistically significant as depicted in table 16.

STRENGTHS

1. The current study explores the relationship between corrected calcium and anemia
2. The current study explores the relationship between serum phosphate and anemia
3. The current study is one of the few studies that explores the relationship between various bone mineral density biochemical parameters between pre dialysis and post dialysis states
4. The current study shows the relationship of biochemical parameters between pre dialysis and post dialysis states across various age groups through sub group analyses.

LIMITATIONS

i. Sample size attained is smaller when compared to similar observational prospective studies in the existing literature

ii. Selection bias is bound to happen in such hospital-based studies.

iii. Post dialysis biochemical parameters would have shown better results if the four-week duration post dialysis was reduced.

iv. Behavioural factors might have played a role in the four-week period that can have an effect on the biochemical parameters post dialysis.

CONCLUSION

Anemia is a common complication of chronic kidney disease. With advancement in stage of CKD in the patients, the bone mineral density composition derangement starts to set in. All the patients in this study were in the stage 3, 4 or 5 of Chronic Kidney Disease (CKD). Anemia was found to be present in almost all the study participants. Biochemical parameters such as Serum phosphate, haemoglobin, Blood urea, serum creatinine and eGFR showed a statistically significant mean difference between the pre dialysis and post dialysis states among the study participants.

Moreover, the biochemical parameters such as Serum calcium, serum phosphate, haemoglobin, Blood urea, serum creatinine and eGFR were found to be positively correlated between the pre dialysis and post dialysis states among the study participants and was also found to be statistically significant.

Unlike corrected calcium, the serum phosphate and haemoglobin were positively correlated at both pre dialysis and post dialysis states in the current study and with very high statistical significance. Hence, phosphate appears to play a crucial role in determining the bone mineral density and indirectly in the progression of anemic status of a CKD patient. But this cannot be completely proved in the current study as it is an observational study. Further studies are required to explore the role of corrected calcium and phosphate in the progression of anemia in CKD patients.

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A. STUDY PROFORMA

GOVT KILPAUK MEDICAL COLLEGE, CHENNAI

DEPARTMENT OF GENERAL MEDICINE

Serial No :

Name :

Age :

Gender :

PRE-DIALYSIS

Serum Calcium (mg/dl) :

Serum Albumin (g/dl) :

Corrected calcium (mg/dl) :

Serum phosphate (mg/dl) :

Serum alkaline phosphatase (U/l) :

Hemoglobin (g/dl) :

Blood Urea (mg/dl) :

Serum creatinine (mg/dl) :

eGFR (ml/min/1.73m2) :

POST-DIALYSIS

Serum Calcium (mg/dl) :

Serum Albumin (g/dl) :

Corrected calcium (mg/dl) :

Serum phosphate (mg/dl) :

Serum alkaline phosphatase (U/l) :

Hemoglobin (g/dl) :

Blood Urea (mg/dl) :

Serum creatinine (mg/dl) :

eGFR (ml/min/1.73m2) :

B. PATIENT INFORMATION SHEET

Dear Sir / Madam,

We are conducting a study on **"Relationship between bone mineral metabolism and anemia in advanced chronic kidney disease prior to dialysis initiation, a cross sectional study in a tertiary care centre"** in the Department of General medicine, KMCH, Chennai. This study will not affect your treatment in any way. The privacy of the patients in the research will be maintained throughout the study. In the event of publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is completely your choice. If you decide to participate, you will be asked to sign the consent form. Kindly sign the consent form only when you understand the information given in the form and have had your questions answered to your complete satisfaction and understanding.

You are free to withdraw from this study at any point of time. We assure you that withdrawal from the study will not affect the rest of your treatment in any way and it will be continued as per the recommended treatment.

Any questions about the study or clarification can be cleared with the principal investigator or with the other co-investigators of this study.

We request you to participate in this study. However, please note that your participation is completely voluntary and that you can withdraw from the study at any stage.

Signature of the investigator

Signature of the participant

Place :

Date :

C. CONSENT FORM

Study detail:

“Relationship between bone mineral metabolism and anemia in advanced chronic kidney disease prior to dialysis initiation, a cross sectional study in a tertiary care centre”

Study centre : KILPAUK MEDICAL COLLEGE, CHENNAI

Patients Name :

Patients Age :

Identification 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, radiological tests.

Signature/thumb impression:

Place :

Date :

Patients Name and Address:

Signature of investigator:

Study investigator's Name:

Place :

Date :

சுயஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு:

இடம்: பொது மருத்துவத்துவ துரை
அரசு கீழ்பாக்கம் மருத்துவ கல்லூரி மருத்துவமனை
சென்னை

பங்குபெறுபவரின் பெயர் :

பங்குபெறுபவரின் வயது : **பங்குபெறுபவரின் எண் :**

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த சட்டசிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக்கொள்ளல்லாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில்பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக்கொள்ள மறுக்க மாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ஆய்வாளரின் கையொப்பம்

இடம் :

தேதி :

D. MASTER CHART

			PRE-DIALYSIS			
S .no	Age (years)	Gender	Serum calcium (mg/dl)	Serum Albumin (g/dl)	Corrected calcium (mg/dl)	Serum phosphate (mg/dl)
1	62	F	10.6	3.9	10.7	4
2	55	M	8.4	3	9.2	3.7
3	35	F	9.7	3.5	10.1	3.8
4	57	F	7.2	3.9	7.3	4.3
5	60	M	8.7	3.6	9	3
6	56	M	9.2	3.6	9.5	3
7	59	M	9.8	3	10.6	2.5
8	47	F	8.6	3.5	9	2.3
9	55	M	9.5	3.2	10.1	3.1
10	60	M	8.9	3.5	9.3	3.7
11	75	F	8.5	3.5	8.9	3.6
12	45	F	8.4	4.1	8.3	2
13	67	M	8.9	4	8.9	2.6
14	38	M	7.9	4	7.9	4.2
15	50	M	8.8	3.2	9.4	6.3
16	62	F	7.8	4.2	7.6	8.9
17	79	M	8	3.5	8.4	8.5
18	63	F	8.3	3.8	8.5	4.5
19	57	F	8.3	4	8.3	4.8
20	67	M	6.2	2.1	7.7	5
21	60	F	8.2	3.5	8.6	6.7
22	48	M	8.2	4	8.2	7.1
23	39	M	9.7	3.4	10.2	7.1
24	67	M	9	4.2	8.8	8.2

			PRE-DIALYSIS			
S .no	Age (years)	Gender	Serum calcium (mg/dl)	Serum Albumin (g/dl)	Corrected calcium (mg/dl)	Serum phosphate (mg/dl)
25	69	M	8.4	3.1	9.1	6.2
26	45	M	8.5	3.2	9.1	3.6
27	56	F	9.1	3.2	9.7	3.8
28	48	M	8.8	3.7	9	4.3
29	77	M	9	4.1	8.9	10.2
30	59	M	7.6	3.5	8	9.7
31	60	F	8.4	3.9	8.5	4.3
32	47	M	9.7	4.2	9.5	4
33	66	M	8.4	3.8	8.6	3.5
34	69	F	9.3	3.7	9.5	3
35	53	M	8.8	3.8	9	3.9
36	67	M	6.2	2.1	7.7	5
37	60	F	8.2	3.5	8.6	6.7
38	50	M	8.8	3.2	9.4	6.3
39	62	F	7.8	4.2	7.6	8.9
40	75	F	8.5	3.5	8.9	3.6
41	45	F	8.4	4.1	8.3	2
42	67	M	8.9	4	8.9	2.6
43	38	M	7.9	4	7.9	4.2
44	50	M	8.8	3.2	9.4	6.3
45	45	M	8.5	3.2	9.1	3.6
46	56	F	9.1	3.2	9.7	3.8
47	48	M	8.8	3.7	9	4.3
48	77	M	9	4.1	8.9	10.2

			PRE-DIALYSIS			
S .no	Age (years)	Gender	Serum calcium (mg/dl)	Serum Albumin (g/dl)	Corrected calcium (mg/dl)	Serum phosphate (mg/dl)
49	59	M	7.6	3.5	8	9.7
50	56	M	9.2	3.6	9.5	3
51	59	M	9.8	3	10.6	2.5
52	47	F	8.6	3.5	9	2.3
53	55	M	9.5	3.2	10.1	3.1
54	60	M	8.9	3.5	9.3	3.7
55	60	F	8.2	3.5	8.6	6.7
56	48	M	8.2	4	8.2	7.1
57	39	M	9.7	3.4	10.2	7.1
58	67	M	9	4.2	8.8	8.2
59	69	M	8.4	3.1	9.1	6.2
60	62	F	10.6	3.9	10.7	4
61	55	M	8.4	3	9.2	3.7
62	35	F	9.7	3.5	10.1	3.8
63	57	F	7.2	3.9	7.3	4.3
64	60	M	8.7	3.6	9	3
65	62	F	7.8	4.2	7.6	8.9
66	79	M	8	3.5	8.4	8.5
67	63	F	8.3	3.8	8.5	4.5
68	57	F	8.3	4	8.3	4.8
69	67	M	6.2	2.1	7.7	5
70	60	F	8.4	3.9	8.5	4.3
71	47	M	9.7	4.2	9.5	4
72	66	M	8.4	3.8	8.6	3.5
73	69	F	9.3	3.7	9.5	3

	PRE-DIALYSIS				
S .no	Serum alkaline phosphatase (U/l)	Hemoglobin (g/dl)	Blood Urea (mg/dl)	Serum creatinine (mg/dl)	eGFR (ml/min/1.73m2)
1	56	6.6	157	15	2
2	120	6.9	97	10	5
3	70	9.4	85	7.7	6
4	61	10	144	8.8	5
5	44	6.1	189	9.5	5
6	39	6.1	136	10.5	5
7	102	4.4	187	14.9	3
8	60	5.5	105	8.7	5
9	74	7.1	154	7.8	7
10	69	7.3	86	8	7
11	52	7.2	174	9.1	4
12	48	6.4	103	7	6
13	62	6.6	198	8.9	6
14	83	4.5	212	10	6
15	91	10.2	178	11.1	5
16	55	10.5	145	8.5	5
17	64	9.6	123	7.9	6
18	83	9.1	184	8	5
19	106	10	169	9.3	4
20	33	7.8	143	11	4
21	46	7.5	121	8.1	5
22	57	7.5	119	10.3	5
23	107	9.8	198	11	5
24	95	11	125	16.6	3

	PRE-DIALYSIS				
S .no	Serum alkaline phosphatase (U/l)	Hemoglobin (g/dl)	Blood Urea (mg/dl)	Serum creatinine (mg/dl)	eGFR (ml/min/1.73m2)
25	83	9	176	9	5
26	44	8.2	166	7.4	8
27	61	8.5	122	8.5	5
28	73	9.8	167	8.8	6
29	88	7	177	8.9	5
30	46	7.6	183	9.5	5
31	35	9.6	121	7.6	5
32	83	9.2	154	7.8	7
33	96	8.3	184	11	4
34	100	6.9	188	8.9	4
35	71	7.1	153	12.5	4
36	43	7.8	143	11	4
37	65	7.5	121	8.1	5
38	106	10.2	178	11.1	5
39	33	10.5	145	8.5	5
40	46	7.2	174	9.1	4
41	57	6.4	103	7	6
42	107	6.6	198	8.9	6
43	95	4.5	212	10	6
44	83	10.2	178	11.1	5
45	44	8.2	166	7.4	8
46	61	8.5	122	8.5	5
47	73	9.8	167	8.8	6
48	88	7	177	8.9	5

	PRE-DIALYSIS				
S .no	Serum alkaline phosphatase (U/l)	Hemoglobin (g/dl)	Blood Urea (mg/dl)	Serum creatinine (mg/dl)	eGFR (ml/min/1.73m2)
49	46	7.6	183	9.5	5
50	35	6.1	136	10.5	5
51	83	4.4	187	14.9	3
52	96	5.5	105	8.7	5
53	100	7.1	154	7.8	7
54	71	7.3	86	8	7
55	43	7.5	121	8.1	5
56	65	7.5	119	10.3	5
57	120	9.8	198	11	5
58	70	11	125	16.6	3
59	61	9	176	9	5
60	44	6.6	157	15	2
61	39	6.9	97	10	5
62	102	9.4	85	7.7	6
63	60	10	144	8.8	5
64	74	6.1	189	9.5	5
65	69	10.5	145	8.5	5
66	52	9.6	123	7.9	6
67	48	9.1	184	8	5
68	62	10	169	9.3	4
69	83	7.8	143	11	4
70	91	9.6	121	7.6	5
71	55	9.2	154	7.8	7
72	64	8.3	184	11	4
73	83	6.9	188	8.9	4

	POST-DIALYSIS			
S .no	Serum calcium (mg/dl)	Serum Albumin (g/dl)	Corrected calcium (mg/dl)	Serum phosphate (mg/dl)
1	10.2	3.2	10.8	3.7
2	9.7	3.9	9.8	4.1
3	8.1	3.9	8.2	4.7
4	8.1	3.8	8.3	5.9
5	8.9	3.6	9.2	2.8
6	9.7	3.6	10	2.4
7	9.2	3	10	2.8
8	8.1	3.5	8.5	2.5
9	9.7	3.2	10.3	2.6
10	9.3	3.5	9.7	3
11	8.2	3.5	8.6	3.1
12	8.8	3.7	9	2.6
13	8.2	3.9	8.3	2
14	8	4.2	7.8	3.7
15	8.3	3	9.1	5.4
16	8	3.7	8.2	7.4
17	8.9	3.2	9.5	7
18	9.2	3.7	9.4	4.3
19	7.8	3.5	8.2	4.9
20	7	3.2	7.6	4.4
21	8.7	3.5	9.1	5.9
22	8.9	3.8	9.1	7
23	8.2	3.2	8.8	6.8
24	9.2	4	9.2	8

	POST-DIALYSIS			
S .no	Serum calcium (mg/dl)	Serum Albumin (g/dl)	Corrected calcium (mg/dl)	Serum phosphate (mg/dl)
25	8.9	3.7	9.1	6.7
26	7.9	3.1	8.6	4
27	9.8	3	10.6	3.5
28	9.2	3.5	9.6	3.8
29	9.1	4	9.1	9.6
30	8	3.8	8.2	9
31	9	4.2	8.8	4
32	8.5	4	8.5	4.1
33	8.9	3.5	9.3	3
34	9	3.9	9.1	2.7
35	9	4	9	3.5
36	7	3.2	7.6	4.4
37	8.7	3.5	9.1	5.9
38	8.3	3	9.1	5.4
39	8	3.7	8.2	7.4
40	8.2	3.5	8.6	3.1
41	8.8	3.7	9	2.6
42	8.2	3.9	8.3	2
43	8	4.2	7.8	3.7
44	8.3	3	9.1	5.4
45	7.9	3.1	8.6	4
46	9.8	3	10.6	3.5
47	9.2	3.5	9.6	3.8
48	9.1	4	9.1	9.6

	POST-DIALYSIS			
S .no	Serum calcium (mg/dl)	Serum Albumin (g/dl)	Corrected calcium (mg/dl)	Serum phosphate (mg/dl)
49	8	3.8	8.2	9
50	9.7	3.6	10	2.4
51	9.2	3	10	2.8
52	8.1	3.5	8.5	2.5
53	9.7	3.2	10.3	2.6
54	9.3	3.5	9.7	3
55	8.7	3.5	9.1	5.9
56	8.9	3.8	9.1	7
57	8.2	3.2	8.8	6.8
58	9.2	4	9.2	8
59	8.9	3.7	9.1	6.7
60	10.2	3.2	10.8	3.7
61	9.7	3.9	9.8	4.1
62	8.1	3.9	8.2	4.7
63	8.1	3.8	8.3	5.9
64	8.9	3.6	9.2	2.8
65	8	3.7	8.2	7.4
66	8.9	3.2	9.5	7
67	9.2	3.7	9.4	4.3
68	7.8	3.5	8.2	4.9
69	7	3.2	7.6	4.4
70	9	4.2	8.8	4
71	8.5	4	8.5	4.1
72	8.9	3.5	9.3	3
73	9	3.9	9.1	2.7

	POST-DIALYSIS				
S .no	Serum alkaline phosphates (U/l)	Hemoglobin (g/dl)	Blood Urea (mg/dl)	Serum creatinine (mg/dl)	eGFR (ml/min/1.73m2)
1	56	7.2	124	13.7	3
2	120	8	80	9.2	6
3	70	9.8	85	7.2	7
4	61	9.8	87	8.2	5
5	44	6.6	146	7.1	8
6	39	8.1	98	9.6	5
7	102	6.4	157	11.2	4
8	60	7.1	90	7.4	6
9	74	9	108	6.8	8
10	69	8.8	80	7.4	7
11	52	8.6	113	8.4	4
12	48	7.2	99	6.4	7
13	62	6.9	167	8	6
14	83	5.8	177	8.5	7
15	91	10	150	10	5
16	55	10.1	129	7.6	5
17	64	9.4	89	7.2	7
18	83	9.2	116	7.1	6
19	106	10.5	115	8.7	5
20	33	8.2	80	9.5	5
21	46	8	103	7.5	5
22	57	7.9	98	9	6
23	107	11	172	10.2	6
24	95	11.5	116	14	3

	POST-DIALYSIS				
S .no	Serum alkaline phosphates (U/l)	Hemoglobin (g/dl)	Blood Urea (mg/dl)	Serum creatinine (mg/dl)	eGFR (ml/min/1.73m2)
25	83	9.2	129	7.6	7
26	44	10	142	6.4	10
27	61	9	100	7.1	6
28	73	9.5	127	7	8
29	88	6.8	99	8.1	6
30	46	8	140	9	6
31	35	10.2	106	7.2	6
32	83	9.6	91	5.9	10
33	96	9	117	8.4	6
34	100	7.5	105	7.8	5
35	71	7	89	10.2	5
36	43	8.2	80	9.5	5
37	65	8	103	7.5	5
38	106	10	150	10	5
39	33	10.1	129	7.6	5
40	46	8.6	113	8.4	4
41	57	7.2	99	6.4	7
42	107	6.9	167	8	6
43	95	5.8	177	8.5	7
44	83	10	150	10	5
45	44	10	142	6.4	10
46	61	9	100	7.1	6
47	73	9.5	127	7	8
48	88	6.8	99	8.1	6

	POST-DIALYSIS				
S .no	Serum alkaline phosphates (U/l)	Hemoglobin (g/dl)	Blood Urea (mg/dl)	Serum creatinine (mg/dl)	eGFR (ml/min/1.73m2)
49	46	8	140	9	6
50	35	8.1	98	9.6	5
51	83	6.4	157	11.2	4
52	96	7.1	90	7.4	6
53	100	9	108	6.8	8
54	71	8.8	80	7.4	7
55	43	8	103	7.5	5
56	65	7.9	98	9	6
57	120	11	172	10.2	6
58	70	11.5	116	14	3
59	61	9.2	129	7.6	7
60	44	7.2	124	13.7	3
61	39	8	80	9.2	6
62	102	9.8	85	7.2	7
63	60	9.8	87	8.2	5
64	74	6.6	146	7.1	8
65	69	10.1	129	7.6	5
66	52	9.4	89	7.2	7
67	48	9.2	116	7.1	6
68	62	10.5	115	8.7	5
69	83	8.2	80	9.5	5
70	91	10.2	106	7.2	6
71	55	9.6	91	5.9	10
72	64	9	117	8.4	6
73	83	7.5	105	7.8	5