EVALUATION OF CHRONIC KIDNEY DISEASE BY USING VISUAL EVOKED POTENTIAL AND UREMIC MARKERS

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In partial fulfillment of the regulations

For the award of the degree of

M.D. (PHYSIOLOGY)

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BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"EVALUATION OF CHRONIC KIDNEY DISEASE BY USING VISUAL EVOKED POTENTIAL AND UREMIC MARKERS''** is a Bonafide record work done by **Dr.P.Shanmuga Priya,** under my direct supervision and guidance, submitted to The Tamil Nadu Dr. M. G. R. Medical University in partial fulfillment of University regulation for **M.D., Branch-V (Physiology).**

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DECLARATION

I, **DR.P.SHANMUGA PRIYA,** solemnly declare that the dissertation titled **"EVALUATION OF CHRONIC KIDNEY DISEASE BY USING VISUAL EVOKED POTENTIAL AND UREMIC MARKERS''** has been prepared by me. I also declare that this work was not submitted by me or any other, for any award, degree, diploma to any other University board either in India or abroad. This is submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of **M.D degree Branch-V (Physiology)** to be held in **April-2015.**

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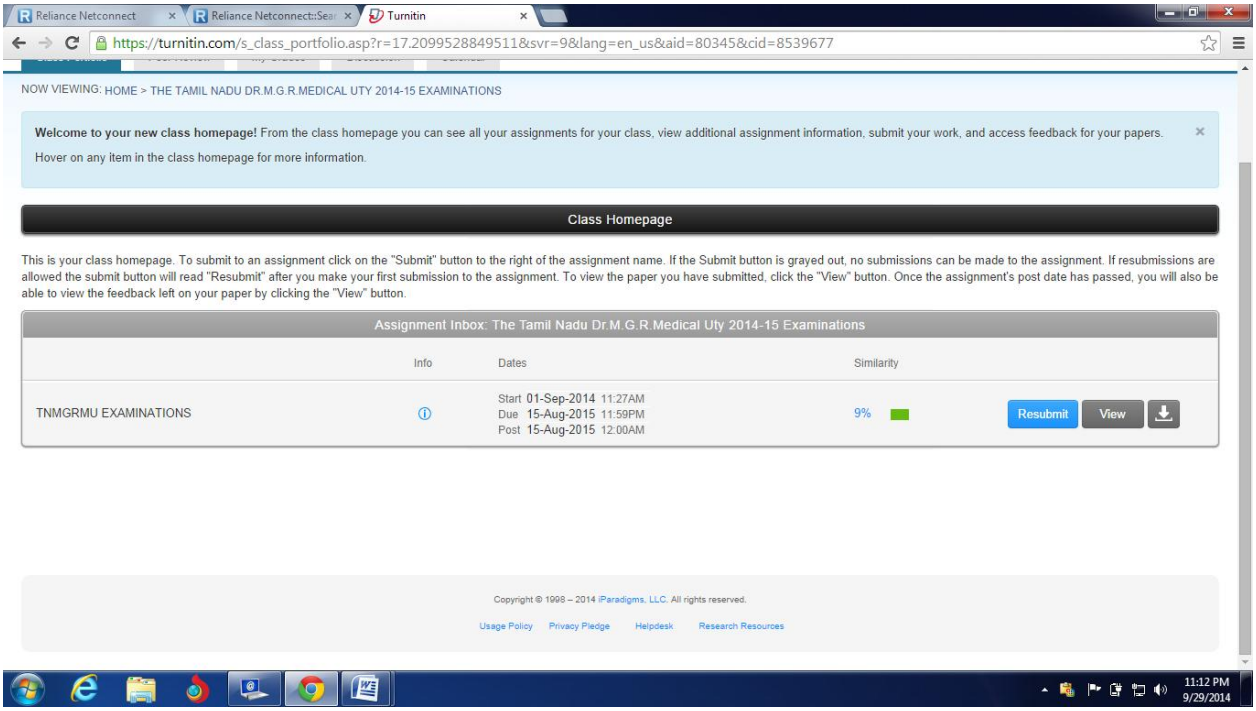
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Title of Work : Visual Evoked Potentials in Chronic Kidney Disease

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The request for an approval from the institutional ethical committee (IEC) was considered on the IEC meeting held on10.01.2014 at the Modernised Seminar Hall, Stanley Medical College, Chennai - 2 at 10am.

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ABBREVATIONS

ADH	Anti diuretic hormone
ARF	Acute renal failure
AVF	Arterio venous fistula
BUN	Blood urea nitrogen
CaR	Calcium sensing receptors
CKD	Chronic kidney disease
CKD 5D	Chronic kidney disease stage 5 on Dialysis
CNS	Central nervous system
CRF	Chronic renal failure
CSF	Cerebro-spinal fluid
CT	Collecting tubule
CVC	Central Venous Catheter
DCT	Distal convoluted tubule
EEG	Electroencephalography
EMG	Electromyography
ESRD	End-stage renal disease
FGF-23	Fibroblast growth factor-23
GABA	Gamma amino butyric acid

GFR	Glomerular filtration rate
GIT	Gastrointestinal tract
GSA	Guanidino succinic acid
HD	Haemodialysis
HIV	Human immunodeficiency virus
HIVAN	Human immunodeficiency virus associated nephropathy
iPTH	Intact Parathyroid hormone
KDOQI	Kidney Dialysis Outcomes Quality Initiative
MG	Methyl guanidine
MNCV	Motor nerve conduction velocity
NMDA	N-methyl-d-aspartate
P_{Cr}	Concentration of Serum Creatinine
PCT	Proximal convoluted tubule
PSVEP	Pattern shift Visual Evoked Potentials
PTH	Parathyroid hormone
RF	Renal failure
ROS	Reactive oxygen species
SHPT	Secondary hyperparathyroidism
SNCV	Sensory Nerve Conduction Velocity

SPSS	Statistical package for social services
UE	Uremic encephalopathy
VEP	Visual Evoked Potentials
VDR	Vitamin D receptor

EVALUATION OF CHRONIC KIDNEY DISEASE BY USING VISUAL EVOKED POTENTIAL AND UREMIC MARKERS

Abstract:

BACK GROUND:Chronic Kidney Disease is often unrecognized health problem due to less awareness,less health care facilities.Due to its progressive and irreversible course it may presents with serious complications involving all systems including the central nervous system of our body.

AIM AND OBJECTIVE: The aim of the present study was to "evaluate the involvement of central nervous system(CNS) in Chronic kidney disease (CKD) patients by doing Visual Evoked Potentials(VEP) and the estimation of blood levels of uremic markers (Uremic neurotoxins) like Blood Urea, Serum Creatinine. Serum Parathyroid hormone(PTH) in comparison with age matched controls". The objectives of the study were " to determine the subclinical involvement of central nervous system in CKD patients by doing Visual Evoked Potentials and compare it with controls,to assess the uremic neurotoxin's role in uremic encephalopathy by measuring the blood levels of uremic markers(uremic neurotoxins) like Blood Urea,Serum Creatinine,Serum Parathyroid hormone in CKD patients and compare it with controls,to find out the most vulnerable group of CKD patients by comparing the VEP parameters and blood levels of uremic markers(uremic neurotoxins) among the two CKD groups (CKD3-5 on medical therapy, CKD5D on dialysis and to find the correlation between the Visual Evoked Potential(VEPs) parameters and blood level of uremic marker in Chronic Kidney Disease(CKD) patients".

MATERIAL AND METHODOLOGY:60 diagonsed as CKD (30-CKD3-5,30-CKD5D) were recruited from Department of Nephrology ,Stanley medical college,Chennai.30 normal subjects were recruited from Master health check-up, Stanley medical college,Chennai.Ethical committee approval was

obtained.Informed and wtitten consent was obtained.After explaining the procedure ,VEP recording was done with the RMS Polyrite apparatus.The blood investigation done for the measurement of uremic markers.

RESULTS: Means, standard deviations, chi square and 'p' values were calculated by One way ANOVA and ‘t’ test. Chi-square test was used to experiment the importance of disparity among the consolidated (quantitative) variables.Prolonged latencies with highly significant p-value ($p<0.0001$) of all VEP parameters and reduced amplitude with significant p-value (<0.05) was noticed. Elevated blood levels of all uremic markers was noticed.This altered variables was higher among CKD3-5 with significant p-value($p<0.05$) in comparison with CKD 5D. Correlation was noticed but not significant between VEP parameters and blood levels of uremic markers.

DISCUSSION:The altered parameters of VEP and Uremic markers may predict the subclinical involvement of central nervous system involvement in CKD patients.

CONCLUSION:In order to reduce the morbidity and mortality in CKD patients ,VEP recording and the estimation of blood levels of uremic markers may used s a screening tool to identify the subclinical involvement of central nervous system in future.

KEY WORDS:Chronic kidney disease, Uremic markers, Visual evoked potentials.

1. INTRODUCTION

Chronic kidney disease (CKD) is a common disorder and is an often unrecognized health problem. People with CKD either remain undiagnosed because of absence of definite signs and symptoms or they present themselves in a very late stage with complications . The central nervous system(CNS) involvement is the most dreadful complication.

The word chronic kidney disease refers to the development of gradual irreversible decline in functioning nephron, and characteristically belongs to final stages of CKD[1]. The term uremia refers to the symptomatic stage of patients with chronic kidney disease[2].

The term ESRD (end-stage renal disease) stands for a phase of CKD with the accumulated uremic toxins, and many electrolytes which are usually removed by the functioning kidneys leading to the uremic syndrome. Mortality in CKD is due to the buildup of toxic excretory products that are not cleared by any form of renal replacement therapy like dialysis or transplantation of kidney.

Accumulation of uremic toxin have harmful effects on all the systems, the severity pertains much to the central nervous system (CNS).[3-7] Though the synaptic dysfunction and neuronal axonal degeneration is found to be the pathological basis of the neural symptoms, the exact basis for CNS abnormality is still vague and unclear. It has been assumed that the accumulation of organic and inorganic substances such as urea, creatinine, uric acid, carnitine polyamines, indolic acid, myoinositol, guanidine compounds sulfate and phosphate, hippurate, acetone, glucuronate, hypocalcemia induced secondary hyperparathyroidism have an effect on the central nervous system.

The worldwide prevalence of CKD is estimated to be 8–16%. In India given its population in billions ,because of the scarce resources, disproportionate patient –health care system and cost expensive treatment, the patients with CKD does not receive sufficient treatment facilities. Though the exact level of the problem of chronic kidney disease(CKD) or end-stage renal disease(ESRD) is not recognized, the crude and age- accustomed ESRD incidence rates by Indian population-based study was found to be 151 and 232 per million population, correspondingly.[8,9] It is anticipated that 1,00,000 new patients of end stage renal disease (ESRD) go into renal replacement therapies yearly in India[10].

Owing to the lack of community based screening programmes, lack of knowledge of the disease, among people and Health personals, the incidence

rate of CKD with mortality is still undertermined cause in addition to environmental factors. Renal transplantation is found to be the correct line of management because of late presentation and it is dependent on living donors which is not a possibility.

In addition to the above factors some other factors like less healthcare availability, leads to a failure of introducing appropriate precautionary procedures. Kidney failure is generally more progressed by the time patients consult a physician and they may go to a worst state with major side effects including neuropathy and multiple organ failure and necessitating an urgent dialysis. It has been proved that management with any modality like medical management or renal replacement therapy either dialysis or renal transplant can stop or holdup the sequence of CKD.

The Indian government has integrated care for renal disease in its 12th 5-year plan cycle, and is at present in the progression of mounting a structure for both dialysis and transplantation.

Preventive nephrology stress early detection of renal disease and the organization of procedures to delay its evolution to final stage. Treatment by any modality should start before the commencement of harmful complication. The dangerous complications of progressive CKD involving central nervous

system like uremic encephalopathy can be predicted earlier by the alterations in parameters of Visual Evoked Potential(VEP)[11-16]

Because of the progressive and the irreversible nature of the disease in CKD it is advisible to evaluate the complications as early as possible by both VEP parameters and the estimation of blood levels of uremic neurotoxins (uremic markers).

The possible uremic markers could be blood urea, serum creatinine, serum uric acid, serum parathyroid hormone as they can sense the CNS complication earlier along with the abnormalities with visual evoked potentials in CKD patients.

The Visual Evoked Potential is an uncomplicated, easy, non-invasive test that may predict the involvement of central nervous system, like uremic encephalopathy at the earliest by the altered parameters.

Hence this research study was carried out to enlighten the consequences of altered Visual Evoked Potentials (VEP),Uremic markers in CKD stage 3-5 and CKD 5D (on Dialysis) in order to detect the serious complication as early as possible and start any form of replacement treatment therapy. This might be helpful to provide early intervention in order to prevent morbidity and mortality.

REVIEW OF LITERATURE

2. REVIEW OF LITERATURE

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2.8. Mechanism underlying uremic encephalopathy

2.9. Haemodialysis

2.10. Visual Evoked Potential

2.11. Literatures

2.1. HISTORICAL ASPECTS OF KIDNEY

1913: John Abel, a well-known pharmacologist at John Hopkins University published an editorial regarding hemodialysis among animals to eliminate toxins that were accumulated in the blood.

1933: The foremost documented human cadaveric kidney transplant was done in Russia.

1936: UVoronoy (Starzl TE, 1990) did a primary human kidney transplant from an allograft.

1943: The young Dutch physician Dr. Willem Kolff is thought to be the father of dialysis who created the initial drum dialyzer (artificial kidney) which is still the basis behind current dialysis.

2.2. HISTORICAL ASPECTS OF VISUAL EVOKED POTENTIAL (VEP)

1934: With the light stimuli Adrian and Matthew observed probable alteration of the occipital EEG.

1961: The primary categorization of occipital EEG components was urbanized by Ciganek.

1965: The checkerboard type of visual stimulation was handled by Spehlmann to illustrate VEPs in human beings .

1972: The initial quantifiable research was concluded by Halliday and colleagues in subjects with retrobulbar neuritis.

2.3. PHYSIOLOGICAL ANATOMY OF KIDNEY

The two kidneys, which weigh about 150 gms each in adults are positioned in the superior dorsal part of the abdominal cavity retro peritoneally, on both side of the vertebrae. On vertical section, it shows cortex which is situated outer and inner placed medulla which have 10-12 pyramids ending in the renal papillae[17].Papillae in turn divide into calyces which come out all the way through the renal pelvis of kidney to the broad end of the ureter.

The nephron is the functional component of kidney. There are approximately 1.3 million nephrons in each kidney[18] (Fig:1). The different parts of the nephron are, Bowmans's capsule with tuft of capillaries, the proximal convoluted tubule (PCT), the loop of Henle, the distal convoluted tubule (DCT) and the collecting tubule (CT).

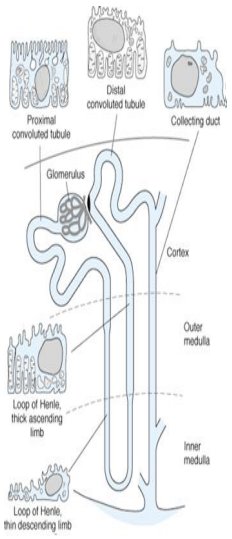


Fig : 1 - STURCTURE OF NEPHRON

2.4 FUNCTIONS OF THE KIDNEY

The ultrafiltration of blood, reabsorption, and secretion of substances are the major functions of kidney. Filtration, which occur at the renal corpuscle is the ultrafiltration which means free from huge proteins and cells of the blood. Reabsorption is the process by which water and solutes move into the blood. Secretion is the process by which substances are passed out from the blood into the urine. The two major functions of kidney are

A. EXCRETORY FUNCTION

B. NON- EXCRETORY FUNCTION

2.4 A. EXCRETORY FUNCTION

Normally the functioning kidneys excrete a range of metabolic waste products formed from protein catabolism such as, urea and uric acid - the nitrogenous waste products. The major function of the kidney is the formation and concentration of urine which is mainly due to the hair pin model of the tubules, the permeability of the descending limb and impermeability of the ascending limb of loop of Henle to water, active transport of solutes out of the ascending loop, countercurrent multiplication system, countercurrent exchange by the vessels.

2.4. B. NON-EXCRETORY FUNCTIONS

I. Acid-base homeostasis

II. Osmolality regulation

III. Blood pressure regulation

IV. Hormone secretion

I. ACID-BASE HOMEOSTASIS

The kidney can maintain the acid-base balance by reabsorption of bicarbonate (HCO3) from the urine, and excretion of hydrogen(H^+ ions).

II.OSMOLALITY REGULATION

In response to raised plasma osmolality, which is sensed immediately by the hypothalamus, inturn triggers the posterior pituitary gland to synthesize antidiuretic hormone (ADH), ADH act on the principal cells of the collecting ducts which subsequently move aquaporins to the apical membrane, allowing water to be reabsorbed into the vasa recta, thereby raising the plasma volume of the body and creating a concentrated urine.

III. BLOOD PRESSURE REGULATION

The kidneys play a major role in long-term control of blood pressure predominantly via the renin-angiotensin system.

IV. HORMONE SECRETION

The functioning kidneys secrete a range of hormones, such as

- Erythropoietin which causes erythropoiesis in the bone marrow.
- 1,25 dihydroxycholicalciferol, the active type of vitamin D, cause absorption of calcium from the intestine and the reabsorption of phosphate from the renal tubules[19].
- Renin
- Synthesis of prostaglandins.
- Formation of tissue Kallikerin.
-

2.5. CHRONIC KIDNEY DISEASE – A REVIEW

Chronic kidney disease (CKD) is a medical state in which the kidneys do not succeed to sufficiently remove waste products from the blood by filtration[1]. CKD is characterized by a decline in glomerular filtration rate(GFR).This is identified by the reduced ability or total failure to urinate and by the estimation of waste products (creatinine or urea) in the blood.

2.5.1. PATHOGENESIS OF CHRONIC KIDNEY DISEASE

The pathogenesis of CKD include

(1) Initial insult particular to the primary cause (e.g., of inflammatory intermediaries and immune complexes in some forms of nephritis or toxins induced interstitial kidney diseases.

(2) Another one is a progressive effect due to hyperfiltration and hypertrophy of the residual functioning nephrons, leading on to a progressive reduction in nephron number, (Fig 2)regardless of primary cause mediated by cytokines, growth factors, vasoactive hormones. Finally, these leads to sclerosis and failure of the left over nephrons. Augmented role of the renin- angiotensin pathway found to be the basic pathology behind the above two mechanisms. Recently, transforming growth factor (TGF-β) appeared to have a role in progressive damage to the kidney[1].

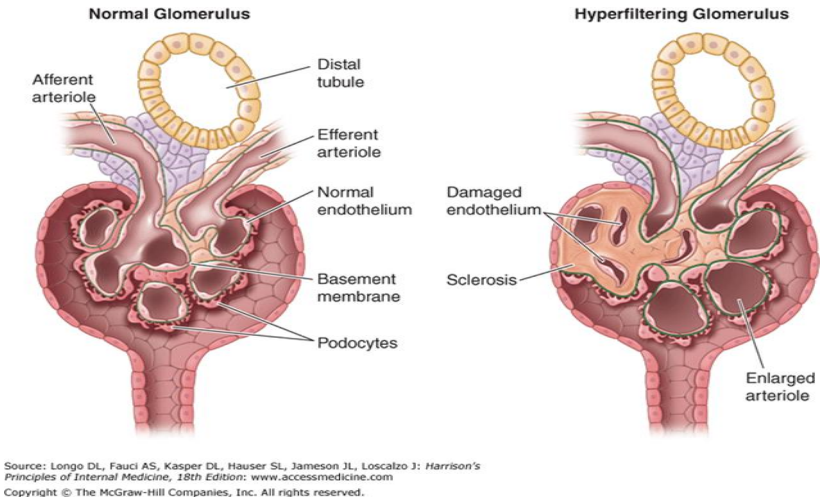


Fig : 2 –NORMAL AND HYPERINFILTRATING GLOMERULUS

2.5.2. SIGNS AND SYMPTOMS OF CHRONIC KIDNEY DISEASE

Stages 1-3 of CKD patients usually do not present with any symptoms. If they become symptomatic, it is mandatory to diagnose the degree of insult to the kidney. A clinician's interpretation is necessary if patients present with the following signs and symptoms:

- Fatigue
- Weakness of muscles
- Muscle cramps
- Edema - swollen feet and ankle
- Puffiness around the eyes

- A need to pass urine more often than normal
- Pale due to anemia
- Metallic taste in mouth
- GIT (gastrointestinal tract)involvement: Anorexia, vomiting, diarrhea.
- Shortness of breath
- Dizziness & Trouble Concentrating
- Skin appearance: Dry skin, ecchymosis and pruritis
- Augmented somnolence[20]

2.5.3. CAUSES OF CHRONIC KIDNEY DISEASE

1. Diabetes mellitus
2. Hypertension.[21]
3. Polycystic kidney disease
4. Immunologic - Polyarteritis Nodosa, Glomerulonephritis, Lupus
5. Nephrotoxins
6. Drugs –Non steroidal anti-inflammatory drugs (NSAID)[22]
7. Infectious causes - Tuberculosis, Pyelonephritis, Hantavirus[23]
8. In people of African basis, the APOL1 gene has been expected as a considerable genetic risk[24-26]

2.5.4. CHRONIC KIDNEY DISEASE- STAGES

On the basis of current guiding principle of the National Kidney Foundation [Kidney Dialysis Outcomes Quality Initiative (KDOQI)], Clinical Practice Guidelines for Chronic Kidney Disease[1] (CKD) stages are distinct according to the GFR estimation

GFR estimation was done using these following formulas:

- **The Modification of Diet in kidney disease**

  Estimated Glomerular Filtration Rate=$1.86\times(\text{Pcr})^{-1.154}\times(\text{age})^{-0.203}$

  multiply by 0.742 for females.

- **Cockcroft- Gault formula(usually followed)**

  Estimated GFR=(140-age) × weight in kg divided by 72xPcr multiply by 0.85 for females

  Where,

  Pcr- Concentration of Serum Creatinine

  GFR- Glomerular filtration rate

STAGE	GFR (mL/min per 1.73 m^2)
0	>90[a]
1	90[b]
2	60–89
3	30–59
4	15–29
5	<15

[a] - Risk factors like older age, Diabetes Mellitus (DM) , family history of any kidney disease, African ancestry, Systemic hypertension, Autoimmune disorders , a preceding incident of acute kidney damage.

[b] - Associated with established kidney harm (e.g., constant proteinuria, nonstandard urine and blood biochemistry, unusual urine sediment, atypical imaging studies).

The usual yearly noticeable turn down in Glomerular filtration rate from thehealthy individuals is 1ml/min/year/ 1.73 m^2, getting an average value of 70 ml/min/1.73 m^2 at the 70 years of age. The average GFR is lesser in females compared to male.

2.6. PATHOPHYSIOLOGY OF UREMIA

Uremia explains the last stage of progressive renal failure and the consequential multiorgan failure. It results from buildup of metabolites of proteins and amino acids and associated failure of renal catabolic, metabolic, and endocrinologic course. No solitary metabolite has been recognized as the

exclusive source of uremia. Uremic encephalopathy (UE) is one of the complication of renal failure (RF).[24] Several harmful toxic substances like urea and creatinine have been found to be accumulated in uremic syndrome. Other nitrogenous waste products like guanido compounds, polyamines, benzoates, products of nucleic acid metabolism, urates, hippurates, uric acid, myoinositol, phenols and indoles are also involved. In addition, plasma estimation of substances such as insulin, prolactin, glucagon, parathyroid hormone (PTH), and sex hormones are altered due to urinary retention and reduced degradation. Finally inflammation is also linked with progressive renal failure associated with elevated C-reactive protein. As a whole, the pathophysiology of the uremic syndrome can be separated into three phases of dysfunction:

- The toxins that are usually excreted by the kidneys accumulate in blood.
- There is failure of other renal functions like homeostasis of fluid and electrolytes and hormonal regulation.
- Progressive nutritional and vascular problems in account for systemic inflammation[1].

2.7. UREMIC BIO-MARKERS (UREMIC NEUROTOXINS)

A. Urea

B. Creatinine

C. Parathyroid hormone (Calcium, Phosphorous homeostasis)

2.6.A. UREA

It is the product of protein metabolism. It is generally excreted in the urine. A raised level of urea denotes either renal dysfunction or dehydration.

2.6.B. CREATININE

It is an intermediatry product formed by the muscles . A raised level of urea and creatinine indicates renal dysfunction. Among these two, estimation of serum creatinine is considered as a best marker and also used for the staging. Goltch et al declared that the blood level of uremic markers like urea and creatinine has been used as an indicator of uremic retention and its elimination is straightforwardly linked with survival of the patients [28-30].

2.7. PARATHYRPOID HORMONE:

SECONDARY HYPERPARATHYROIDISM (SHPT)

1. INTRODUCTION
2. PATHOPHYSIOLOGY

2.7.1. INTRODUCTION

Chronic Kidney Disease (CKD) leads to reduction in phosphorus excretion and hyperphosphatemia, vitamin D deficiency and hypocalcemia, which inturn leads on to Secondary Hyperparathyroidism (SHPT).[31] In recent times, the increase in fibroblast growth factor-23 (FGF-23) in CKD patients due to phosphorus retention, has been found to increase the calcitriol synthesis which in turn leads to augmented PTH[32]. SHPT remains unrecognized and under-diagnosed at prior stages of CKD. SHPT may be challenging to dietary/ dialytic /medical treatment and may continue even subsequent transplantation.[33]

2.7.2. PATHOPHYSIOLOGY OF SECONDARY HYPERPARATHYROIDISM

There are four parathyroid glands situated in the neck. It synthesises a polypeptide hormone parathyroid hormone (PTH), that maintain the accurate equilibrium of serum calcium and serum phosphorous in the body. The entire molecule is made of a series of eighty four amino acids. SHPT seen in CKD is

due to excess synthesis of this hormone as a consequence of reduced functional capacity of kidney.[34]

A. CALCIUM METABOLISM

The active form of Vitamin D_3 (calcitriol) synthesized in kidney combines with vitamin D receptor (VDR)[32]. Vitamin D3 reduces the production of parathyroid hormone (PTH) either by parathyroid VDR stimulation or by increased activity of the intestinal VDR which in turn ultimately leads to the increased absorption of calcium and increased serum calcium.[36,37]

Due to kidney failure, there is a turn down of renal 1α-hydroxylase action that is responsible for the ultimate hydroxylation reaction in the synthesis of calcitriol. Due to the progressive nature of CKD, 1α-hydroxylation carried out by kidney is reduced, leading to reduced synthesis of active form of vitamin D3 and increased PTH levels.[38]

Decreased active form of vitamin D3 leads to reduced calcium absorption from intestine. This hypocalcemia in turn leads to secondary hyperparathyroidism early in CKD[39,40]

B. PHOSPHORUS METABOLISM

In progressive CKD, there will be a noticeable alteration in the excretion of phosphorus ion. Initially, functioning nephrons work in excess in order to

compensate for the damaged, non-functioning nephrons. With progression of the disease this compensatory mechanism fails leading to hyperphosphatemia.

Secondary Hyperparathyroidism is due to hypocalcemia in progressive CKD. In the serum, as the levels of one or both ions (calcium or phosphorous) increases, there is more chance for an ionic bond to form, leading to an insoluble complex. Therefore, PTH synthesis and release may be motivated by hypocalcemia, hyperphosphatemia, and vitamin D deficiency.[41,42]

2.8. MECHANISMS UNDERLYING UREMIC ENCEPHALOPATHY

Signs and symptoms of encephalopathy include headache, asterixis, visual abnormalities, chorea, tremor and seizures, mild sensorial clouding to delirium uremic twitch convulsion and even coma[43]. Both forms the acute or chronic kidney disease may lead to uremic encephalopathy but along with acute kidney failure(ARF) the signs and symptoms are added up and steps forward very speedily.[44,45] Yet in CKD patients who are neurologically asymptomatic, unnatural cognitive involvement can be disclosed by event-related potentials.

2.8.1. PATHOPHYSIOLOGY OF UREMIC ENCEPHALOPATHY

The pathophysiology of uremic encephalopathy is vague, but various factors have been recognized.[46]

A. Hormonal disturbances

B. Accumulation of metabolites

C. Oxidative stress

D. Disparity in excitatory and inhibitory neurotransmitters.

A. HORMONAL DISTURBANCES

Serum estimation of numerous substances like glucagon , gastrin prolactin, growth hormone ,parathyroid hormone, thyrotrophin, insulin and luteinizing hormone are raised in patients with kidney failure.[48] Heath et al noticed the significant role of PTH(Parathyroid hormone) in the progress of centrol nervous system uremic encephalopathy th[49,50] In chronic kidney disease(CKD), PTH level is prominently elevated with associated raised calcium level in the cerebral cortex. This hypothesis is evidenced by a study which confirmed the irregularity of brain calcium content in dogs with renal failure that are inhibited by parathyroidectomy, so these alterations appear to be PTH-dependent.[51]

B. ACCUMULATION OF METABOLITES

Chronic kidney disease(CKD) leads to the accumulation of a range of uremic toxins, like Urea, creatinine, guanidine, guanidinosuccinic acid (GSA), and methylguanidine (MG).[53]

C. OXIDATIVE STRESS

Reactive oxygen species (ROS) are measured to be one of the significant mediators of the pathophysiology of uremic encephalopathy. Numerous studies illustrated that these toxic substances generate a inflammatory reaction in CKD via the creation of a disparity between raised production of ROS and imperfect or reduced antioxidant capacity[52]

D. DISPARITY IN EXCITATORY AND INHIBITORY NEUROTRANSMITTERS

Chronic kidney disease(CKD) also leads to biochemical changes and metabolic derangements which may be the cause for the behavioral deficits[54-56] Disparity by means of raised levels of excitatory *N*-methyl-d-aspartate (NMDA) receptors and simultaneous hang-up of inhibitory GABA(A) neurotransmitters have been anticipated as fundamental cause.Recent studies suggested that creatinine may operate as aggressive opponent at the neurotransmitter appreciation location of the GABA-A receptor[57],which was also exposed in several extra endogenous GCs with convulsive action.[58-60]

2.9. HAEMODIALYSIS

1. DEFINITION
2. PRINCIPLE
3. TECHNIQUES-
    1. An intravenous catheter -Non-tunnelled, tunneled

2. An arteriovenous fistula (AV)

3. A synthetic graft.

4. TYPES:

    1. Conventional hemodialysis

    2. Daily hemodialysis

    3. Nocturnal hemodialysis.

5. COMPLICATIONS - Immediate & Late

6. PRECAUTIONS TO AVOID SIDE EFFECTS

7. ADVANTAGES AND DISADVANTAGES

8. HAEMODIALYSIS MACHIENE

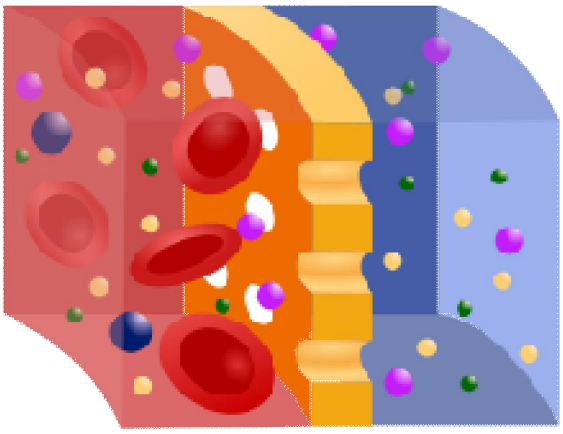
2.9.1. DEFINITION

One among the three modalities of replacement therapies for kidney failure is hemodialysis. Hemodialysis (also Haemodialysis-HD) is a technique that is used in kidney failure individuals to attain the elimination of metabolic intermediatary products like urea, creatinine and free water from the blood . The remaining modalities are peritoneal dialysis and kidney transplantation. It can be carried out as an outpatient remedy or inpatient therapy.[61]

2.9.2. PRINCIPLE

It involves the passage of solutes via a semi permeable membrane (Fig3). It make use of counter current flow, which preserve the concentration gradient across the membrane and increases the effectiveness of the haemodialysis.

Fig : 3 - SCHEME OF SEMIPERMEABLE MEMBRANE



red = blood, blue = PD fluid yellow = membrane

2.9.3. TECHNIQUES

There are 3 primary techniques applied to achieve way in to the blood[62] .

A. Catheter
B. Arteriovenous fistula (AV)
C. Arteriovenous synthetic graft.

A. AN INTRAVENOUS CATHETER

It is occasionally named a CVC (Central Venous Catheter) made upof a plastic one had two lumens which is introduced through a greater vein (generally the inferior vena cava, the femoral vein and the internal jugular vein) to permit great stream of blood to be removed from one side of the lumen, to go into the dialysis machine , and to come back by the use of the additional lumen.

They are generally set up in two common type

- Tunnelled

- Non-tunnelled.

NON-TUNNELLED

This type is used only for temporary use, mostly for single setting of dialysis or may be used for 10 days. The point of introduction and the outlet site was the same in this type.

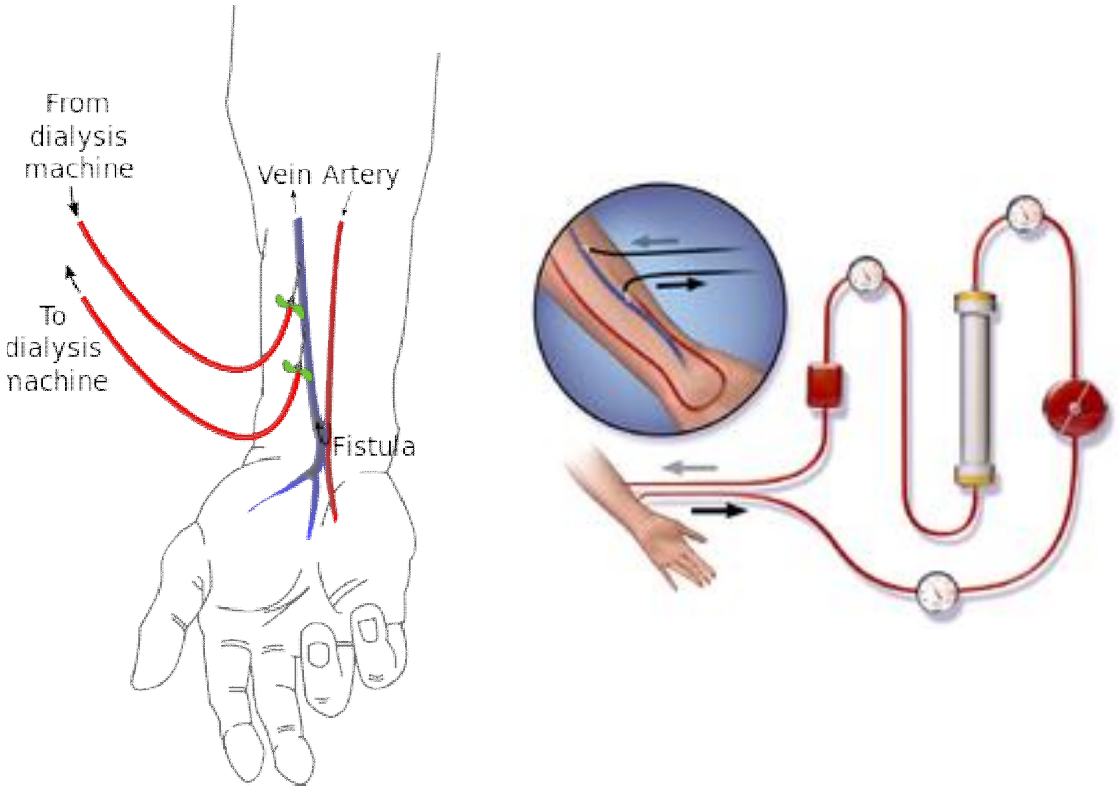
TUNNELLED

It involves a lengthy type of catheter. There was some distance between the summit point and the outlet point. This is frequently positioned in the neck (summit of introduction is at internal jugular vein) and the chest wall was the outlet site. They are used frequently. In addition it acts as a barrier to attack microbes.

B. AV (ARTERIOVENOUS) FISTULA

It is a most acceptable method. An artery and a vein are communicated via an anastomosis that bypasses the capillaries to create a fistula (Fig 4). Blood flows speedily in the course of the fistula.

FIG - 4 - ARTERIO VENOUS (AV) FISTULA



LOCATION OF FISTULA

Fistulas are frequently created in arm. It acquires 4–6 weeks time for the fistula to mature. The usual sites may be

a. The hand at the level of the snuffbox

b. The forearm - radiocephalic fistula or Brescia-Cimino fistula in which the radial artery is joined to the cephalic vein.

c. The elbow - A brachiocephalic fistula.

d. At the level of groin .

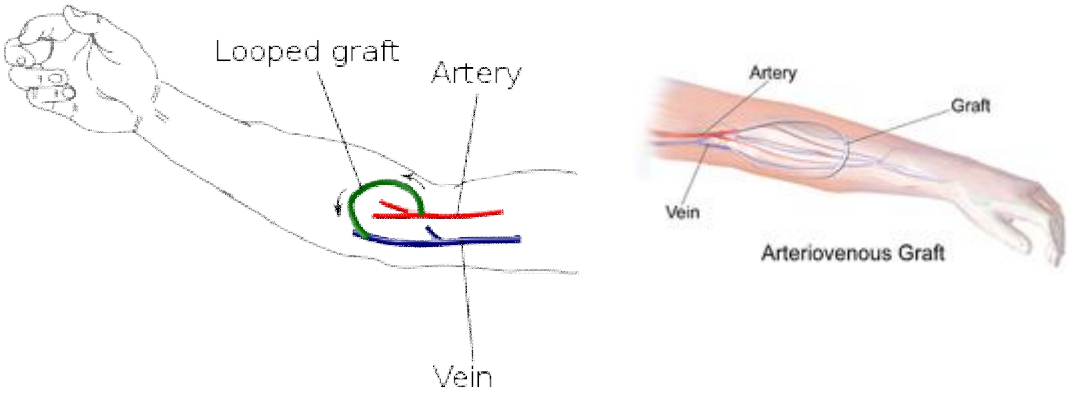
METHOD OF FISTULA OPERATION

Two needles are introduced into the fistula, one to withdraw the blood and another one to push back blood.

C. AV (ARTERIOVENOUS) GRAFTS

A synthetic material is used as a graft to join the artery and vein (Fig 5). It matures very quickly.

FIG : 5 -ARTERIO VENOUS (AV GRAFT)



2.9.4. TYPES OF HEMODIALYSIS

A. Usual, regular type (Conventional) of hemodialysis

B. Daily hemodialysis

C. Nocturnal hemodialysis.

A. USUAL, REGULAR TYPE OF HEMODIALYSIS

- It is regularly carried out as thrice in a week nearly three to four hours during each session.
- The kidney failure individual's blood is drained away all the way via the tube at a speed of 200-400 ml/min.
- The blood is first to passed via the dialyzer, and then it is passed back into the individual's circulation via one more tube .

- The blood pressure is strictly monitered, and if it is reduces, or if the patient had some other signs of low blood volume like nausea, the dialysis attendant can run more fluid all the way through the machine.
- With this procedure, the subject's whole volume of blood nearly 5000 ml pass throughout the apparatus once in fifteen minutes.

B. EVERY DAY HEMODIALYSIS

- It is usually carried out at home.
- It is more placid.
- It needs more frequent procedures.
- This is usually carried out with catheters very easily, but difficult with AVF or grafts.
- It is usually lasts for two hours per each session, six days in a week.

C. NOCTURNAL HEMODIALYSIS

- It is analogous to usual hemodialysis
- It is done 3-6 nights in a week and lasting for about 6-10 hours per sitting while the subject sleeps.[63]

2.9.5. COMPLICATIONS OF HAEMODIALYSIS

A. IMMEDIATE

B. LATE

C.

A. IMMEDIATE COMPLICATIONS

- Too much removal or too rapid removal leads to fatigue, reduced blood pressure, leg-cramps ,headaches, chest pains, , nausea.
- Sepsis
- Infection of the heart valves leading to endocarditis.
- Infection affecting the bones --osteomyelitis.
- Bleeding can also occur
- Heparin allergy is a rare problem, that may lead to reduced platelet count.

B. LATE COMPLICATIONS

- Amyloidosis,
- Neuropathy
- Heart disease. Due to excess fluid accumulation in these subjects.

2.9.6. PRECAUTIONS TO AVOID SIDE EFFECTS

- Fatigue, reduced blood pressure, leg-cramps , chest pain, nausea. – Can be minimized by restraining fluid ingestion or increasing the frequency of dialysis.
- Infection can be diminished by sticking to the infection control.
- Bleeding as a consequences of dialysis may vary according to the kind of modality we use. By following careful , finest method ,it may be

reduced . Even in some patients this procedure may done without the use of anticoagulant substances.

2.9.7. ADVANTAGES AND DISADVANTAGES

ADVANTAGES

- Less mortality rate
- Minimal dietary limitation
- Enhanced solute removal result for the everyday haemodialysis
- Enhanced acceptance and fewer side effects with extra recurrent dialysis[64]

DISADVANTAGES

- Needs always some person's support.
- Needs extra equipment like superior water system and the provision of excellent electrical power.
- Needs consistent machinery.
- This practice is complex and needs additional awareness.
- More expenditure had to be spent for the maintenance of the equipment.

2.9.8. HAEMODIALYSIS MACHINE

This apparatus propel the subject's blood via the dialyzer machine (Fig 6,7). The latest apparatus are extremely programmed and constantly check an arrangement of some features like analysis of the dialysate for evidence of blood leakage, blood and dialysate flow rates, temperature, pH, dialysis solution conductivity, and the existence of air. Anything that is changed from the normal value generates an alarm to aware paramedical staffs who is supervising the procedure.

FIG : 6 -HAEMODIALYSIS MACHINE

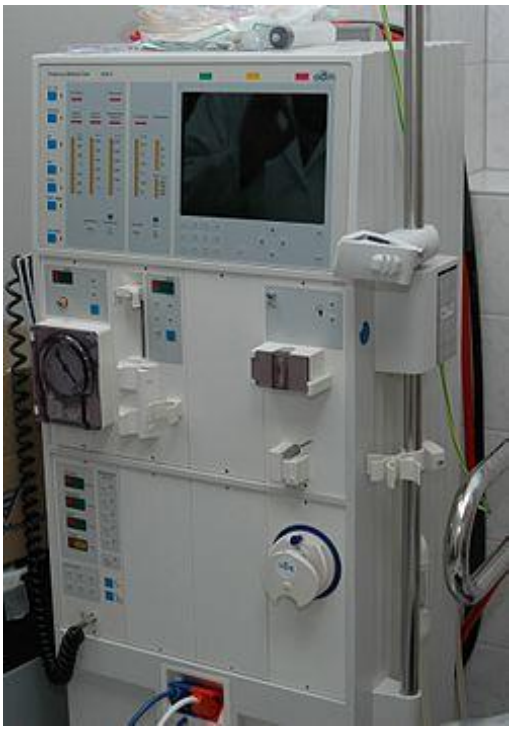
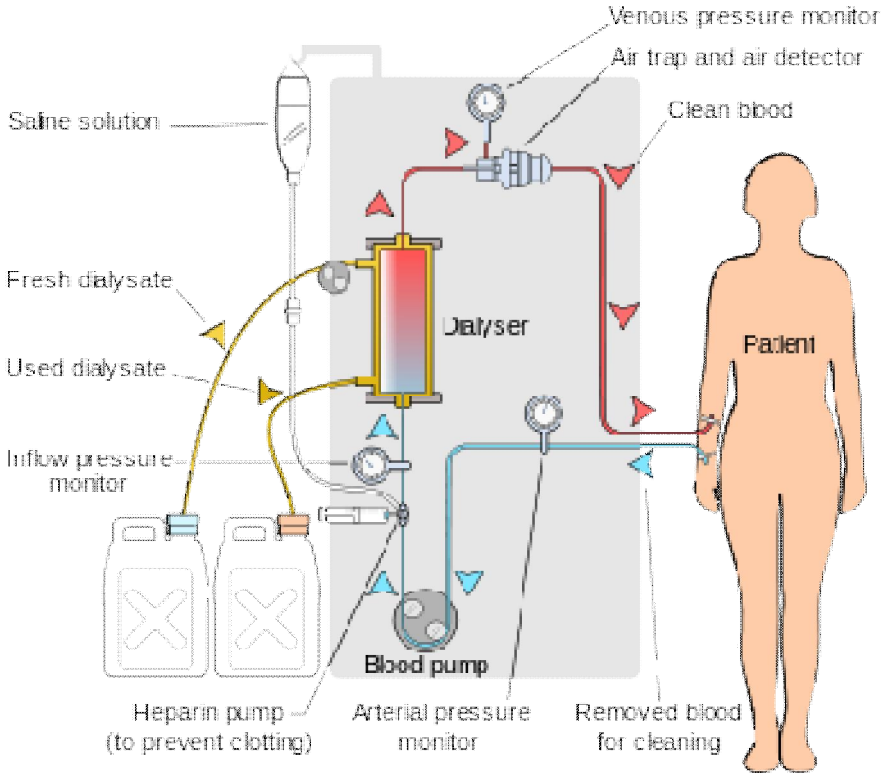


FIG:7-SCHEMATIC OF A HEMODIALYSIS CIRCUIT



2.10. VISUAL EVOKED POTENTIALS

2.10.1.DEFINITION OF EVOKED POTENTIAL

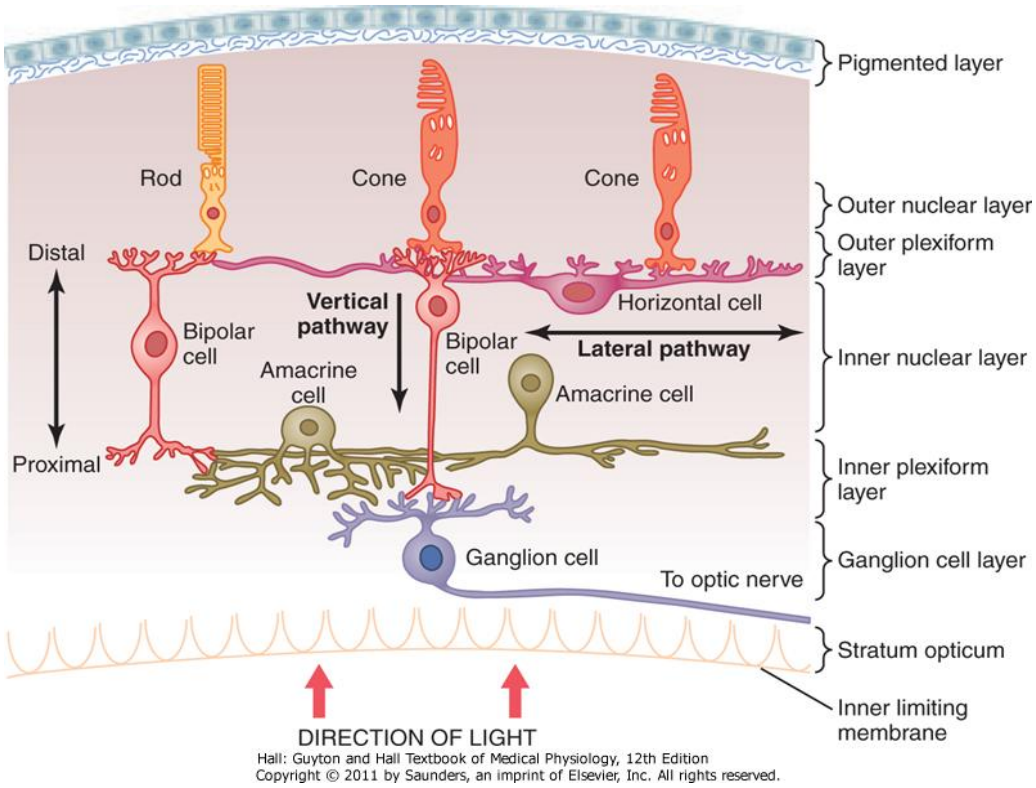
An evoked potential or evoked response is a type of electrical response documented from the human as well as from the animal's nervous system in response to a stimulus.

Visual evoked potentials (VEP) are electrical response documented from the vertex in reply to visual stimuli[65]. It represents the gathering reaction of the cortical and probably subcortical areas. A normal cortical response is recorded when the entire visual pathway is normal.

2.10.2. ANATOMICAL BASIS OF VISUAL PATHWAY

The retina has ten layers (Fig 8). The outermost layer is the pigment epithelium. The rods and cones lie next to this layer. They synapse with the inner nuclear or bipolar cells, which inturn project to the ganglion cell layer. The axons of the ganglion cells form the optic nerve. The rods and cones are the receptors that are stimulated by the light mpulses and the information is conveyed through the bipolar and ganglion cells via optic nerve to the lateral geniculate body via the optic chiasma, which in turn project to the visual cortex through the optic radiation.

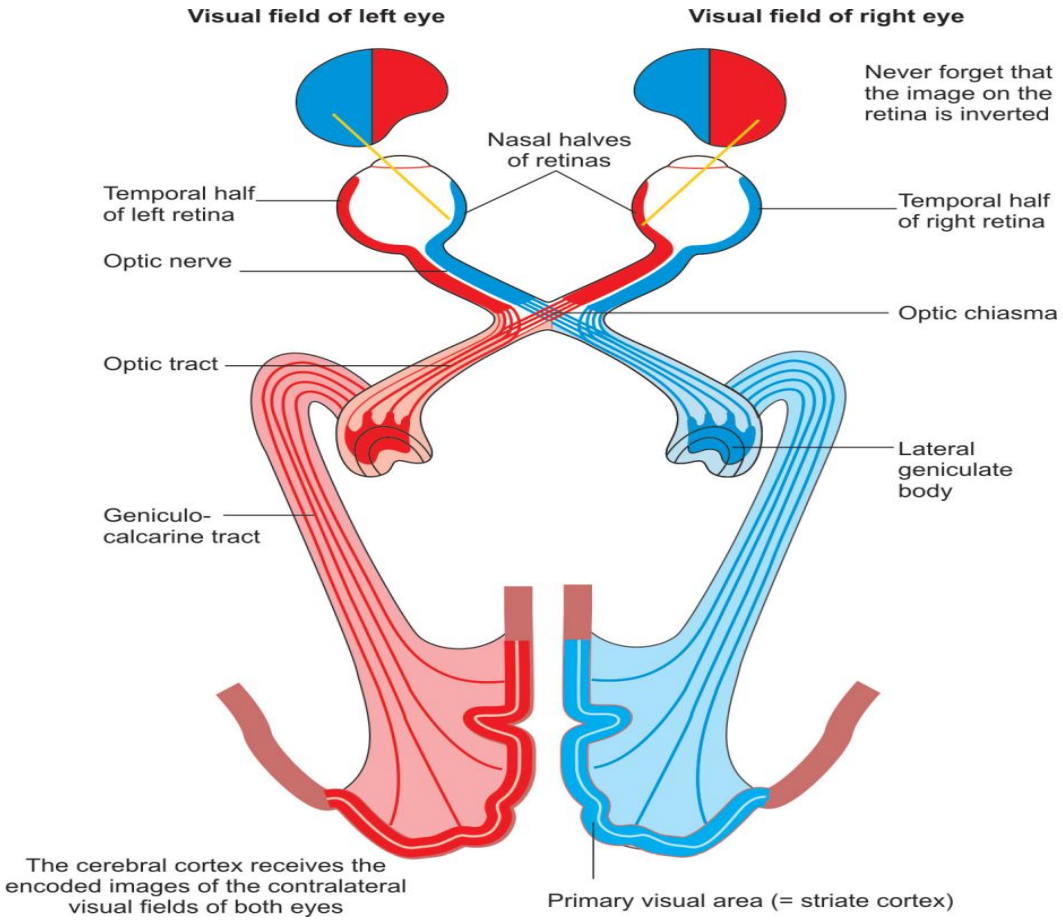
FIG: 8-LAYERS OF RETINA



2.10.3. PHYSIOLOGICAL BASIS OF VEP

The P_{100} waveform of VEPs is generated in the occipital cortex by the activation of the primary visual cortex and activation of areas surrounding the visual cortex by thalamocortical fibres (Fig 9).The retinal ganglion cell are of three types: X,Y and W. The X cells are small ganglion cells that mediate the function of cone systems. They have small diameter axons and small receptive fields. They are present in the central visual field and exhibit lateral inhibition. They provide the substrate for pattern VEPs via the geniculate pathway. The Y cells are large ganglion cells that mediate functions of rod system. They have large diameter axon with a large receptive field. They are present in the peripheral visual field and grant things via the extrageniculate pathway for flash VEPs .It primarily represent the motion originating in the central part of visual pathway, which is linked to the exterior of the occipital cortex. The central part of retina (fovea centralis) has greater cortical illustration in the visual cortex and events in the central visual field magnify the VEPs.

FIG:9 -VISUAL PATHWAY



2.10.4. METHODS AND INSTRUMENATION

A. BASIC INSTRUMENTATION FOR DATA ACQUISITION

AMPLIFERS

Instrument must be with amplitudes down to 0.1 micro volts and band with from below 1Hz to 10KHz.The impedance of electrodes should be below 5kΩ.

B. FILTERS

Low cut filters at 1-3Hz and high cut filter at 100-300Hz are available. The filter setting should be kept constant.

C. ELECTRODES

These are fixed to the forehead & scalp by paste .It is necessary to check the impedence of each electrode.

D. STIMULATORS

They are the basic part of the apparatus. The stimuli are coordinated to the sampling epoch and the trigger point highly developed or postponed from the start of the epoch to help showing the data on the screen.

E. DISPLAY

The recording are displayed on an oscilloscope. The statistics are manipulated by digital techniques prior to being displayed in colour on a VDU. Latencies and amplitudes can be recorded from the displayed data either automatically or by cursor measurements.

D. STIMULATION

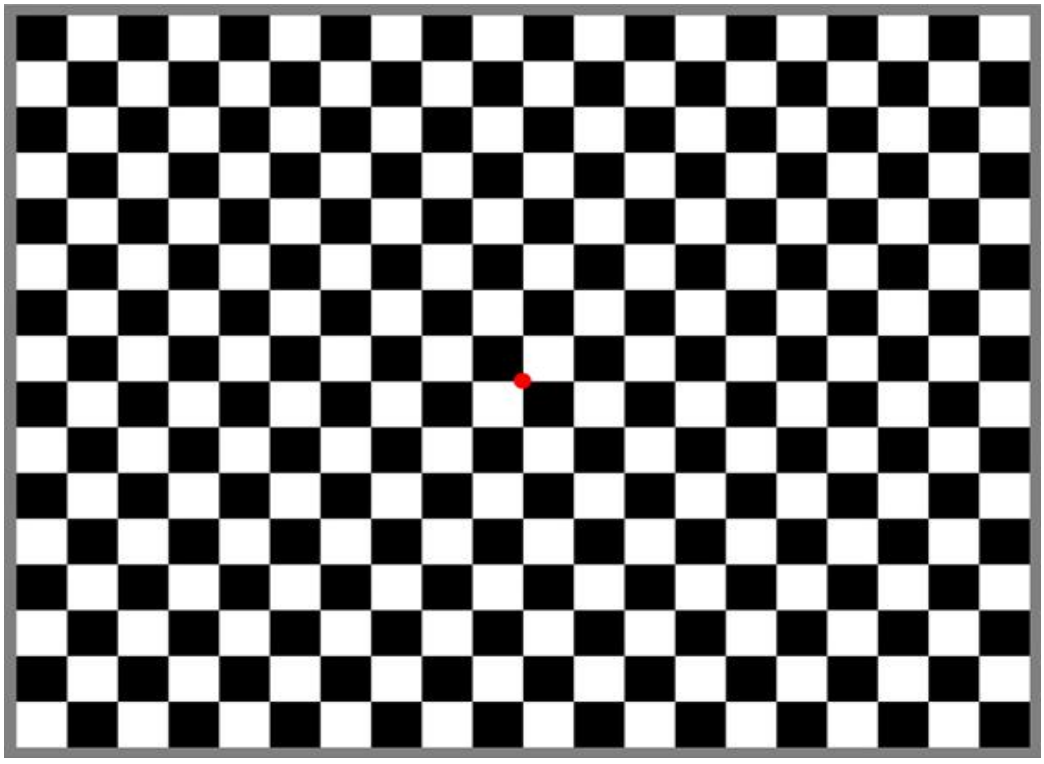
- VISUAL STIMULATION
- FLASH

The most frequently used is the stroboscope flash. It can be a single or repetitive flash.

E. PATTERNS AND PICTURES

Stationary or changing pattern such as checker board reversal can be used (Fig 10).

FIG : 10 -CHECKER BOARD



F. ANALYSIS TIME AND RATE

They are available with latencies 70-150msec.

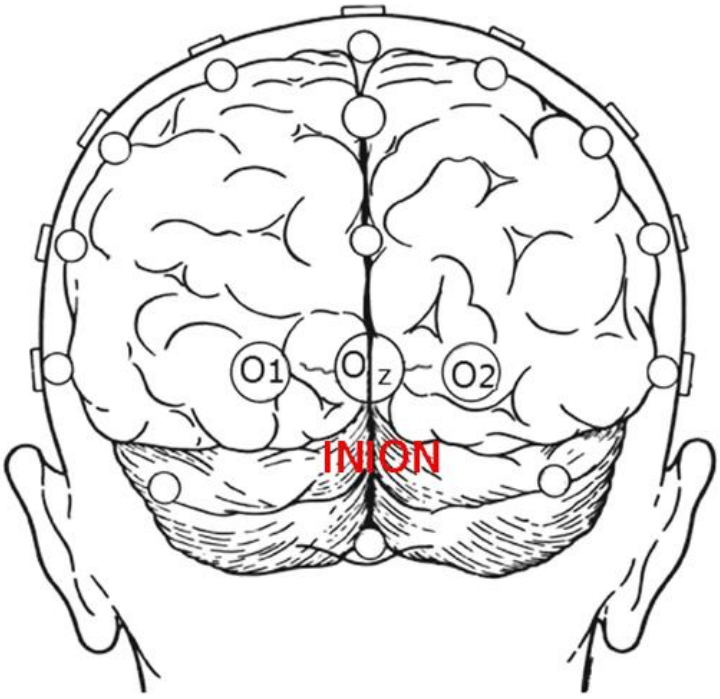
G. DURATION OF SWEEP

They kept at the 250-500ms.

H. ELECTRODE PLACEMENT

Most widely used method for keeping the electrodes is the- 10-20 International System where the head size is used as a parameter (Jasper, 1958)[63]. The active electrode (OZ) located in the midline (Fig 11). The space above the inion considered as 3-4 cm in adults which is about 10 % of the distance connecting the inion and nasion. The reference electrode is placed 12cm from the nasion. The ground electrode is placed in the middle of the forehead .

FIG:11 -OCCIPITAL SCALP ELECTRODE LOCATIONS



Occipital scalp electrode locations using 10-20 International System. The INION is the skull location at the position shown. The Nasion is on the bridge of the nose

I. GAZE FIXATION

This procedure needs full cooperation of the individuals. They are instructed to fix their eye at a centre of the checkerboard. Monocular stimulation is done by closing the other unstimulated eye with the patch or any other type of covering.

2.10.5. NORMAL WAVEFORM OFVEPs

The VEPs consists of a series of waveforms of opposite polarity. The negative wavesare denoted by N and positive waves by P which is followed by the pproximate latency in ms. The commonly seen waveforms are N_{75},$P_{100}$and N_{145}.

- N_{75} mainly consequences from foveal area activity and originates in primary visual region 17.
- P_{100} from the visual area nineteen (19).
- N_{145} be a sign of the activity of visual area eighteen (18).

2.10.6. FACTORS THAT INFLUENCE VEP

AGE:

The amplitude of P_{100} is high in infants and children which is almost the adult value. The adult value is reached in 5-7 years. After 50 years, the amplitude decreases.

GENDER:

The P_{100} latency is longer in men, which may be due to bigger head size in men. The P_{100} amplitude is greater in women, which may be due to hormonal influences.

DRUGS:

The drugs that cause miosis (pupillary constriction) like pilocarpine increases the P_{100} latency, which is due to decreased area of retinal illumination. The use of mydriatics decrease P_{100} latency

EYE DOMINANCE:

The duration and amplitude of P_{100} is shorter if recorded by stimulating the dominant eye compared to the non-dominant eye. This is attributed to the neuroanatomic asymmetries in the human visual cortex.

EYE MOVEMENTS:

The P_{100} amplitude is decreased by eye movements but the latency remains unaffected.

VISUAL ACUITY:

With poor visual acuity the amplitude of P_{100} is decreased but the latency remains normal.

2.11. LITERATURES: STUDIES RELEATED TO UREMIC ENCEPHALOPATHY

P.M Rossini et al stated that the altered latencies and amplitude were noticed in 53.6% of the study subjects. Patients on prolonged dialysis showed elevated levels of parameters in visual evoked potential. Positive correlation was noticed between pattern VEP and blood urea ($P < 0.001$) .They concluded that the measurement of both VEP, blood levels of uremic markers was used as a tool for deduction of the early involvement of an encephalopathic uraemia[67] .

E.G Lewis et al stated that the altered VEP recordings was noticed in both dialysed as well as in transplanted patients. It showed prolonged latencies and altered amplitude when compared to control groups. They documented that there was no consistent connection between blood estimation and VEP parameters in the correlational investigation [68].

Cosmo L et al concluded that the chronic kidney disease individuals who on medical therapy may have symptoms range from soft sensorial clouding to delirium and even coma. These complication may be due to advanced disease itself or by dialysis itself like dialysis dementia, the dialysis disequilibrium syndrome, and progressive intellectual dysfunction. Secondary HyperParathyroidism was noticed in progressive kidney disease in response to

hypocalcemia, also may be a uremic neurotoxin. The parathyroid hormone can impose on calcium transport in the brain was evidenced by the research study on synaptosomes. They explained in the task of parathyroid hormone in the pathogenesis of uremic encephalopathy in kidney failure patients[69].

Victor Lorenzo et al mentioned about the role of PTH as a uremic toxin. Hypocalcemia was encountered in CKD patients can lead to secondary hyperparathyroidism which can act as a uremic toxin by altering the cell calcium levels .Calcium is an input intracellular pointer required for typical cell function. SHPT was begins to start at very early stages of CKD itself. As the disease progresses, there is a decrease in the number of vitamin D receptors (VDR) and also calciums sensing receptors (CaR) in the parathyroid glands[70].

R. Dyer et al mentioned about the role of visual evoked potentials (VEP) to neurotoxicity research. It showed a significant change in their latency and amplitude in VEP parameters [71].

Bijen Nazliel et al did their study research in patients on dialysis by recording VEP. Nearly eight study subjects showed prolonged P100 latency at least in one examined eye. They concluded that VEP can be used in CKD patients to find out the subclinical involvement of central nervous system. They analysed the consequence of haemodialysis on VEP parameters. They noticed that there was no correlation between VEP parameters and dialysis duration,

creatinine, parathyroid hormone, serum blood urea nitrogen (BUN), and haematocrit levels. They concluded that Visual evoked potential is a reliable, simple and non-invasive technique that can be used for the analysis and follow up of subclinical involvement of visual pathways in those patients [72].

Another study done by **A. Ducati et al** in CKD children on dialysis. They noticed an altered latency and amplitude in VEP . But no corrrelations was found among blood chemistry markers and VEP parameters. He concluded that the VEP can be taken as the most amenable than EEG to distinguish a central nervous system (CNS) abnormality in these uremic patients[73].

Tschan PE et al did their research in renal failure patients with many valuable electrophysiologic and cognition-dependent probes. They concluded that the altered potentials correlated directly with the stage of renal failure[74].

Giselli Scaini et al explained about the pathophysiology of uremic encephalopathy. The pathophysiology of uremic encephalopathy till now is unsure, but numerous factors has to be concerned; it is a complex and almost has a multi factorial course. Hormonal disturbances, accumulation of metabolites, oxidative stress imbalance in excitatory and inhibitory neurotrans-mitters, and disturbance of the intermediary metabolism have been focused as causal feature. In spite of uninterrupted therapeutic advancement, the majority neurological problems of uremia, like uremic encephalopathy, be unsuccessful

to fully reply to dialysis and many are draw out or provoked by dialysis or renal transplantation. One study showed that antioxidant therapy could be used as an adjuvant therapy for the treatment of these neurological complications [75].

Di Paolo B et al did VEP, estimation of urea, creatinine, cholesterol, triglycerides, lipid electrophoresis, uric acid, glucose, PTH in 29 CKD patients. Based on their research, they concluded serum PTH has a significant neurotoxin role. Because there was a significant direct relationship between evoked potentials and serum PTH. So they recommended the VEP recording to detect preclinical variation in the central nervous system when there is 40% renal function.[76]

Seymen P et al did the estimation of VEP in CKD patients with varied management methods. T hey divided 39 study subjects into three groups as pre-dialysis group, HD group and CAPD group. They observed that there was prolonged latency in both dialysis groups. There was no significant difference between VEPs of the CAPD and HD groups. They noticed that the diminished VEPs demonstrating visual neuronal damage, when CRF progresses. This study concluded that the CNS abnormalities can be analyzed and supplementary therapeutic modalities could be followed using VEPs during the treatment of CKD[77].

Veysi Demirbilek et al stated that the role of VEP as a tool to find out the subclinical involvement in CKD pediatric patients and looking for a possible relationship between serum parathyroid hormone (PTH) and creatinine levels and PR-VEP parameters. They noticed significant alteration in VEP parameters and a positive correlation between VEP results and serum estimation of PTH and creatinine[78].

AIM AND OBJECTIVES

3. AIM AND OBJECTIVES

Aim: To evaluate the subclinical involvement of central nervous system in Chronic kidney disease (CKD) patients and analyse the association with their uremic status.

The objectives of the study

1. To evaluate the subclinical involvement of central nervous system in CKD patients belonging to stages 3-5 on medical therapy and stage 5D on dialysis by recording Visual Evoked Potentials(VEP).

2. To measure the blood levels of uremic markers namely Urea, Creatinine and Parathyroid hormone in these patients.

3. To correlate the central nervous system involvement with the severity of their uremic status.

4. To assess the variation in the CNS involvement among the two CKD groups.

5. To record VEP and measure blood parameters in the age and gender matched controls.

MATERIALS AND METHODS

4. MATERIALS AND METHODS

The research study has been carried out in the Neuro Physiology Research Lab, Department of Physiology, Stanley Medical College, Chennai.

SAMPLE SIZE :

60 study subjects (30- CKD3-5, 30-CKD5D) and 30 controls.

STUDY DESIGN:

Case-control study

PLACE OF STUDY:

Neuro Physiology Research Lab, Department of Physiology.

SUBJECT GROUP:

30 diagonsed Chronic Kidney Disease(CKD) stage3-5 on medical treatment, 30 study subjects on stage 5D(on dialysis) who fulfilled the above norms, were recruited from the Department of Nephrology, Stanley Medical College Hospital, Chennai.

Regarding the collection of study subjects the following inclusion and exclusion criteria were followed.

INCLUSION CRITERIA:

Chronic Kidney Disease (CKD) patients of both gender belongs to stage 3-5 on medical treatment, stage 5D (on dialysis-Haemodialysis was only carried out in nephrology department, Stanley medical college). Staging was done by the estimated GFR ml/min per $1.73m^2$ using recommended equation for calculating GFR with serum creatinine (P_{cr}), Age, Sex, Body weight.

- Cockcroft- Gault formula

  Estimated GFR=(140-age) × weight in kg divided by 72 x Pcr which is multiply by 0.85 for females.

EXCLUSION CRITERIA:

Acute causes of renal failure, Demyelinating disease like Multiple sclerosis, Optic neuritis, Ischemic optic neuropathy due to central nervous system vascualitis, Temporal arteritis, HIV infections, Nutritional optic neuropathy.

CONTROL GROUP:

30 Normal subjects (control) age and gender matched with study subjects were recruited from the Master Health Checkup Department in Stanley Medical College Hospital, Chennai.

ETHICAL CONSIDERATION:

Ethical committee approval was obtained from Stanley Medical College, Chennai for this research study. Informed and written consent was obtained from the individuals following the thorough method and principle of the study was clarified to them.

All the practice of recordings, time duration, apparatus were preserved consistently throughout the study. The study subjects were made to settle down and comfortable preceding to the test. Thorough history and clinical examination of the study individuals was done.

METHODOLOGY:

PHYSICAL AND GENERAL EXAMINATION:

Usual regular height and weight was recorded exclusive of footwear.

VEP RECORDING:

PROCEDURE:

By means of the typical RMS ENMG EP MARK II apparatus VEP recordings were done.

PRE- REQUISITES:

- Avoid hair oil application after hair wash.
- If study subjects has refractory error, the normal routinely used power glasses are put on throughout the procedure.
- Avoid the usage of any miotic or mydriatics drug 12 hours prior to the procedure

APPARATUS ARRANGEMENT FOR VEP RECORDING:

MONTAGE:

FPz - Reference electrode

Cz - Ground electrode

Oz - Active electrode

APPARATUS SETUP:

Filter	:	high filter cut :100-300Hg
Amplification range	:	20000-10000
Sweep duration	:	300 msecs
Number of epochs	:	100 are averaged
Electrode impedence	:	less than 5 KΩ

STIMULATION:

Black and White Checkerboard is utilized. Contrast -80%, Distance between individuals and monitor is 100 cms. Size of pattern element - 14×16mintue. Rate of stimulation-4-8 Hz.

METHOD OF RECORDING:

- The study subject was instructed to sit comfortably on a chair with their footwear.
- Each eye was recorded separately. The other eye is covered with an eye shield, with no entry of light into that eye.
- The skin at the point of keeping the electrodes is thoroughly cleaned.
- Three surface disc type electrodes are used-

  Reference, Recording (active) and Ground electrode.
- The active electrode is kept at Oz-5cm above the inion (ridge between the skull and the back of neck
- The reference electrode is kept at FPz-12 cms from the nasion (in between forehead and nose)
- The ground electrode is placed at the middle in forehead.
- The electrodes are linked via the pre amplifier to the cathode ray oscilloscope.
- The study subjects were guided to fix the gaze at the centre of the monitor.
- The lights are switched off.

- The visual stimulus is send by photo stimulator at frequency of 10 flashes/sec.
- The results got is showed on the TV monitor and the peak latency and peak to peak amplitude of the recorded waves are calculated

ESRIMATION OF UREMIC MARKERS (UREMIC NEUROTOXIN)

- BLOOOD UREA
- SERUM CREATININE
- SERUM CALCIUM
- SERUM PHOSPHOROUS
- SERUM PARATHYROID HORMONE

Done in Biochemistry Department, Stanley Medical College, Chennai.

BLOOD UREA

METHOD : Urease method[76]

SAMPLE : Unhaemolysed serum/plasma(heparin)

PROCEDURE : 500µl reagent mixed with 5µl sample. Read in semiautonalyser at 340nm after mixed well.

REAGENT COMPOSITION : R_1- α Ketoglutarate, urease, Glutamate dehydrogenase, Adenosine diphosphte, Sodium azide, R_2 – NADH (Nicotinamide adenine dinucleotide reducd, Sodium azide

PRINCIPLE : The rate of decrease in absorbance of NADH is read at 340nm and it proportional to the urea concentration in the sample [77,78.]

REFERENCE RANGE : 15-39 mg/dl or 2.5-6.4mmol/L[79].

SERUM CREATININE

METHOD : Jaffe's kinetic method[80]

SAMPLE : Unhaemolysed serum/plasma(heparin)

PROCEDURE : 1 ml of reagent mixed with 0.1 ml of sample and incubated for 15mints.Reading was done at 520nm.

REAGENT COMPOSITIO: R_1- Picric acid reagent

PRINCIPLE : Creatinine present in the sample react with picric acid in alkaline medium forming orange yellow coloured creatinine picrate. The absorbance is measured at 520nm and the intensity is proportional to the concentration of creatinine in the sample[81].

REFERENCE RANGE : Male--- 0.7-1.4 mg/dl, Female-- 0.6-1.2 mg/dl[79]

SERUM CALCIUM

METHOD : O-Cresolphthalein complexone method

SAMPLE : Unhaemolysed serum

PROCEDURE : 500µl of reagent was added to 12.5 µl of sample and incubated at room temperature for 15 mint.

REAGENT COMPOSITION : AMP buffer PH 10.7,Colour regent- O-Cresolphthalein complexone

PRINCIPLE : Calcium fors a purple coloured complex with ortho-Cresolphthalein Complexone in an alkaline medium [82,83]. Hydrochloric acid

(Hcl) helps to release calcium bound to proteins and 8 hydroxy quinoline eliminates the interference magnesium.2 amino-2methyl,1-propanol(AMP) provides the alkaline medium for the colour reaction and also act as phosphate acceptor. The intensity is measured at 570-580nm.

REFERENCE RANGE : 8.5-10.4 mg/dl

SERUM PHOSPHORUS

METHOD : UV Molybdate, End point assay.

SAMPLE : Fasting serum sample is preferable.

PROCEDURE : 500µl of reagent was added to 5 µl of sample and incubated at room temperature for 5 .mint.

REAGENT COMPOSITION: Molybdate reagent, Sample blan reagent

PRINCIPLE : In acidic medium inorganic phosphorus reacts with ammonium molybdate to form phosphomolybdate complex[84]

This colorless complex is measured at 340nm and is directly propotional to the concentration of inorganic phosphorus in the serum sample.

REFERENCE RANGE : 2.5- 4.5 mg/dl

SERUM PARATHYROID HORMONE

This is done by ECLIA method .-Electro Chemiluminescent Linked Immuno Assay[85].Based on the principle that " Chemiluminesence is the name given to light emission produced during a chemical reaction".

PHOTOGRAPH:1

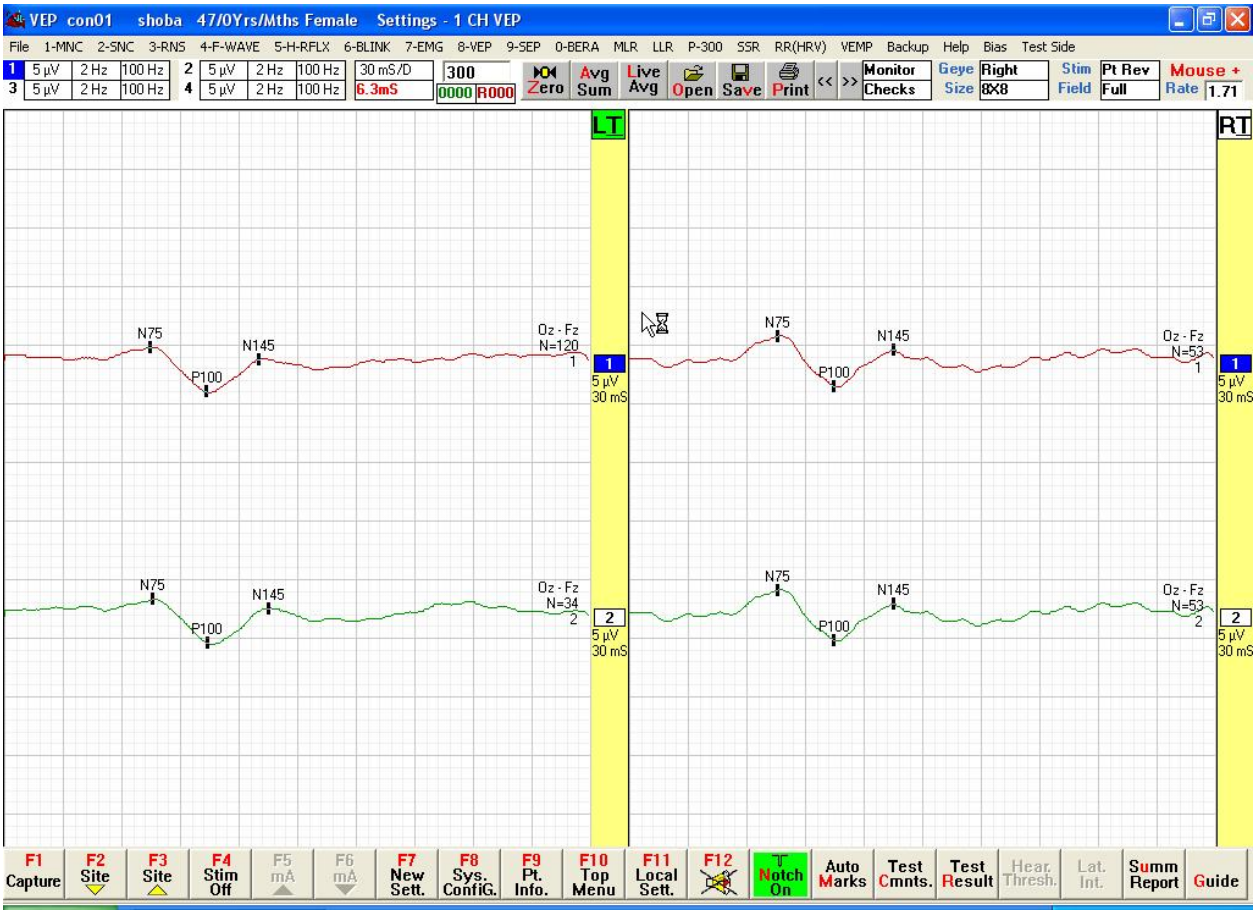
RMS EMG EP MARK-II MACHINE

NEUROPHYSIOLOGY RESEARCH LAB

DEPARTMENT OF PHYSIOLOGY

PHOTOGRAPH:2

VEP RECORD



STATISTICAL ANALYSIS

5. STATISTICAL ANALYSIS

In this study research 60 Chronic Kidney Disease (CKD) patients, 30 on medical therapy (CKD3-5) and 30 on Dialysis(CKD5D) who fulfilled the inclusion criteria were analysed with anthropometric measurements, Visual Evoked Potential parameters(VEPs), Blood uremic markers (uremic toxins like Blood Urea, Serum Creatinine, Serum Parathyroid hormone(PTH))levels among themselves and they are compared with 30 controls.

STATISTICAL TOOLS

The information collected concerning all the preferred study subjects were documented in a Master Chart. With the use of computer by by means of Epidemiological Information Package (EPI 2010), Statistical Software SPSS 16 and Sigma Stat 3.5 version data analysis was done.

By means of this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated by One way ANOVA and ‘t’ test. Chi-square test was used to experiment the importance of disparity among the consolidated (quantitative) variables.

P -value <0.001 –Highly significant

and < 0.05 - significant .

RESULTS

6. RESULTS

From the above study the following results were obtained and analysed.

* **COMPARISON OF BASIC PARAMETERS (AGE, SEX, BMI) BETWEEN CASES AND CONTROL (TABLE1,2)**

* **COMPARISON OF MEAN VALUES OF VEP PARAMETERS BETWEEN CKD CASES AND CONTROL (TABLE: 3)**

* **COMPARISON OF MEAN VALUES OF UREMIC MARKERS BETWEEN CASES AND CONTROL (TABLE:4)**

* **COMPARISON OF MEAN VALUES OF VEP PARAMETERS BETWEEN STAGES CKD3-5 AND CKD 5D PATIENTS (TABLE: 5)**

* **COMPARISON OF MEAN VALUES OF BLOOD UREMIC MARKERS BETWEEN CKD STAGES 3-5 AND CKD 5D PATIENTS (TABLE: 6)**

* **CORRELATON BETWEEN VEP PARAMETERS AND BLOOD UREMIC MARKERS (TABLE : 7 - 10)**

TABLE – 1

COMPARISON OF BASIC PARAMETERS (MEAN±SD) BETWEEN CKD CASES AND CONTROL.

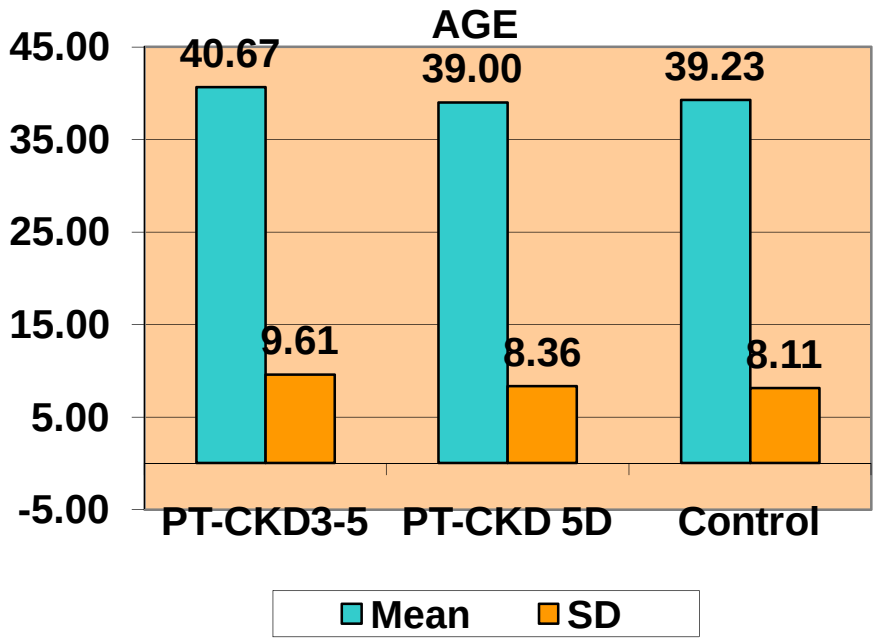
PARAMETER	GROUPS	MEAN	SD	p-Value
AGE	CKD3-5	40.67	9.61	0.726
	CKD5D	39.00	8.36	
	CONTROL	39.23	8.11	
BMI (Wt/htm^2)	CKD3-5	22.17	2.64	0.985
	CKD5D	22.27	1.59	
	CONTROL	22.20	2.54	

**-----Highly significant, * ----- Significant

No significant difference between study groups and controls.

CHART-1

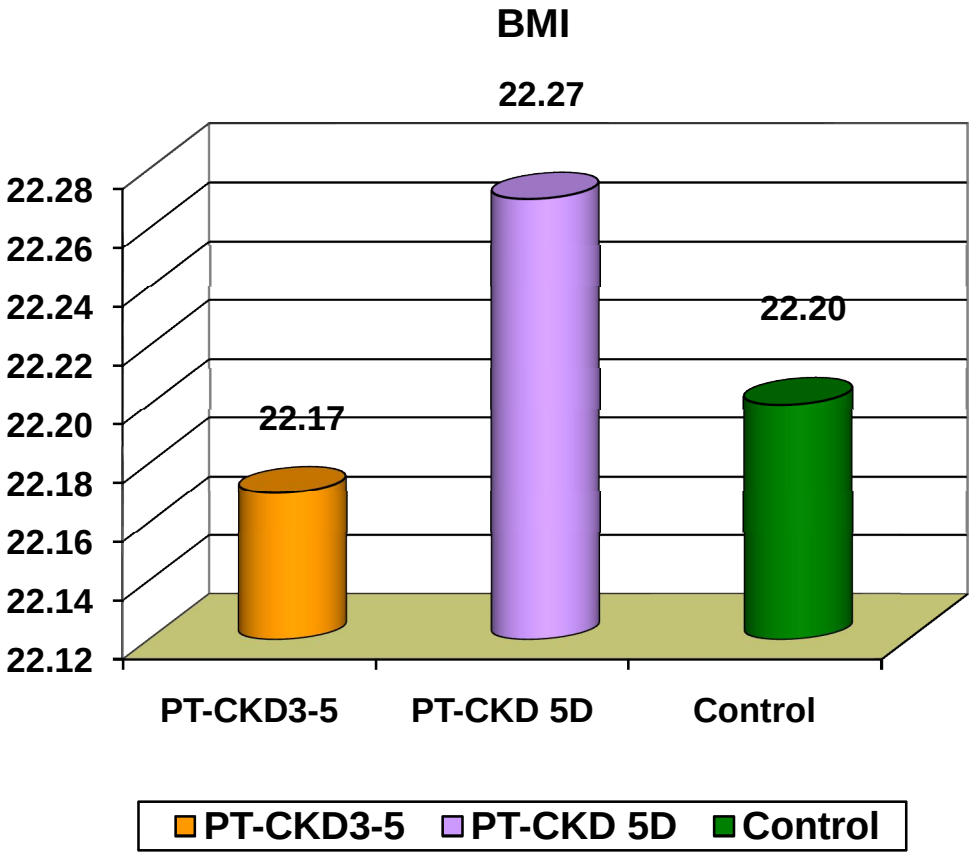
COMPARISON OF AGE (MEAN±SD) BETWEEN CKD STUDY GROUPS AND CONTROLS



No significant difference between study groups and controls.

CHART - 2

COMPARISON OF BODY MASS INDEX (BMI-MEAN±SD) BETWEEN CKD STUDY GROUPS AND CONTROLS



No significant difference between study groups and controls.

TABLE : 2

SEX DISTRIBUTION

			GROUP					
		CKD3-5		CKD5D		CONTROL		Chi square test
		N	%	N	%	N	%	p-value
SEX	MALE	16	53.3	16	53.3	16	53.3	1.000
	FEMALE	14	46.6	14	46.6	14	46.6	Not
TOTAL		30	100	30	100	30	100	significant

**-----Highly significant, * ----- Significant

No significant difference between study groups and controls.

CHART - 3:

SEX DISTRIBUTION AMONG CKD STUDY GROUPS AND CONTROLS

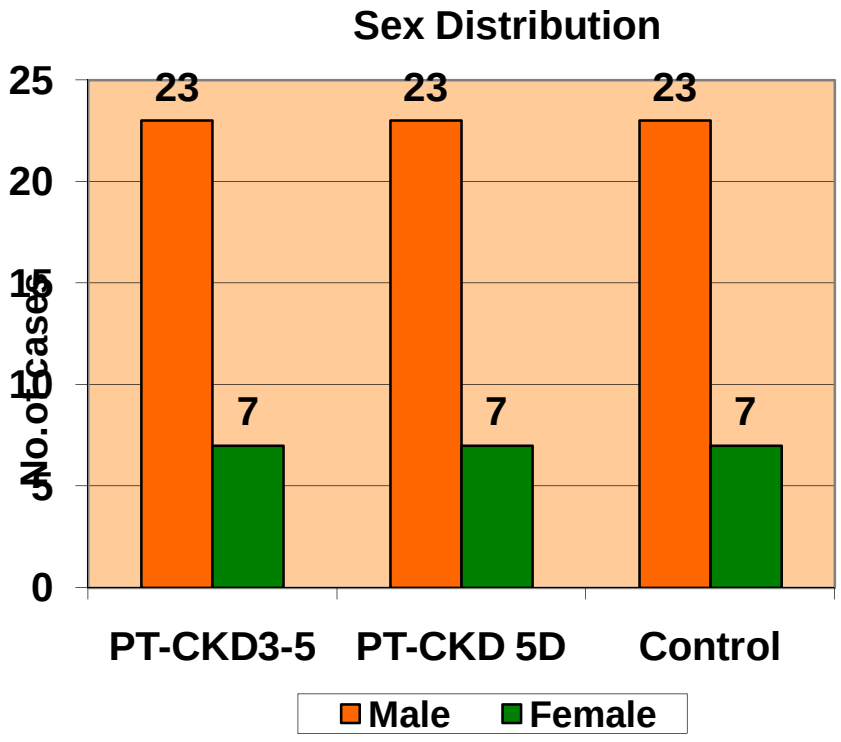


TABLE : 3

COMPARISON OF MEAN VALUES OF VEP PARAMETERS BETWEEN CKD CASES AND CONTROL

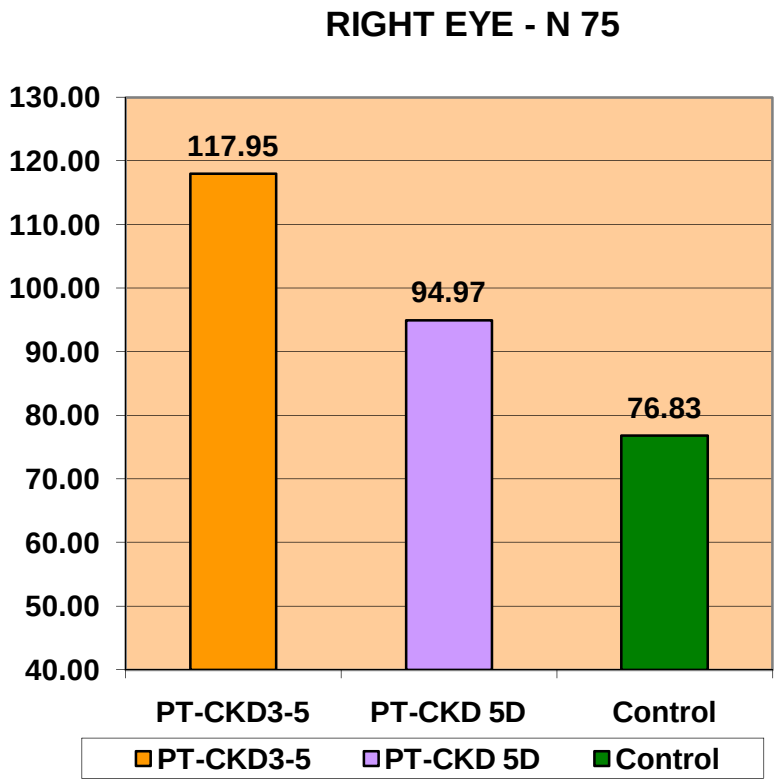
PARAMETER	EYE	GROUPS	MEAN	SD	p-value
		CKD3-5	117.95	39.61	
N_{75}	RT EYE	CKD3-5	94.97	35.24	0.001**
		CONTROL	76.83	76.83	
		CKD3-5	92.39	36.55	
	LT EYE	CKD3-5	114.21	41.52	0.001**
		CONTROL	68.57	7.16	
		CKD3-5	134.29	34.29	
	RT EYE	CKD3-5	120.76	31.61	0.001**
P_{100}		CONTROL	103.78	24.17	
		CKD3-5	110.54	40.36	
	LT EYE	CKD3-5	131.09	41.37	0.001**
		CONTROL	93.67	93.67	
		CKD3-5	157.16	32.82	
	RT EYE	CKD3-5	122.67	37.45	0.001**
N_{145}		CONTROL	137.23	25.88	
		CKD3-5	123.11	41.63	
	LT EYE	CKD3-5	154.75	44.36	0.002*
		CONTROL	131.02	9.23	
		CKD3-5	2.83	1.16	
P_{100}- N_{75}	RT EYE	CKD3-5	3.16	1.66	0.001**
		CONTROL	9.35	2.42	
		CKD3-5	3.17	1.15	
	LT EYE	CKD3-5	7.42	15.49	0.048*
		CONTROL	8.73	0.31	

**-----Highly significant, * ----- Significant

Significantly prolonged latency of VEP parameters (N_{75} , N_{145}, P_{100}) and reduced amplitude of P_{100}- N_{75} were observed in both groups of cases when compared to controls.

CHART - 4

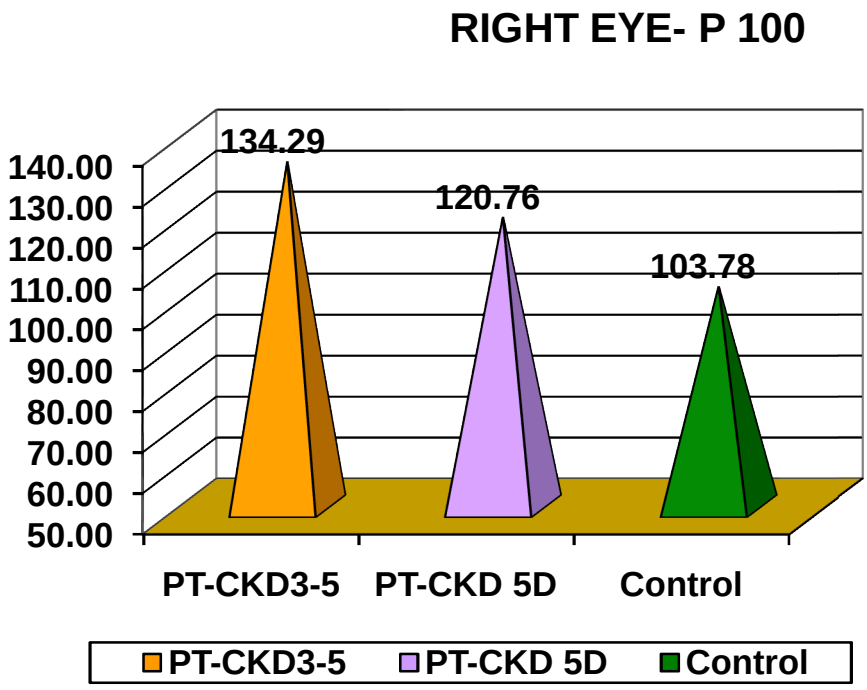
COMPARISON OF MEAN VALUES OF VEP PARAMETERS-N_{75} (RIGHT EYE) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 5

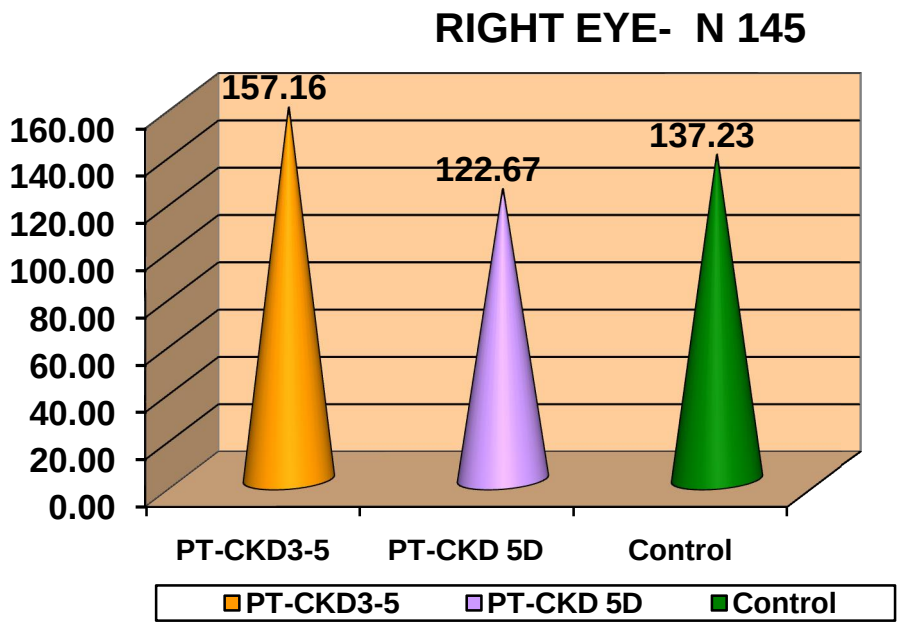
COMPARISON OF MEAN VALUES OF VEP PARAMETERS-P_{100} (RIGHT EYE) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 6

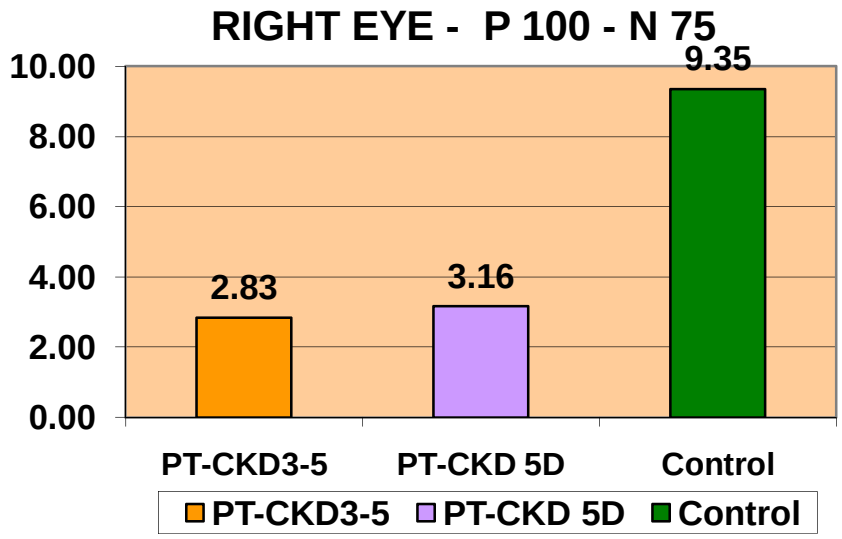
COMPARISON OF MEAN VALUES OF VEP PARAMETERS-N_{145} (RIGHT EYE) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 7

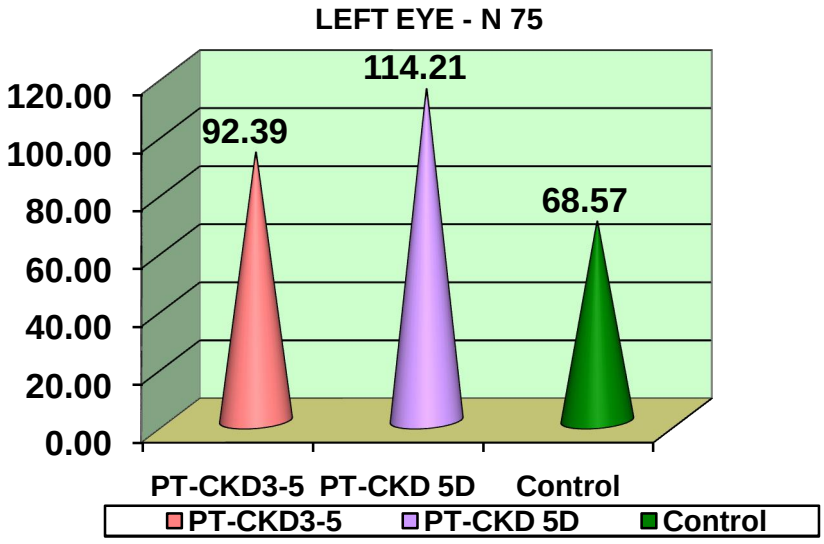
COMPARISON OF MEAN VALUES OF VEP PARAMETERS-P_{100}-N_{75} (RIGHT EYE) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 8

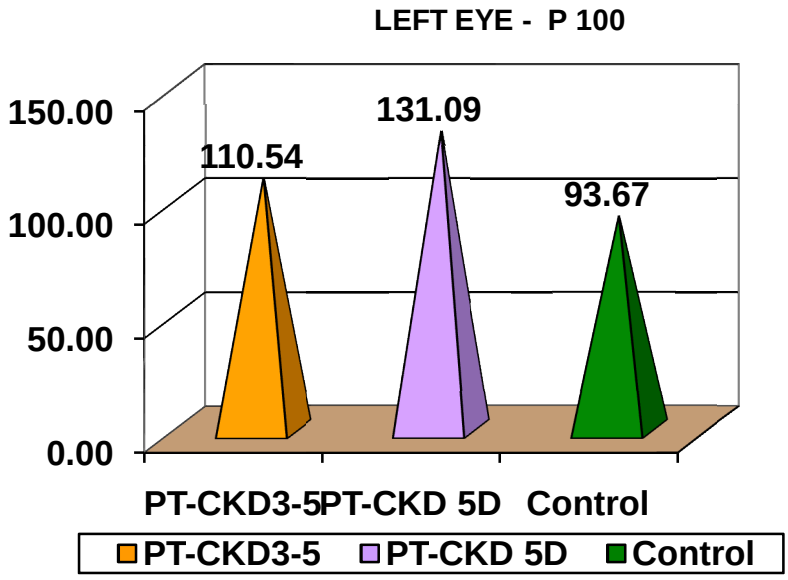
COMPARISON OF MEAN VALUES OF VEP PARAMETERS-N_{75} (LEFT EYE) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 9

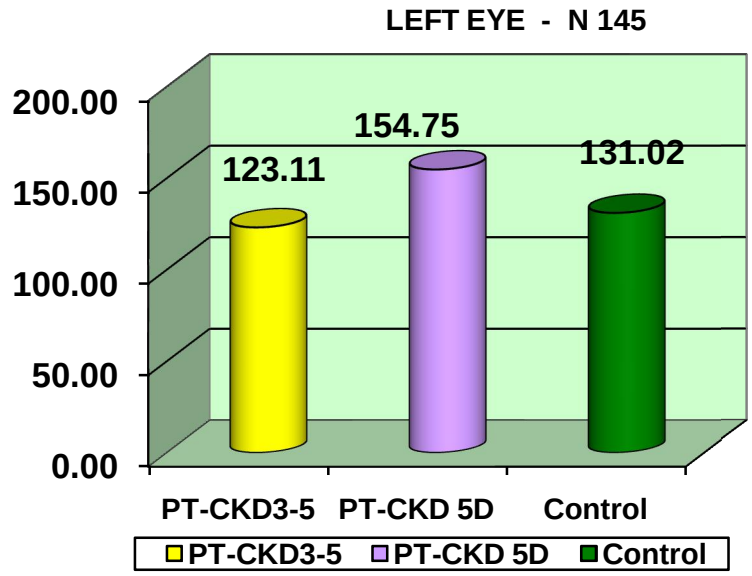
COMPARISON OF MEAN VALUES OF VEP PARAMETERS-P_{100} (LEFT EYE) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 10

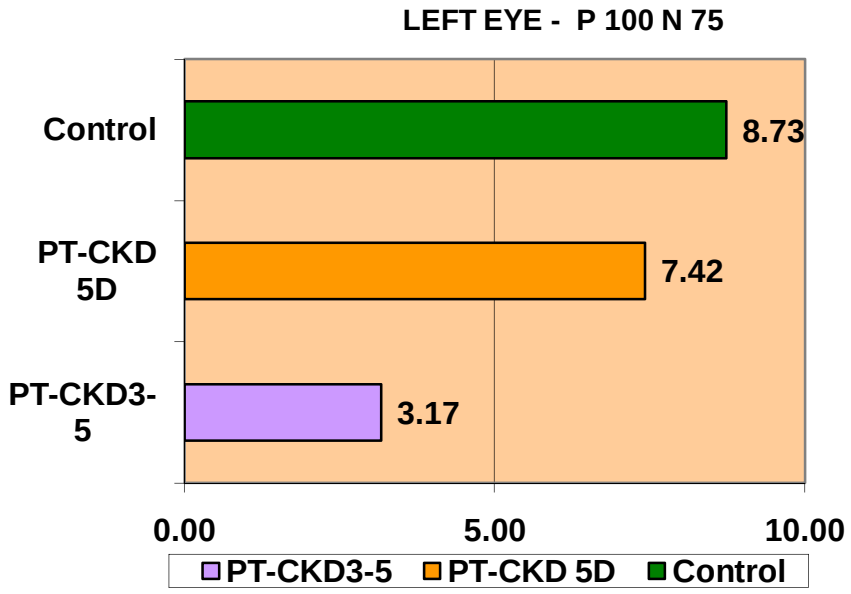
COMPARISON OF MEAN VALUES OF VEP PARAMETERS-N_{145} (LEFT EYE) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 11

COMPARISON OF MEAN VALUES OF VEP PARAMETERS-P_{100}-N_{75} (LEFT EYE) BETWEEN CKD STUDY GROUPS AND CONTROL



Significant difference between study groups and controls was observed.

TABLE : 4

COMPARISON OF MEAN VALUES OF UREMIC MARKERS BETWEEN CKD CASES AND CONTROL

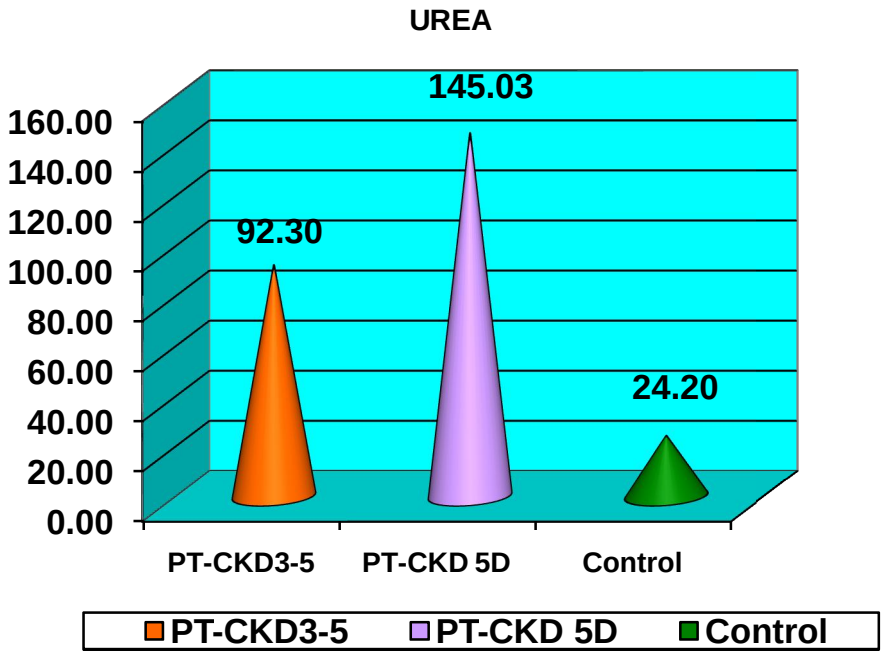
PARAMETER	GROUPS	MEAN	SD	p-value
	CKD3-5	92.30	43.95	
UREA	CKD3-5	145.03	35.40	0.001**
	CONTROL	24.20	0.81	
	CKD3-5	6.54	0.54	
CREATININE	CKD3-5	5.66	1.13	0.001**
	CONTROL	9.09	0.28	
	CKD3-5	6.54	0.54	
SERUM CALCIUM	CKD3-5	5.66	1.13	0.001**
	CONTROL	9.09	0.28	
	CKD3-5	4.12	0.43	
SERUM PHOSPHOROUS	CKD3-5	4.01	0.49	0.02*
	CONTROL	3.84	0.13	
	CKD3-5	84.70	18.61	
PTH	CKD3-5	110.56	30.50	0.001**
	CONTROL	50.00	0.83	

**-----Highly significant, * ----- Significant

Blood parameters were significantly elevated in patients compared to controls.

CHART - 12

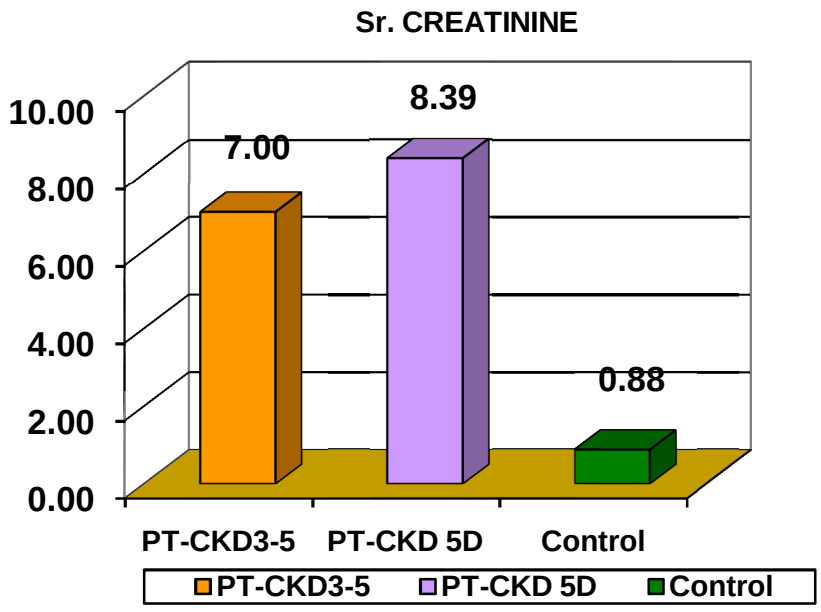
COMPARISON OF MEAN VALUES OF BLOOD UREA (mg/dl) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 13

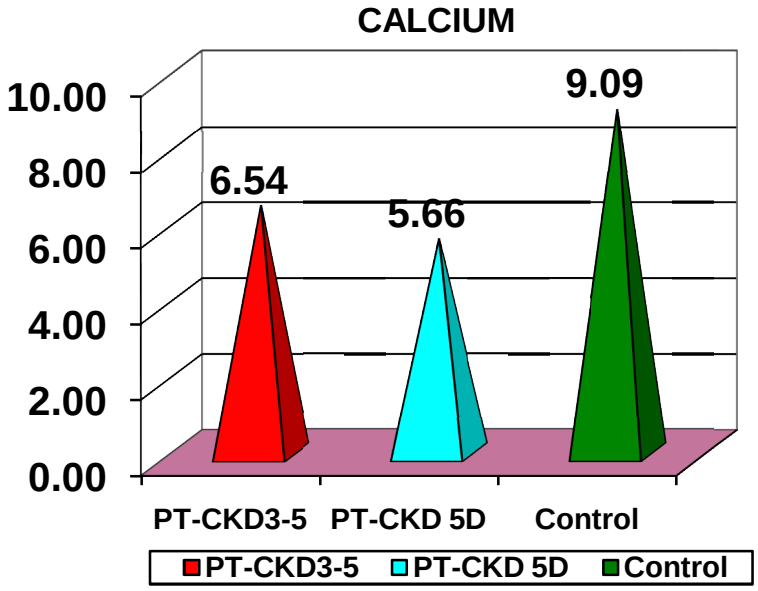
COMPARISON OF MEAN VALUES OF SERUM CREATININE (mg/dl) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 14

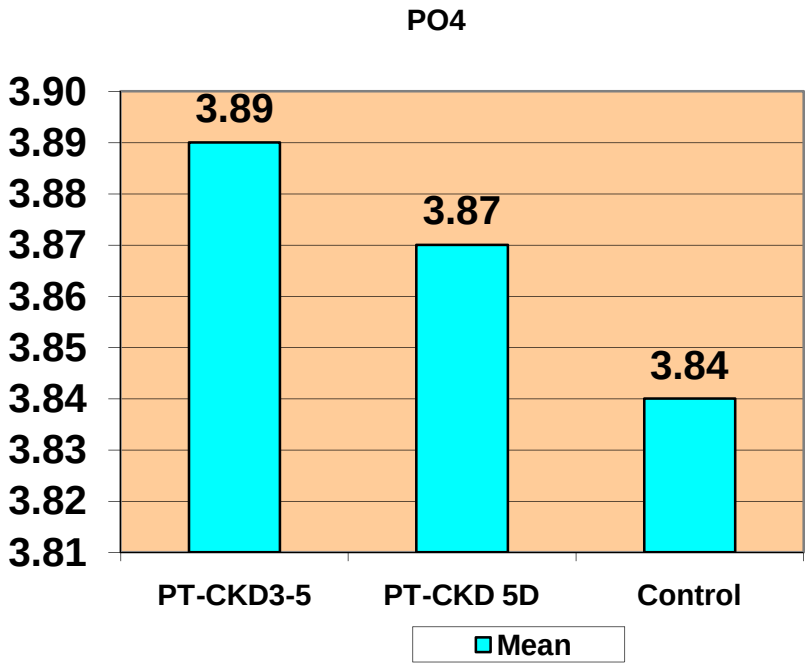
COMPARISON OF MEAN VALUES OF SERUM CALCIUM (mg/dl) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 15

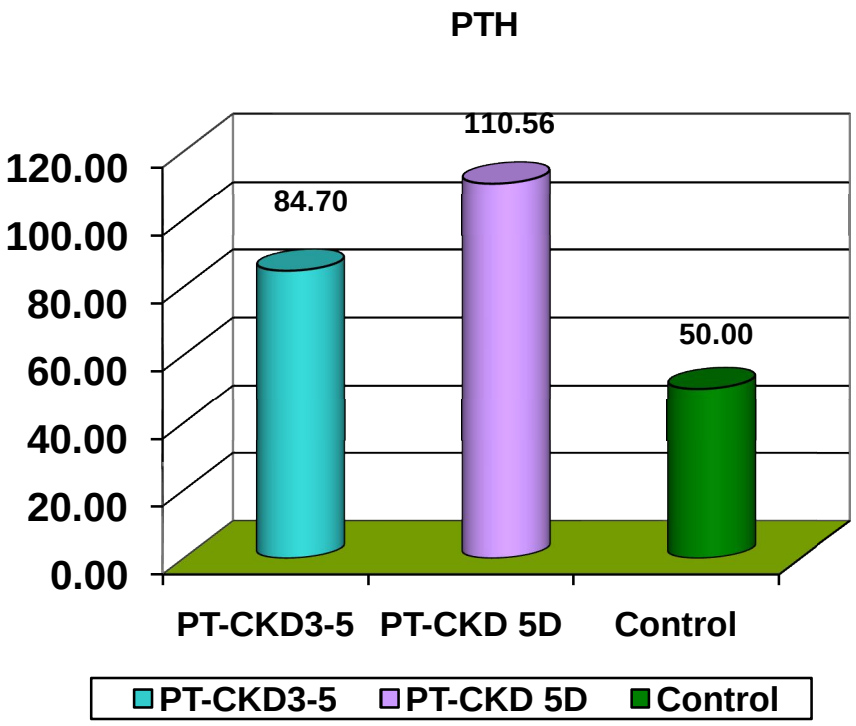
COMPARISON OF MEAN VALUES OF SERUM PHOSPHOROUS (mg/dl) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

CHART - 16

COMPARISON OF MEAN VALUES OF SERUM PARATHYROID HORMONE (pg/dl) BETWEEN CKD STUDY GROUPS AND CONTROL.



Significant difference between study groups and controls was observed.

TABLE : 5

COMPARISON OF MEAN VALUES OF VEP PARAMETERS BETWEEN CKD 3-5 AND CKD 5D

PARAMETER	EYE	GROUPS	MEAN	SD	p-value
		CKD3-5	117.95	39.61	
N_{75}	RT EYE	CKD3-5	94.97	35.24	0.010*
		CKD3-5	92.39	36.55	
	LT EYE	CKD3-5	114.21	41.52	0.017*
		CKD3-5	134.29	34.29	
	RT EYE	CKD3-5	120.76	31.61	0.058*
P_{100}		CKD3-5	110.54	40.36	
	LT EYE	CKD3-5	131.09	41.37	0.028*
		CKD3-5	157.16	32.82	
	RT EYE	CKD3-5	122.67	37.45	0.001**
N_{145}		CKD3-5	123.11	41.63	
	LT EYE	CKD3-5	154.75	44.36	0.002*
		CKD3-5	2.83	1.16	
P_{100}- N_{75}	RT EYE	CKD3-5	3.16	1.66	0.001**
		CKD3-5	3.17	1.15	
	LT EYE	CKD3-5	7.42	15.49	0.048*

**-----Highly significant, * ----- Significant

Significantly prolonged latency of VEP parameters (N_{75} , N_{145}, P_{100}) and reduced amplitude of P_{100}- N_{75} were observed in CKD stages3-5 compared to CKD 5D.

CHART - 17

COMPARISION OF MEAN VALUES VEP PARAMETER-N_{75},P_{100} (RT EYE)BETWEEN CKD3-5 AND CKD5D

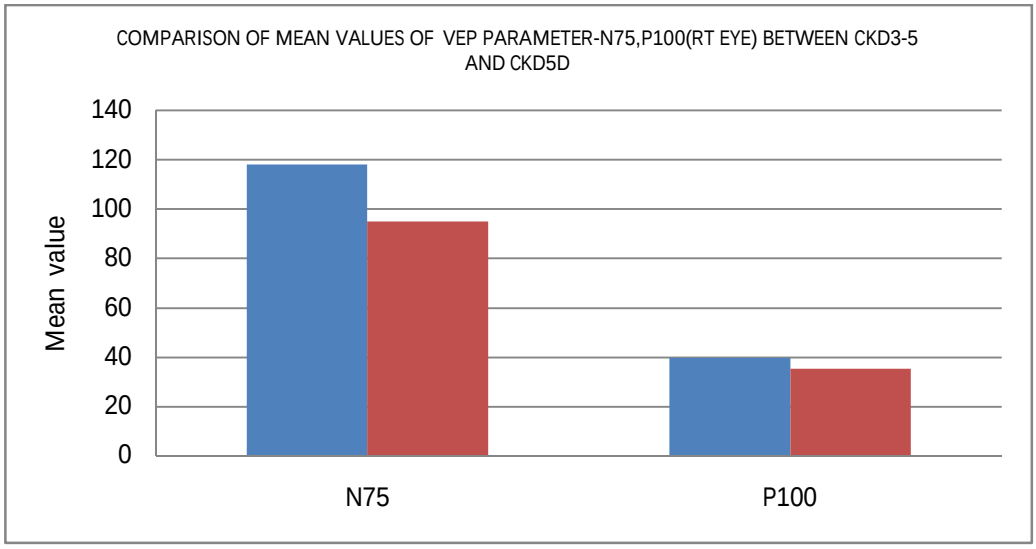


CHART - 18

COMPARISION OF MEAN VALUE OF VEP PARAMETER- N_{145} (RT EYE) BETWEEN CKD3-5 AND CKD5D

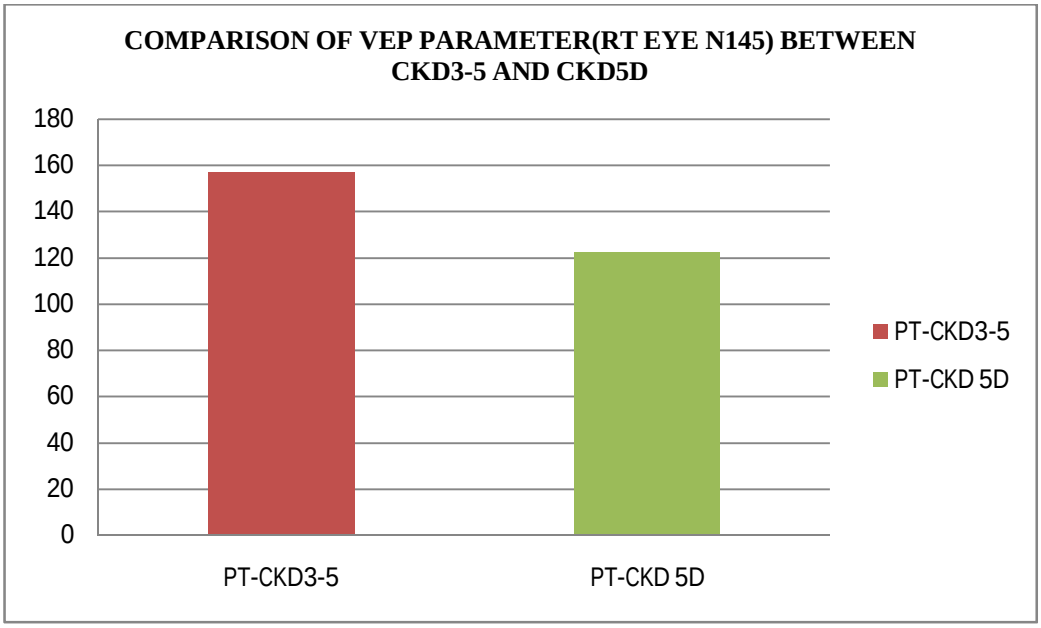


CHART - 19

COMPARISION OFMEAN VALUES OF VEP PARAMETER (RT EYE P_{100}-N_{75}) BETWEEN CKD3-5 AND CKD5D

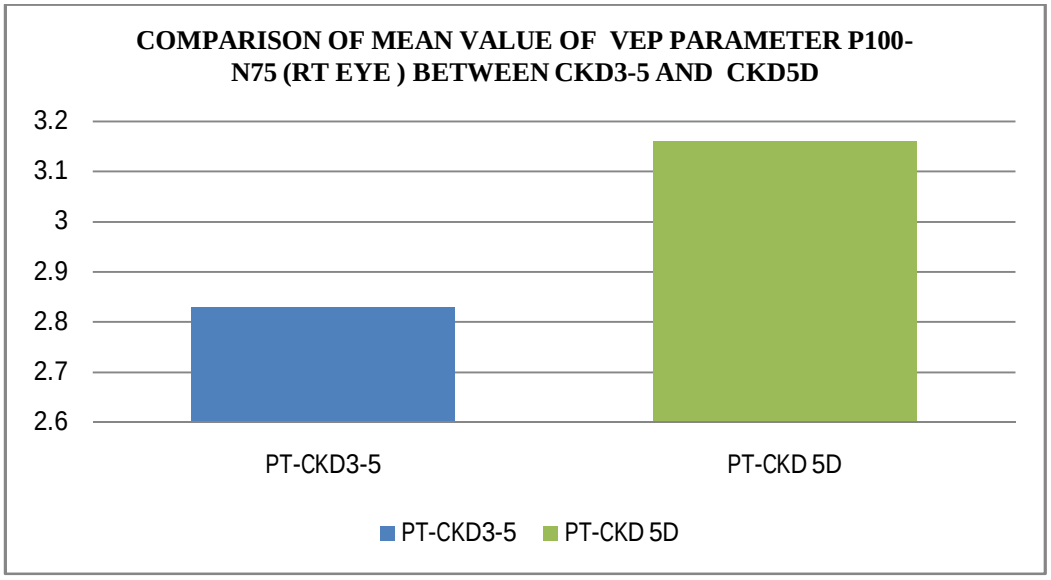


CHART - 20

COMPARISION OF VEP PARAMERTER (N_{75},P_{100}-LT EYE) BETWEEN CKD3-5,CKD5D

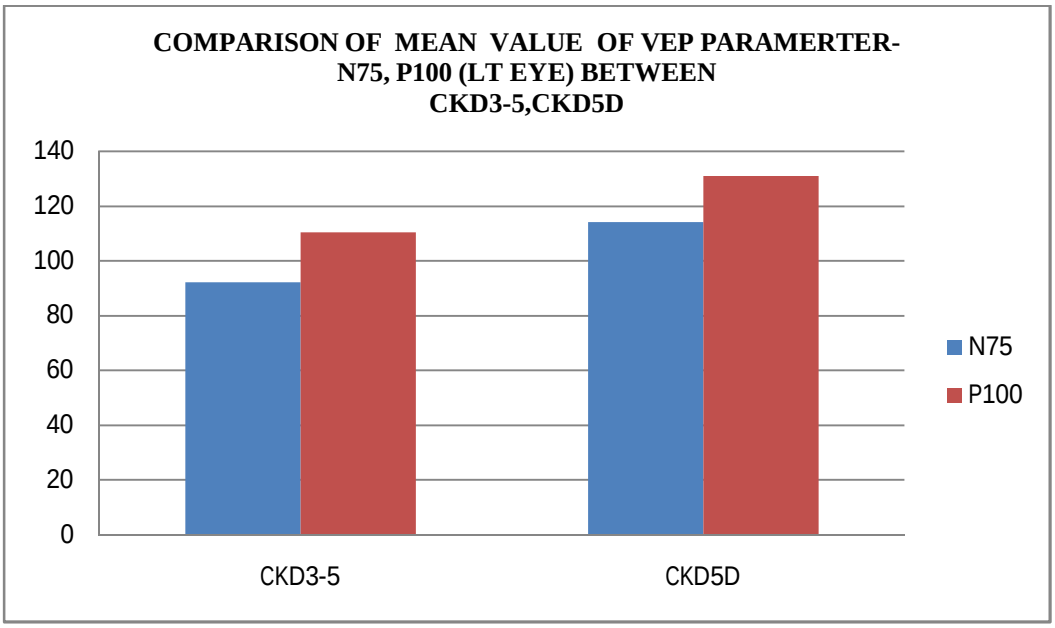


CHART - 21

COMPARISON OF MEAN VALUE OF VEP PARAMERTER – N_{145}(LEFT EYE) BETWEEN CKD3-5,CKD5D

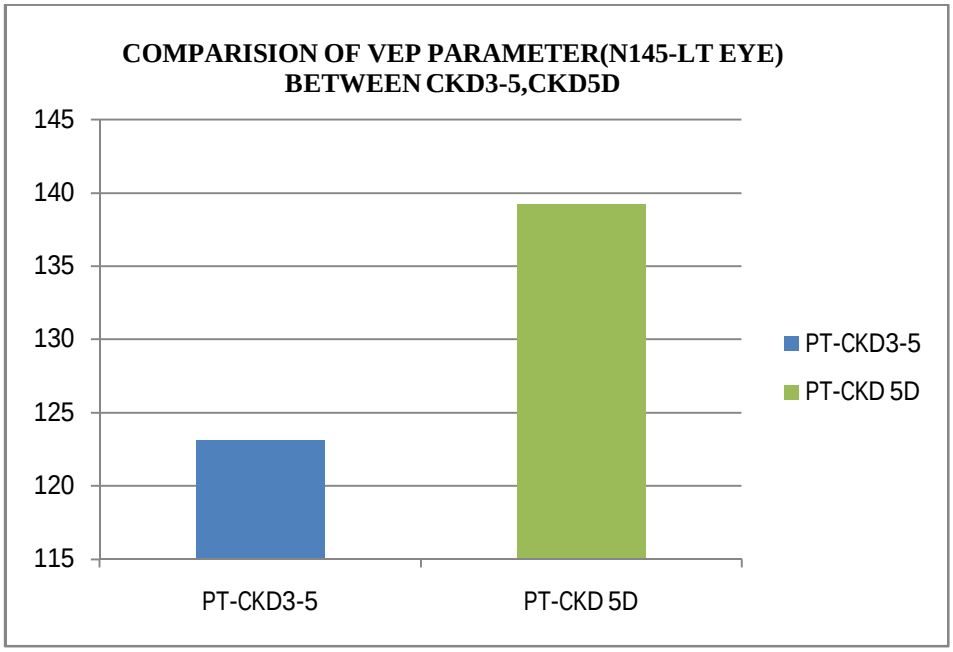


CHART - 22

COMPARISON OF MEAN VALUE OF VEP PARAMERTER –P_{100}-N_{75} (LEFT EYE) BETWEEN CKD3-5,CKD5D

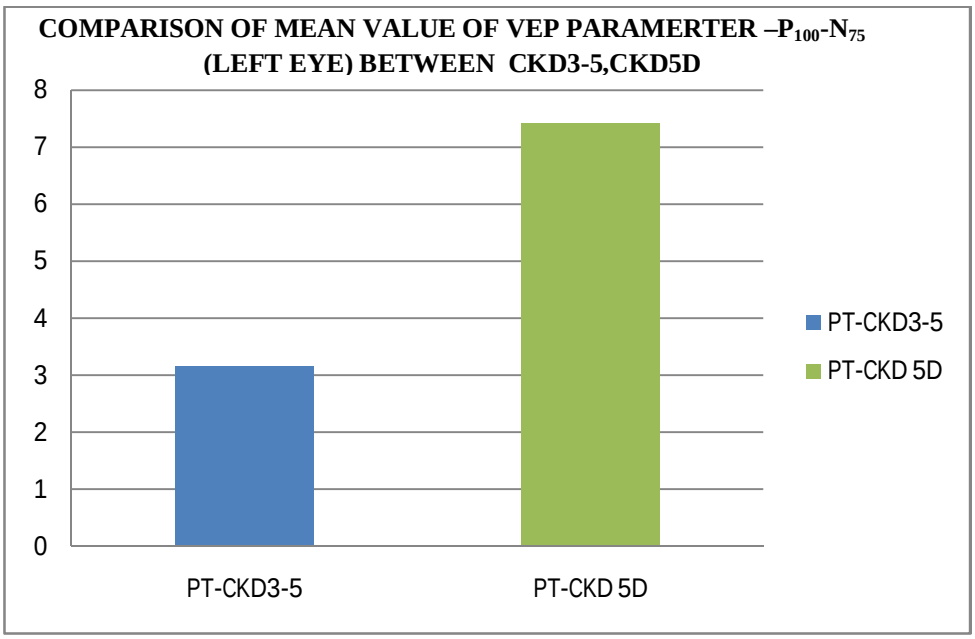


TABLE : 6

COMPARISION OF MEAN VALUES OF BLOOD UREMIC MARKERS BETWEEN CKD3-5 AND CKD 5D

PARAMETER	GROUPS	MEAN	SD	P-value
B.UREA	CKD3-5	92.3	43.95	3.6943
	CKD5D	145.03	35.40	
Sr. CREATININE	CKD3-5	7.0	8.44	0.2001
	CKD5D	8.39	2.96	
Sr. CALCIUM	CKD3-5	6.54	0.54	0.0026*
	CKD5D	5.66	1.13	
Sr. PHOSPHOROUS	CKD3-5	3.89	0.16	0.2294
	CKD5D	3.87	1.04	
Sr.PTH	CKD3-5	84.7	18.61	0.0001**
	CKD5D	110.56	30.50	

**-----Highly significant, * ----- Significant

Blood parameters were significantly elevated in CKD patients stage 5D compared to stages CKD 3-5.

CHART - 23

COMPARISON OF MEAN VALUES OF BLOOD UREA BETWEEN CKD3-5 AND CKD5D

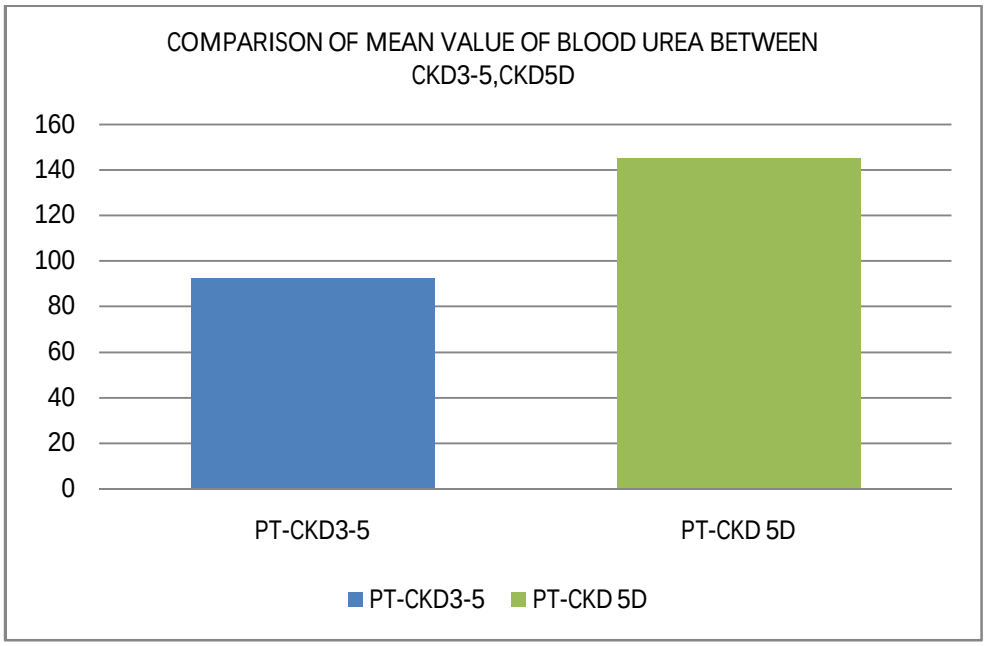


CHART - 24

COMPARISON OF MEAN VALUES OF SERUM CREATININE BETWEEN CKD3-5 AND CKD5D

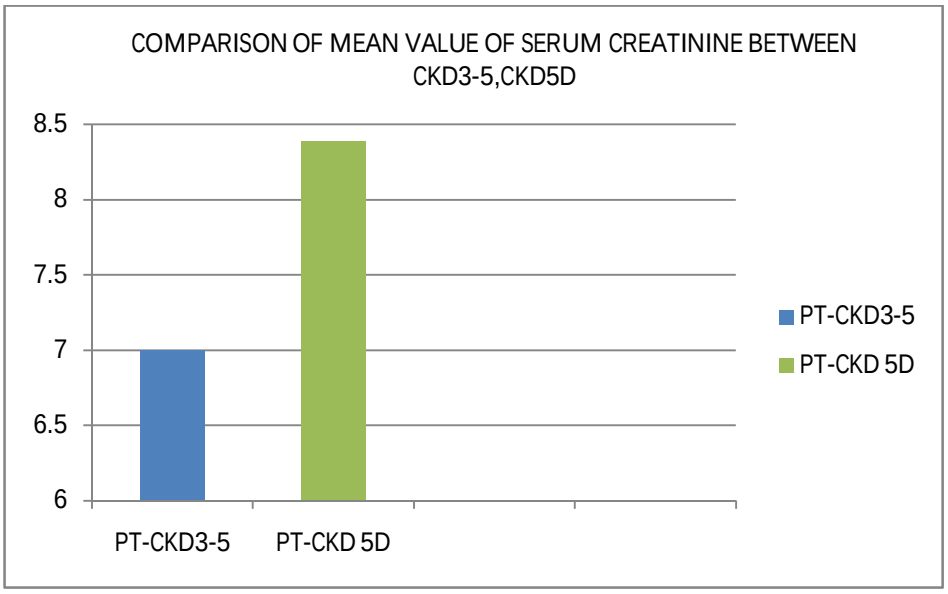


CHART - 25

COMPARISON OF MEAN VALUES OF SERUM CALCIUM BETWEEN CKD3-5 AND CKD5D.

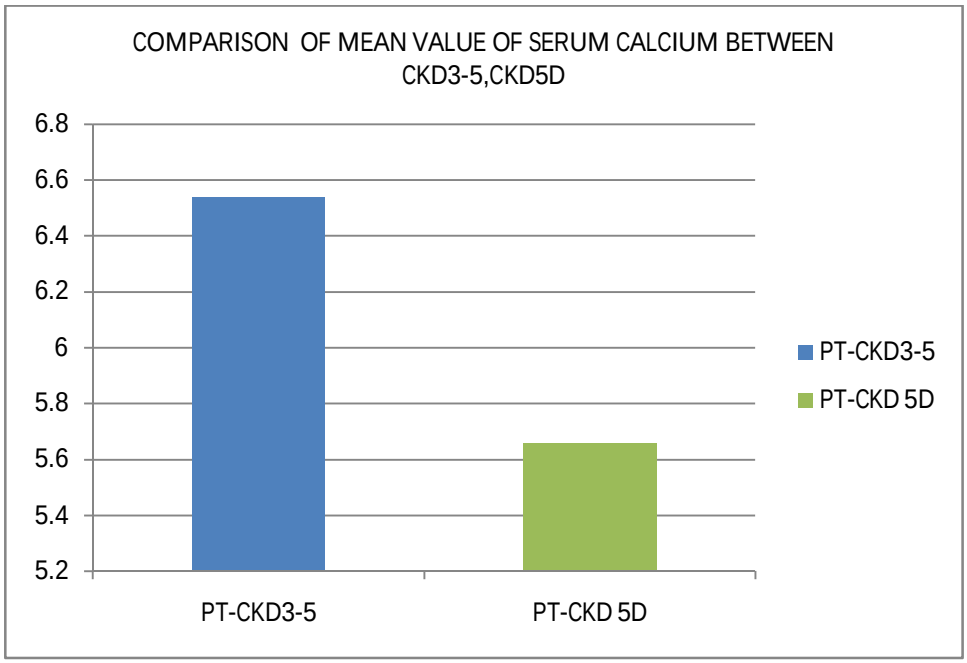


CHART - 26

COMPARISON OF MEAN VALUES OF SERUM PHOSPHOROUS BETWEEN CKD3-5 AND CKD5D.

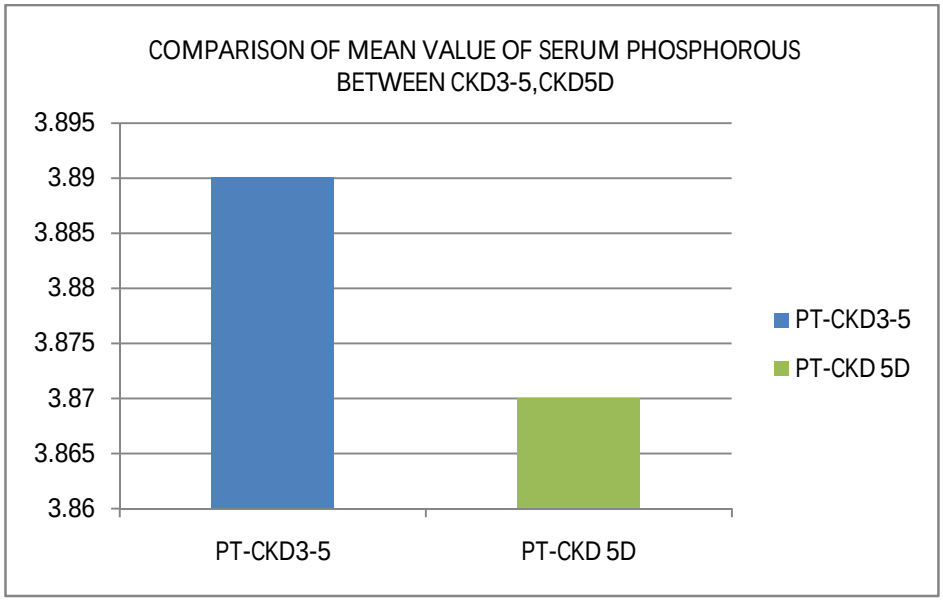
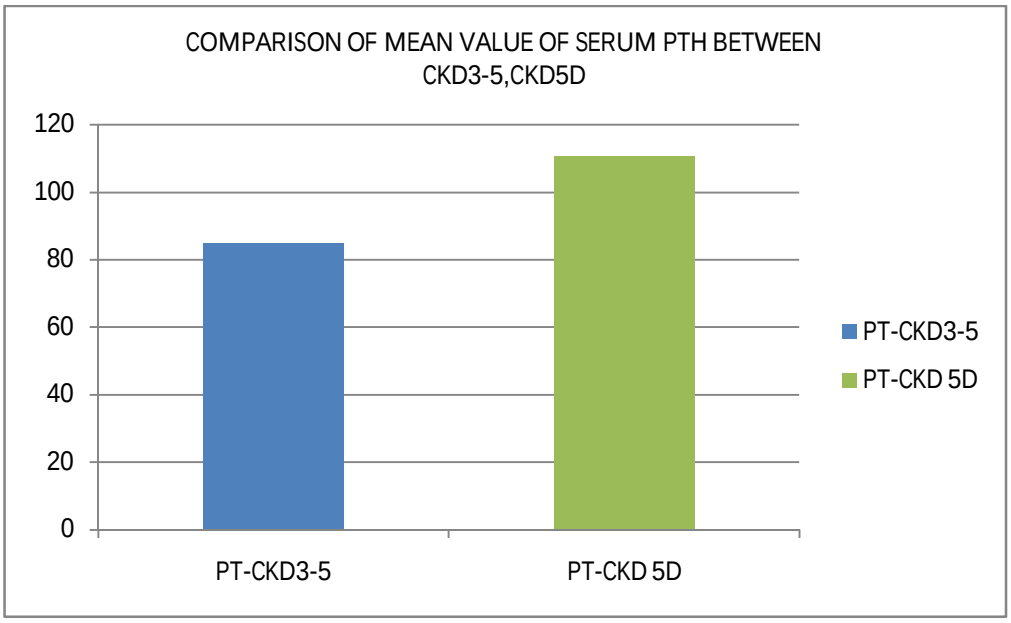


CHART - 27

COMPARISON OF MEAN VALUES OF SERUM PARATHYROID HORMONE (PTH) BETWEEN CKD3-5 AND CKD5D.



CORRELATION BETWEEN VEP PARAMETERS AND BLOOD UREMIC MARKERS (TABLE 7-10)

The following tables shows correlation between VEP Parameters (N_{75},P_{100},N_{145},P_{100}-N_{750}) and Blood uremic markers(Blood urea, Serum creatinine, Serum Parathyroid hormone)

TABLE : 7

CORRELATION BETWEEN N_{75} AND BLOOD UREMIC MARKERS IN CKD3-5 AND CKD5D

PARAMETER		GROUPS	Correlation coefficient and p value
CORRELATION BETWEEN N_{75} AND BLOOD UREA	RIGHT EYE	CKD3-5	r = -0.016, p =0.02
		CKD5D	r= -0.219, p= 2.089
	LEFT EYE	CKD3-5	r= -0.021,P= 0.992
		CKD5D	r= -0.037,p= 0.005
CORRELATION BETWEEN N_{75} AND SERUM CREATININE	RIGHT EYE	CKD3-5	r= 0.074, p= 6.190
		CKD5D	r= -0.028, p= 4.605
	LEFT EYE	CKD3-5	r= 0.376,P=7.641
		CKD5D	r= -0.113, p= 1.884
CORRELATION BETWEEN N_{75} AND SERUM PTH	RIGHT EYE	CKD3-5	r= 0.317, p= 0.001
		CKD5D	r= -0.514 ,p= 0.072
	LEFT EYE	CKD3-5	r= -0.080, P= 0.309
		CKD5D	r= -0.141, p= 0.699

CORRELATION COEFFICIENT AND p- VALUE INTERPRETATION

There was a correlation between N_{75} and blood uremic markers but it was not significant.

TABLE - 8

CORRELATION BETWEEN P_{100} AND BLOOD UREMIC MARKERS IN CKD3-5 AND CKD5D

PARAMETER		GROUPS	Correlation coefficient and p value
CORRELATION BETWEEN P_{100} AND BLOOD UREA	RIGHT EYE	CKD3-5	r = 0.029,p = 0.0001
		CKD5D	r= 0.149, p= 0.039
	LEFT EYE	CKD3-5	r= -0.097,p= 0.099
		CKD5D	r= 0.090,p= 0.234
CORRELATION BETWEEN P_{100} AND SERUM CREATININE	RIGHT EYE	CKD3-5	r= 0.039,p= 1.152
		CKD5D	r= -0.140,p= 2.442
	LEFT EYE	CKD3-5	r= 0.236, p= 1.000
		CKD5D	r= 0.001,p= 3.633
CORRELATION BETWEEN P_{100} AND SERUM PTH	RIGHT EYE	CKD3-5	r= 0.194,p= 1.195
		CKD5D	r= -0.457,p= 0.208
	LEFT EYE	CKD3-5	r= 0.075,p= 0.002
		CKD5D	r= -0.011p= 0.033

CORRELATION COEFFICIENT AND p- VALUE INTERPRETATION

There was a correlation between P_{100} and blood uremic markers but it was not significant.

TABLE : 9

CORRELATION BETWEEN N_{145} AND BLOOD UREMIC MARKERS IN CKD3-5 AND CKD5D

PARAMETER		GROUPS	Correlation coefficient and p value
CORRELATION BETWEEN N_{145} AND BLOOD UREA	RIGHT EYE	CKD3-5	r = -0.172,p = 2.981
		CKD5D	r = 0.135,p= 0.045
	LEFT EYE	CKD3-5	r= 0.012,p= 0.001
		CKD5D	r= -0.200,p= 7.756
CORRELATION BETWEEN N_{145} AND SERUM CREATININE	RIGHT EYE	CKD3-5	r= -0.105,p= 1.550
		CKD5D	r= 0.192,p= 9.764
	LEFT EYE	CKD3-5	r= -0.086,p= 2.986
		CKD5D	r= -0.352,p= 5.984
CORRELATION BETWEEN N_{145} AND SERUM PTH	RIGHT EYE	CKD3-5	r= 0.071,p= 8.180
		CKD5D	r= -0.131,p= 0.134
	LEFT EYE	CKD3-5	r= 0.019,p= 6.800
		CKD5D	r= -0.333,p= 0.014

CORRELATION COEFFICIENT AND p- VALUE INTERPRETATION

There was a correlation between P_{100} and blood uremic markers but it was not significant .

TABLE : 10

CORRELATION BETWEEN P_{100}- N_{75} AND BLOOD UREMIC MARKERS IN CKD3-5 AND CKD5D

PARAMETER		GROUPS	Correlation coefficient and p value
CORRELATION BETWEEN P_{100}-N_{75} AND BLOOD UREA	RIGHT EYE	CKD3-5	r = 0.028,p =5.226
		CKD5D	r = 0.090,p=9.732
	LEFT EYE	CKD3-5	r= 0.079,p= 5.709
		CKD5D	r= -0.037,p= 0.005
CORRELATION BETWEEN P_{100}-N_{75} AND SERUM CREATININE	RIGHT EYE	CKD3-5	r= -0.327,p= 0.011
		CKD5D	r= -0.026,p= 7.392
	LEFT EYE	CKD3-5	r= -0.352,p= 0.019
		CKD5D	r= 0.271,p= 0.738
CORRELATION BETWEEN P_{100}-N_{75} AND SERUM PTH	RIGHT EYE	CKD3-5	r= -0.164,p= 8.239
		CKD5D	r= 0.364,p= 3.926
	LEFT EYE	CKD3-5	r= 0.088,p= 9.244
		CKD5D	r= -0.035,p= 3.092

CORRELATION COEFFICIENT AND p-VALUE INTERPRETATION

There was a correlation between P_{100} and blood uremic markers but it was not significant.

DISCUSSION

7. DISCUSSION

All the subjects (both CKD3-5,CKD5D) included in the study had fulfilled the inclusion criteria .

7.1 CHARACTERISTICS OF STUDY SUBJECTS

The age of the subjects were in the range of 20-60 years for both the study and control groups. The mean and SD of the subjects were (40.67 ± 9.61) for CKD3-5, (39.0 ± 8.36) for CKD5D and (39.23 ± 8.11) for the control group. The mean age in Derici U et al, Schindler S et al and Toupchizadeh et al were almost similar to that of our study [72,89,90].

The mean value for height of subjects were (157.80 ± 3.01) for CKD3-5,(160.73 ± 4.98) for CKD5D and (160.5 ± 7.38) for control group. The mean value for weight of subjects were (54.17 ± 5.17) for CKD3-5, (55.37± 5.47) for CKD5D and (56.00 ± 6.37) for the control group. The mean value of body mass index(BMI) in the CKD3-5 group were (22.17±2.64) for CKD5D, (22.27± 1.59) and (22.20± 2.54) for control group. This was similar to other studies like, Toupchizadeh et al with mean value of height (159.80± 3.11), weight (54.17± 5.17) and BMI (23.27± 1.69)[90]. The ratio of the gender in both the control and study groups were found to be matched.

The patients in the present study were mostly in the adult age group. Henceforth there is a possibility that the noticeable VEP parameter changes and blood estimation of uremic markers are mainly due to progressive nature

and etiology related rather than age-related. This result was found to be similar as observed by toupchizadeh at al[90]. The observations in our study are advantageous and superior than those reported in other studies because the result was achieved with gender in ratio of 1:1 between the study and control group unlike Derici et al, schinder et al with 1.4: 1[72].

7.2 VISUAL EVOKED POTENTIAL STUDY

The subjects without any clinical features of CNS involvement were chosen. Hence the main parameters that were used in assessing the abnormalities of central nervous system were the decreased amplitude and prolonged latency of VEP paramerters (N_{75},P_{100},N_{145},P_{100}-N_{75}) . since the present study record the early changes that occur in the central nervous system (CNS) caused by the progressive, irreversible nature of chronic kidney disease (CKD) the abnormalities observed in this study subjects could be due to the already mentioned nature of CKD and due to the accumulation of uremic neurotoxins (uremic markers).

The mean value of N_{75} , P_{100}, N_{145} was observed with the highly significant (p0.001) value with the mean value of N_{75} in the CKD3-5 group was (117.95± 39.61), for CKD5D (94.97± 35.24) and for the control group it was (76.83± 25.37) in the right eye. The mean value in the CKD3-5 group was (92.39± 36.55), for CKD5D was (114.21± 41.52) and for the control group it

was(68.57± 7.16) in the left eye. With the highly significant P-value (P 0.001) in left eye. P_{100} latency recorded in the right eye was found to be significantly prolonged in CKD3-5 group (134.29 ± 34.29), CKD5D (120.76 ± 31.61) compared with the control group (103.78 ± 24.17) with p 0.001. Also latency recorded in the left eye was observed to be (92.39 ± 36.55)in CKD3-5 group, (114.21 ± 41.52) in CKD5D and for the control group it was (68.57± 7.16) with a highly significant p-value 0.001. The mean value of in the CKD3-5 group was (157.16± 32.82), for CKD5D was (122.67± 37.45) and for the control group it was (137.23± 25.88) in the right eye with the highly significant P-value (P <0.001) . The mean value of N_{145} in the CKD3-5 group was (123.11± 41.63), for CKD5D was(139.24± 53).64 and for the control group (131.02± 9.23) in the left eye with the significant P-value (P 0.002). The mean value of P_{100}- N_{75} in the CKD3-5 group was (2.83±1.16), for CKD5D (3.16± 1.66) and for the control group (9.35± 2.42) in the right eye with the highly significant P-value (P<0.001).In left eye with the mean (3.17 ± 1.15), for CKD5D (7.42 ± 15.49) and for the control group (8.73 ± 0.31) with the significant p-value (P-0.048).

The prolonged latencies of VEP parameters like N_{75},P_{100},N_{145} and decreased amplitude of P_{100}-N_{75} was observed in our study similar to Derici U et al where he found altered P_{100} latencies in dialysis patients. The altered VEP suggests axonal degeneration of central nervous system [72].

According to Di Paolo B et al who concluded that it is possible to sense the CNS complications by various evoked potentials and an elevated PTH supporting my study. The altered VEP parameters in our study were suggestive of neural degeneration which correlated well with the uremic status of the patients[76].

Seymen P et al noticed prolonged latency and altered amplitude of VEP parameter in their research. In his study fifty-nine patients diagnosed with CKD of different etiologies were separated into 3 sets according to the treatment modalities as pre-dialysis group, HD group and CAPD group. There was no considerable disparity between VEPs of the CAPD and HD groups. Diminished VEPs demonstrating visual neuronal system damage were observed, when CRF progresses. This study concluded that the CNS abnormalities can be analyzed and supplementary therapeutic modalities could be followed using VEPs during the treatment of CRF [77].

Mahnaz Talebi b et al stated that in comparison with the control group, there were exclusively significant prolonged N_{145} and P_{100} latencies in hemodialysis and peritoneal dialysis group. He concluded that optic pathway can be affected by chronic renal failure and there would be no marked difference in optic pathway involvement between patients undergoing hemodialysis and peritoneal dialysis. This may indicate the equal effects of hemodialysis and peritoneal dialysis upon subclinical damages of optic pathway[72]. My study was done only on haemodialysis subjects where we noticed prolonged latencies of P_{10O} ,N_{75} ($P < 0.001$) and reduced P_{100} amplitude($P < 0.001$) [91].

Toupchizadeh Vahideh et al in their study showed VEP abnormality in 35% of hemodialysed patients. They concluded that the **etiologic factors associated with abnormality might be circulating toxins or demyelination.** So this research suggest that the CNS involvement could be due to demyelination or uremic toxins[90].

Kuba et al. assessed that there was significant prolonged P_{100} latency and decreased P_{100} amplitude in hemodialysis group, compared to controls .On the other hand, the outcome of current study established that there was significant prolonged P_{100} latency and decreased P_{100} amplitude in hemodialysis group, compared to controls [92] .

7.3 BLOOD ESTIMATION OF UREMIC MARKERS(UREMIC NEUROTOXINS)

Due to the progressive nature of CKD, the central nervous system complications can be sensed by the estimation of uremic markers(uremic neurotoxins).The main parameters that were used in assessing the abnormalities of central nervous system apart from the evoked potential were the blood levels of uremic markers (Blood Urea, Serum creatinine, Serum Parathyroid hormone(PTH).In order to explain the pathogenesis of secondary hyperparathyroidism (SHPT) blood levels of serum calcium, serum phosphorous was estimated.

The mean value of Blood Urea in the CKD3-5 group was (92.30± 43.95), for CKD5D (145.03± 35.40) and for the control group (24.20± 0.8) with the significant P-value ($P < 0.001$) . The mean value of Serum Creatinine in the CKD3-5 group was (7.00± 8.44), for CKD5D was (8.39 ± 2.96) and for the control group (0.88± 0.05) with the significant P-value ($P < 0.001$). The

mean value of Serum Calcium in the CKD3-5 group was (6.54± 0.54), for CKD5D (5.66 ± 1.13) and for the control group (9.09± 0.28) with the highly significant P-value (p<0.001) . The mean value of Serum Phosphorous in the CKD3-5 group was (7.00± 8.4), for CKD5D was (8.39± 2.96) and for the control group (0.88± 0.05) with the significant P-value (P <0.001) . The mean value of Serum Parathyroid hormone in the CKD3-5 group was (84.70± 18.61), for CKD5D (110.56 ± 30.50) and for the control group (50.00 ± 0.83)with the significant P-value (P <0.001). The mean value of Serum Parathyrid hormone in the CKD3-5 group was (84.70± 18.61), for CKD5D (110.56±30.50) and for the control group (50.00 ± 0.83) with the highly significant P-value (P <0.001) .

The mean value of Blood Urea in the CKD3-5 group was (92.3±43.95), for CKD5D was (145.03 ±35.40) with the P value (P 3.69) which is not significant. The mean value of Serum Creatinine in the CKD3-5 group was (7.0 ±8.44), for CKD5D (8.39 ±2.96) with the P value (P 0.2001) which is not significant. The mean value of Serum calcium in the CKD3-5 group was (6.54 ±0.54), for CKD5D (5.66 ±1.13) with the significant P value (P 0.001). The mean value of Serum phosphorous in the CKD3-5 group was (3.89 ±0.16), for CKD5D (3.87±1.04) with the P value (P 0.2294) which is not significant. The mean value of Serum parathyroid hormone (PTH) in the CKD3-5 group was

(84.7 ±18.61), for CKD5D (110.56 ± 30.50) with the P value (P - 0.0001) which is highly significant.

M.H. Rahman et al noticed a significant elevation of PTH (P <0.001), significantly lowered serum calcium levels (P<0.001), significantly raised serum phosphorous levels (P <0.001) in ESRD patient. He concluded that increased PTH levels occur even in the beginning path of CRF and progressive hypocalcemia and hyperphosphatemia are the commencing factors for the progress of hyperparathyroidism which concurs with our study.

Cosmo L.Fraser et al, Smogorzewski M, et al, Barbara Rever, MD et al ,Sprague SM et al stated that the nervous system dysfunction serves as a main cause of morbidity and mortality. They observed that there was an elevated Parathyroid hormone among their study subjects[69,94,95,96].

The blood levels of uremic markers (uremic neurotoxins) like urea, creatinine, parathyroid hormone were elevated in both CKD3-5 on medical treatment and CKD5D on dialysis compared to controls. When compared among study groups it was greatly elevated in the CKD5D groups. These uremic markers along with secondary HPT are more frequently noticed in progressive CKD which may be challenging to dietary, medical or dialytic treatment and may even continue subsequent to renal transplantation [33].

There was a positive correlation between VEP parameters (N_{75},P_{100},N_{145},P_{100}-N_{75}) and blood uremic markers (uremic neurotoxins like Urea, Creatinine, Parathyroid hormone(PTH) in our study concurring with Rossini et al and Di Paolo et al[67,76].

Thus from this study we end up stating that the subclinical involvement of central nervous system can be assessed by VEP and uremic markers in patients with progressive stages of CKD3-5 and CKD5D.

CONCLUSION

8. CONCLUSION

From this study it is evident that there is a definite central nervous system impairment as shown by the prolonged latency and reduced amplitude of VEP parameters N_{75},P_{100},N_{145},P_{100}-N_{75} in the CKD patients. In both the CKD groups, stages 3-5 and stage 5D, there are significant abnormalities in the VEP recordings. Even though there is a positive correlation between the VEP parameters and the severity of uremic status, it is not statistically significant in this study.

The subclinical central nervous system involvement could be due to the progressive accumulation of uremic neurotoxins which predispose to the underlying pathology, axonal degeneration and demyelination. As the severity of the disease based on the blood levels of uremic toxins correlate with the VEP abnormalities , it is suggested that VEP can be done as a routine screening tool to detect the early subclinical involvement of central nervous system in these patients. This will enable us to plan for appropriate management for preventing eventual development of uremic encephalopathy in them. Due to the progressive and irreversible nature of CKD, these patients have to be considered for renal transplantation which is better than medical treatment or dialysis in improving their uremic status.

Thus it can be concluded, that the routine screening by recording of VEP in CKD patients for neurological involvement will be useful in planning

their effective management which will reduce the morbidity and can improve the quality of their life.

SUMMARY

9. SUMMARY

This study was conducted to evaluate the central nervous system involvement by recording VEP in CKD patients ,30 patients stages3-5 on medical therapy and 30 patients stage 5D on dialysis. Their uremic status was assessed by the blood levels of uremic markers namely urea , creatinine and parathyroid hormone(PTH).These findings were compared with that of a group comprising 30 age and gender matched controls.

The altered VEP parameters with prolonged latency of N_{75},P_{100},N_{145} and reduced amplitude of P_{100}-N_{75} was noticed in both CKD groups. The blood levels of uremic markers was elevated significantly when compared to controls. This suggests that the involvement of central nervous system in these patients. By recording VEP, we can identify the central nervous system involvement at an early stage

The impairment of the central nervous system correlate with the level of uremic status which is going to produce the neurological impairment in CKD patients.

From the results, significant influence of uremic markers and changes in VEP proves central nervous system involvement. This study suggests that in

future the recording of Visual Evoked Potential may be utilized as a routine screening test for CKD patients. It also clearly indicates both study groups CKD stages 3-5 on medical therapy and stage 5D on dialysis may be considered for renal transplantation.

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ANNEXURES

PROFORMA

Proforma for the study subjects:

1.S.No.

2.I.D(given by investigator):

3.Name:

4.Age:

5.Sex:

6.In patient/Out patient:

7.Address&Contact No:

8.Occuption:Not working/Housewife/Professional/Others:

9.Educational Qualification:uneducated/educated

10.Per capita income:Number of family members: Net family income:

11.Complaints:

12.Past history:

13.Family history:

14.Social habits:smoker/non-smoker/alcoholic/non- alcoholic

15.Treatment history:

16.General examination:O/E:

Height :

Weight :

Built :

Nourishment :

BMI :

Respiratory rate :

Pulse rate :

Blood pressure :

Temperature :

Clinical examination:

17.Investigation:

Blood investigation:

BLOOD UREA -----

SERUM CREATININE -----

SERUM CALCIUM -----

SERUM PHOSSPHOROUS ------

SERUM PARATHYROID HORMONE----

நோயாளி தகவல் தாள்

ஒளியினால் தூண்டப்படும் மின் அதிர்வுகளை சிறுநீரகம் பழுதடைந்த நோயாளிகளுக்கு பதிவு செய்யும் ஆய்வு.

நோயாளிகளுக்கான தகவல்:

இது ஆற்றல் மிக்கதாகவும், பாதுகாப்பாகவும் இருப்பதாக அறியப்படுகிறது. இந்த ஆய்வின் மூலம் பெறப்படும் அறிவானது, உங்களைப் போன்று பல்லாயிரக்கணக்கான நோயாளிகளுக்கு நன்மை தருவதாக அமையும்.

ஆய்வு நடைமுறைகள்:

இந்த ஆய்வில் ஒளியினால் தூண்டப்படும் மின் அதிர்வுகளை சிறுநீரகம் பழுதடைந்த நோயாளிகளுக்கு பதிவு செய்கிறோம்.

பதிவேடுகளை இரகசியமாக பாதுகாத்தல்:

உங்கள் மருத்துவ பதிவேடுகள் மிகவும் இரகசியமாக வைத்துக் கொள்ளப்படும். மற்றும் பிற மருத்துவர்கள், விஞ்ஞானிகள், இந்த ஆய்வின் தணிக்கையாளர்கள் அல்லது ஆராய்ச்சி ஆதரவாளர்களின் பிரதிநிதிகள் ஆகியோரிடம் அவை வெளிப்படுத்தப்படும். பெயரை வெளியிடாமல் இந்த ஆய்வின் முடிவுகள் அறிவியல் பத்திரிக்கைகளில் பிரசுரிக்கப்படும்.

ஆய்வில் உங்கள் பங்கேற்பு மற்றும் உங்கள் உரிமைகள்:

இந்த ஆய்வில் உங்கள் பங்கேற்பு தன்னிச்சையாக மற்றும் காரணங்கள் எதையும் கூறாமலேயே நீங்கள் இந்த ஆய்விலிருந்து எந்த ஒரு நேரத்திலும் விலகிக் கொள்ளலாம். உங்களை கவனித்துக் கொள்ளும் மருத்துவருடன் முழுமையாக ஒத்துழைக்க வேண்டுமென கேட்டுக் கொள்கிறோம்.

(ஆய்வில் பங்கேற்பவர் கையொப்பம் அல்லது பெருவிரல் பதிவு)

ஒப்புதல் படிவம்

திரு / திருமதி ..... ஆகிய நான் இந்த மருத்துவ பரிசோதனைக்கு உட்பட மனப்பூர்வமாக ஒப்புதல் தெரிவிக்கிறேன். இந்த மருத்துவ ஆய்வின் நோக்கம், ஒளியினால் தூண்டப்படும் மீன் அதிர்வுகளை சிறுநீரகம் பழுதடைந்த நோயாளிகளுக்கு பதிவு செய்வதாகும்.

இந்த மருத்துவ பரிசோதனையில் கேட்கப்படும் கேள்விகளுக்கு பதிலளிக்க வேண்டுமென்றும், இங்கு சேகரிக்கப்பட்ட அனைத்து விபரங்களும் எந்த ஒரு அறிவியல் கூட்டத்திலும் தெரிவிக்கலாம் என்பதையும் தெரிந்து கொண்டேன். எந்த ஒரு சூழ்நிலையிலும் இந்த ஆய்விலிருந்து விலகிக் கொள்ளலாம் என்பதனையும், அதன் பின்னரும் எந்தவித இடையூறுமின்றி மருத்துவ சிகிச்சையை இந்த மருத்துவமனையில் தொடர்ந்து மேற்கொள்ளலாம் என்பதையும் புரிந்து கொண்டேன்.

(ஆய்வில் பங்கேற்பவர் கையொப்பம் அல்லது பெருவிரல் பதிவு)

MASTER SHEET

CKD STAGES 3 TO 5 ON MEDICAL THERAPY

S.NO	AGE	SEX	HT	WT	BMI	RT EYE				LT EYE				Urea	Sr.Cr	Ca	Po4	PTH
						N75	P100	N145	P100-N75	N75	P100	N145	Pioo-N					
1	45	M	155	54	32	88.8	118.1	160.6	5.19	157.5	173.1	185.6	5.39	89	5.2	6.8	3.9	99
2	60	M	155	52	23	86.9	100	107.5	6.46	8.75	100	105	2.47	85	3.1	6.7	3.8	89
3	30	M	156	52	23	75	188.8	203.8	3.26	69.4	62.5	96.9	3.8	86	3.2	6.7	3.8	80
4	60	M	154	53	22	195.6	206.9	221.3	2.07	70	81.9	93.1	3	59	2.8	6.8	3.9	125
5	23	M	162	50	20	105.6	119.4	128.1	2.12	101.3	102.5	110	2.94	188	5.2	6.9	3.8	110
6	32	M	162	50	20	100.6	124.4	140.6	4.37	89.4	236.9	266.9	5.67	58	2.8	6.8	3.7	109
7	60	M	156	50	21	205	112.5	226.3	0.96	103.1	90.6	100.6	0.17	58	1.8	6.2	3.8	99
8	45	M	158	50	20	142.5	155	163.1	2.38	105	118.1	126.9	2.5	43	6.3	6.3	3.8	87
9	25	F	154	50	21	106.3	118.1	126.9	3.14	150.1	170.6	181.9	2.92	136	6.8	6.1	4.1	57
10	44	M	162	68	26	108.8	118.1	127.5	2.67	51.9	65	71.3	4.52	100	4.6	6.8	3.9	88
11	45	M	156	56	23	124.4	135	150.6	1.73	130	136.9	142.5	1.88	75	31.2	6.5	3.8	90
12	20	M	156	56	20	157.5	170.6	178.1	2.15	88.1	100.6	115.6	3.39	140	6.7	6.6	3.9	89
13	40	M	156	54	22	105	120	142.5	2.33	62.5	83.1	104.4	4.16	100	3.4	6.7	3.8	88
14	44	M	162	68	26	69.4	82.5	96.9	2.68	33.1	46.9	63.1	4.25	37	1.8	6.8	3.8	67
15	45	F	153	60	24	75.6	104.4	135	4.16	74.4	103.1	130	3.78	180	9.6	6.8	3.9	102
16	40	M	160	55	24	73	96	126	2.59	100	108.9	117.5	4.38	49	3.9	6.9	3.8	56
17	37	F	165	65	24	200.4	224	238	4.03	184	191.3	206.9	2.63	78	1.8	6.9	3.9	60
18	37	F	158	50	24	141.9	154.4	167	4.41	54.4	64.4	71.3	1.61	124	3.8	3.9	4	60
19	36	F	160	50	20	70.6	100	159.4	3	88.8	100	105	2.91	60	1.9	6.6	4.3	56
20	33	M	162	50	20	105.6	119.4	128.1	2.12	101.3	102.5	110	2.94	188	5.2	6.9	3.8	110
21	44	F	158	50	20	142.5	155	163.1	2.38	105	118.1	126.9	2.5	43	6.3	6.3	3.8	87
22	44	M	156	56	20	157.5	170.6	178.1	2.15	88.1	100.6	115.6	3.39	140	6.7	6.6	3.9	89
23	46	F	156	56	23	124.4	135	150.6	1.73	130	136.9	142.5	1.88	75	31.2	6.5	3.8	90
24	35	F	158	50	20	142.5	155	163.1	2.38	105	118.1	126.9	2.5	43	6.3	6.3	3.8	87
25	37	F	160	50	20	70.6	100	159.4	3	88.8	100	105	2.91	60	1.9	6.6	4.3	56
26	37	F	156	54	22	105	120	142.5	2.33	62.5	83.1	104.4	4.16	100	3.4	6.7	3.8	88
27	46	F	156	56	20	157.5	170.6	178.1	2.15	88.1	100.6	115.6	3.39	140	6.7	6.6	3.9	89
28	46	F	156	54	22	105	120	142.5	2.33	62.5	83.1	104.4	4.16	100	3.4	6.7	3.8	88
29	40	F	160	50	20	70.6	100	159.4	3	88.8	100	105	2.91	60	1.9	6.6	4.3	56
30	44	F	156	56	23	124.4	135	150.6	1.73	130	136.9	142.5	1.88	75	31.2	6.5	3.8	90

CKD STAGE 5D ON DIALYSIS

S.NO	AGE	SEX	HT	WT	BMI	RT EYE				LT EYE				Urea	Sr.Cr	Ca	PO4	PTH
						N75	P100	N145	P100-N75	N75	P100	N145	P100N75					
1	30	F	156	44	18	44.4	62.1	98.8	4.77	60	83.3	130	63.84	184	11.5	6	3.8	186.4
2	44	M	156	52	21	89.4	108.1	130.6	2.78	126.3	137.5	147.5	1.24	190	12.1	5.9	3.9	120
3	47	F	156	55	23	56.3	73.8	95	2.47	128.1	178.1	2.35	7.28	192	11.9	6.4	3.9	156
4	25	F	156	52	21	90	100.6	112.5	2.67	125	136.3	143.1	2.68	136	6.8	6.3	3.2	86
5	39	F	160	50	20	88.1	100	105.6	7	90	100	106.3	7.08	104	6.8	6.1	3.1	120
6	32	M	156	54	22	106.3	118.1	124.4	1.93	108.8	118.1	130.6	2.47	123	14.3	6.2	3.8	98
7	55	M	156	54	22	70.6	82.5	92.5	2.04	164.4	153.1	143.1	0.94	139	6.8	6.1	3.8	99
8	31	M	156	48	20	65	81.3	113	1.93	210.6	225	240	2.06	136	6.8	6.2	3.2	124
9	32	F	156	56	24	93.8	130	88.1	2.38	123.8	136.3	150.6	4.64	60	10.8	6.5	3.8	124
10	39	M	160	55	22	88.1	100	117.5	2.9	199.4	211.3	232.5	3.05	181	10.3	6.5	3.8	111
11	38	M	160	55	22	155	180	212.5	6.07	130.9	146.9	164.4	1.31	114	9.69	6.8	6.6	134
12	47	F	153	60	24	75.6	104.4	135	4.16	74.4	103.1	130	3.78	180	9.6	6	3.8	156
13	26	M	160	55	23	141.3	153.4	165.6	2.66	105	110.1	126.3	1.48	180	10.2	6	3.9	87
14	37	F	160	55	24	123.8	136.9	147.5	2.83	88.8	100	100.5	2.44	166	8.4	6.2	3.9	88
15	19	M	168	55	20	141.9	152.5	168.8	2.6	80.8	149	169.8	2.92	156	9	6.1	3.1	92
16	36	M	160	55	22	196.9	200.1	214	1.84	75.9	100.9	128.9	2.52	124	10.1	6.8	3.9	85
17	38	F	168	55	22	86.3	130	76	3.9	69.4	81.3	88.8	2.03	104	9.9	6.8	3.9	100
18	35	M	168	55	23	105.6	116.9	131.9	7.5	129	100.3	123	3.82	124	5.2	6.8	3.9	99
19	55	M	168	55	22	72.5	140	90	2.15	121.1	136.4	141	2.29	104	5.8	4.3	5.6	85
20	44	F	168	55	23	89.4	100.6	118.3	6.37	87.5	100.6	105.6	2.7	94	4.6	4.7	3.5	100
21	44	F	168	55	22	71.9	130	96.3	1.31	105.6	117.5	123.8	1.1	104	5.8	4.1	4.2	88
22	40	M	160	55	21	155	159.4	172	2.09	212.4	232	256	9.88	124	5.2	4.1	3.9	86
23	40	M	165	65	24	85	120	118.8	2.12	140	160	176	6.45	124	5.2	3.2	3.6	86
24	44	F	165	65	24	83.1	106.3	154.4	2.09	68.8	99.4	156.9	3	156	6.2	3.2	5.5	88
25	44	M	165	65	24	80	138	66	1.88	69.4	100.6	189	3.76	124	3.2	4.2	4.6	85
26	44	F	165	65	24	125.6	139.9	142.5	1.51	90	81.9	143.1	3.25	156	6.1	3.9	3.9	85
27	44	M	165	65	24	78	135	68	2.8	124.4	135	148.1	2.16	146	3.8	6.8	4.4	86
28	30	F	156	44	20	44.4	139	98.8	4.77	60	83.3	130	63.84	184	11.5	6	3.8	186.4
29	44	M	156	52	24	89.4	108.1	130.6	2.78	126.3	137.5	147.5	1.24	190	12.1	5.9	3.9	120
30	47	F	156	55	23	56.3	73.8	95	2.47	128.1	178.1	2.35	7.28	192	11.9	6.8	3.3	156

CONTROL

S.NO	AGE	SEX	HT	WT	BMI	RT EYE				LT EYE				Urea	Sr.Cr	Ca	PO4	PT
						N75	P100	N145	P100-N75	N75	P100	N145	P100-N75					
1	40	F	153	70	29	66.3	93.8	137.5	8.4	66.4	92.5	126	8.89	24	0.9	8.9	3.9	5
2	44	M	153	65	27	65	92.5	118.6	10.47	65	91.3	120	8.89	24	0.9	9	4	5
3	47	F	164	66	25	114.4	144.4	196.3	6.92	90	93	135	9.02	26	0.9	9.2	3.9	5
4	25	M	166	66	24	79.4	139.9	167.4	15.58	67	99	139	8.9	24	0.8	9.3	3.8	4
5	39	M	166	66	24	127.6	152.5	205	5.73	70	91.3	145	8.9	26	0.9	8.9	3.8	4
6	32	F	164	62	23	117.5	124.4	135	8.34	69	99	135	9.02	22	0.9	9	3.5	5
7	55	M	152	52	22	168.1	191.3	211.8	8.02	69	100	138	8.89	24	0.9	9.2	4	4
8	31	F	156	52	21	118.9	130	150	9.9	91.3	113.1	136.3	8.67	26	0.8	9.3	3.7	4
9	32	M	134	50	21	68.1	88.8	120.6	8.85	86.3	99	139	8.73	24	0.8	9	3.5	5
10	39	F	155	52	22	66.9	92.8	111.3	7.39	69	93.8	135	8.89	26	0.7	9.2	4	5
11	38	M	160	55	22	66.3	93.8	137.5	7.9	66.4	92.5	135	7.89	24	0.9	8.9	3.9	4
12	47	M	153	60	24	64.9	92.5	118.7	10.45	65	91.3	120	8.89	24	0.9	9	3.8	5
13	26	F	160	55	21	66.2	93.8	137.5	9.9	66.4	92.5	130	8.79	24	0.9	8.9	3.7	5
14	37	M	160	55	21	65	92.5	118.8	10.43	65	91.3	120	8.89	24	0.9	9.9	4	4
15	19	M	168	55	20	66.4	93.8	137.5	0.3	66.4	92.5	139	8.29	24	0.9	8.9	3.9	4
16	36	F	160	55	22	65	92.5	118.9	10.47	65	91.3	120	8.89	24	0.9	9	3.8	5
17	38	M	168	55	19	66.2	93.8	137.5	8.9	66.4	92.5	140.3	8.92	24	0.9	8.9	3.9	5
18	35	M	168	48	19	65.1	92.5	118.8	10.47	65	91.3	120	8.89	24	0.9	9	3.8	5
19	55	F	168	55	19	66.1	93.8	137.5	8.6	66.4	92.5	135	9.02	24	0.9	8.9	3.9	5
20	44	M	168	47	19	64.9	92.5	118.9	10.47	65	91.3	120	8.89	24	0.9	9	3.8	4
21	44	M	168	55	19	66.3	93.8	137.5	10.2	66.4	92.5	143	8.29	24	0.9	8.9	3.9	4
22	40	F	160	48	21	65	92.5	118.5	10.46	65	91.3	120	8.89	24	0.9	9.4	3.9	5
23	40	F	165	55	24	66.2	93.8	137.5	10.6	66.4	92.5	143	8.29	24	0.9	8.9	3.8	5
24	44	F	165	55	24	64.9	92.5	118.7	10.44	65	91.3	120	8.89	24	0.9	9	3.9	5
25	44	M	165	55	24	66.4	93.8	137.5	10.3	66.4	92.5	139	8.29	24	0.9	8.9	3.7	4
26	44	M	165	55	24	64.8	92.5	118.8	10.46	65	91.3	120	8.89	24	0.9	9.4	3.9	5
27	44	F	165	65	24	66.3	93.8	137.5	10.5	66.4	92.5	139	8.09	24	0.9	8.9	3.9	5

28	30	F	156	44	18	65.1	92.5	118.8	10.49	65	91.3	120	8.89	24	0.9	10	3.8	5
29	44	M	156	52	21	66.3	93.8	137.5	8.9	66.4	92.5	139	8.39	24	0.9	8.9	3.9	5
30	44	F	156	55	23	65.2	92.5	118.8	10.44	65	91.3	120	8.89	24	0.9	9	3.9	5