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To study Serum Vitamin D3, Intact Para-Thyroid Hormone & Osteocalcin In All Stages Of Chronic Kidney Disease Patients

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Abstract

Chronic kidney disease (CKD) is become major health problem in world wide. Progressive loss of kidney funcations leads to reduced production of calcitriol (1,25 dihydroxyvitamin D) and imbalance in serum calcium and phosphorous levels which are associated with progression of renal failure. **Aim:** - The present study aim is to study Serum, Vit.D_3, Intact parathyroid hormone & Osteocalcin in all stages of chronic kidney disease patients.

Material and Methods:- The case control study was carried out in Department of Biochemistry in association with Department of Nephrology, Bharati Vidyapeeth (Deemed To Be University) Medical College and Hospital, Sangli., Maharashtra, India during the period of 2018 to 2020 with approval of Intuitional Ethical commette. 175 patients of CKD (35 patients of each stage) in the age group of 20 to 60 years were included. Besides the kidney funcation parameters serum VitD_3, iPTH.& Osteocalcine were measured on Maglumi 800 Chemiluminescence immunoassay. The statistical analysis was done using the ANOVA , "t" and Chi-Square test.

Results:- The results exhibited significant reduction in Serum Vit.D_3, level with significant increase in iPTH & Osteocalcin in all stages of CKD patients as compared to normal levels..

Conclusion:- The results exhibited the reduction of Vit.D_3 levels lead to development of severe secondary hyperparathyroidism and osteodystrophy with progression in kidney disease

Keywords: CKD ,Serum. Vit D3, Serum Osteocalcin & Serum Intact parathyroid hormone (iPTH)

Introduction

Chronic kidney disease (CKD) is become major health problem in world wide. (1) CKD is characterized by progressive deterioration of kidney function, which develops over months or years leads eventually to end stage renal failure. [1,2] The KDOQI guidelines CKD is classified in 5 stages based of GFR.[2]The high mortality rate among patients in end stages of CKD who finally requires dialysis.[2,3] CKD is associated with many kinds of metabolic changes, cardiovascular disease and bone mineral disorders. The term CKD associated mineral bone disease is abnormalities in bone and mineral seen in progressive kidney disease which altered levels of calcium, phosphorous, parathyroid hormone and vitamin D. The kidney and the skeleton have intimate biological relationships that can affect bone strength as well as renal physiological functions.[3,4]

PTH is the primary calcium- and phosphate regulating hormone produced by chief cells in the parathyroid glands. PTH is the major storage, secreted, and biologically active form of the hormone, and molecular weight is 9500 Dalton.

The hormonal gene product of parathyroid cells is 115 amino acid i.e. pre-Proparathyroid hormone. In cisternal space of endoplasmic reticulum the ezyme

clipase removes the presequence, leaving 90 amino acid Proparathyroid hormone structure. Proparathyroid hormone is converted to parathyroid hormone in golgi apparatus by proteolytic removal of the remaining 6 amino acids at the amino terminal, here 84 amino acids polypeptide is secretion in secretory granules or its free form.[5,6] 1-84 PTH which actually induces hormonal action within the target cells, various PTH fragement of other lengths are also found in the systemic circulation. 7-84 PTH is directly secreted from parathyroid cells and binds to PTH-1 receptors with a binding affinity comparable to 1-84 PTH. The extracellular calcium levels critically affects the switching of 1-84 PTH and 7-84 PTH secretion in parathyroid cells. The total PTH level is increased under a hypocalcaemia condition. The change in 1-84 PTH levels is enhanced by the extracellular calcium levels because the extracellular calcium levels sensed by calcium sensing receptor. Cinacalcet hydrochloride (CH) binds to the calcium sensing receptor and it transmit false information of elevated extracellular calcium levels into cells, as a result CH suppresses the parathyroid secretion and production in parathyroid cells. This calcium sensing receptor is hypothesized by CH, so secretion of 1-84 PTH is suppressed and 7-84 PTH secretion is promoted. The intact PTH assay detects both 1-84 PTH and 7-84 PTH fragments.[5,6] Enhanced PTH secretion occurs in response to hypocalcaemia, hypophosphatemia, and decrease in serum 1,25dihydroxyvitamin D (1,25(OH)2D)level, whereas high serum levels of calcium, calcitriol, orFGF23 suppress PTH secretion. The extracellular concentration of ionized calcium is the most essential determinant of the minute to minute oscillatory secretion of PTH, which tends to be blunted in CKD patients. Once secreted, PTH is rapidly cleared from plasma through cellular up take by liver and kidneys, where PTH undergoes intracellular proteolysis into active amino- and in active carboxyl-terminal PTH fragments. PTH fragments is the N-terminal PTH fragment rapidly degraded in by the liver and kidney, where carboxyl-terminal (C-terminal) PTH fragments are mainly released into the blood and eventually excreted by the kidney. N-terminal PTH fragments have short plasma half-lives between 2 and 4 minutes, whereas the C-terminal PTH fragments have a half-life of several hour even longer in patients with CKD due to decreased renal clearance.[5]In chronic kidney disease patients not undergoing dialysis have shown a slight increases in parathyroid hormone. PTH levels are associated with an increased cardiovascular risk, regardless of the serum levels of calcium and phosphorus and vitamin D therapy. The monitoring PTH levels from the early stages of CKD is important and preventing any mineral metabolism disorders. [6]

Vitamin D is a pre hormone obtained through sunlight via skin synthesis and diet. It is activated in 2 step process, involving first 25-hydroxylation in liver to produce25-(OH)vitamin D and then 1-hydroxylation, which occur in the kidney, to produce the active product 1,25 vitamin D or calcitriol. The traditional dogma was that the 1,25 renal activated end product is responsible for all effects of the active vitamin D hormone in the body. These effects were restricted to regulation of bone and mineral metabolism. The kidney is major target organ for both the classical and non-classical actions of vitamin D, The non-classical effects of vitamin D may play a relevant role in the mortality and morbidity of patients with CKD, specifically affecting the possible progression of renal disease and cardiovascular disease, which is major cause of death.[7] Abnormalities in vit.D metabolism play a major role in the pathogenesis of secondary hyperparathyroidism in CKD because the gradual and progressive decline in 1,25-dihydroxyvitamin D in the course of CKD.(8)As kidney disease develops, there is decreased functional renal mass and a reduction in renal 1α-hydroxylase activity and thus in renal production of calcitriol at very early CKD stages. .Life expectancy in patients with CKD is limited by development of disturbances of mineral metabolism, during the progression of their disease. It is associated with bone loss and fractures, cardiovascular disease, immune suppression, and increased mortality.[7,8]

Osteocalcin (OC) is a 49-amino acid, vitamin K-dependent calcium-binding protein which was secreted by mature osteoblasts. It is a specific biomarker of bone turn-over and bone formation. OC plays a critical role in maintaining the bone mineralization rate and inhibiting hydroxyapatite crystallization and cartilage mineralization.[9,10] It is also implicated in calcium ion homeostasis. Osteocalcin acts as a hormone in the body, act as sex hormone in male and causing beta cells in pancreas to

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release more insulin. Some studies shows that higher serum osteocalcin levels are relatively well correlated with increases in bone mineral density (BMD) during treatment with anabolic bone formation drugs for osteoporosis. In many studies, Osteocalcin is used as a preliminary biomarker on the effectiveness of a given drug on bone formation to measure of osteoblasts activity[11,12] The Biochemical parameters i.e Serum Vit.D_3 , intact-parathyroid hormone(iPTH), & Osteocalcin is useful to monitor the CKD patients.

Aim: - The present study aim is to study Serum, Vit.D_3, Intact parathyroid hormone & Osteocalcin in all stages of chronic kidney disease patients.

Material And Methods:-

The present study was carried out at the Department of Biochemistry and Department of Nephrology Bharati Vidyapeeth (Deemed To Be University) Medical College and Hospital, Sangli., Maharashtra, India during the period 2018 to 2020 with approval of Institute of Ethical Committee (IEC/ Dissertation 2017-18/246). In period over 2 year. 175 of CKD patients. (35 patients of each stage) in the age group of 20-60 yrs, will be included. Staging of CKD and other than factors will be done by Nephrologists. Patients information was filled in Performa. Estimation of VitD_3, iPTH & Osteocalcin was done by Maglumi 800 Chemiluminescence immunoassay. Serum Vit.D3, Osteocalcin, & iPTH values are compared with standard and controls of kit.

Statistical Analysis:-

Statistical comparisons were performed with spreadsheet software (Excel, Microsoft) .The statistical analysis was done using the ANOVA , "t" and Chi-Square test. All results were calculated as mean ± SD and a "p" value of <0.05 was considered statistically significant.

Results :-

In this study 175 Diagnosed patients of chronic kidney disease of I to V stages. (35 patients of each stage) in the age group of 20-60 yrs, in which 117 Male & 58 Female will be included

Table no- 1) Stagewise values of biochemical parameter in CKD patients

Sr. No	Stage	S.Vit.D_3 (ng/ml)	S.Osteocalcin (ng/ml)	S.Intact parathyroid Hormone iPTH) (pg/ml)
1	I	38.93±20.35	8.13±13.65	9.76±23.48
2	II	31.00±16.67	10.45±11.74	11.52±13.59
3	III	27.55±11.84	12.94±20.54	21.44±24.00
4	IV	24.63±12.38	18.95±9.93	53.16±26.85
5	V	20.80±16.73	39.67±22.60	73.08±42.51

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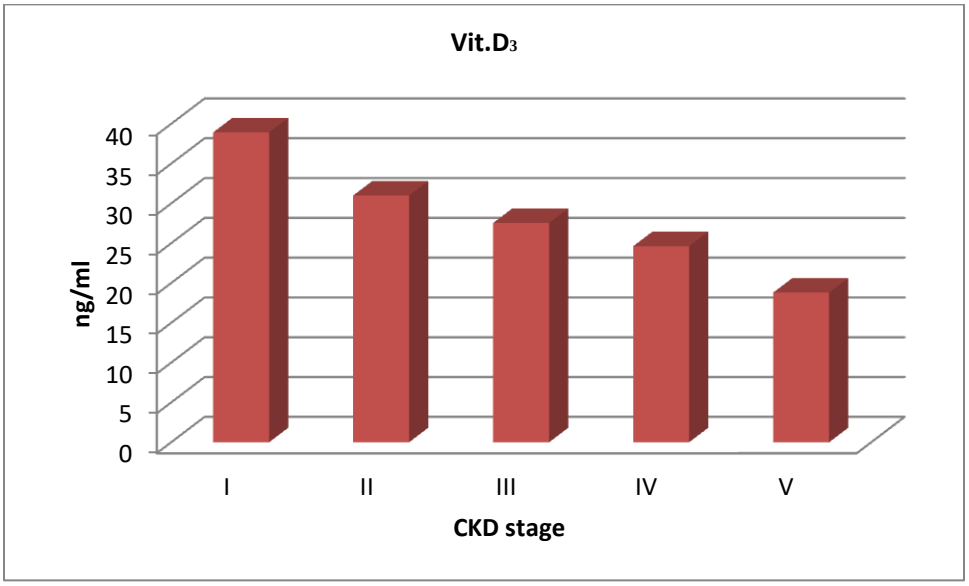
		F=4.100	**F=22.417**	**F=37.427**	
		(p=0.003)	**(p=0.000)**	**(p=0.00)**	

Table No.1:- Table and graph shows Serum Vit.D3, Osteocalcin,& iPTH Mean±SD values in I to V stagesin CKD patients. S. Vit.D_3 is significant ($p<0.003$) in all stages as compared to I to V stages. S. Osteocalcin & S. iPTH is highly significant.($p<0.000$) in all

Table No.1:- Table and graph shows Serum Vit.D3, Osteocalcin & iPTH Mean±SD values in I to V stages in CKD patients. S. Vit.D_3 is significant decreased values ($p<0.003$) and S. Osteocalcin & S. iPTH is significant ($p<0.000$) increased in all stages as compared to I to V stages. Serum Vit.D_3, Osteocalcin,& iPTH values are compared with standard and controls of kit.

Graph no-1. Stage wise values of S.Vit.D_3 in CKD patients



Graph no-2. Stage wise values of S.Osteocalcin in CKD patients

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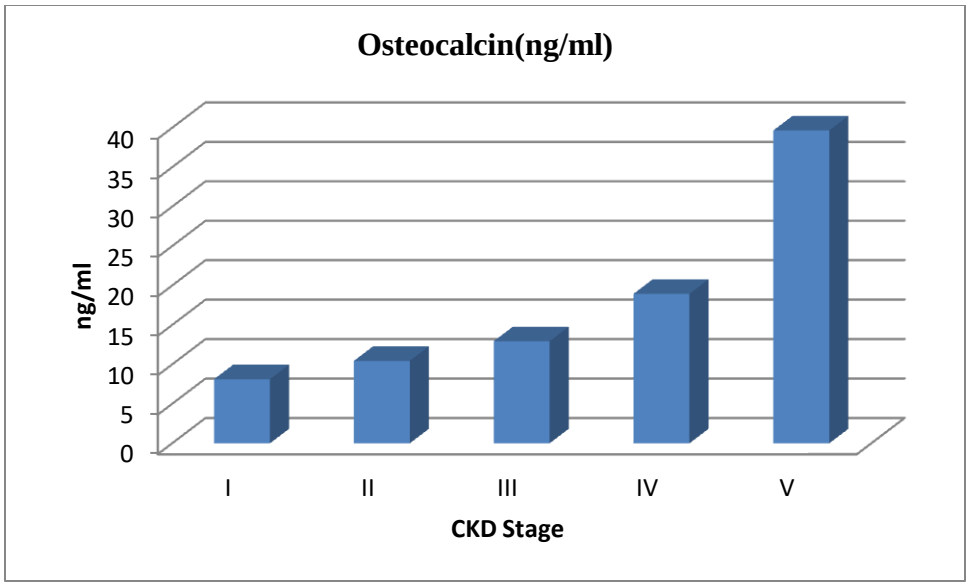
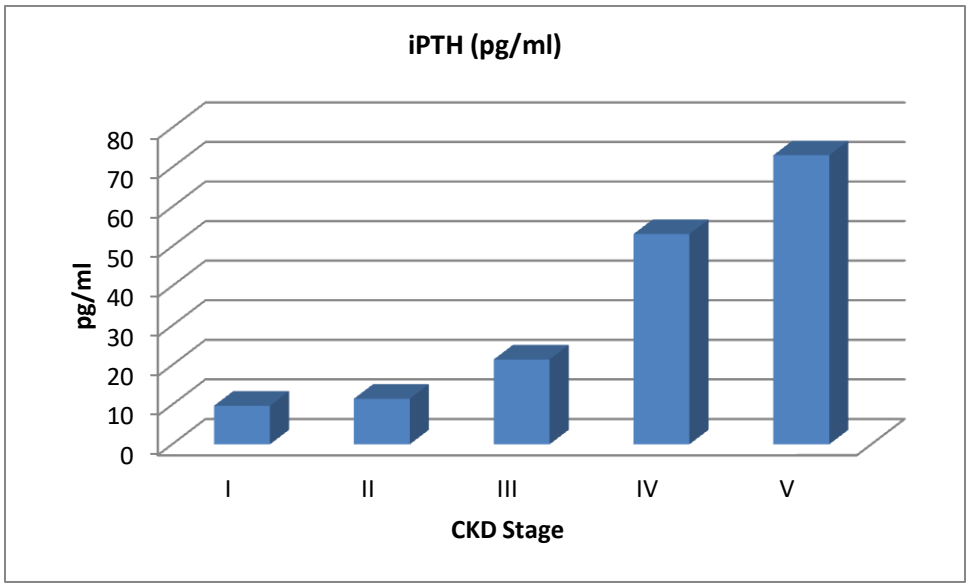


Graph no-3. Stage wise values of S. Intact Parathyroid Hormone (iPTH) in CKD patients



Discussion:-

Chronic kidney disease is a modern day global epidemic and it is now recognized as public health issue has significant morbidity and mortality implications. Mineral and bone disorders are common in CKD mineral and bone disorder (MBD). These abnormalities begin to appear even in early stages of CKD. [13]In present study we observed S. Vit.D3 is significant in all stages ($p<0.003$) increase values in as compared to I to V stages. S. Osteocalcin & S. iPTH in I to V stages is highly significant. ($p<0.000$). Serum Vit.D3, Osteocalcin,& iPTH values are compared with standard and controls of kit. Serum Vit.D3 levels is low and increased levels of iPTH seen due to progression in stages of CKD. The kidney function decrease and glomerular filtration rate falls ultimately the kidney decrease

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phosphate excretion. The increase levels of FGF23 reduce the activity of 1 α hydroxylase which converts 25D to active 1.25D. 1.25D acts to regulates secretion of parathyroid hormone. The decrease levels of 1.25D and low levels of calcium leads rise in PTH levels. The increased PTH levels of 1.25D and low levels of calcium leads affect bone metabolism causing a bone disease associated with increased bone turnover. [7,8]Alteration in vitamin D metabolism is one of the key features of CKD–MBD is major clinical disorder. The kidneys are rich with vitamin D receptors and play a major role in turning vitamin D into active form to maintain balance of calcium and phosphorus in body by controlling absorption of these minerals from the food you eat and regulates parathyroid hormone (PTH). In CKD patients their ability to activate vitamin D is lost. Without the activated vitamin D to control calcium and phosphorus levels in blood, iPTH will try to maintains and go out of range.[13,14,15]The excess calcium in the blood stream. calcium can deposit in soft tissues. These deposits or calcifications cause cardiovascular and bone complications in CKD the parathyroid glands may sense that there is not enough calcium in the blood and produce excess parathyroid hormone which tells the body to pull calcium out of the bones and put it in the bloodstream. This excess of iPTH can cause secondary hyperparathyroidism which can result in bone pain and weak bones that fracture easily. So it is necessary to monitored PTH levels every three months or more. [16,17]

Table no-1 and graph shows increased levels of serum Osteocalcin in progression stages of CKD patients. The increased levels of serum Osteocalcin patients with CKD can be related to decreased renal clearance and increased bone metabolism. Osteocalcin contains three residues of the amino acid gammacarboxyl glutamic acid (Gla). The Gla residues, in the presence of calcium, facilitate its binding to hydroxyapatite and eventual deposition in the mineralized bone matrix. To analyze the effectiveness of emerging bone forming anabolic agents, serum levels of Osteocalcin are used to determine the bone formation rate. The Osteocalcin is present either as carboxylated or as under carboxylated forms. CKD patients usually present with complications of bone anomalies that vary from fractures due to increased bone fragility to extra skeletal calcification due to mineral ion deregulation. These skeletal anomalies in CKD–mineral bone disorder (CKD–MBD) are partly related to decreased osteoblastic differentiation that impairs the anabolic responses of the bone[9,10,11] The accumulation of serum Osteocalcin in patients with CKD can be related to decreased renal clearance and increased bone metabolism or a combination of both.. In patients with CKD, the progressive increase in serum Osteocalcin levels closely corresponded with intact PTH and alkaline phosphates levels [9] The abnormalities in bone in CKD include the effects of high levels of PTH on bone, which results in the high and low turnover bone disease and skeletal abnormality. Some cases shows that the demonstrate mineralization defects and show frank osteomalacia. This skeletal abnormality can give rise to hyperparathyroidism on bone together with mineralization defects, and is known as mixed renal osteodystrophy.[18,19,20] This study is designed to examine the frequency and severity of the skeletal demineralization in patients of I to V stages of CKD by measurements of serum levels of S. Vit.D_3, Osteocalcin & iPTH.

Conclusion -.

The results of our study indicate that serum levels of Osteocalcin & iPTH is higher and Vit.D_3 is decreased when progression in CKD stages. The results exhibited the reduction of Vit.D_3 levels lead to development of severe secondary hyperparathyroidism and osteodystrophy with progression in kidney disease

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