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Efficacy of Intravenous Vitamin-D Selective Receptor Activator (Paricalcitol) In Management of Secondary Hyperparathyroidism in Hemodialysis Patients, Single Center Experience.

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ABSTRACT

Background: secondary hyperparathyroidism (SHPT), a complication of chronic kidney disease (CKD) and is characterized by not only increased serum levels of intact parathyroid hormone (iPTH), but also may cause skeletal and cardiovascular complications. Deficiency of calcitriol (1, 25-hydroxy vitamin D) caused by impaired renal function, a main factor in the pathogenesis and pathophysiology of secondary hyperparathyroidism (SHPT) is associated with poor outcomes in hemodialysis patients. Therapy with vitamin D receptor (VDR) activators, including calcitriol or the selective VDR activator paricalcitol, has been associated with improved survival in patients with CKD on hemodialysis.

PATIENTS AND METHODS: single center cross over observational study of 28 patients on regular Hemodialysis in nephrology unit in Dubai hospital, the patient stopped all vitamin-D supplementations and calcium containing phosphate binder for 2 weeks prior to initiation and for the whole study period, non calcium based phosphate binder was continued. Initial dose of selective VDRA (PARICALCITOL) is 0.04 to 0.1 mcg/kg body weight (average total dose 2.8 – 7 mcg) administered as a bolus dose post hemodialysis twice to three times per week according to initial parathyroid hormone level Titration weekly dose (micrograms) calculated by dividing most recent i-PTH level (pg/ml)/80.

RESULTS : analyzing the data at start and end of trial period 48 weeks showed that there was significant reduction of serum I-PTH from (491.210±144.690 pg/dl) at start of the trial to (142.610 ±41.519pg/dl) at 48 weeks with *P- value (<0.001)* . Serum calcium increased from (8.343± 0.654mg/dl) at the start of the study to (8.629±0.534mg/dl) at 48 weeks but without statistical significance *P- value (0.006),* same occurred with serum phosphate which showed insignificant rise with phosphate level at start of the test(7.264±1.695mg/dl) and at 48 weeks (7.279±1.800mg/dl) with *P-value(0.975).*

CONCLUSION: It could be concluded that use of intravenous vitamin D selective receptor activator (Paricalcitol) is effective in reducing serum I-PTH level in hemodialysis patients. Serum Ca++ and phosphorus levels were statistically insignificant.

Key words: Paricalcitol, vitamin D selective receptor activator, secondary hyperparathyroidism, Hemodialysis.

INTRODUCTION

Abnormalities in calcium, phosphorus, PTH, and vitamin D metabolism (collectively referred to as disordered mineral metabolism) are common in patients with chronic kidney disease (CKD). Changes in the laboratory parameters of chronic kidney disease – bone mineral disease (CKD–MBD) may begin in CKD stage 3, but the presence of abnormal values, the rate of change, and the severity of abnormalities are highly variable among patients. To make the diagnosis of CKD–MBD, one or more of these laboratory abnormalities must be present however the other two essential components for the diagnosis are bone abnormalities and vascular calcification. [1, 2] Secondary hyperparathyroidism (SHPT), a complication of chronic kidney disease (CKD) is characterized by not only increased serum levels of intact parathyroid hormone (i-PTH), but also may cause skeletal and cardiovascular complications .[3-4] SHPT is associated with increased mortality in end-stage kidney disease as well as in earlier stages of CKD .[5,6]

Deficiency of calcitriol (1, 25-hydroxy vitamin D) caused by impaired renal function, a main factor in the pathogenesis and pathophysiology of secconrady hyperparathyroidism (SHPT) is

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associated with poor outcomes in hemodialysis patients. Therapy with vitamin D receptor (VDR) activators, including calcitriol or the selective VDR activator Paricalcitol, has been associated with improved survival in patients with CKD on hemodialysis. Evidence from epidemiological studies further suggests that the causes for the survival benefit from VDR activator therapy go beyond the control of iPTH and calcium–phosphorus homoeostasis. [7,8]

Hypercalcemia is a common side effects associated with high dose vitamin d therapy , however the selective vitamin d activator such as Paricalcitol have less incidence of hypercalcemia associated with its use especially in Hemodialysis patients , it is also associated with improved outcome in this cohort of patients than the use of conventional calcitriol .[9,10]

An alternative approach to the treatment of SHPT in patients on Hemodialysis is the use of cinacalcet a calcimimetic agents acting by stimulation of the calcium sensing receptors in the parathyroid gland thus suppressing IPTH level with low dose vitamin D to counteract tendency to hypocalcaemia associated with its use .[11-13]

A large multicenter randomized trial published recently have studied the effect of using vitamin d selective receptor activator (Paricalcitol) versus the use of cinacalcet with low dose vitamin D in the management of secondary hyperparathyroidism and concluded that Paricalcitol based therapy with or without supplemental cinacalcet compared with the combination of cinacalcet and low-dose vitamin D provides superior reduction of iPTH to target levels with minimal effects on calcium in patients with SHPT requiring Hemodialysis . [14]

In order to study the effect of using the VDRA (PARICALCITOL) on serum i-PTH in our cohort of patients we conducted study on patients receiving hemodialysis in our center.

PATIENTS AND METHODS

Single center cross over observational study of 28 patients on regular hemodialysis in nephrology unit in Dubai hospital. Patient inclusion criteria done on patients of 18 years old or older, on CKD on regular HD for at least 3 month, were on conventional vitamin D therapy (calcitriol) without satisfactory effects. Informed consent was signed by the patient enrolled in the study and local ethical committee approval of the trial was obtained. Patient's results confidentiality were assured.

The patient stopped all vitamin-D supplementations and calcium containing phosphate binder for 2 weeks prior to initiation and for the whole study period, non calcium based phosphate binder was continued. Initial dose of selective VDRA (PARICALCITOL) is 0.04 to 0.1 mcg/kg body weight (average total dose 2.8 – 7 mcg) administered as a bolus dose post hemodialysis twice to three times per week according to initial parathyroid hormone level Titration dose (micrograms) most recent iPTH level (pg/ml) divided by 80 , If a satisfactory response is not observed, the dose may be increased by 2 to 4 mcg / week at 2- to 4-week intervals during any dose adjustment period, serum calcium and phosphorus levels should be monitored more frequently every 2 weeks , and if an elevated calcium level > 10.5 or a Ca × P product greater than 75 is noted, the drug dosage immediately reduced or interrupted until these parameters are normalized, see diagram (1&2). Afterwards should be reinitiated at a half previous dose , from twice weekly back to once weekly or omit for 1-2 weeks till normalize Ca^{++} and Ca x Ph (wash out period). Our primary end point was achievement of target I-PTH level of 3-9 times reference range as recommended by K-DIGO CKD-MBD (the kidney disease initiatefes for global outcome, chronic kidney disease mineral bone disease) management guidelines. [1]

All data were then tabulated, computerized and statistically analyzed using SPSS 16 software.

RESULTS

Table 1 shows that 28 patients were on regular HEMODIALYSIS with mean age (52.955±10.986) years and of them, 17 patients were female (60.7%) and 11 patients were male (39.3%).

Table (2) shows the data at start and end of trial period (48 weeks). This indicates that there was significant reduction of serum I-PTH with values of 491.210±144.690 pg/dl at start of the

trial compared to 142.610 ±41.519 pg/dl at 48 weeks with *P- value (<0.001)* .
Serum calcium (8.343± 0.654mg/dl) and serum phosphorus (7.264±1.695mg/dl) at the start of the study were statistically insignificantly increased compared to their values (8.629±0.534mg/dl) for calcium and (7.279±1.800mg/dl) for phosphorus at 48 weeks.

Table (3) and figure (2) shows a significant rise in serum calcium at 12 weeks of therapy (9.379±0.984 mg/dl) from the baseline at start with *(P- value <0.001)* , and stayed at higher values throughout the study with tendency to normalization at 48 weeks which we attribute to the higher doses of Paricalcitol used in initial phases of the trial and lower maintenance doses reached at end of trial period with most patients achieving target I-PTH level .
Simultaneously Serum phosphate showed initial rise at the initial phase of the trial however statistically insignificant.
On the other hand, serum intact parathyroid hormone I-PTH showed initial significant drop at 12 weeks (253.93±82.944pg/dl) from the baseline level (491.21±144.690 pg/dl) with *P-value* (<0.001) . There was consistent reduction of I-PTH throughout the follow up period with tendency for homogenous distribution of the study cohort as shown in figure (1) which illustrates the distribution of I-PTH values throughout the study period and the achievement of target levels at 48 weeks.

.DISCUSSION

The current study demonstrated the efficacy of VDRA (Paricalcitol) in reduction of serum I-PTH levels and that associated hypercalcemia and/or hyperphosphatemia is insignificant especially if instructions to the patients were clearly given to avoid all vitamin D and Calcium supplementation and strict compliance to the non calcium containing phosphate binders prescribed.
Data of the present study are largely supported by the work of *MARKUS et al*, in the IMPACT trial that showed similar results both in the intravenous and oral Paricalcitol strata. (14)
ROSE et al, have shown similar results in a cohort of patients on HEMODIALYSIS and peritoneal dialysis with achievement of the target end point without significant side effects. (15)

Shinaberger et al, correlate the high initial serum I-PTH and the use of initial higher dose of Paricalcitol to the occurrence of hypercalcemia and hyperphosphatemia in his cohort of patient, a conclusion we could not yield in our study. (16)
Teng et al , in a survival study demonstrated the beneficial effect of using vitamin D and vitamin D receptor activator (Paricalcitol) in improving the outcome and survival benefit in patient on regular Hemodialysis , we could not yield such conclusion in our study due to limited duration and small sample size .(17)

CONCLUSION

From ongoing results and discussion it could be concluded that the use of intravenous vitamin D selective receptor activator (Paricalcitol) is effective in reducing serum I-PTH level in Hemodialysis patients while calcium and phosphorus levels statistically insignificant. Weak point of this trial was the small sample size and the lack of control group to demonstrate the drug effects clearly and omit other factors that may share in reduction of I-PTH level.
In addition and as CKD-MBD is the main target in treatment of patient with secondary hyperparathyroidism further studies including risk reduction for fractures and vascular calcifications and long term survival benefit should be conducted.

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Tables and figures

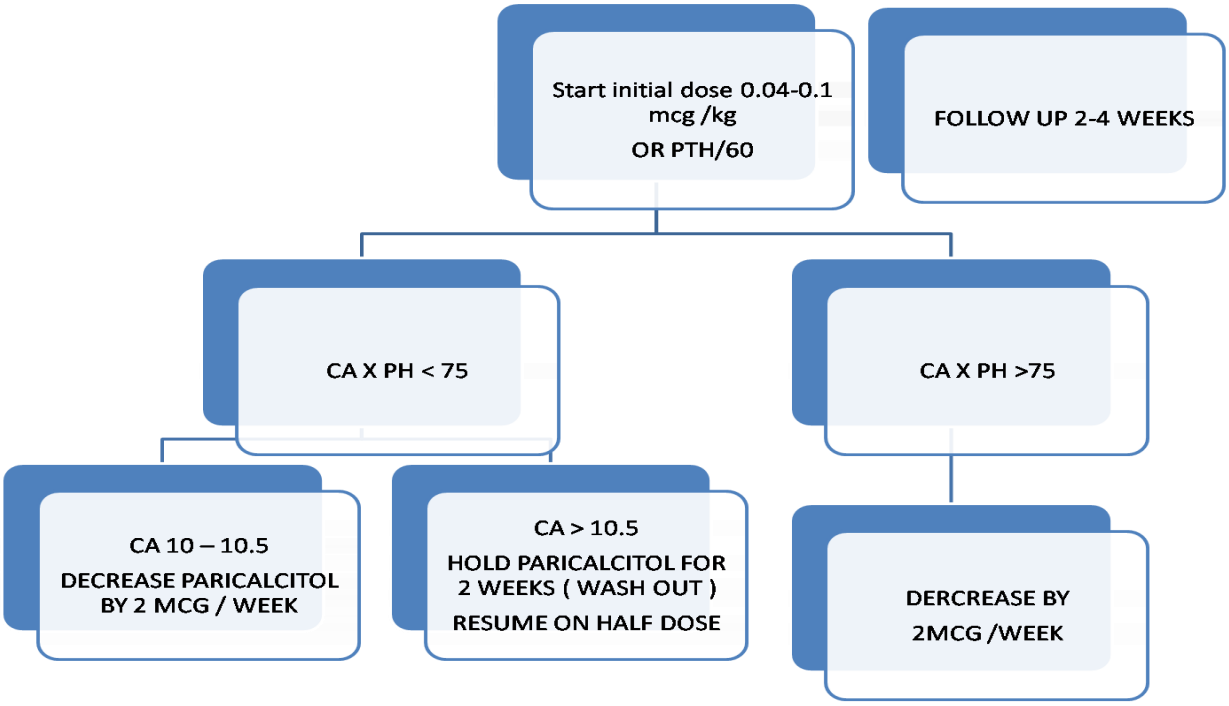


Diagram (1) showing initial dosing and dose adjustement in study design

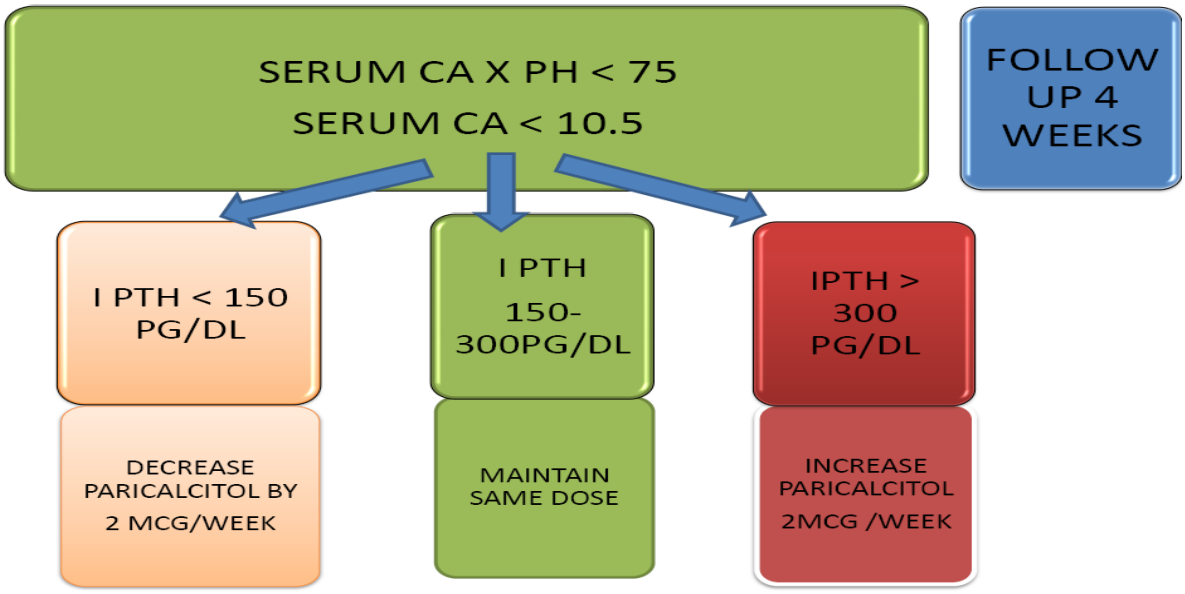


Diagram (2) follow up at 4 weeks and dose adjustement in according to I-PTH LEVEL Table and figures

TABLE (1) DESCRIPTIVE STATISTICS OF THE STUDY GROUP				
	Minimum	**Maximum**	**Mean**	**Std. Deviation**
AGE (years)	**38**	**72**	**52.955**	**10.986**
CALCIUM (mg/dl) 0 WEEK	**6.8**	**9**	**8.3429**	**0.654**
PHOSPHATE(mg/dl) 0 WEEK	**5**	**10.9**	**7.2643**	**1.69**
PARATHYROID (pg/dl) **HORMONE 0 WEEK**	**298**	**710**	**491.21**	**144.68**
CALCIUM(mg/dl) 12 WEEKS	**7.9**	**11**	**9.3786**	**0.984**
PHOSPHATE(mg/dl) 12WEEKS	**5.6**	**11.3**	**7.8143**	**1.553**
PARATHYROID HORMONE(pg/dl) **12WEEKS**	**153**	**415**	**253.9**	**82.943**
CALCIUM(mg/dl) 24 WEEKS	**6.9**	**10.5**	**9.0071**	**0.924**
PHOSPHATE (mg/dl)24 WEEKS	**4.7**	**9.5**	**6.7786**	**1.357**
PARATHYROID HORMONE (pg/dl) **24WEEKS**	**91**	**352**	**209**	**66.782**
CALCIUM (mg/dl)36 WEEKS	**7.9**	**10**	**9.05**	**0.571**
PHOSPHATE(mg/dl) 36 WEEKS	**4.5**	**9.7**	**6.8679**	**1.697**
PARATHYROID HORMONE(pg/dl) **36WEEKS**	**90**	**515**	**232.93**	**121.08**
CALCIUM(mg/dl) 48 WEEKS	**7.9**	**9.7**	**8.6286**	**0.533**
PHOSPHATE (mg/dl)48 WEEKS	**3.4**	**9.7**	**7.2786**	**1.799**
PARATHYROID HORMONE(pg/dl) **48 WEEKS**	**30**	**195**	**123.75**	**51.34**

Table(2) T -test comparing the studied patients at start (0weeks) and end (48) weeks of the study

		Mean	**Std. Deviation**	**Std. Error Mean**	**t**	**Sig. (2-tailed)**
Pair 1	**CALCCIUM(mg/dl) 0 WEEK**	**8.343**	**0.654**	**0.124**	**-1.912**	**0.066**
	CALCIUM (mg/dl)48 WEEKS	**8.629**	**0.534**	**0.101**		
Pair 2	**PHOSPHATE(mg/dl) 0 WEEK**	**7.264**	**1.695**	**0.320**	**-0.032**	**0.975**
	PHOSPHATE (mg/dl)48 WEEK	**7.279**	**1.800**	**0.340**		
Pair 3	**PARATHYROID HORMONE 0 WEEK**	**491.210**	**144.690**	**27.344**	**12.227**	**<0.001****
	PARATHYROID HORMONE(pg/dl) **48 WEEKS**	**142.610**	**41.519**	**7.846**		

*P- VALUE <0.005 SIGNIFICANT

**P VALUE <0.001 HIGHLY SIGNIFICANT Pair 1,2&3 compare levels of calcium , phosphate , PTH at start (0week) and end (48week) of study

TABLE (3) COMPARISON BETWEEN SERUM CALCIUM VALUES THROUGH THE STUDY PERIOD

		Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)
Pair 1	CALCCIUM (mg/dl)0 WEEK	8.343	0.654	0.124	-5.312	<0.001**
	CALCIUM (mg/dl)12 WEEKS	9.379	0.984	0.186		
Pair 2	CALCIUM (mg/dl)12 WEEKS	9.379	0.984	0.186	3.033	0.005
	CALCIUM (mg/dl)24 WEEKS	9.007	0.924	0.175		
Pair 3	CALCIUM (mg/dl)24 WEEKS	9.007	0.924	0.175	-0.296	0.769
	CALCIUM(mg/ dl) 36 WEEKS	9.050	0.572	0.108		
Pair 4	CALCIUM (mg/dl)36 WEEKS	9.050	0.572	0.108	4.621	<0.001**
	CALCIUM (mg/dl)48 WEEKS	8.629	0.534	0.101		
	**P- VALUE <O.OO5 significant*					
	*** P VALUE < 0.001 HIGHLY significant* *Pair 1,2,3&4 compare changes in calcium level at 12 weeks interval during trial period*					

TABLE (4) COMPARISON BETWEEN SERUM PHOSPHATE VALUES THROUGH THE STUDY PERIOD

		Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)
Pair 1	PHOSPHATE (mg/dl)0 WEEK	7.264	1.695	0.320	-1.766	0.089
	PHOSPHATE (mg/dl)12 WEEKS	7.814	1.553	0.294		
Pair 2	PHOSPHATE (mg/dl)12 WEEKS	7.814	1.553	0.294	6.033	< 0.001**
	PHOSPHATE (mg/dl)24 WEEKS	6.779	1.357	0.256	6.033	
Pair 3	PHOSPHATE (mg/dl)24 WEEKS	6.779	1.357	0.256	-0.364	0.719
	PHOSPHATE (mg/dl)36 WEEKS	6.868	1.697	0.321	-0.364	
Pair 4	PHOSPHATE (mg/dl)36 WEEKS	6.868	1.697	0.321	-1.260	0.218
	PHOSPHATE (mg/dl)48 WEEKS	7.279	1.800	0.340	-1.260	

**P- VALUE < 0.005 SIGNIFICANT **P VALUE< 0.001 HIGHLY SIGNIFICANT*
Pair 1,2,3&4 compare changes in phosphate level at 12 weeks interval during trial period

TABLE (5) COMPARISON BETWEEN SERUM PARATHYROIDHORMONE VALUES THROUGH THE STUDY PERIOD

		Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)
Pair 1	PARATHYROID HORMONE(pg/dl) 0 WEEK	491.21	144.690	27.344	6.578	**0.001
	PARATHYROID HORMONE (pg/dl) 12 WEEKS	253.93	82.944	15.675		
Pair 2	PARATHYROID HORMONE(pg/dl) 12 WEEKS	253.93	82.944	15.675	1.990	0.057
	PARATHYROID HORMONE (pg/dl) 24 WEEKS	209.00	66.783	12.621		
Pair 3	PARATHYROID HORMONE (pg/dl) 24 WEEKS	209.00	66.783	12.621	-0.901	0.375
	PARATHYROID HORMONE (pg/dl) 36WEEKS	232.93	121.081	22.882		
Pair 4	PARATHYROID HORMONE (pg/dl) 36WEEKS	232.93	121.081	22.882	4.468	**0.001
	PARATHYROID HORMON E(pg/dl) 48WEEKS	142.61	41.519	7.846		

***P- VALUE < 0.005 SIGNIFICANT **P VALUE< 0.001 HIGHLY SIGNIFICANT**

Pair 1,2,3&4 compare changes in parathyroid hormone PTH level at 12 weeks interval during trial period

FIGURE (1) HISTOGRAM OF DISTRIBUTION OF SERUM PARATHYROID HORMONES DURING(0 , 12,24,36 & 48) WEEKS

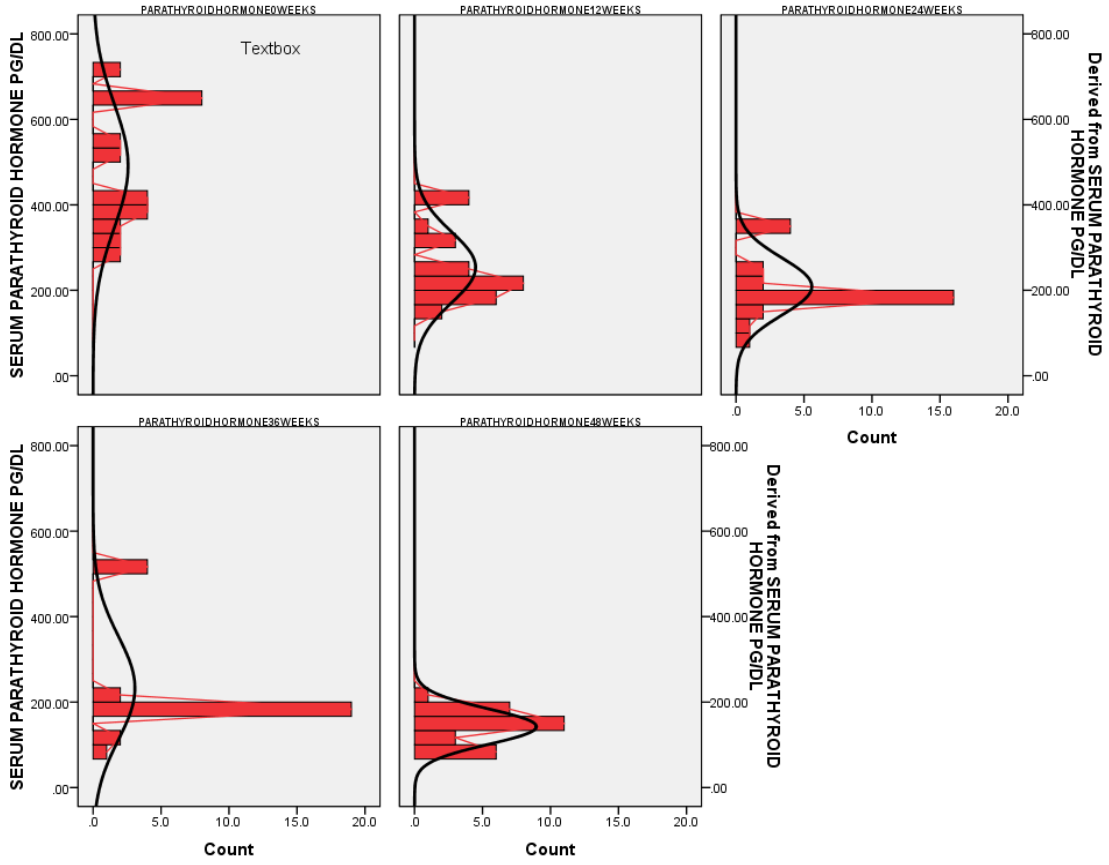
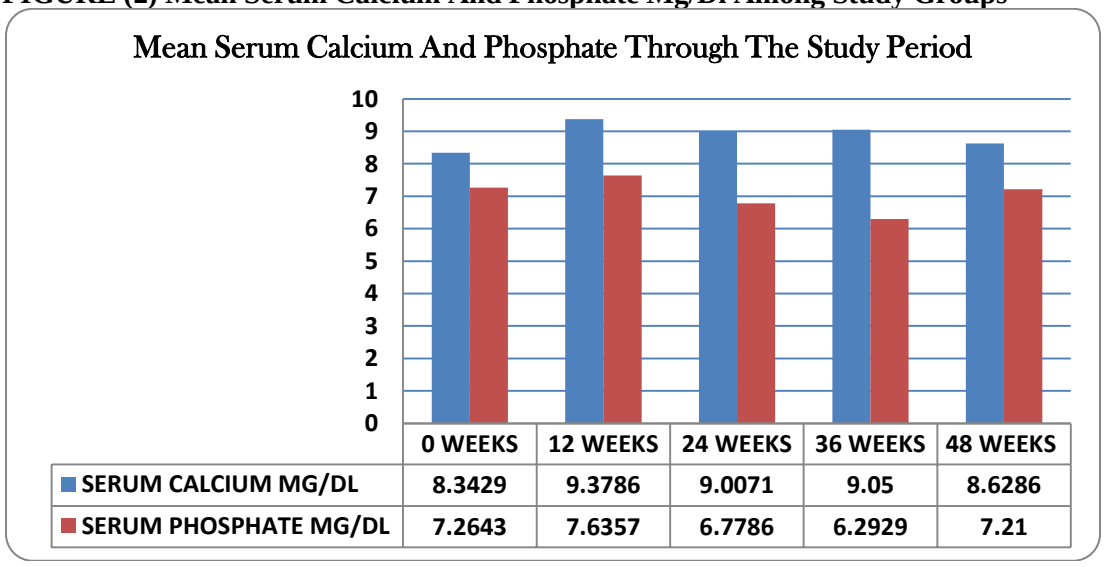


FIGURE (2) Mean Serum Calcium And Phosphate Mg/Dl Among Study Groups



	0 WEEKS	12 WEEKS	24 WEEKS	36 WEEKS	48 WEEKS
SERUM CALCIUM MG/DL	8.3429	9.3786	9.0071	9.05	8.6286
SERUM PHOSPHATE MG/DL	7.2643	7.6357	6.7786	6.2929	7.21