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RESEARCH ARTICLE

STUDY OF RADIOGRAPHIC FEATURES OF RENAL OSTEODYSTROPHY IN CHRONIC KIDNEY DISEASE (CKD) AND THEIRCORRELATION WITH CLINICAL AND BIOCHEMICAL PARAMETERS

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Abstract

Background: Although frequently silent, mineral and bone disease (MBD) is one of the most precocious complication of chronic kidney disease (CKD) and is omnipresent in patients with CKD stage 5. In recognition of the identical, our study was designed and conceived to review the Radiographic features of Renal Osteodystrophy in CKD and their correlation with Clinical and Biochemical Parameters thus helping in improving the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines.

Methods: This Observational study was undertaken on a total of 75 patients (both Male & Female) who have been diagnosed with CKD and attended Emergency/OPD or those who were admitted (IPD) seeking medical attention at SAIMS Hospital, Indore, M.P.

Results: Most patients with belonged to 55 – 65 years of age group with M/F ratio being 1.8:1. Majority belonged to Stage 5. Out of 44 patients of CKD stage 5, 37(77.1%) had bone changes. PTH levels were maximum in CKD stage 5. Osteopenia (low bone density) was the commonest Xray finding by subperiosteal resorption of the phalanges. Other findings include pathological fracture, subchondral sclerosis and soft tissue calcification. The levels of the Biochemical parameters i.e. Low calcium, High Phosphorus and High PTH levels was also positively correlated.

Conclusions: The adoption of a clear definition and an improved classification scheme of CKD – MBD, will help in improving the care and outcomes of kidney disease patients worldwide.

Introduction:-

Chronic kidney disease (CKD) is a global public health problem affecting 5- 10% of the planet population withthe expected incidence being 5-8% every year.[1] Persons with CKD have significantly higher rates of morbidity, mortality, hospitalizations, and healthcare utilization due to the adverse outcomes, including progressive loss of kidney function, cardiovascular disease, and premature death. The prevalence of CKD Stages 2–5 has continued

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to increase since 1988 as have the prevalence of diabetes and hypertension, which are respectively etiologic in approximately 40% and 25% ofCKD cases.[2]

The kidney plays a leading role in calcium and phosphorus homeostasis in association with other organs, i.e., the parathyroid gland, intestines, and bones. As kidney function declines, there is a progressive deterioration in mineral homeostasis with disruption of normal serum concentrations of phosphorus, calcium, and changes in circulating levels of hormones like parathyroid hormone (PTH) and Vitamin D3.[3,4] Disturbances in the mineral metabolism leading to bone disease are common complications of CKD which is an important cause of morbidity and decreased quality of life. Importantly, there's increasing evidence suggesting that these disorders in mineral and bone metabolism are associated with increased risk for cardiovascular calcification, morbidity, and mortality.[5]

The underlying mechanisms for this linkage aren't completely understood but are probably associated with a bearing on vascular calcification (VC) leading to changes in cardiovascular structure and function.[6,7] Evaluation of extraskeletal calcification therefore becomes an essential component in the workup and classification of the mineral andbone disorders in patients with CKD.

Optimal management of patients with chronic renal disorder (CKD) requires appropriate interpretation and useof the markers and stages of CKD, early disease recognition, and collaboration between primary care physicians and nephrologists. Since multiple terms have been applied to chronic kidney disease (CKD), eg, chronic renal insufficiency, chronic renal disease, and chronic renal failure, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative™ (NKF KDOQI™) has defined the all-encompassing term, CKD.[4]

Renal osteodystrophy is the term that has been used traditionally to explain the abnormalities in bone morphology that develop in CKD.[8-11] In 2002, KDOQI published its classification of the stages of chronic uropathy as shown in Table 1.[12]

Table 1:- Classification of the stages of chronic uropathy (KDOQI, 2002).

Stage	Level of Chronic Uropathy
Stage 1	Kidney damage with normal or increased GFR (>90mL/min/1.73m^2)
Stage 2	Mild reduction in GFR (60 -89mL/min/1.73m^2)
Stage 3	Moderate reduction in GFR (30-59mL/min/1.73m^2)
Stage 4	Severe reduction in GFR (15-29 mL/min/1.73m^2)
Stage 5	Kidney failure (GFR<15mL/min/1.73m^2)

Patients with chronic renal disease stages 1-2 are generally asymptomatic; clinical manifestations typically appear in stages 3-5. Disturbances in mineral metabolism in CKD which result in a multisystem disorder have now been given a different identity as CKD-MBD (CKD-mineral and bone disorder) by Kidney Disease Improving Global Outcomes (KDIGO) 2009[12] (Figure1). CKD-MBD, the new terminology used for renal osteodystrophy and renal bone disease (also known as uremic osteopathy), is a constellation of musculoskeletal abnormalities that occurs in patients with chronic renal failure. It includes Osteomalacia (adults)/rickets (children), Secondary hyperparathyroidism: abnormal calcium and phosphate metabolism, Bone Resorption, Osteosclerosis. Radiographic findings are many and varied such as Subperiosteal resorption: characterized by typical subperiosteal resorption on radial aspects of middle phalanges of index and long fingers, Rugger jersey spine: sclerosis of the vertebral body endplates, insufficiency fractures, Looser zone, Biconcavity of vertebral bodies and bending deformities of long bone.

In addition to bone histology and serum biomarkers, imaging has been an crucial component of evaluating bone disease within the past and remains the main tool in assessing extraskeletal calcification in CKD patients.[17] (Figure 2) Ongoing developments in non-invasive imaging techniques almost certainly will lead to their improved and more widespread use in clinical diagnosis and decision-making within the near future.[18]

In recognition of the identical, our study was designed and conceived to review the Radiographic features of Renal Osteodystrophy in CKD and their correlation with Clinical and Biochemical Parameters. The adoption of a clear definition and an improved classification scheme of CKD – MBD, will help in improving the care and

outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines.

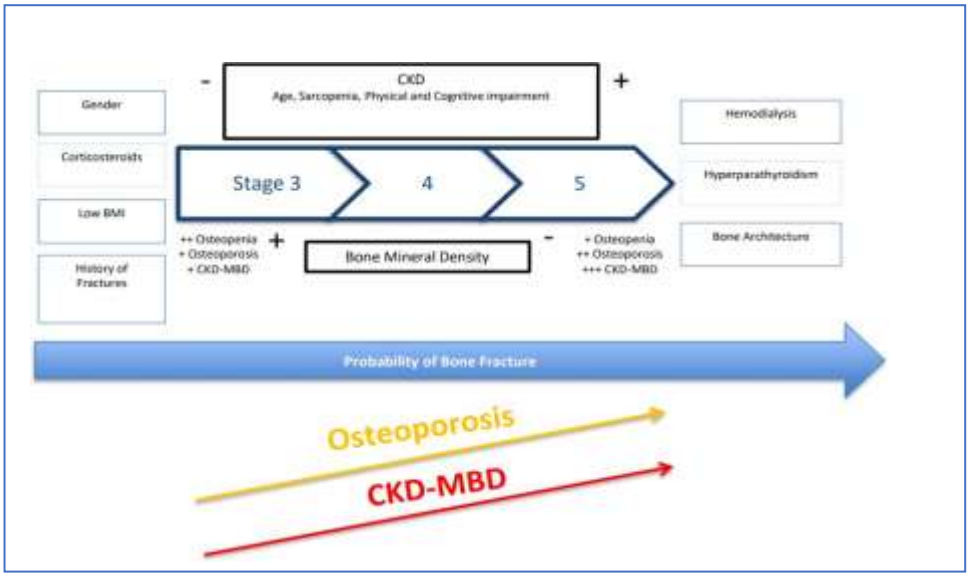

Figure 1:- CKD progression: risks factors for bone fragility in CKD stages. In stage 3 it is more likely to have a more relevant contribution of osteoporosis to bone fragility. On the other hand, in stage 5 CKD-MBD and osteoporosis may have a more relevant role. Abbreviation: BMI, body mass index.

Material & Methods:-

This Observational study was undertaken in the Department of General Medicine at Sri Aurobindo Medical College & PG Institute, Indore (MP) after valid approval of ethics committee of the institution between December 2019to September 2021 on 75 patients (both Male & Female) who attended in patients (IPD) and out patients (OPD) at SAIMS Hospital Indore seeking medical attention and were diagnosed to have CKD were included in this study.

Inclusion Criteria:

All patients (Both males and female) with Age>15 years and have been Diagnosed of C.K.D. on Clinical, Biochemical and USG parameters irrespective of Etiology**.** Patients presenting with Clinical Features suggestive of Renal Osteodystrophy like Pain over Upper and Lower Extremities, Backache, over Clavicle, Loin, etc., Bony deformities**,** Restriction of mobility of joint, small joint, spine and abnormalities in Bone growth and development

Exclusion Criteria:

Cases Of AKI , Patients with History of bone injuries, Fractures , History of other con- cominant Bone diseases like Tumor, Bony Dysplasia, TB, Hypo/Hyper thyroidism and Patient known to be taking drugs like steroids, calcium supplements and Phosphate binders.

Method:-

After taking pre-Informed written consent from the patient, a prestructured proforma was used to collect the desired baseline data. Detailed clinical examination was done and biochemical tests were done on all patients as per the protocol. All the relevant details of history, general physical examination, laboratory and technical investigation reports were noted down from time to time. The clinical profile was assessed with procured data.

Investigations planned:

Venous blood sample were obtained for Routine Investigations like Complete Blood Count (CBC). Serum Urea was done using the UreaL kit- 04460715 190 while Serum Creatinine (measured using alkaline pictrate method), SGOT, SGPT was done by Vitros-5.1/FS machine. Serum Electrolyte done by Automated analysis method using ABL 800 Basic machine. Calcium done using the Calcium Gen 2 kit- 05061482 190 from Roche, and analysed using cobas c 311 analyzer while PO_4 were assessed using Phosphate ver.2 kit- 03183793 122 from Roche, on

Cobas c 311 analyser, The iPTH assay was carried out using the 2 site Electro Chemi Luminescence Immuno Assay with the kit ms-11972103122 on Cobas e 411analyser. XRAY & USG (W/A) was also done.

Statistical methods

The data was coded and entered into Microsoft excel 2010 (Microsoft corp.), analysed using excel 2010 and SPSS 20.0 for Windows (SPSS inc). Prevalence of an outcome variable along with 95% confidence limits was calculated. A descriptive analysis of the population will be carried out. The categorical or dichotomous variables will be expressed as absolute values and percentages, and will be compared with Pearson test. The continuous variables with a normal distribution will be described as the mean +/-(SD). The correlation between two quantitative variables will becarried out by using KARL PEARSON'S/ SPEARMEN'S coefficient of correlation. A P value less than .05 will considered statistically significant whereas a P value > 0.05 will be taken as non-significant difference.

Results:-

In the present study, majority of the population belonged to 56-65 years i.e., 41.3%/31 (Table 3). Male to female ratio of 1.88:1 was observed (Table 4). 69.3% were having Abnormal while, 30.7% had Normal PTH. 37.3% of participants belonged to CKD stage 5B (Stage 5 patients on Hemodialysis) while only 17.3% belonged to 3rd stage. Majority i.e 64% presented with Abnormal X ray findings.

Age Group	Frequency	Percent
18-25 Years	0	0.0
26-35 Years	6	8.0
36-45 Years	19	25.3
46-55 Years	16	21.3
56-65 Years	31	41.3
>=66 Years	3	4.0
Total	75	100.0

Table 3:- Distribution Based on Age Group.

54.7% of respondents had Abnormal while, 45.3% had Normal Calcium Level with base value as 8 – 11 mg/dl.

For PO4 levels, 69.3% had Abnormal while 30.7% had Normal i.e., between 2.5 – 4.6 mg/dl. 70.7% of respondents had Abnormal Ca*Po4 Level. Normal calcium phosphorous product taken as <55mg/dl. Osteopenia was the most common X ray finding with 54.7% prevalence followed by Subperiosteal resorption 9.3%, fracture 5.3%, Soft tissue calcification and Osteosclerosis shows equal percentage 2.7% and least was Subchondral sclerosis 13%. Pathological fracture was seen in 4 i.e., 5.3% of the patients. (Table 4)

X ray Finding	Frequency	Percent (N=75)
Osteopenia	41	54.7%
Subperiosteal resorption	7	9.3%
Pathological Fracture	4	5.3%
Soft tissue calcification	2	2.7%
Subchondral sclerosis	1	1.3%
Osteosclerosis	2	2.7%

Table 4:- Presence of different X ray finding in patients.

A statistically significant ($p<0.05$) association was found between the CKD stages & Calcium, PO4 & PTH status, showing a direct variation. While patients in CKD stage 5 showed higher percentage (70.5%) for Abnormal Ca

Level & (93.2%) for PO_4 levels while Patients falling in CKD Stage 3 showed minimum 30.8% & 23.1% for Ca & PO_4 respectively (Table 5). Patients having Abnormal PTH Status showed the highest percentage (31.3%) for CKD Stage 5A while, the lowest percentage 8.3% of patients for Stage 3. X ray finding and CKD stages showed a positive correlation too. Patients having Abnormal X ray finding showed the highest percentage (31.3%) for CKD Stage 5A while 8.3% of patients were in Stage 3 (Table 7). Further, a statistically significant ($p<0.05$) association was also foundbetween the X ray findings and Ca & Po4 Status, showing a direct variation. While 72.9% patients having Abnormal Xray had Abnormal Ca Level, 83.3% had abnormal PO_4 levels. Patients having Normal Xray Finding showed higher percentage (55.6%) for Normal Po4 Status while, 44.4% of patients for Abnormal Po4 Status.

Calcium Level	**CKD Stages**						**Total**	
	3		**4**		**5**			
	Abnormal	**Normal**	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**	**Normal**
Count (%)	4 (30.8%)	9(69.2%)	6 (33.3%)	12 (66.7%)	31 (70.5%)	13 (29.5%)	41 (54.7%)	34 (45.3%)
Pearson Chi-Square	Value		Df		P Value		Result	
	10.727		2		0.005		**Significant**	
PhosphorousLevel	**CKD Stages**						**Total**	
	3		**4**		**5**			
	Abnormal	**Normal**	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**	**Normal**
Count (%)	3 (23.1%)	10 (76.9%)	8 (44.4%)	10 (55.6%)	41 (93.2%)	3 (6.8%)	52 (69.3%)	23 (30.7%)
Pearson Chi-Square	Value		Df		P Value		Result	
	30.096		2		0.000		**Significant**	

Table 5:- Association between CKD Stages & Calcium & Po4 level.

PTH Status	CKD stages				Total
	3	4	5A	5B	

Abnormal	Count	5 (38.5%)	9 (50%)	15 (93.8%)	23 (82.1%)	52 (69.3%)
Normal	Count	8 (61.5%)	9 (50%)	1 (6.3%)	5 (17.95)	23 (30.7%)
Total	Count	13 (100%)	18 (100%)	16 (100%)	28 (100%)	75 (100%)
Pearson Chi-Square		Value	df	P Value	Result	
		15.639	3	0.001	**Significant**	

Table 6:- Association between CKD Stages & PTH Status.

CKD stages		**X ray Finding**		**Total**
		Abnormal	**Normal**	
3	Count	4 (8.3%)	9 (33.3%)	13 (17.3%)
4	Count	7 (14.6%)	11 (40.7%)	18 (24%)
5A	Count	15 (31.3%)	1 (3.7%)	16 (21.3%)
5B	Count	22 (45.8%)	6 (22.2%)	28 (37.3%)
	Count	48 (100%)	27 (100%)	75 (100%)
Pearson Chi-Square	Value	Df	P Value	Result
	19.884	3	0.000	**Significant**

Table 7:- Association between X ray Finding & CKD stages.

PTH Status		**X ray Finding**		**Total**
		Abnormal	**Normal**	
Abnormal	Count	45 (93.8%)	7 (25.9%)	52 (69.3%)
Normal	Count	3 (6.3%)	20 (74.1%)	23 (30.7%)
	Count	48 (100%)	27 (100%)	75 (100%)
Pearson Chi-Square	Value	Df	P Value	Result
	37.385	1	0.000	**Significant**

*P value < 0.05: Statistically Significant

Table 8:- Association between X ray Finding & PTH Status.

Duration Of Disease		**X ray Finding**		**Total**
		Abnormal	**Normal**	
<1 Years	Count	4 (8.3%)	10 (37%)	14 (18.7%)
1-5 Years	Count	28 (58.3%)	14 (51.9%)	42 (56%)
>= 5 Years	Count	16 (33.3%)	3 (11.1%)	19 (25.3%)
Total	Count	48 (100%)	27 (100%)	75 (100%)
Pearson Chi-Square	Value	Df	P Value	Result
	11.125	2	0.004	**Significant**

*P value < 0.05: Statistically Significant

Table 9:- Association between Duration of Disease and X ray Findings.

A statistically significant ($p<0.05$) association was found between the Xray Finding & PTH Status. Patients having Abnormal Xray Finding showed higher percentage (93.8%) for Abnormal PTH Status while, 6.3% of patients for Normal PTH Status. A significant positive correlation was also observed between duration of disease and X ray findings. Respondents having Abnormal X ray Finding showed the highest percentage (58.3%) for 1-5 years, while thelowest percentage 8.3% of respondents for <1 Year (Table 9).

A comparison of Mean scores of Calcium based on CKD Stages in present study showed that the difference among the three CKD Stages was statistically significant (P<0.05), showing that mean scores of Calcium change significantly with CKD Stages. The mean score of Calcium of respondents having CKD Stage 3 (9.077) is found to be the highest and it shows the lowest score for respondents having CKD Stage 5 (7.930). Identically for Po4 levels, a statistically significant (P<0.05) difference was found showing that mean scores of Po4 change significantly with CKD Stages. A positive correlation was also observed between the three CKD Stages and mean scores of PTH. The mean score of PTH of respondents having CKD Stage 5 (216.770) is found to be the highest and it shows the lowest score for respondents having CKD Stage 3 (65.718). A statistically significant (P<0.05) difference was found in all the pairs exceptin the pair of Po4 3 & 4.

Discussion:-

Renal osteodystrophy as a consequence of CKD is seen with increasing frequency with the advent of replacement therapy. This is because the longer duration of life and prolonged dialysis exposes the bones to worsening alterations of the divalent metabolism. Dialysis does the excretion work of the kidney but not the endocrine function. The age of onset of renal osteodystrophy depends on the age of the onset of renal failure, the duration and progression of renal failure, the duration and efficacy of dialysis and the control of the divalent ion abnormality Types of abnormalities detected radiologically vary with patient age, type of management, and duration of hemodialysis, as well as with techniques and type of film used and interest of the radiologist.[19]

In addition to bone histology and serum biomarkers, imaging has been an crucial component of evaluating bone disease within the past and remains the main tool in assessing extraskeletal calcification in CKD patients [(17)]. Ongoing developments in non-invasive imaging techniques almost certainly will lead to their improved and more widespread use in clinical diagnosis and decision-making within the near future [(18)]. There is limited data on CKD- BMD from India, particularly in early stages of CKD. Present study was prospectively conducted to assess biochemical and parathyroid hormone profile in patients with various stages of CKD. In recognition of the identical, our study was designed and conceived to review the Radiographic features of Renal Osteodystrophy in CKD and their correlation with Clinical and Biochemical Parameters.

A total of 75 patients with CKD were evaluated with age ranging from 26 years to 70 years. Highest percentage (41.3%) belonged to 56-65 years followed by 25.3% and 21.3% in 36-45 years and 46-55 years respectively. Our resultswere in accordance with study done by **Mc Clellan et al** [(20)]**, Agarwal S k et al** [(19)] and **Memos et al** [(21)] in which renal bone disease was seen in an older age group (mean age 49.2 + 11.2 years). This is due to the fact that prompt treatment and adequate dialysis has prolonged the life expectancy of patients. males outnumbered females with M: F 1.8:1. The results of our study were comparable to studies done by **Agarwal et al** [(19)] and **Nissenson et al** [(22)].

PTH levels showed a marked increase with 52 (69.3%) cases having PTH more than 65 pg/ml with maximum level found to be 795.3 pg/ ml and remaining 23 patients have PTH levels within the normal range. The findings are similar to **Block et al** [(23)] study, a significant increase in PTH levels was observed in CKD. They also identified high PTH levels as a significant correlate of all-cause mortality. They concluded that elevations in serum PTH might be associated with increased risk of death from cardiac causes. **Amann K et al** [(24)] studies also implicated parathyroid hormone as a permissive factor that promotes cardiac fibroblast activation and inter-myocardiocytic fibrosis. For early diagnosis, staging of CKD is required and was done by CKD-EPI equation and the levels of PTH, Calcium and Phosphorus of patients in various stages of CKD are as follows; In **Stage III CKD**, there is marginal elevation in PTH and phosphorus levels; and fall in calcium levels. In **Stage IV CKD**, there is further elevation in PTH and phosphorus levels; and further decrease in the calcium level. In **Stage V CKD,** there is significant increase in PTH levels; moderate increase in phosphorus levels and fall in calcium levels.

Osteopenia was the commonest X ray finding followed by Subperiosteal resorption, osteosclerosis, soft tissue calcification & Subchondral sclerosis. Additionally, most patients with X ray changes had increased PTH levels and lowcalcium levels. While in patients with soft tissue calcification, calcium level was found to be significantly high. This was in concordance to study done by **Rizvi et al** [(25)], where they found osteopenia (decreased bone density) in 55.22% of theircases. In study done by **Thimmappa et al** [(26)], they observed subperiosteal resorption in 6% of the cases. In Gupta et al, they observed soft tissue calcification in 10% of the cases. Pathological Fracture too was observed in 2(4%) of the casesdone by **Thimmappa et al** [(26)].

Patients with osteopenia were found to have low calcium levels as compared to patients having normal X ray findings. The results of the study were comparable to earlier studies done in early 1970s found osteitis fibrosa in almost50% of cases on dialysis [27-29] and which studies done by Kaushal et al [30] and Parfitt et al [31]. Kaushal et al [30] in 1989 reported osteitis fibrosa in 20% of patients on dialysis. The prevalence of osteosclerosis varied widely from 0% to 54%[31,32]. Parfitt, et al [31] in 1977 observed osteomalacia in 20% of Australian patients with renal bone disease. Soft tissue calcification which was seen in only 2 patients. Both patients had significant higher calcium phosphorous product levelthat may indicate metastatic calcification in patients of CKD. X Ray findings and stage of CKD had a significant association in our study. The patients having X ray abnormalities were found to increase with increase in the progression of the disease. Of the 16 patients of CKD stage 5A, 15 were found to have X- ray changes while 22 patients out of the 28 patients of CKD stage 5 B presented with same.

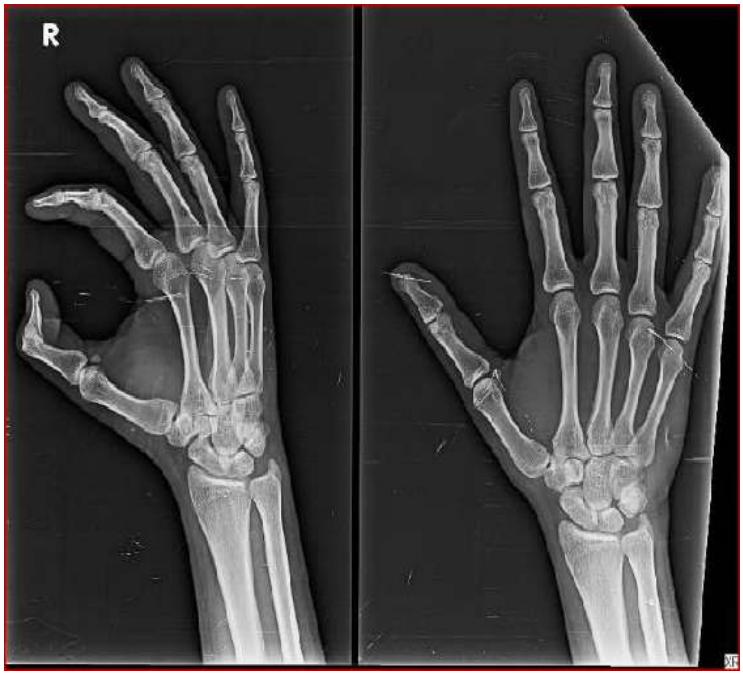

Figure 3:- Periarticular osteopenia (Subperiosteal bone resorption of radial aspect of middle phalynx).

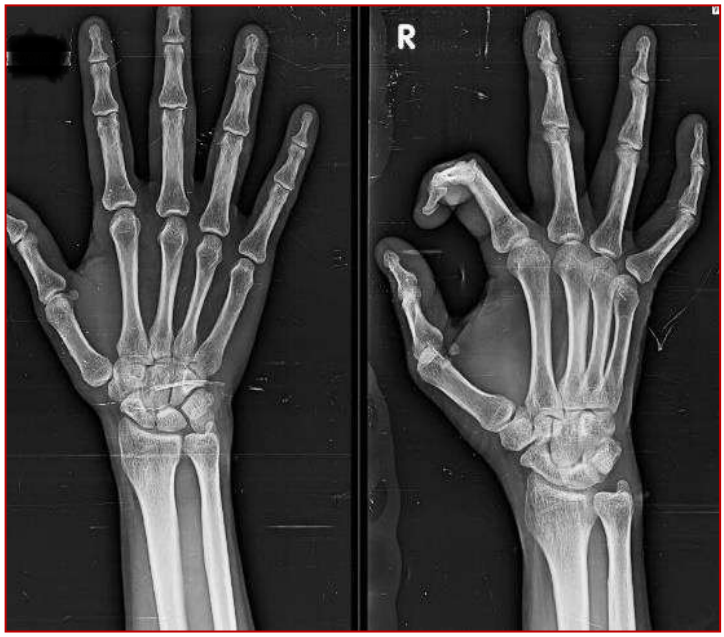

Figure 4:- Osteopenia + subperiosteal bone resorption of radial side of middle phalynx.

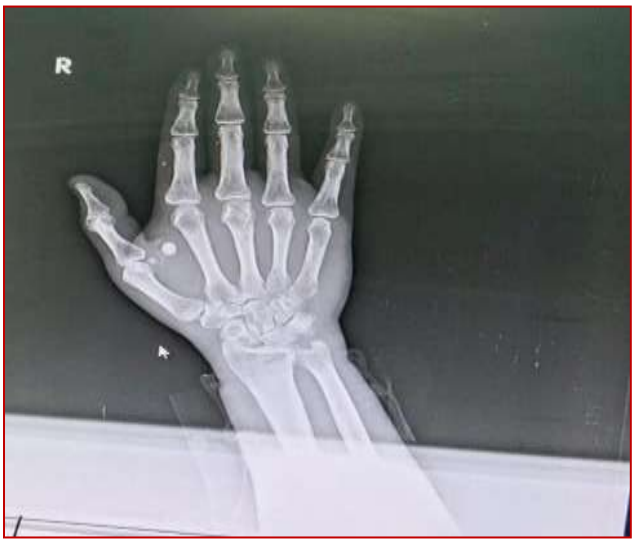

Figure 5:- Periarticular osteopenia with Soft tissue calcification.

Conclusion:-

X- Ray despite being a primitive tool, is readily available and being inexpensive can be used for detection of Renal Osteodystrophy. The presence of renal osteodystrophy can help in identifying the disease and for starting early prevention and treatment of the disease and complication. Bone biopsy is the gold standard for identifying Renal Osteodystrophy and thus should be used whenever available, but being invasive and costly still not profoundly used and thus Other non-invasive techniques are needed to have early diagnosis of renal osteodystrophy having high sensitivity and predictability of the disease. The adoption of a clear definition and an improved classification scheme of CKD – MBD, will help in improving the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines**.**

Limitations

As the major part of the study was done in the Covid – 19 pandemic era, when the patients were taking many multi – vitamins and immunity boosters, so results like calcium and protein can vary. Further, the conventional X-ray is a primitive tool to identify renal bone disease. The exact bone disease can only reliably be known by histomorphometric study. But bone histology being invasive and costly could not be used. Lastly, Due to economic constraints other investigations like Vit D , alkaline phosphatase and DEXA scan could not be performed

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