Evaluation of Bone Turnover in Children with Chronic Renal Failure in Egypt

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Abstract: Background: Renal osteodystrophy is a multifactorial and universal disorder of bone metabolism in advanced chronic kidney disease. It is a spectrum of bone mineral changes that could range from the high turnover lesions of secondary hyperparathyroidism to the low turnover lesions of adynamic bone disease. Objective: to evaluate the bone turnover, estimated by the measurement of some serum biochemical markers and bone mineral density in children with chronic renal failure either on conservative therapy or regular hemodialysis. Methods: The study included 35 children suffering from chronic renal failure, 20 out of them on regular hemodialysis (group I) & the other 15 on conservative therapy (group II). Each group was subdivided into three subgroups according to iPTH values. In addition to 20 apparently healthy children served as a control group. All children underwent thorough history taking, physical examination, routine, specific laboratory& radiological investigations as serum Ca, P, ALP, iPTH , β_2-microglobulin & DEXA scan. Results: both of groups I &II had significant increase in SBP, DBP, serum β_2-microglobulin and iPTH than the controls. Meanwhile, no statistical significant differences in serum β_2-microglobulin & iPTH levels were found between groups I & II. BMD was measured using DEXA scan revealed that osteopenia was found in 50% group I and 53% of group II. The frequencies of LTBD estimated by iPTH in groups I & II were 20% and 27%, respectively. Meanwhile, the HTBD frequencies were 60 % in the both groups. Children with CRF in the subgroups with high iPTH had significantly higher SBP and DBP than those with low iPTH either in group I or II. Serum β_2-microglobulin showed a significant increase in high iPTH subgroup than low iPTH subgroup only in group I. iPTH correlated positively with SBP, DBP & β_2-microglobulin. Meanwhile, negatively with Ca & BMD Z-score in groups I & II. Conclusions: Maintenance of normal bone turnover may be important in prevention of irreversible bone disabilities and CVD. The preserving of normal BMD is a challenge for pediatric nephrologists so, continuous and regular monitoring systems by combination of iPTH, serum Ca, ALP, β_2-microglobulin & BMD Z-score could be early, accurate and non invasive assessment of the skeletal system in children with CRF.

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1. Introduction

Renal osteodystrophy is a multifactorial and universal disorder of bone metabolism in advanced chronic kidney disease (CKD)[(1)]. It is a spectrum of bone mineral changes that could range from the high-turnover lesions of secondary hyperparathyroidism to the low-turnover lesions of adynamic bone disease [(2)]. Despite the fact that bone biopsy is the gold standard for the diagnosis of renal osteodystrophy, it has not been routinely performed mainly because it requires an invasive procedure to obtain a bone sample and needs special equipment and expertise [(3)].

Hyperparathyroidism is a common finding in patients with renal insufficiency [(4)]. Parathyroid hormone (PTH) is considered a uremic toxin responsible for many of the abnormalities of the uremic state and bone disease [(5)]. The interpretation and significance of intact PTH (iPTH) levels in the individual patient is further complicated by skeletal resistance to PTH in chronic renal failure, it is confirmed in the epiphyseal cartilage growth plate of uremic rats. Therefore, additional tests or new markers of bone remodeling are needed, that allow a correct and dynamic non invasive diagnosis of bone turnover. These biochemical markers have to be compared and/or combined with iPTH plasma values to evaluate their potential interest [(6)]. β_2-microglobulin is a low molecular weight protein produced by all nucleated cells at a constant rate. It is freely filtered by the glomerulus, reabsorbed and catabolized by proximal tubular cells [(7)]. β_2-microglobulin was proposed as a potential bone

growth factor. Studies evaluating the microglobulin effects on bone have been performed utilizing different experimental models on cells obtained from different animal species and using varying doses of β_2- microglobulin. In these studies the bone cells undergo a series of developmental stages such as proliferation, differentiation and apoptosis [8].

Radiological studies are of little diagnostic utility, because biochemical changes precede radiological changes. They are useful as the first step in the study to detect vascular calcifications and amyloidosis due to β_2- microglobulin and in symptomatic and at risk patients to detect vertebral fractures [9]. Bone densitometry: dual energy x-ray absorptiometry (DEXA) is the standard method to determine bone mineral density. It provides information on changes in bone mineral content, but not on the type of underlying bone disease. It is useful for follow up of bone mass or for the study of bone mass changes in the same patient [10].

Aim of the work was to evaluate the bone turnover, estimated by the measurement of some serum biochemical markers and bone mineral density in children with chronic renal failure either on conservative therapy or regular hemodialysis

2. Subjects and Methods

The present study was carried out on 55 children from Tanta and Menoufiya Universities Hospitals, divided into 3 groups: group I (dialysis group) included 20 children (8 males & 12 females) with mean age ±SD 13.7± 2.3 years with end stage renal failure (ESRF), on regular hemodialysis therapy. This group was subdivided into three subgroups according to iPTH values; subgroup with low iPTH levels which was less than the target range, subgroup with iPTH levels within the target range and subgroup with high iPTH levels which was above the target range. The target range defined according to the NKF/KDOQI guidelines. Group II (conservative group) included 15 children (6 males & 9 females) with mean age ±SD 12.7 ±4.6 years. Also, they were subdivided into three subgroups according to iPTH values as before in group I where the target range defined according to the NKF/KDOQI guidelines. The cut-off values of 150 pg/mL and 300 pg/mL represent low-turnover and high-turnover disease respectively [11]. The values between150-300 pg/mL could be considered within the "safe" limits of iPTH ("controlled" ROD). In addition to 20 apparently healthy children, age and gender matched served as a control group. All patients were given calcium-based phosphate binders and calcitriol. Exclusion criteria included malignancy, history of parathyroidectomy, sever trauma & biochemical evidence of obstructive jaundice.

All subjects were subjected to thorough clinical examination including weight, height, BMI and blood pressure. Laboratory & radiological investigations as serum Ca, P, ALP, iPTH, β_2-microglobulin, & DEXA scan. Informed consents were obtained from all participants' parents.

Samples collection and preparation

Immediately before a dialysis session, 5 ml of venous blood were withdrawn and the sample divided as follow: 2 ml of whole blood were allowed to clot, the serum separated in a refrigerated centrifuge, and stored at -20 ºC for later determination of iPTH. The other 3 ml of whole blood were allowed to clot, centrifuged & serum sample were divided in two aliquots, one of them kept immediately at-20 ^{0}C for determination of β_2-microglobulin & the other aliquot for determination of total and direct bilirubin, albumin, urea, creatinine, Ca, P ,and ALP.

Laboratory Methods:

- Total & direct bilirubin, albumin, urea,creatinine, Ca, P and ALP assayed on Synchron Cx9 (Beckman Instrument. Inc. Fullerton, California USA.).
- iPTH assayed by the DAI Intact PTH Immunoassay (IBL GESELLSCHAFT. HAMBURG,GERMANY) which is a two-site enzyme-linked immunosorbent assay for the measurement of the biologically intact 84 amino acid chain of PTH. Two different goat polyclonal antibodies to human PTH have been purified by affinity chromatography to be specific for well defined regions on the PTH molecule.
- β_2-microglobulin was assayed by indirect solid phase enzyme immunometric assay (ELISA, ORG 5BM, ORGENTEC DIAGNOSTIKA Gmbh). The microplate is coated with highly purified anti-β_2 microglobulin antibodies where any present β_2-microglobulin bind to the immobilized antibodies. With the addition of anti-h- β_2 microglobulin-hoseradish peroxidase conjugate, it recognizes β_2-microglobulin molecules bound the immobilized anti-β_2 microglobulin forming the sandwich complexes.

Radiological investigations:

Bone mineral density (BMD): BMD at lumbar spinal region (L2-L4) was measured in all children using DEXA(Challenger envision osteodensitometer). BMD was classified according to Bakr [12], on the basis of BMD Z-score which were calculated from the following equation: Z-score = [BMD (g/cm^3) of the patient—BMD predicted for age and sex/SD for BMD (age, sex and height matched)]. A patient was considered osteopenic if the Z-score was <–1.0. If the Z-score was≤ –2.5 the patient was classified as

having severe osteopenia.

The statistical analysis was undertaken using SPSS software (version 17; SPSS Inc., Chicago, IL, USA). Descriptive statistics in the form of mean and standard deviation for parametric data were used. ANOVA test for comparison between three groups having quantitative variables normally distributed followed by LSD (least significant difference). Kruskal-Wallis test for comparison between three groups not normally distributed having quantitative variables. Pearson correlation coefficient (r) was used to test correlation between two quantitative variables. The level of significance was set at 0.05.

3. Results and Discussion:

Renal failure is a growing problem that involves a large part of the population and has a great social impact, with often incapacitating complications, mainly related to mineral bone disorders referred to as renal osteodystrophy [13]. Changes in mineral metabolism and bone structure are linked to abnormalities in the metabolism of calcium, phosphate, vitamin D, and parathyroid hormone levels [11].

In the current work, the obtained results revealed a presence of a statistical significant difference between group I and the control group regarding BMI. While, no statistical significant difference was found neither between group II and the control groups nor group I and group II regarding BMI. In a study done by ***Gupta et al.,*** [14], they found that Kuwaiti patients with ESRF had a lower body mass index when compared with the controls**.**

In the present study both groups of chronic renal failure had statistical significant increase in SBP, DBP, serum β_2-microglobulin and iPTH than the control group. Meanwhile, no statistical significant increase in SBP, DBP, β_2-microglobulin and iPTH levels was found between both groups of chronic renal failure. In a study done by ***Michelis et al.,*** [15] they found that the salivary and serum β_2 microglobulin concentrations were 90.7% higher in CKD patients compared with healthy controls. In healthy individuals, β_2-microglobulin is synthesized at a constant rate, but retention of it occurs in renal failure [16].

In the present study, the BMD at lumbar spinal region (L2-L4) was measured using DEXA revealed the presence of statistical significant difference between both groups of renal failure and the control group. While no statistical significant difference was found between both groups of renal failure as regard the same parameter. DEXA Z-score results revealed that osteopenia was found in 53% of group II and 50% of group I. This high frequency is probably related to the high rates of bone growth and the remodeling process that are characteristic of the immature skeleton.

Ziolkowska et al.,[17] reported that 48.4% of children with CRF were osteopenic. One-third of these patients were treated conservatively while two-thirds were on dialysis. ***Bakr*** [12] demonstrated that osteopenia was present in about 62% of 21 children with predialysis CRF and 59% of 44 children with ESRF. In a study done by ***Gupta et al.,*** [14], they found that the ESRF Kuwaiti patients had a lower BMD than the controls.

In most clinical settings, it is not necessary to identify the specific form of renal osteodystrophy but rather determine if bone turnover activity is high or low. In children with CKD stage 5, a combination of serum PTH and calcium can distinguish between high (eg, osteitis fibrosa cystica) and low (eg, adynamic bone disease) turnover bone disease [9]. The high PTH subgroup represents high turnover bone disease (HTBD) and low PTH subgroup which represent low turnover bone disease (LTBD), while normal PTH group represent controlled ROD.

In the present work, the frequencies of LTBD estimated by serum iPTH in groups I & II were 20% and 27%, respectively. Meanwhile, the frequencies of HTBD estimated by serum iPTH were 60 % in both groups I & II. The other 20 % of group I and 13 % of group II could be considered within the "safe" limits of iPTH ("controlled" ROD). ***Avila-Diaz et al.,*** [18] reported that there were 20 (48.8%) children with PTH <150 pg/ml were classified as having LTBD; the remaining 21 (51.2%) children were classified as having no LTBD. In previous reports, the prevalence of LTBD by biopsy in children undergoing dialysis was 27% in Poland [19] & 29% in Turkey [20].

In the current study, there was no significant difference between high and low PTH subgroups as regard duration on dialysis in group I. Meanwhile, there was a significant differences between high and low iPTH subgroups in group II regarding duration of renal impairment, this may be attributed to longstanding high calcium intake and over treatment with 1,25-dihydroxyvitamin D. This finding agreed with ***Avila-Diaz et al.,*** [18].

The clinical relevance of LTBD in children undergoing dialysis treatment or on conservative management is related mainly to growth retardation. In the present study, no significant statistical

differences in height and weight were found between the three subgroups of groups I & II. This may explained by the wide range of age at the onset of renal failure, which has a significant effect on linear growth. In accordance with the present study, ***Avila-Diaz et al***., [18] reported that LTBD group has lower weight and height than HTBD group but not statistically significant.

The present results revealed that only patients with CRF in the subgroup with high iPTH had significantly higher SBP and DBP levels than the patients in the subgroup with low iPTH either in group I or II. The results of the current study run parallel with the results of the ***Ávila-Diaz et al.,***[18]. Moreover, the present results revealed a significant positive correlation between iPTH levels and DBP & SBP among groups I & II. Elevated PTH is associated with a greater prevalence and incidence of CV risk factors and predicts a greater likelihood of prevalent and incident disease, including mortality. PTH represents an important new CV risk factor that adds complementary and independent predictive value for CV disease and mortality. As well, this may be attributable to PTH-induced increased intracellular Ca^{++} affecting vascular endothelial function that leads to increased vascular tone and stiffness [21]. Another explanation stated that the increase in phosphorus, calcium, inflammatory mediator and uraemia levels have been observed to promote smooth muscle cells transforming into osteogenic lineage cells. These cell produce collagen matrix, which is later mineralized [9].

The current study shows that low iPTH subgroup has significant elevated serum calcium than high iPTH subgroup in groups I & II. Meanwhile, no significant statistical differences as regard serum phosphorus in the three subgroups either in group I or group II. These obtained results run parallel with those of study carried by ***Salusky et al.***, [22]. The present results supported the ***Ávila-Diaz et al.,***[18]. hypothesis who has defined patients with LTBD, by PTH <150 pg/ml and total Ca >10 mg/dl and patients without LTBD, as defined by PTH >150 pg/ml and total Ca <10 mg/dl. Furthermore, there were significant negative correlations between iPTH level and serum calcium among groups I & II which is comparable to the results of ***Inaba et al***., [23]. So, determination of serum calcium considered to has a high discriminatory value between LTBD and HTBD.

In the present study, patients with LTBD had lower levels of ALP than those with HTBD in both groups I &II. The same results were obtained by ***Piscitelli et al.,*** [24] & ***Avila-Diaz et al.,*** [18] found that ALP in children with LTBD was significantly lower than those without LTBD. As well, the obtained results revealed a significant positive correlation between serum iPTH and ALP in group I but not group II.

As regard serum β_2-microglobulin, the obtained results showed a significant increase in serum β_2-microglobulin in high iPTH subgroup than low iPTH subgroup of group I but not group II which were partially comparable to the results of ***Ferreira and DrÜeke***[6] who observed that patients with HTBD have higher serum levels of β_2-microglobulin than patients with normal bone or LTBD. Also, a significant positive correlation was found between serum iPTH and β_2-microglobulin in groups I & II. This association of high serum β_2-microglobulin with high serum markers of bone turnover suggests that β_2-microglobulin could be either a direct or an indirect activator of bone cells or at least another marker of bone cell activity. So, determination of serum β_2-microglobulin could be considered to have a discriminatory value between HTBD and LTBD.

In the present study, group II showed no statistical significance in Z-score between high and low iPTH subgroups which run parallel with the results of ***Andrade et al***.,[2] **.** On the other hand, a statistical significant difference in Z-score was found between high & low iPTH subgroups of group I which were similar to that of ***Bakr*** [12]**.** In the present study, Z-scores at lumbar spines were significantly negatively correlated with iPTH in groups I & II and with ALP in group I but not in group II. Besides, positively correlated with Ca in group I but not in group II. On the other hand, no statistical significant correlations were found between Z-scores at lumbar spines and duration of renal impairment & dialysis, BMI, weight, height, phosphorus or ß2-microglobulin. ***Waller et al.,*** [25] found that in patients with CRF the BMD Z-score did not correlate with any biochemical markers such as serum iPTH, Ca, ALP and P. The inconsistencies in the results as regard relation between DEXA findings and other biochemical parameters of bone turnover are possibly due to small patient's number and varying patient's characteristics as well as differing therapeutic management strategies affecting bone turnover.

It seems likely that the maintenance of normal serum PTH levels is an important factor in preserving normal BMD which supported by the current results which showed normal BMD in patient with normal PTH value in groups I & II which could be explained by adequate treatment with calcitriol.

Disturbances involving phosphate excretion, vitamin D3 metabolism, hypocalcemia , increased PTH, and acid base disturbances are known pathophysiological factors in patients with ROD . These factors lead to the loss of bone mass, destruction of bone micro architecture, and subsequently increase bone turnover due to increased bone formation and resorption. This could explain the correlation observed between Z-score values and some biochemical markers of bone activity, as DEXA measures the amount of mineral in the scanned area [12]. Measuring of BMD Z-score alone is considered of variable value as HTBD showed more osteopenia than LTBD but not reach significance in group II.

Table (1): Comparison between the studied groups regarding the clinical data, biochemical variables and BMD Z-score

Parameter	*Group 1 (N=20) X± SD*	*Group II (N=15) X± SD `*	*Control group (N=20) X± SD*	*P- value*
Age (years) ∞	13.77±2.39	12.73±4.68	12.4±3.56	>0.05 for all
Weight (kg) ∞	32.22±9.04	43.27±14.11	42.95±13.41	P1<0.001** P2>0.05* P3<0.05
Height (cm) ∞	136±12.08	136.8±28.89	147.1±13.95	>0.05 for all
BMI (kg/m2) ∞	17.12±3.12	17.34 ±1.9	19.33±3.6	P1<0.05* P2>0.05 P3>0.05
SBP (mmHg) ∞	126.7±14.35	129.33±15.79	115±19.6	P1<0.05* P2<0.05* P3>0.05
DBP (mmHg) ∞	84.25±9.9	88.66 ± 9.53	73.5±6.09	P1<0.001** P2<0.001** P3>0.05
GFR (ml/min/1.73 m2) ∞	9.62±1.31	20.84±10.95	238.22±78.38	P1<0.001** P2<0.001** P3>0.05
Total calcium (mg/dl) ∞	8.73±1.33	9.03±1.24	9.45±0.40	P1<0.05P2>0.05 P3>0.05
Phosphorus (mg/dl) ∞	4.98±1.05	5.24±0.78	4.74±0.54	P >0.05 for all
Intact PTH (pg/ml) ♦	791.9±689.75	546.34±532.91	36.8±14.56	P1<0.001** P2<0.001** P3>0.05
ALP (IU/L) ∞	255.15±139.9	172.4±101.2	142.2±56.63	P1<0.001** P2>0.05 P3<0.05*
ß2-microglobulin (mg/l) ∞	6.99±3.48	6.77±3.44	0.98±0.37	P1<0.001** P2<0.001** P3> 0.05
BMD Z-score♦	*-1.63±1.13*	*-1.63±0.51*	*-0.03±0.28*	P1<0.001** P2<0.001** P3 >0.05

♦Kruskal walls test ∞ ANOVA TEST N= number

P1 between control and dialysis group P2 between control and conservative group P3 between dialysis group and conservative group P>0.05 = not significant P< 0.001**= highly significant P<0.05 = significant

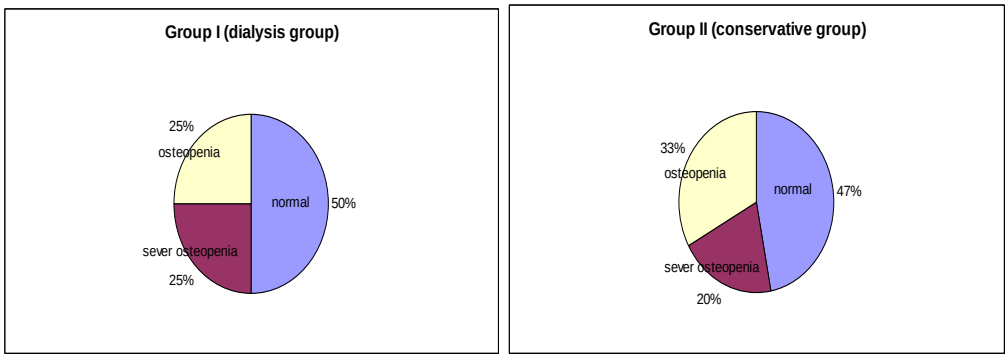

Fig. (1): Frequency of the osteopenia degree in group I& group II

Table (2): Clinical characteristics, biochemical variables, bone mineral density Z-score of group I classified according to iPTH values:

Parameter	Low iPTH (N=4) X ± SD	Normal iPTH (N=4) X ± SD	High iPTH (N=12) X ± SD	p- value
iPTH (pg/ml) ♦	86±49.81	219.7±46.5	1217.9±567	P1 <0.05* P2 <0.001** P3 <0.001**
Duration of dialysis (months) ♦	43.5±29.13	19.25±19.2	32.91±20.98	P> 0.05 for all
Weight (kg) ∞	31.62±7.8	33±13.8	35.25±9.56	P>0.05 for all
Height (cm) ∞	132.08±12.1	134.7±12.3	143±12.35	P>0.05 for all
BMI (kg/m2) ∞	16.4±2.2	16.89±4.57	17.4±3.0	P>0.05 for all
SBP (mmHg) ♦	115±5.7	118.7±11.8	133.3±13.7	P1 > 0.05 P2 <0.05* P3 > 0.05
DBP (mmHg) ♦	75±5.77	80±8.16	88.75±9.07	P1 >0.05 P2 <0.05* P3>0.05
Total calcium (mg/dl) ∞	10.62±0.27	9.37±0.61	7.89±0.85	P1 < 0.05* P2 <0.001** P3 <0.005**
Phosphorus (mg/dl) ∞	5.07±2.02	4.97±0.45	4.95±0.86	P>0.05 for all
ALP (U/L) ♦	72±31.02	207.75±37.86	332±117.21	P1 <0.001** P2 < 0.001** P3 <0.05
ß2-microglobulin (mg/l) ♦	3.8±1.17	4.97±2.33	8.72±3.25	P1 >0.05 P2 < 0.001** P3 <0.05*
BMD Z-score♦	-0.82±0.39	-0.72±0.35	-2.19±1.12	P1 >0.05 P2 <0.05* P3 <0.05*

♦ Kruskal wallies test N= number
P1 between low & normal ∞ ANOVA test
P2 between low & high P3 between normal & high
P>0.05 = not significant P<0.05 = significant

Table (3): Clinical characteristics, biochemical variables, bone mineral density Z-score of group II classified according to iPTH values:

Parameter	Low iPTH (N=4) Mean ± SD	Normal iPTH (N=2) Mean + SD	High iPTH (N=9) Mean + SD	p- value
iPTH (pg/mL) ♦	27.52+35.01	150+70.71	865+455.88	P1 >0.05 P2 <0.001** P3 <0.05*
Duration of renal impairment (months) ∞	42+15.49	43+16.97	18.44+13.48	P1 >0.05 P2 < 0.05* P3 <0.05*
Weight (kg) ♦	31.77+14.67	37+4.24	38.5+14.88	P>0.05 for all
Height (cm) ∞	129.11+29.11	162+28.2	141.5+31.68	P> 0.05 for all
BMI (kg/m2) ∞	16.05+1.36	17.94+2.24	17.78+1.96	P> 0.05 for all
SBP (mmHg) ∞	115+17.32	125+7.07	136.66+12.24	P1 >0.05 P2 < 0.001** P3 >0.05
DBP (mmHg) ∞	77.5+9.57	90+0.0	93.33+6.12	P1 >0.05 P2 < 0.001** P3 >0.05
Total calcium ∞ (mg/dL)	10.8+0.14	9.550+.07	8.13+0.41	P1 <0.001** for all
Phosphorus (mg/dL) ∞	5.5+0.91	4.95+0.07	4.96+0.72	P>0.05 for all
ALP (IU/L) ♦	57.5+9.57	225+106.06	211.77+86.44	P1 <0.001** P2 <0.001** P3 >0.05
ß2-microglobulin♦ (mg/l)	4.29+2.34	6.4+0.28	7.96+3.73	P> 0.05 for all
BMD Z-score ♦	-1.27+0.55	-0.80+0.14	-1.96+1.87	P>0.05

♦Kruskal wallies test P1 between low & normal ∞ ANOVA test
P1 between low & normal P2 between low & high P3 between normal & high P3 between normal & high
P>0.05 = not significant P< 0.001**= highly significant P<0.05* = significant

Table (4): Correlation between DEXA Z score and clinical& laboratory data in group I&II

Parameter	***group I***		***group II***	
	R	***P***	***r***	***P***
Duration of renal impairment and dialysis	***0.15***	***P >0.05***	***0.05***	***P >0.05***
BMI (kg/m2)	***-0.36***	***P >0.05***	***0.08***	***P >0.05***
Weight (kg)	***-0.19***	***P >0.05***	***-0.33***	***P >0.05***
Height (cm)	***-0,07***	***P >0.05***	***0.38***	***P >0.05***
SBP (mmHg)	***-0.65***	***P <0.001****	***-0.31***	***P >0.05***
DBP (mmHg)	***-0.62***	***P<0.001****	***-0.29***	***P >0.05***
Total calcium (mg/dL)	***0.78***	***P <0.001****	***0.34***	***P >0.05***
Phosphorus (mg/dL)	***- 0.15***	***P >0.05***	***-0.19***	***P >0.05***
ß2-microglobulin (mg/l)	***-0.29***	***P >0.05***	***-0.23***	***P >0.05***
iPTH (pg/mL)	***-0.61***	***P <0.001****	***-0.68***	***P <0.001****
ALP (IU/L)	***a-0.48***	***P <0.05****	***-014***	***P >0.05***

r: Pearson correlation coefficient P>0.05 = not significant
P< 0.001**= highly significant P<0.05* = significant

Table (5): Correlation between iPTH and clinical& laboratory data in group I&II

parameter	*group I*		*group II*	
	r	*P*	*r*	*P*
BMI (kg/m2)	*0.01*	*P >0.05*	*0.26*	*P >0.05*
Duration of renal impairment and duration of dialysis	*0.19*	*P >0.05*	*-0.29*	*P >0.05*
Weight (kg)	*-0.01*	*P >0.05*	*-0.28*	*P >0.05*
Height (cm)	*-0,01*	*P >0.05*	*-0.39*	*P >0.05*
SBP (mmHg)	*0.63*	*P <0.001***	*0.55*	*P <0.05**
DBP (mmHg)	*0.71*	*P <0.001***	*0.56*	*P <0.05**
Total calcium (mg/dl)	*-0.73*	*P <0.001***	*-0.76*	*P <0.001***
Phosphorus (mg/dl)	*-0.17*	*P >0.05*	*-0.32*	*P >0.05*
ß2-microglobulin (mg/L)	*0.79*	*P <0.001***	*0.57*	*P <0.05**
ALP (IU/L)	*0.81*	*P <0.001***	*0.44*	*P >0.05*

r: Pearson correlation coefficient P>0.05 = not significant P< 0.001**= highly significant
P<0.05* = significant

Conclusions: Maintenance of normal bone turnover may be important in prevention of irreversible bone disabilities & CVD. The preserving of normal BMD is a challenge for pediatric nephrologists so continuous and regular monitoring systems by combination of iPTH, serum Ca, ALP, β_2-microglobulin & BMD Z-score could be early, accurate and non invasive assessment of the skeletal system in children with CRF.

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