

Original Research Article

Bone metabolism assessment in hemodialysis patients by using Carboxy-terminal cross-linked telopeptide of type I collagen

ABSTRACT

Aims: To evaluate the carboxy-terminal telopeptide of type I collagen (CTX I) as a serum bone metabolism marker in hemodialysis patients

Study design: Cross-sectional observational.

Place and Duration of Study: Hemodialysis unit of Tanta University Hospital, between October 2018 and March 2020.

Methodology: 80 male patients aged from (18-65y) on regular hemodialysis were included. All patients were subjected to: history taking, full clinical examination, laboratory investigations including: Serum calcium, serum phosphorus, serum albumin, alkaline phosphatase (ALP), Intact parathyroid hormone (iPTH), serum carboxy-terminal cross linking telopeptide (CTX I) and dual energy X ray absorptiometry (DEXA) scan of the lower third of the right fibula to evaluate bone mineral density (BMD) and patient were divided according to bone mineral density T score into two groups "normal and osteopenic groups"

Results: There is significant difference between normal and osteopenic groups according to iPTH ($p = 0.001$) and ALP ($p = 0.001$) and CTX I ($p = 0.001$), but there is non-significant difference between normal and osteopenic groups according to serum calcium ($p = 0.239$), serum phosphorus ($p = 0.672$), serum albumin ($p = 0.749$) and corrected serum calcium ($p = 0.314$). There was negative significant correlation between CTX I and DEXA scan, and between DEXA scan and iPTH and ALP. There was positive significant correlation between CTX I and iPTH, ALP and serum albumin and there was positive significant correlation between iPTH and ALP. At cutoff 2.0 ng/ml CTX I can significantly diagnose osteopenia in hemodialysis patients with 93% sensitivity, 95% specificity and accuracy of 92%. It had positive predictive value of 95% and negative predictive value of 83%, in multiple regression analysis the increase in iPTH and CTX I was the significant predictor of osteopenia.

Conclusion: This study showed high association between CTX I and other established markers of bone metabolism and BMD by DEXA demonstrating the potential utility of CTX I as marker of bone resorption in renal bone disease

Keywords: Hemodialysis, bone metabolism, DEXA scan, carboxy-terminal telopeptide of type I collagen (CTX I)

1. INTRODUCTION

"Chronic kidney disease (CKD) is currently a public health problem. More than 60 million worldwide people lose their lives annually due to the risk of kidney failure"⁽¹⁾

"Metabolic bone disease is a common complication of CKD and is part of broad spectrum disorders of mineral metabolism that occur in this clinical setting during dialysis"⁽²⁾.

"In the course of **CKD** most of the metabolic bone diseases are characterized by alteration in the bone resorption / formation balance as secondary hyperparathyroidism, osteoporosis, mixed bone diseases, osteomalacia, a dynamic osteopathy, and extra skeletal calcifications"⁽³⁾.

The presence of high levels of circulating calcium can promote the deposition of calcium in the arterial walls, including the aorta, leading to vascular calcification. Vascular calcification poses significant cardiovascular risks for hemodialysis patients, as it is associated with increased arterial stiffness, hypertension, and an increased risk of cardiovascular events, such as heart attacks and strokes.⁽³⁾

"There are biochemical markers currently available for the assessment of bone turnover include enzymes and non-enzymatic peptides derived from the cellular and non-cellular compartments of bone metabolism, these markers which are formed during the bone resorption phase of bone remodeling include products of osteoclasts activity released during bone resorption"⁽⁴⁾.

"Carboxy-terminal cross-linked telopeptide of type I collagen (CTX I) is a biochemical marker widely used in assessing bone metabolism. It plays a crucial role in the evaluation of bone turnover and the management of skeletal health in various clinical settings".⁽⁵⁾

"Bone metabolism is a dynamic process involving continuous bone formation and resorption, which is tightly regulated by various factors. Collagen type I is the major component of bone tissue, and its degradation products, such as CTX I, can be measured in the blood and urine to provide insights into bone turnover. CTX I specifically represents the C-terminal telopeptide of type I collagen, which is released during bone resorption".⁽⁶⁾

Hemodialysis patients frequently experience alterations in bone metabolism due to multiple factors, including renal osteodystrophy, chronic inflammation, mineral and hormonal imbalances, and the use of certain medications. Renal osteodystrophy, a complex bone disorder, is prevalent in these patients and is characterized by a spectrum of bone abnormalities, ranging from low bone turnover to high bone turnover.⁽⁷⁾

CTX I serves as a valuable marker for evaluating bone turnover in hemodialysis patients. Elevated CTX I levels indicate increased bone resorption, while decreased levels suggest reduced bone turnover. Monitoring CTX I levels can aid in diagnosing and classifying renal osteodystrophy, assessing treatment response, and guiding therapeutic interventions to optimize skeletal health.^(5, 6)

The present study evaluate the **carboxy-terminal** telopeptide of type I collagen (CTX I) as a serum bone metabolism marker in **hemodialysis** patient. By monitoring CTX levels, clinicians can better understand bone turnover and make informed decisions regarding the management of skeletal health. This knowledge can contribute to the prevention of bone-related complications and ultimately improve the quality of life for individuals undergoing hemodialysis

2. METHODOLOGY

The study carried on 80 male **CKD** patients on regular hemodialysis between October 2018 and March 2020. **A written** informed consent was obtained from all participants before

inclusion in the study, explaining the value of the study, plus the procedures that was commenced. **Approval** from Ethical Committee of Tanta Faculty of Medicine was obtained before starting the study. **Confidentiality** and personal privacy was respected in all levels of the study. **Participants** are free to withdraw from the study at any time without any consequences. **Collected** data were not and will not be used for any purpose.

2.1. Inclusion criteria:

Adult male patients who are on regular hemodialysis due to CKD.

2.2. Exclusion criteria:

1. Patients suffer from chronic inflammatory disease.
2. Patients with past history of renal transplantation.
3. Patients with past history of parathyroidectomy.
4. Patients with past history of fracture.
5. Patients with acute illness.
6. Female patients due to hormonal effect on bone metabolism.
7. Medication that affect calcium metabolism.

All patients were subjected to the following:

1. Through history taking.
2. Complete clinical examination.
3. Laboratory investigations including:

A- Routine laboratory investigation: **serum** calcium, **serum** phosphorus, **serum** albumin, alkaline phosphatase (ALP), Intact **parathyroid** hormone (iPTH) ,

B- Specific laboratory investigation: Serum **carboxy-terminal** cross linking telopeptide.

dual energy X ray **absorptiometry** scan (DEXA) of the lower third of the right fibula to evaluate bone mineral **density** (BMD) and patient were divided according to bone mineral density

4. Imaging:

Abdominal and pelvic ultrasonography **and DEXA scan. BMD** of the distal third of right fibula was assessed by DEXA scan. BMD T and Z scores were classified according to World Health Organization criteria and T-score < -1 , which was below the expected range for age, was indicative of the diagnosis of **osteopenia**. In the T-score scale, 0 represents normal, healthy bone density of T-scores above 0 and slightly below 0 are within the normal range. T-score of -2.3 shows lower bone density than a score of -1.8. The T-score is a radiographic diagnosis, meaning it is an X-ray diagnosis and doesn't imply anything about the cause of osteoporosis. T-scores mean different things on the different DEXA scans.

- A T-score of -1 to 0 and above is considered normal bone density.
- A T-score between -1 and -2.5 is diagnosed as osteopenia.
- A score of -2.5 or below is diagnosed as osteoporosis

2.3. Statistical Analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 22.0. Quantitative data were expressed as mean± standard deviation (SD). Mean value, Standard student "t test", The Mann-Whitney U test, Linear Correlation Coefficient [r] (z test), ROC-curve, the subject of multivariate analysis deals with the statistical analysis of the data collected on more than one (response) variable. ⁽⁸⁾

3. RESULTS AND DISCUSSION

Table (1) showed that: There is significant difference between normal and osteopenic groups according to iPTH with p.value (0.001) and ALP with p.value (0.001).

No significant difference between two groups as regard serum Ca with p.value (0.239), serum PO₄ with p.value (0.672), serum albumin with p.value (0.749) and corrected serum Ca with p.value (0.314).

Table 1: Comparison between Normal and Osteopenic groups according to serum Calcium, phosphorus, parathyroid hormone, albumin, alkaline phosphatase, Corrected Calcium

		Range	Mean ± S. D	t. test	p. value
Ca mg/dl	Group A	7.5 – 10	8.40 ± 0.75	1.407	0.239
	Group B	6.8 – 10	8.61 ± 0.73		
PO ₄ mg/dl	Group A	3.3 – 6.9	5.08 ± 1.14	0.180	0.672
	Group B	2.5 – 7.7	5.21 ± 1.21		
PTH pg/ml	Group A	170 – 612	309.48 ± 126.16	16.513	0.001*
	Group B	45 – 2500	643.68 ± 385.30		
ALP U/L	Group A	214 – 720	376.26 ± 137.45	14.476	0.001*
	Group B	350 – 2900	769.77 ± 486.96		
Albumin gm/dl	Group A	2.2 – 3.4	2.86 ± 0.32	0.103	0.749
	Group B	2.1 – 3.9	2.89 ± 0.46		
Corrected Ca mg/dl	Group A	8.14 – 10.5	9.30 ± 0.82	1.027	0.314
	Group B	7.08 – 10.96	9.50 ± 0.77		

Ca =calcium. PO₄= phosphorus. PTH= parathyroid hormone. ALP= alkaline phosphatase.

Table (2) showed that: There is difference between Normal (group A) and Osteopenic (group B) groups according to BMD.

Table 2: Comparison between Normal and Osteopenic groups according to bone mineral density by using T score obtained by dual energy X ray absorptiometry scan.

		Mean	±	S. D	t. test	p. value
BMD	Group A	0.72	±	0.40	30.949	0.001
	Group B	-2.04	±	0.34		

BMD: bone mineral density

Table (3) showed that: There is difference between Normal and Osteopenic groups according to CTX I with mean± S. D (1.85±0.19) for normal group and mean± S. D (42.04±42.71) for osteopenic groups with P. value (0.001).

Table 3: Comparison between Normal & Osteopenic groups according to carboxy-terminal cross linking telopeptide

	Normal Group	Osteopenic group	U test	P
CTX I	1.8 ± 0.19	42.04 ± 42.71	6.798	0.001

CTX I: carboxy-terminal cross linking telopeptide

Table (4) shows:

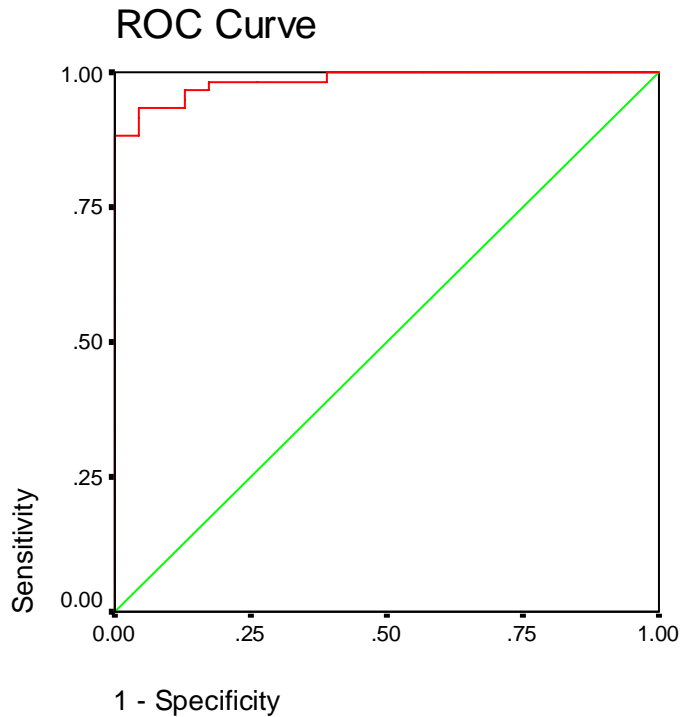
- Negative significant correlation between CTX I and DEXA scan with r (-0.520).p (0.001).
- Negative significant correlation between DEXA scan and iPTH with r (-0.444) , p(0.001) & Alp with r (-0.417) p(0.001).
- Positive significant correlation between CTX I and iPTH with r (0.590) p (0.001), ALP with r (0.575) and p(0.001) & Albumin with r (0.339) and p(0.002).
- Positive significant correlation between iPTH & ALP with r (0.930) and p (0.001).

Table 4: Correlation between carboxy-terminal cross linking telopeptide, dual energy X ray absorptiometry scan & intact parathyroid hormone and other items

	CTX I		DEXA scan		iPTH	
	r	P	r	p	R	p
DEXA scan	-0.520	0.001			-0.444	0.001
Age in years	0.020	0.854	-0.054	0.627	-0.163	0.141
Ca in mg/dl	0.096	0.390	-0.157	0.157	0.162	0.143
PO4 in mg/dl	0.105	0.343	-0.014	0.901	0.180	0.104
PTH in pg/ml	0.590	0.001	-0.444	0.001		
Alp in U/L	0.575	0.001	-0.417	0.001	0.930	0.001
Albumin in gm/dl	0.339	0.002	-0.101	0.362	0.148	0.183
Corrected Ca in mg/dl	-0.058	0.599	-0.108	0.332	0.077	0.487

Ca = calcium. PO4= phosphorus. iPTH = intact parathyroid hormone ALP = alkaline phosphatase.
 CTX I: carboxy-terminal cross linking telopeptide
 DEXA: dual energy X ray absorptiometry scan

Figure (1): Receiver Operating Characteristics Curve to Carboxy-Terminal Cross Linking Telopeptide for Prediction of Osteopenia



ROC: Receiver Operating Characteristics
 CTX I: carboxy-terminal cross linking telopeptide

Table (5): Receiver Operating Characteristics Curve to Carboxy-Terminal Cross Linking Telopeptide for Prediction of Osteopenia.

HCC C&D	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
CTX I	2.0	0.984	93	87	95	83	92

PPV: positive predictive value, NPV: negative predictive value, AUC area under curve

Table (5) and Figure (1): showed that at cutoff 2.0 ng/ml, area under curve (AUC): 0.984, CTX I can detect osteopenia with Sensitivity: 93%, Specificity: 87%, positive predictive value (PPV): 95%, negative predictive value (NPV): 83% and accuracy: 92%.

Table (12) of multiple regression show that analysis for the parameters for detection of osteopenia shows that: the increase in PTH with p value 0.001 and CTX I with p value 0.027 are the most predictors for osteopenia in hemodialysis patients.

*The predictors of osteopenia are PTH and CTX I

Table (6) of multiple regression show that analysis for the parameters for detection of osteopenia shows that: the increase in PTH with p value 0.001 and CTX I with p value 0.027 are the most predictors for osteopenia in hemodialysis patients.

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Table (6): Multi regression analysis for predictors of osteopenia

	OR	95% CI	P value
Age	1.028	0.960 – 1.101	0.423
Ca	1.161	0.394 – 3.420	0.787
PO4	0.928	0.448 – 1.920	0.840
PTH	1.011	1.006 – 1.017	0.001
ALP	1.032	0.992 – 1.073	0.118
Albumin	0.135	0.012 – 33.502	0.071
Corrected Ca	2.426	0.138 – 42.621	0.544
CTXI	1.954	1.199 – 4.521	0.027

Ca =calcium. PO4= phosphorus. PTH= parathyroid hormone.

ALP= alkaline phosphatase.

CTX I: carboxy-terminal cross linking telopeptide

Discussion:

In current study, there is no significant difference between normal and osteopenic groups according to age. This may be due to the limited number of young adults (i.e., those with peak bone mass) in our study population compared with the studies from the general population.

In harmony with our study *Barreto et al.* and *Park et al.* found that age was not significantly different in relation to BMD changes^(9,10).

However, *Slouma et al.*, found that patients with osteoporosis were older than patients without osteoporosis⁽¹¹⁾.

Also, in disagreement with current study, *Avramovski and Sikole*, detected “a high prevalence of osteoporosis in a relatively young hemodialysis patient population. Bone loss likely begins much earlier and progresses more rapidly in hemodialysis patients”⁽¹²⁾.

In our study, there was no significant difference between osteopenic and non-osteopenic groups regarding calcium, phosphorus and albumin levels.

Similarly, *Malluche et al.*, found no significant relation between baseline BMD and serum calcium or phosphorus⁽¹³⁾.

Also, another study done by *Lai et al.*, showed that “there was no relationship between serum albumin, alkaline phosphatase, phosphate levels and femoral neck BMD in dialysis patients and albumin was not a useful predictor of BMD”⁽¹⁴⁾.

Another similar result was reported by studies found that “hypoalbuminemia independently associated with bone loss as serum albumin is a marker of systemic inflammatory status among dialysis patients”^(14, 15).

In disagreement with our study, *Huang et al.*, found “a positive correlation between serum albumin levels and femoral neck BMD in dialysis patients”⁽¹⁶⁾.

Moreover, *Polymeris et al.*, investigated the BMD and bone metabolism in hemodialysis patient and found serum phosphorus levels was high in cases with lower BMD⁽¹⁷⁾.

In current study, iPTH was significantly higher in osteopenic groups than normal cases (643.68 ± 385.30 pg/ml versus 309.48 ± 126.16 pg/ml respectively, $p=0.001$).

These results were in harmony with *Slouma et al.*, study which included total of 90 patients and reported that iPTH levels were significantly increased in patients with osteoporosis⁽¹¹⁾.

Also, *Taal et al.*, showed that the BMD had a negative correlation with PTH⁽¹⁸⁾.

Similarly, BMD was significantly and negatively correlated with serum intact PTH as reported by *Okuno et al.*,⁽¹⁹⁾.

This results was supported by *Brunerová et al.*, study revealed that, “serum markers of bone resorption and formation were high in the majority of patients with low BMD and in almost 70% of them secondary hyperparathyroidism was present”⁽²⁰⁾.

In contrast to these results, *Ueda et al.*, compared between HD patients with and without reduction in radius BMD in serum PTH and bone metabolic markers, they found serum PTH was not significantly different between the two groups ($p = 0.4603$)⁽²¹⁾.

In current study, ALP was significantly higher in oosteopenic groups than normal cases (769.77 ± 486.96 U/L versus 376.26 ± 137.45 U/L respectively, $p=0.001$).

This was in accordance with a study done by *Ueda et al.*, which included 137 HD patients, and reported that, serum bone ALP was significantly higher in those with BMD reduction than in those without.⁽²¹⁾

Moreover, according to study by *Malluche et al.*, baseline BMD correlated with iPTH and bone-specific ALP⁽¹¹⁾.

In line with our study, *Ureña and de Vernejoul*, reported that, uremic patients usually exhibit high plasma iPTH and high serum concentration of biochemical markers of bone metabolism such as ALP⁽²²⁾.

In harmony with current work, *Nybo et al.*, reported that, BMD correlated with levels of iPTH and ALP⁽²³⁾.

Also, *Park et al.*, found that serum ALP was negatively correlated with bone mineral density assessed by DEXA scan in hemodialysis patients⁽¹⁰⁾.

In a single-center cohort study, *Iimori et al.*, investigated 485 hemodialysis patients, and their results also showed that higher values of serum ALP are a predictor of fragility in those patients⁽²⁴⁾.

However, *Barreto et al.*, study data revealed no correlation between BMD and ALP in hemodialysis patients⁽⁹⁾.

In current study, there was Positive significant correlation between iPTH & ALP.

In agreement with the present study, *Barreto et al.*, found a positive correlation was found between iPTH and ALP levels ($r=0.0408$, $P=0.001$)⁽⁹⁾.

Similarly, *Polymeris et al.*, found that, serum iPTH correlated significantly in a positive manner with serum ALP ($R = 0.690$; $p < 0.001$)⁽¹⁷⁾.

In current study, there is negative significant correlation between CTX I and DEXA scan, positive significant correlation between CTX I and PTH, Alp & albumin.

In agreement with our study, *Reichel et al.*, found that, serum CTX I was significantly correlated with various iPTH assays ($r > 0.56$) and with alkaline phosphatase ($r = 0.404$)⁽²⁴⁾.

Also, *Pagani et al.*, found the positive correlation of serum CTX I with serum iPTH clearly indicates that the increase in CTX I also results from enhanced bone turnover due to secondary hyperparathyroidism⁽²⁵⁾.

Moreover, *Maeno et al.*, found that serum NTX I and CTX I, but not other bone markers, correlated significantly with the rate of forearm bone loss during a subsequent 2-year period in hemodialysis patient⁽²⁶⁾.

Also, *Okuno et al.*, found that, “serum CTX I showed significant and negative correlation with BMD change, Serum CTX I was also found to have significant and positive correlations with iPTH ($r=0.60$, $P < 0.01$) and alkaline phosphatase (ALP) ($r=0.66$, $P < 0.01$)”⁽¹⁹⁾.

Moreover, *Herrmann and Seibel*, have also demonstrated that CTX I concentrations are raised in patients with CKD-5D and correlate well with BMD measurements⁽²⁷⁾.

However, in contrast to our results, another study by *Ueda et al.*, showed that serum CTX I levels were not different between patients with and without loss of BMD at the distal radius⁽²¹⁾.

Another study done by *Slouma et al.*, disagreed with our results as it found that there was no significant difference between patients with osteoporosis, those with osteopenia, and those with normal T-scores regarding bone turnover markers including serum CTX I levels⁽¹²⁾.

In current study, multiple regression analysis for predictor of osteopenia the parameters shows that, the increase in iPTH and CTX I was the significant predictor of osteopenia in hemodialysis patients. Otherwise, age, Ca, PO₄, ALP, albumin were not significantly predicted osteopenia in hemodialysis patients. CTX I is significantly higher in osteopenic groups than normal cases (42.04 ± 42.71 versus 1.85 ± 0.19 respectively, $p=0.001$).

We reported that, at a cutoff 2.0 and AUC of 0.984, CTX I significantly diagnosed osteopenia in hemodialysis patients with 93% sensitivity, 95% specificity, and accuracy of 92%. It had PPV of 95% & NPP of 83%.

These results were supported by many studies reported that, high sensitivity and specificity as a bone resorption marker is provided by a newly developed assay for

degradation fragments of the C-terminal telopeptide of type I collagen that contain the b-isomerized octapeptide (CTX I)^(28, 29).

Moreover, in study by *Maeno et al.*, The sensitivity of the highest quartiles as cutoff points for identification of those hemodialysis patients who had lost bone mass in the distal third of the radius was 45% for CTX I, the specificity was 82%, the positive predictive values was 46% for CTX I, and the negative predictive values was 81% for CTX I Although its value was lower than our study⁽²⁶⁾.

Okuno et al., shows “the sensitivity of the highest quartile as a cut-off point for identifying those hemodialysis patients who had lost bone mass was 41% for CTX I, The specificity was high at 83% for CTX I, The positive predictive value of serum bone marker values was 55% for CTX I & the negative predictive value of serum marker values was 73% for CTX I”⁽¹⁹⁾.

5. CONCLUSION:

We found a significantly increase CTX I in osteopenic group and high association between CTX I and other established markers of bone metabolism demonstrating the potential utility of CTX I as marker of bone resorption in hemodialysis patients

CONSENT:

Any unexpected risks appeared during the course of the research will be cleared to the participants, their parents and the ethical committee on time. There are adequate measures to maintain the privacy of participants and confidentiality of the data: A code number to every patient with the name and address will be kept in a special file. The patient name will be hidden when using the research. The results of the study will be used only in a specific manner and not to use in any other aims. Informed consent will be obtained from patients 18 years old or older. "All authors declare that „written informed consent was obtained from the patient (or other approved parties) for publication of this research and accompanying images".

ETHICAL APPROVAL

“All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.”

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