Review Form 1.7

Journal Name:	**Journal of Advances in Medicine and Medical Research**
Manuscript Number:	**Ms_JAMMR_102954**
Title of the Manuscript:	**Bone metabolism assessment in hemodialysis patients by using Carboxy-terminal cross-linked telopeptide of type I collagen**
Type of the Article	**Original Research Article**

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty'**, provided the manuscript is scientifically robust and technically sound.
To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(https://www.journaljammr.com/index.php/JAMMR/editorial-policy)

PART 1: Review Comments

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Compulsory REVISION comments **1. Is the manuscript important for scientific community?** (Please write few sentences on this manuscript) **2. Is the title of the article suitable?** (If not please suggest an alternative title) **3. Is the abstract of the article comprehensive?** **4. Are subsections and structure of the manuscript appropriate?** **5. Do you think the manuscript is scientifically correct?** **6. Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form.** **(Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)**	1. Yes, this study, is so important, although pioneering and with a smaller number of subjects, investigates a combination of two biomarkers, one clinical (**Carboxy-terminal cross-linked telopeptide of type I collagen**) and the other imaging diagnostic, DEXA. 2. YES 3. Yes 4. YES 5. YES, after corrections that the authors need to do. 6. Yes 7.	
Minor REVISION comments **1. Is language/English quality of the article suitable for scholarly communications?**	1. YES The authors have to correct all my notes according I suggested, point-by-point. Line 9: Please correct to "carboxy – terminal". Please correct in all further text. Please correct to "hemodialysis". …serum calcium, serum phosphorus, serum albumin…please correct as I suggested. Please correct "absorbtiometry" to "**absorptiometry".** **Please correct to "density".** Please correct to (normal and osteopenic). Please correct to "normal and osteopenic group" Please replace "oesteopenic" to "osteopenic" in all further text.	

	You use “PTH” but it is not abbreviate before. Please abbreviate previously, “intact parathyroid hormone” not “intact para thyroid” with abbreviation iPTH. After that you may use its abbreviation…according to the iPTH (p = 0.001). Please delete “value” after “p”. Please insert a space between “phosphatase” and “(ALP)”. Please explain the used abbreviation DEXA in its first order of appearance. Please use the same word for abbreviation, “CTX I” instead “CTXI”. Keep attention of missed space between the joined words. Please explain the used abbreviations PPV and NPP in their first order of appearance. If they did not appeared in the further text in the abstract, you not have to abbreviate them. It is better to use “and” than “&”, PTH and ALP, instead PTH & ALP. Please check for that in all text. The part **Introduction** is too short, about 15 lines. Please insert at least 30 lines, about bone turnover in haemodialysis patients and carboxy-terminal cross-linked telopetide I collagen. Please use some sentences as I suggested: Carboxy-terminal cross-linked telopeptide of type I collagen (CTX) 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. 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, can be measured in the blood and urine to provide insights into bone turnover. CTX specifically represents the C-terminal telopeptide of type I collagen, which is released during bone resorption. 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. CTX serves as a valuable marker for evaluating bone turnover in hemodialysis patients. **Elevated CTX levels indicate increased bone resorption, while decreased levels suggest reduced bone turnover.** Monitoring CTX levels can aid in diagnosing and classifying renal osteodystrophy, assessing treatment response, and guiding therapeutic interventions to optimize skeletal health. Please insert a few sentence about the progression of the bone mineral density loss in dialysis patients: **https://eprints.uklo.edu.mk/id/eprint/8437/** **https://eprints.uklo.edu.mk/id/eprint/8437/1/13.%20KOREAN%20J%20INT%20MED%2C%20The%20progression%20of%20BMD%20loss....pdf** 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. Please write something about BMD and aortic calcification. https://pubmed.ncbi.nlm.nih.gov/26467382/	

In hemodialysis patients, disturbances in **bone turnover** can lead to the movement of calcium from the bone to the aorta, a process known as vascular calcification.

Chronic kidney disease and hemodialysis-related factors contribute to an imbalance in bone metabolism, resulting in increased bone resorption and reduced bone formation. The excess release of calcium from bone due to accelerated bone resorption can contribute to elevated calcium levels in the bloodstream. 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.

Please cite 1-3 new references with would be in connections of the new inserted text in the INTRODUCTION. Please rewrite the introduction to be wider.

Methodology

Line 37: You previously abbreviate “chronic kidney disease” – line 19. Now, please use the abbreviation, only.

Line 38: Please insert a space between joined words “A” and “written”, and after “commenced” (line 40), and after “study.”. Please check all joined words and missed spaces everywhere in the further text (line 40, line41, line42, line 43, line 45).

Line 46: Please rewrite the sentence.

Line 62: Star sentence with big letter, Dual energy…

absorptiometry is correct, not absorbtiometry.

Line 63: Please correct “density” to “density. Do not repeat the full name “bone mineral density” that you previously abbreviated (BMD). Please use onlu the abbreviation BMD, now.
Line 66, 68: Please use only the abbreviation DEXA, before you were explained before.
Line 70: Please correct to “osteopenia”.
Line 79: Missed space between…
Line 80: Please cite appropriately the used statistical software SPSS v.22
IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Line 82: Please explain the mean of the used abbreviation ROC (receiver operating characteristics).

Example one

Variable	Normal Group	Osteopenic group	t - test	p
Ca, mmol/L	8.40 ± 0.75	8.61 ± 0.73	1.407	0.239
PO_4	5.08 ± 1.14	5.21 ± 1.21	0.180	0.672
PTH				

In the bottom of the tables provide the abbreviations explanations:
Ca, calcium; PO_4 not PO4, phosphorus. PTH, parathormon…ALP, and insert…
The results are expressed as mean and standard deviation (SD).
Beside the variables please provide the units of measure according SI. Ca, mmol/L.

	You did not provide the unit of measure for the variables. Please coreect that, BMI (kg/m^2). Table 2: Please do not use abbreviations in the table title, BMD replace with bone mineral density, and DEXA, too. The columns range is not necessary, the mean and SD are sufficient descriptive statistics. Please redraw the tables with columns that I suggested. Please delete a "Range" column and reconstruct the table as "example one". Please do it for all tables. Please delete the cells with "mean ± SD" only. In the bottom of the table you have to provide: **The results are expressed as mean and standard deviation (SD).** In this way, as I suggested, the tables are more understandable and clear. Please reconstruct all tables. Table 3: Please delete the asterisk (*) beside 0.001 for p-value. Please provide the unit of measure beside all variables according SI. Age, years, ca,Po4,PTH… Please explain the used abbreviation ROC in the title of Figure 1. In the bottom of the table you explain the used abbreviation PPV and NPV. Where they are in the figure. Tell me the purpose of their display. Please insert a legend what is red and what is green line (line of equality). In discussion you discus about the results of BMD, PTH, ALP, but you did not provided any unit of measure for those variables. Please provide beside all results the units of measure according to the SI. Line 239: Where is multiple regression analysis? I did not seen any results from this statistical method. What is strengths and limitations of your study? Please provide several limitations and strengths. MAJOR REVISO	
Optional/General comments		

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

PART 2:

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Are there ethical issues in this manuscript?	*(If yes, Kindly please write down the ethical issues here in details)*	

Reviewer Details:

Name:	**Petar Avramovski**
Department, University & Country	**St. Klement Ohridski University, North Macedonia**