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Assessment of Some Bone Turnover in Chronic Kidney Disease Patients in Tikrit/Iraq

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ABSTRACT

The present study aimed to assess some bone turnover in chronic kidney disease with and without hemodialysis. 50 individuals were involved in the study and divided into three groups; the first two groups were patients with chronic kidney disease (15 were with hemodialysis, and 15 were without hemodialysis), and the third group involved 20 healthy individuals as a control group. Some bone turnovers like parathyroid hormone, vitamin D3, insulin-like growth factor-1, osteopontin, fibroblast growth factor-23, and calprotectin were analyzed using serum from all individuals. The serum concentration of parathyroid hormone was significantly lower ($P<0.05$) in chronic kidney disease with non-hemodialysis compared to chronic kidney disease with hemodialysis group and healthy individuals. While serum concentrations of vitamin D3, insulin-like growth factor, and osteopontin were significantly lower in both chronic kidney disease groups compared to healthy individuals. The serum concentration of fibroblast growth factor showed a non-significant difference ($P>0.05$) in both chronic kidney disease groups compared to healthy individuals. While serum concentration of calprotectin showed a significant increase ($P<0.05$) only in the chronic kidney disease without hemodialysis group compared to both other groups.

Keywords: *Kidney, Disease, Assessment, Group*

INTRODUCTION

Chronic Kidney Disease (CKD) is a worldwide health issue, and about 13.4% of the global population has the disease.

CKD is classified into 5 stages, the first 3 stages were asymptomatic, while the last two stages were symptomatic, and patients undergo hemodialysis (1). The majority, 79 percent, were in advanced stages of the disease (stages 3–5); however, the actual proportion of people with early CKD (stages 1 or 2) is likely to be much higher because early kidney disease is clinically silent (2).

The most critical variables in the classification of patients with CKD are bone mineral density (BMD) and bone turnover. Variations in kidney function can lead to changes in serum biochemical values due to communication pathways between the bone, kidney, and parathyroid glands (3). Controlling biochemical parameters of CKD-MBD patients has been reported to be critical in these individuals.

Radeef et al. (2020) show a significant increase in both serum Parathyroid hormone (PTH), and Vitamin D3 (VD3) among CKD (4), while Gallieni et al. (2016) show the opposite (5).

Several studies indicate that some bone turnover biomarkers are affected in CKD. Teppala et al. (2010) show that the serum Insulin-like growth factor decreased among CKD (6), while Nishi et al. (2022) show the opposite (7). Shamsulddin et al. (2020) show a significant increase in serum Osteopontin (OPN) among Iraqi CKD (8). Ameen and Ali, (2018) showed increased serum levels of Fibroblast growth factor-23 (FGF-23) among CKD (9). There are rare studies about serum calprotectin among CKD, also, locally in Iraq, this is the first study about calprotectin among Iraqi CKD. As well as the effect of CKD on these bone turnover biomarkers is still not clear, as well as the effects of hemodialysis and non-hemodialysis.

So, the current study aimed to assess serum levels of bone turnover biomarkers, and serum calprotectin among hemodialysis and non-hemodialysis Iraqi CKD.

MATERIALS AND METHOD

The design of the study

The current study involved 30 patients with CKD divided into CKD with hemodialysis and CKD without hemodialysis (each one with 15 patients), also, the current study involved 20 healthy individuals as a control. Both patients and healthy individuals' ages ranged from 18-45 years. Patients with acute chronic disease and healthy subjects who decline consent were excluded from the study.

Blood samples from the study population were aspirated and the serum was used to assess serum PTH, VD3, IGF-1, OPN, FGF-23, and calprotectin.

Evaluation of bone turnover biomarkers

The ELISA technique was used to assess all biomarkers in the study using commercial kits.

Statistical analysis

All results are expressed as Mean±S.D using SPSS (V.23) program, then the differences between all groups were detected using a One-way ANOVA test followed by the Duncan multiple ranges.

RESULTS

Statistical analysis showed a significantly decreased ($P<0.05$) concentration of serum PTH in CKD with hemodialysis and CKD without hemodialysis groups compared to the healthy subjects. As shown in Table 1.

Table 1 shows a significant increase ($P<0.05$) in serum VD3 concentration in both CKD groups compared to the healthy subjects.

As shown in Table 1, the results showed a significant increase ($P<0.05$) in the serum IGF-1 concentration compared to the healthy subjects.

Serum OPN was significantly higher ($P<0.05$) in both CKD groups in the present study compared to the Healthy subjects. As shown in Table 1.

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As shown in Table 1, Serum FGF-23 showed non-significant differences (P>0.05) in both CKD groups compared to the healthy subjects. As shown in Table 1.

Lastly, the current study showed a significant increase (P<0.05) in serum calprotectin in CKD without hemodialysis group compared to both CKD with hemodialysis and the Healthy subjects. As shown in Table 1.

TABLE 1: Assessed serum PTH, VD3, FGF-23, IGF-1, OPN, and calprotectin levels in CKD without hemodialysis, and CKD without hemodialysis patients compared to the healthy subjects.

Parameters	CKD with hemodialysis	CKD without hemodialysis	Healthy subjects	P-value
	Mean±S.D			
PTH pg/ml	27.36±22.22B	18.38±6.25 C	36.63±10.79A	0.001
VD3 ng/ml	60.76±50.19A	54.18±15.99A	27.86±25.74B	0.029
IGF-1 µg/l	21.04±11.38A	21.41±12.02A	29.75±16.32B	0.031
OPN ng/ml	1.61±0.7A	1.9±0.65A	1.13±0.37B	0.005
FGF-23	7.27±1.95A	6.71±1.96A	5.24±2.43A	0.096
Calprotectin ng/ml	4.65±1.79B	5.74±0.78A	4.12±1.24B	0.005

- Different litters indicate significant differences at P-value ≤0.05.

DISCUSSION

Reflecting the elevated occurrence of CKD, the current study was created to provide some proof of some biomarkers of bone turnover in the Iraqi population. The results of the statistical analysis in the present study showed a significant decrease (P<0.05) in the serum of PTH level and a significant increase (P<0.05) in the serum level of VD3.

Many signaling molecules like PTH, VD3 and some other factors regulate both new-bone secretor cells (Osteoclasts, and osteoblast) (10).

Abnormalities in some biomarkers like PTH, and VD3 describe a systemic condition of bone and mineral metabolism caused by chronic kidney disease—mineral and bone disorder (CKD-MBD) (11).

A study by Radeef (2020) presented a significantly higher (P<0.05) concentration of VD3 and PTH in CKD patients (4). Recent findings indicate that kidney disease is associated with a higher incidence rate of vitamin D deficiency or insufficiency, and severely proteinuric patients have a higher incidence rate than the smallest values. However, the current study found that VD3 serum levels were significantly higher (P<0.05) in CKD patients throughout the study. One possible explanation for this increase is that most of these patients received vitamin D supplementation (alfacalcidol) throughout the course of the study.

PTH is indeed the predominant calcium as well as a phosphate-regulating hormone made by PTH chief cells, high serum levels of calcium, calcitriol, or FGF23 limit PTH secretion, whereas hypocalcemia, hyperphosphatemia, and/or a drop in 1,25-dihydroxy vitamin D (1,25(OH)2D) level result in increased PTH secretion (12).

Dawson-Hughes et al. (2016) in their study mentioned that even though patients with CKD have decreased enzyme activity of 1-hydroxylase in the kidneys, the parathyroid gland contains 1--hydroxylase, allowing the metabolically active form of vitamin D to be produced locally in a paracrine/autocrine fashion to inhibit PTH secretion (13).

A pro-hormone called vitamin D (VD) is necessary for higher animals to survive. It is created endogenously in the skin by a photochemical reaction and is only found in a small number of dietary types (14). Ergocalciferol (VD2) and cholecalciferol (VD3) are the two main types of VD, and they both follow comparable metabolic routes (15).

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The most typical sources of VD2 are "fortified" meals and vegetable sources. Although it can be found in animal-based diets, pre-vitamin D3 and then VD3 are mostly produced in the skin by photolytic conversion of cutaneous 7-dehydroxycholesterol by UV radiation (16).

The results of the current study agreed with the study of Naveh-Many and (2017) regarding PTH concentration in CKD (17). Other studies (5,18,19) as these studies have stated that increased serum PTH is common among CKD patients.

Underbjerg et al. (2018) mentioned in their study that hypoparathyroidism is common among CKD patients (20).

This study also aimed to show if the changes in serum IGF-1 levels are correlated with some bone turnover in hemodialysis and non-hemodialysis CDK and total thyroidectomy patients.

Hormones and growth factors like IGF-1 primarily regulate bone turnover by influencing the recruitment, differentiation, and activity of osteoclasts and osteoblasts. How thoroughly bone collagen is calcified during the formation stage of skeletal remodeling is reflected by mineralization. Inadequate vitamin D intake, mineral (calcium or Pi) insufficiency, acidosis, and aluminum toxicity are causes of poor mineralization (21).

Our study showed that the concentration of IGF-1 decreased in CDK patients, and these results are confirmed by Al-khateeb (2013) findings which show that the serum IGF-1 decreased in CDK patients, and he pointed out that this decrease in IGF-1 was correlated with high urea in serum (uremia) (22). Also, this finding confirms studies of (23). The main reason for this is that uremia causes inhibition of both GH and IGF-1(24).

Additionally, aging and insufficient nutrition have been linked to a decrease in IGF-1 mRNA, with one contributing factor being protein restriction, which is frequently imposed as CKD develops (7).

By contrast, a study by Teppala et al. in the USA in 2010 showed that the levels of IGF-1 were increased among adults with CDK (6).

Vasilkova et al. (2020) showed that the levels of IGF-1 were decreased among diabetic CDK patients (25).

IGF-1 is a hormone with a molecular structure resembling that of insulin. It is crucial for a child's development and continues to be anabolic in adults (26). It is well recognized that IGF-1 is a powerful mitogen for renal mesangial cells, which can promote cell migration and the formation of fibronectin, proteoglycan, laminin, and type IV collagen, therefore accelerating the development of CKD in diabetics (27). Prechondrocytes are believed to respond to the hepatic growth factor IGF-1 once they have reached adulthood by proliferating and growing larger, which lengthens the bone (28).

One explanation for reduced IGF-1 levels in CKD and total thyroidectomy patients in this study may be that hypoparathyroidism occurred in both groups as seen in table 1, and this is confirmed by the study of Dura-Trave and Gallinas-Vectoriano (2022) (29).

OPN, a glycol-phosphoprotein present in bone, has also been linked to angiogenesis, renal cancer growth and invasion, lupus nephritis formation in people with systemic lupus erythematosus, and the potential to serve as a marker of acute allograft rejection following kidney transplantation (30). OPN is crucial for controlling vascular calcification and bone mineralization (31).

OPN’s expression is powerfully influenced by PTH. OPN, a secreted glycoprotein, is a prominent bone matrix protein that promotes the adhesion of osteoclasts to the bone matrix regulating the synthesis and resorption of bone (32).

Our findings demonstrate a substantial rise in the plasma level of OPN in CKD patients. These results are in line with earlier CKD investigations that showed increased OPN (33). OPN may be elevated in our patient samples due to MBD or chronic inflammatory conditions, where it is upregulated. It is significant to highlight those high levels of OPN are linked to all-cause mortality in CKD5-HD patients (34).

Shamsulddin et al. (2020) show a significant increase in serum OPN in Iraqi postmenopausal women with osteoporosis (8). As OPN is expressed in bone osteoblasts and osteoclasts cells and related to bone turnover and density BMD. By making it easier for osteoclasts to bind to the bone matrix, OPN performs crucial roles in bone resorption (35).

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The study of Lorenzen et al. (2011) showed a significant increase in the serum levels of OPN among patients with acute kidney injury (36). Also, the study of Nawar et al. (2022) showed a significant increase in the serum levels of OPN among patients with CKD patients (37).

One explanation for increased serum levels of OPN in CKD patients in the present study is that CKD patients suffer from a low Glomerular Filtration Rate, in this in line with some earlier studies (36).

Osteoblasts in bone are crucial for maintaining mineral ion homeostasis and bone mineralization. Osteocytes emit the majority of FGF23, which is a vital factor in the physiological regulation of phosphate. This implies that they may also be responsible for phosphate and bone metabolism disorders (38).

Serum FGF-23 levels were assessed in the present and revealed a non-significant rise in the two CDK groups.

According to the research by Ameen and Ali (2018), CDK patients with hypoparathyroidism had significantly higher levels of FGF-23 (9).

Children with CDK have higher serum FGF-23, according to research by Portale et al. (2016) (39).

FGF23, which has been connected to cardiac hypertrophy, heart failure, and all-cause mortality as early as stage 2 CKD, is one of the first markers to begin rising in the blood (40).

In CKD patients, higher blood FGF23 concentrations have been demonstrated to positively correlate with elevated serum levels of inflammatory markers. Numerous clinical studies have proven the relationships between FGF23 and inflammatory markers in disease conditions (41).

According to Lopez et al. (2011), PTH does not appear to stimulate FGF-23 when there is hypocalcemia (42). this may explain why FGF-23 has not increased in the presence of a decrease in PTH in CKD patients.

From these results, it can be inferred that whereas PTH concentration in CKD patients does not alter the concentration of FGF-23.

Locally in Iraq, the present study to our knowledge is the first study about calprotectin in CDK patients. Serum calprotectin showed a significant increase in CDK without hemodialysis with normal levels in and patients with hemodialysis.

Calprotectin is considered a neutrophil-cytosolic protein, consider a sensitive indicator of neutrophil turnover. It rises during the acute phase of response toward infection. Serum calprotectin increases during infection more than during systematic inflammation (43).

The first report to assess peritoneal calprotectin in patients with peritonitis was by Sevik et al. (2022) who exhibited that the peritoneal calprotectin increased (44). While the study by Heller et al. (2011) showed that urinary calprotectin was 60.7 times higher in intrinsic Acute Kidney Injury (45).

According to our knowledge, the study by Kanki et al. (2020) confirmed the findings of the current study regarding increases in serum calprotectin in CDK patients (46). It also demonstrated a significant increase in plasma calprotectin in patients with CDK and a positive correlation between plasma calprotectin and the concentration of Pi. Calcitonin in CDK has a direct link with serum phosphate (47) because serum phosphate applies its cytotoxicity if it creates insoluble nanoparticles with calcium (49). According to (48), TLR-4-dependent calcitonin secretes cytokines that harm cells, and calprotectin has a pathogenic function by enhancing TLR4/nuclear factor kappa B (NF-B) signaling (49). In light of these data, we can say with some certainty that serum calprotectin may be linked to CDK pathogenesis.

The fact that CPT is an inflammatory protein that may be enhanced with hs-CRP, WBC, or platelet counts in chronic inflammation—one of the key factors critical to the pathogenesis in HD patients may explain a large increase in serum calprotectin in CDK without hemodialysis in the present study.

From these findings, we conclude that serum calprotectin is more affected in CDK without hemodialysis than CDK with hemodialysis.

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CONCLUSIONS

CKD with hemodialysis and CKD with hemodialysis has the same effect on serum IGF-1, OPN, and FGF-23, while PT and calprotectin are more affected in CKD without hemodialysis

CONFLICT OF INTERESTS

no conflict

REFERENCES

1. Evans M, Lewis RD, Morgan AR, Whyte MB, Hanif W, Bain SC, Davies S, Dashora U, Yousef Z, Patel DC, Strain WD. A Narrative Review of Chronic Kidney Disease in Clinical Practice: Current Challenges and Future Perspectives. Advances in Therapy [Internet]. 2021 Nov 5 [cited 2022 Aug 6];39(1):33-43. Available from: https://doi.org/10.1007/s12325-021-01927-z
2. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD. Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. PLOS ONE [Internet]. 2016 Jul 6 [cited 2022 Aug 6];11(7):e0158765.Available from: https://doi.org/10.1371/journal.pone.0158765
3. Fukagawa M, Komaba H, Onishi Y, Fukuhara S, Akizawa T, Kurokawa K. Mineral Metabolism Management in Hemodialysis Patients with Secondary Hyperparathyroidism in Japan: Baseline Data from the MBD-5D. American Journal of Nephrology [Internet]. 2011 [cited 2022 Aug 6];33(5):427-37. Available from: https://doi.org/10.1159/000327654
4. Radeef M. Association between Allelic Variations of -174G/C Polymorphism of Interleukin-6 Gene and Chronic Kidney Disease-Mineral and Bone Disorder in Iraqi Patients. Baghdad Science Journal [Internet]. 2020 Dec 1 [cited 2022 Aug 6];17(4):1145. Available from: https://doi.org/10.21123/bsj.2020.17.4.1145
5. Gallieni M, De Luca N, Santoro D, Meneghel G, Formica M, Grandaliano G, Pizzarelli F, Cossu M, Segoloni G, Quintaliani G, Di Giulio S, Pisani A, Malaguti M, Marseglia C, Oldrizzi L, Pacilio M, Conte G, Dal Canton A, Minutolo R. Management of CKD-MBD in non-dialysis patients under regular nephrology care: a prospective multicenter study. Journal of Nephrology [Internet]. 2015 May 19 [cited 2022 Aug 6];29(1):71-8. Available from: https://doi.org/10.1007/s40620-015-0202-4
6. Teppala S, Shankar A, Sabanayagam C. Association between IGF-1 and chronic kidney disease among US adults. Clinical and Experimental Nephrology [Internet]. 2010 Jun 22 [cited 2022 Aug 6];14(5):440-4. Available from: https://doi.org/10.1007/s10157-010-0307-y
7. Nishi H, Uchida K, Saito M, Yamanaka D, Nagata H, Tomoshige H, Miyata I, Ito K, Toyoshima Y, Takahashi SI, Hakuno F, Takenaka A. Essential Amino Acid Intake Is Required for Sustaining Serum Insulin-like Growth Factor-I Levels but Is Not Necessarily Needed for Body Growth. Cells [Internet]. 2022 May 2 [cited 2022 Aug 6];11(9):1523. Available from: https://doi.org/10.3390/cells11091523.
8. Shamsulddin HH, Salih LA, Eleiwe SA. Relationship Between Osteopontin Biochemical Parameters and BMD Status in Iraqi Postmenopausal Women with Osteoporosis. Iraqi Journal of Science [Internet]. 2020 Oct 28 [cited 2022 Aug 6]:2494-503. Available from: https://doi.org/10.24996/ijs.2020.61.10.6
9. Ameen ZA, Ali S. Effects of Aldosterone, Osteoprotegerin and Fibroblast Growth Factor-23 and Some Biochemical Markers in Chronic Kidney Disease Patients' (Stage II-IV) among Patients with or without Cardiovascular Events. Iraqi Journal of Pharmaceutical Sciences (P-ISSN: 1683 - 3597 , E-ISSN : 2521 - 3512) [Internet]. 2018 Dec 7 [cited 2022 Aug 6]:150-8. Available from: https://doi.org/10.31351/vol27iss2pp150-158
10. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, Alexandersen P, Zerbini CA, Hu MY, Harris AG, Fitzpatrick LA, Cosman F, Christiansen C. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis. JAMA [Internet]. 2016 Aug 16 [cited 2022 Aug 6];316(7):722. Available from: https://doi.org/10.1001/jama.2016.11136
11. Bover J, Cozzolino M. Mineral and bone disorders in chronic kidney disease and end-stage renal disease patients: new insights into vitamin D receptor activation. Kidney International Supplements [Internet]. 2011 Sep [cited 2022 Aug 6];1(4):122-9. Available from: https://doi.org/10.1038/kisup.2011.28
12. Kritmetapak K, Pongchaiyakul C. Parathyroid Hormone Measurement in Chronic Kidney Disease: From Basics to Clinical Implications. International Journal of Nephrology [Internet]. 2019 Sep 17 [cited 2022 Aug 6];2019:1-9. Available from: https://doi.org/10.1155/2019/5496710

13. Dawson-Hughes B, Wang J, Barger K, Bischoff-Ferrari HA, Sempos CT, Durazo-Arvizu RA, Ceglia L. Intra-trial Mean 25(OH)D and PTH Levels and Risk of Falling in Older Men and Women in the Boston STOP IT Trial. The Journal of Clinical Endocrinology & Metabolism [Internet]. 2022 Jan 12 [cited 2022 Aug 6];107(5):e1932-e1937. Available from: https://doi.org/10.1210/clinem/dgac012.
14. Franca Gois P, Wolley M, Ranganathan D, Seguro A. Vitamin D Deficiency in Chronic Kidney Disease: Recent Evidence and Controversies. International Journal of Environmental Research and Public Health [Internet]. 2018 Aug 17 [cited 2022 Aug 6];15(8):1773. Available from: https://doi.org/10.3390/ijerph15081773
15. Gois P, Ferreira D, Olenski S, Seguro A. Vitamin D and Infectious Diseases: Simple Bystander or Contributing Factor? Nutrients [Internet]. 2017 Jun 24 [cited 2022 Aug 6];9(7):651. Available from: https://doi.org/10.3390/nu9070651
16. Wang J, Zhou J, Robertson G, Lee V. Vitamin D in Vascular Calcification: A Double-Edged Sword? Nutrients [Internet]. 2018 May 22 [cited 2022 Aug 6];10(5):652. Available from: https://doi.org/10.3390/nu10050652
17. Naveh-Many T, Volovelsky O. Parathyroid Cell Proliferation in Secondary Hyperparathyroidism of Chronic Kidney Disease. International Journal of Molecular Sciences [Internet]. 2020 Jun 18 [cited 2022 Aug 6];21(12):4332. Available from: https://doi.org/10.3390/ijms21124332
18. Goel N, Pokharna H, Abramowitz MK, Gnanasekaran I. Mineral and Bone Metabolism Disorders in Minority Incident ESRD Patients in an Inner-City Hemodialysis Unit. Einstein Journal of Biology and Medicine [Internet]. 2016 Mar 2 [cited 2022 Aug 6];30(1&2):16. Available from: https://doi.org/10.23861/ejbm201530634
19. Adhikary LP, Pokhrel A, Yadava SK, Khadka D, Thakur R. Relation between Serum Intact Parathyroid Hormone Level and Hematocrit in Chronic Kidney Disease Patients. Kathmandu University Medical Journal [Internet]. 2017 Feb 26 [cited 2022 Aug 6];13(3):220-3. Available from: https://doi.org/10.3126/kumj.v13i3.16811
20. Underbjerg L, Sikjaer T, Rejnmark L. Long-Term Complications in Patients With Hypoparathyroidism Evaluated by Biochemical Findings: A Case-Control Study. Journal of Bone and Mineral Research [Internet]. 2018 Feb 14 [cited 2022 Aug 6];33(5):822-31. Available from: https://doi.org/10.1002/jbmr.3368
21. Ghelichi-Ghojogh M, Fararouei M, Seif M, Pakfetrat M. Chronic kidney disease and its health-related factors: a case-control study. BMC Nephrology [Internet]. 2022 Jan 10 [cited 2022 Aug 6];23(1). Available from: https://doi.org/10.1186/s12882-021-02655-w.
22. Al-Khateeb M. The role of Leptin and Insulin like Growth factor-1 in patients with end stage renal disease under haemodialysis (pre & post dialysis). Mustansiriya Medical Journal [Internet]. 2013 Apr 14 [cited 2022 Aug 6] 12(1), 53. Available from: https://www.iasj.net/iasj/article/75606.
23. Chen Z, Nilsson E, Lindholm B, Heimbürger O, Barany P, Stenvinkel P, Qureshi AR, Chen J. Low plasma insulin-like growth factor-1 associates with increased mortality in chronic kidney disease patients with reduced muscle strength. Journal of Renal Nutrition [Internet]. 2022 Jul [cited 2022 Aug 6]. Available from: https://doi.org/10.1053/j.jrn.2022.06.008.
24. Haffner D, Grund A, Leifheit-Nestler M. Renal effects of growth hormone in health and in kidney disease. Pediatric Nephrology [Internet]. 2021 Jun 18 [cited 2022 Aug 6]. Available from: https://doi.org/10.1007/s00467-021-05097-6
25. Vasilkova VN, Mokhort TV, Pchelin IY, Bayrasheva VK, Naumenko EP, Korotaeva LE, Filiptsova NA. Association between serum insulin like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 levels and chronic kidney disease in diabetic patients. Journal of Renal Injury Prevention [Internet]. 2020 Mar 10 [cited 2022 Aug 6];10(1):e05-e05. Available from: https://doi.org/10.34172/jrip.2021.05
26. Dichtel LE, Cordoba-Chacon J, Kineman RD. Growth hormone and insulin-like growth factor I regulation of nonalcoholic fatty liver disease. The Journal of Clinical Endocrinology & Metabolism [Internet]. 2022 Feb 16 [cited 2022 Aug 6]. Available from: https://doi.org/10.1210/clinem/dgac088
27. Gao ST, Lv ZT, Zhou CK, Mao C, Sheng WB. Association between IGF-1 polymorphisms and risk of osteoporosis in Chinese population: a meta-analysis. BMC Musculoskeletal Disorders [Internet]. 2018 May 10 [cited 2022 Aug 6];19(1). Available from: https://doi.org/10.1186/s12891-018-2066-y
28. Racine HL, Serrat MA. The Actions of IGF-1 in the Growth Plate and Its Role in Postnatal Bone Elongation. Current Osteoporosis Reports [Internet]. 2020 May 15 [cited 2022 Aug 6];18(3):210-27. Available from: https://doi.org/10.1007/s11914-020-00570-x
29. Durá-Travé T, Gallinas-Victoriano F. Vitamin D and Parathyroid Hormone during Growth Hormone Treatment. Children [Internet]. 2022 May 15 [cited 2022 Aug 6];9(5):725. Available from: https://doi.org/10.3390/children9050725

30. Kaleta B. The role of osteopontin in kidney diseases. Inflammation Research [Internet]. 2018 Nov 19 [cited 2022 Aug 6];68(2):93-102. Available from: https://doi.org/10.1007/s00011-018-1200-5
31. Abdalrhim AD, Marroush TS, Austin EE, Gersh BJ, Solak N, Rizvi SA, Bailey KR, Kullo IJ. Plasma Osteopontin Levels and Adverse Cardiovascular Outcomes in the PEACE Trial. PLOS ONE [Internet]. 2016 Jun 10 [cited 2022 Aug 6];11(6):e0156965. Available from: https://doi.org/10.1371/journal.pone.0156965
32. Cheng Y, Li Y, Scherer N, Grundner-Culemann F, Lehtimäki T, Mishra BH, Raitakari OT, Nauck M, Eckardt KU, Sekula P, Schultheiss UT. Genetics of osteopontin in patients with chronic kidney disease: The German Chronic Kidney Disease study. PLOS Genetics [Internet]. 2022 Apr 6 [cited 2022 Aug 6];18(4):e1010139. Available from: https://doi.org/10.1371/journal.pgen.1010139
33. Barreto DV, Lenglet A, Liabeuf S, Kretschmer A, Barreto FC, Nollet A, Slama M, Choukroun G, Brazier M, Massy Z. Prognostic Implication of Plasma Osteopontin Levels in Patients with Chronic Kidney Disease. Nephron Clinical Practice [Internet]. 2010 Nov 12 [cited 2022 Aug 6];117(4):363-72. Available from: https://doi.org/10.1159/000321520
34. Scialla JJ, Kao WH, Crainiceanu C, Sozio SM, Oberai PC, Shafi T, Coresh J, Powe NR, Plantinga LC, Jaar BG, Parekh RS. Biomarkers of Vascular Calcification and Mortality in Patients with ESRD. Clinical Journal of the American Society of Nephrology [Internet]. 2014 Jan 23 [cited 2022 Aug 6];9(4):745-55. Available from: https://doi.org/10.2215/cjn.05450513
35. Wilson SR, Peters C, Saftig P, Brömme D. Cathepsin K Activity-dependent Regulation of Osteoclast Actin Ring Formation and Bone Resorption. Journal of Biological Chemistry [Internet]. 2008 Nov 21 [cited 2022 Aug 6];284(4):2584-92. Available from: https://doi.org/10.1074/jbc.m805280200
36. Lorenzen JM, Hafer C, Faulhaber-Walter R, Kumpers P, Kielstein JT, Haller H, Fliser D. Osteopontin predicts survival in critically ill patients with acute kidney injury. Nephrology Dialysis Transplantation [Internet]. 2010 Aug 23 [cited 2022 Aug 6];26(2):531-7. Available from: https://doi.org/10.1093/ndt/gfq498
37. Nawar AM, Elhendy YA, Nabil M, Sami MM, Salah AM, Allam HM. The Relationship between Serum Osteopontin level and Parameters of Chronic Kidney Disease – Mineral Bone Disease in Patients on Regular Hemodialysis. The Egyptian Journal of Hospital Medicine [Internet]. 2022 Jan 1 [cited 2022 Aug 6];86(1):499-501. Available from: https://doi.org/10.21608/ejhm.2022.213805
38. Guo YC, Yuan Q. Fibroblast growth factor 23 and bone mineralisation. International Journal of Oral Science [Internet]. 2015 Feb 6 [cited 2022 Aug 6];7(1):8-13. Available from: https://doi.org/10.1038/ijos.2015.1
39. Portale AA, Wolf MS, Messinger S, Perwad F, Jüppner H, Warady BA, Furth SL, Salusky IB. Fibroblast Growth Factor 23 and Risk of CKD Progression in Children. Clinical Journal of the American Society of Nephrology [Internet]. 2016 Aug 25 [cited 2022 Aug 6];11(11):1989-98. Available from: https://doi.org/10.2215/cjn.02110216
40. Salanova Villanueva L, Sánchez González C, Sánchez Tomero JA, Aguilera A, Ortega Junco E. Bone mineral disorder in chronic kidney disease: Klotho and FGF23; cardiovascular implications. Nefrología (English Edition) [Internet]. 2016 Jul [cited 2022 Aug 6];36(4):368-75. Available from: https://doi.org/10.1016/j.nefroe.2016.08.001
41. Kazancioğlu R. Risk factors for chronic kidney disease: an update. Kidney International Supplements [Internet]. 2013 Dec [cited 2022 Aug 6];3(4):368-71. Available from: https://doi.org/10.1038/kisup.2013.79
42. López I, Rodríguez-Ortiz ME, Almadén Y, Guerrero F, Oca AM, Pineda C, Shalhoub V, Rodríguez M, Aguilera-Tejero E. Direct and indirect effects of parathyroid hormone on circulating levels of fibroblast growth factor 23 in vivo. Kidney International [Internet]. 2011 Sep [cited 2022 Aug 6];80(5):475-82. Available from: https://doi.org/10.1038/ki.2011.107
43. Seibert FS, Pagonas N, Arndt R, Heller F, Dragun D, Persson P, Schmidt-Ott K, Zidek W, Westhoff TH. Calprotectin and neutrophil gelatinase-associated lipocalin in the differentiation of pre-renal and intrinsic acute kidney injury. Acta Physiologica [Internet]. 2013 Feb 14 [cited 2022 Aug 6];207(4):700-8. Available from: https://doi.org/10.1111/apha.12064
44. Sevik G, Barutcu Atas D, Ilgin C, Asicioglu E, Tuglular S, Velioglu A. Peritoneal calprotectin level in peritoneal dialysis patients. Seminars in Dialysis [Internet]. 2022 Apr 19 [cited 2022 Aug 6]. Available from: https://doi.org/10.1111/sdi.13082

45. Heller F, Frischmann S, Grünbaum M, Zidek W, Westhoff TH. Urinary Calprotectin and the Distinction between Prerenal and Intrinsic Acute Kidney Injury. Clinical Journal of the American Society of Nephrology [Internet]. 2011 Sep 1 [cited 2022 Aug 6];6(10):2347-55. Available from: https://doi.org/10.2215/cjn.02490311
46. Kanki T, Kuwabara T, Morinaga J, Fukami H, Umemoto S, Fujimoto D, Mizumoto T, Hayata M, Kakizoe Y, Izumi Y, Tajiri S, Tajiri T, Kitamura K, Mukoyama M. The predictive role of serum calprotectin on mortality in hemodialysis patients with high phosphoremia. BMC Nephrology [Internet]. 2020 May 4 [cited 2022 Aug 6];21(1). Available from: https://doi.org/10.1186/s12882-020-01812-x
47. Smith ER, Ford ML, Tomlinson LA, Rajkumar C, McMahon LP, Holt SG. Phosphorylated fetuin-A-containing calciprotein particles are associated with aortic stiffness and a procalcific milieu in patients with pre-dialysis CKD. Nephrology Dialysis Transplantation [Internet]. 2012 May [cited 2022 Aug 6];27(5):1957-66. Available from: https://doi.org/10.1093/ndt/gfr609
48. Kuro-o M. A phosphate-centric paradigm for pathophysiology and therapy of chronic kidney disease. Kidney International Supplements [Internet]. 2013 Dec [cited 2022 Aug 6];3(5):420-6. Available from: https://doi.org/10.1038/kisup.2013.88
49. Kuwabara T, Mori K, Kasahara M, Yokoi H, Imamaki H, Ishii A, Koga K, Sugawara A, Yasuno S, Ueshima K, Morikawa T, Konishi Y, Imanishi M, Nishiyama A, Nakao K, Mukoyama M. Predictive Significance of Kidney Myeloid-Related Protein 8 Expression in Patients with Obesity- or Type 2 Diabetes-Associated Kidney Diseases. PLoS ONE [Internet]. 2014 Feb 18 [cited 2022 Aug 6];9(2):e88942. Available from: https://doi.org/10.1371/journal.pone.0088942