



Association between Serum Procollagen Type I N-Terminal Propeptide and Bone Metabolism Markers in Iraqi Patients with Acromegaly: A Cross-Sectional Study

Najlaa Q. Muftin

Department of Chemistry, College of Science, Mustansiriyah University, Baghdad, Iraq.

Article's Information	Abstract
Received: 27.09.2025 Accepted: 17.07.2026 Published: 15.09.2026	Background: Acromegaly is caused by excess secretion of growth hormone (GH) due to a benign pituitary adenoma, which significantly disrupts mineral metabolism and bone turnover. Aims of the study : To compare the serum levels of calcium, phosphorus, 25(OH)D ₃ , and P1NP in patients with acromegaly to those of healthy controls; investigate relationships between P1NP and important metabolic indicators; and use ROC curve analysis to assess P1NP's diagnostic value. Methods: This study is a cross-sectional study, where 60 patients with acromegaly (mean age 46.66 ± 6.75) and 30 age-sex matched healthy controls (mean age 45.10 ± 5.98) were enrolled. The levels of glucose, insulin like growth factor 1 (IGF-1), GH, calcium, phosphorus, 25(OH) D ₃ , and P1NP were evaluated in the serum. Results: The patients with acromegaly demonstrated significantly higher levels of calcium, phosphorus and P1NP and significantly lower levels of 25(OH)D ₃ compared with controls. The bone formation (as measured by P1NP) correlated negatively with age ($r = -0.26$, $p < 0.05$), indicating that bone formation decreases with age even in the presence of excess GH/IGF-1. The independent variables, phosphate levels, and disease duration were inversely correlated, with a correlation coefficient of -0.29 ($p < 0.05$), and calcium was positively correlated with the independent variable of phosphate levels, with a correlation coefficient of 0.38 ($p = 0.01$). ROC analysis of P1NP yielded an AUC of 1.00, indicating strong discriminative ability in this cohort. Conclusion: Changes in bone turnover markers, particularly P1NP, may offer valuable insights into skeletal alterations in acromegaly. While the findings support the potential diagnostic value of P1NP, the cross-sectional design limits causal interpretation. Larger prospective studies are needed to validate these preliminary results and clarify the longitudinal utility of P1NP in clinical practice.

Keywords:

procollagen type 1,
N terminal propeptide,
Vitamin D₃,
Bone turnover rate,
Calcium,
Phosphorus,
Acromegaly.

<http://doi.org/10.22401/ANJS.29.3.05>

*Corresponding author: najlaaqassem9@gmail.com



This work is licensed under a Creative Commons Attribution 4.0 International License

1. Introduction

Acromegaly is a rare illness that arises due to the presence of a benign tumor of the pituitary gland [1]. Significant metabolic complications, such as cardiovascular problems, joint and bone issues, sleep apnea, cancer, diabetes, and others, are linked to acromegaly and are a major cause of death and morbidity. [2]. Bone problems in acromegaly are still poorly understood, despite increased knowledge of these systemic consequences. This represents a significant gap in the clinical treatment of this

disease [3]. Although several studies have investigated bone turnover markers in acromegaly, evidence regarding the relationship between P1NP and mineral metabolism remains inconsistent, particularly in Middle Eastern populations. Furthermore, data from Iraqi patients are currently unavailable. The spread of this disease is very slow, as the number of infected cases per million people is estimated at only three [4,5]. Although many clinical symptoms appear in acromegaly patients, its diagnosis may be delayed for a period that may

range from 7 to 10 years, which exposes patients to many dangerous complications[6]. The GH-IGF-1 axis dysregulation, which has a significant impact on several organ systems, including the skeletal system, is at the heart of the pathophysiology of acromegaly [7]. It was observed that the metabolism of bone including (maintaining calcium balance, bone formation, and restoration) affected by increase in the levels of both growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in acromegalic patients [8]. Significant changes in bone remodeling, such as increased bone turnover, poor bone quality, and microarchitectural deterioration, are seen in acromegalic patients. These changes may eventually lead to secondary osteoporosis, but information on osteoporosis risk and bone mineral density in these patients is still lacking [9,10,11]. As well, it was observed that acromegaly patients have changes in the levels of bone minerals associated with hyperphosphatemia, hypercalcemia, and hypercalciuria [12], whereas 25(OH) D₃ and parathyroid hormone (PTH) data are inconsistent [11]. It is important to know that identifying the older subjects who have a high risk of developing fragility fractures is a significant challenge in osteoporosis management [13]. Despite measuring bone mineral density (BMD) through applying dual-energy X-ray absorptiometry (DXA), to estimate the risk of bones being fractured[14]; but, BMD cannot be used to determine bone turnover rate[15], which can be regulated by secondary hyperparathyroidism resulting from a deficiency of vitamin D [16]. The possibility of losing bone components and breaking easily increases due to high rates of bone turnover [17]. According to epidemiological studies, the high risk of fractures represented by high bone turnover markers (BTMs) that are associated with the rate of bone turnover [18]. One of the BTMs is procollagen type 1 amino-terminal propeptide (P1NP). According to the recommendations of the International Federation of Clinical Chemistry and Laboratory Medicine, P1NP acts as a favored indicator of bone construction, [17, 19]. Elevated levels of GH and IGF-1 in acromegaly stimulate osteoblast activity, resulting in increases P1NP levels. Therefore, P1NP is useful to estimate bone metabolism, follow disease activity, and determine fracture risk as it characterizes osteoblastic activity induced by GH/IGF-1. So this study aimed to detect bone disorders associated with acromegaly by measuring P1NP, additionally, the prospective usage of P1NP in these patients as an indicator for follow-up and diagnosis.

2. Methods

Ninety people were enrolled in this cross-sectional study; among them, 30 were healthy volunteers (16 males and 14 females ;mean age 45.10± 5.98) and 60 had acromegaly (38 males and 22 females; mean age 46.66±6.75). To avoid confounding effects of sex and age, controls were matched to patients. In order to preserve sample homogeneity and remove the confounding pathophysiological effects of altered glucose metabolism and insulin resistance on bone turnover markers and mineral homeostasis, the study's inclusion criteria included subjects with active acromegaly. Active acromegaly was defined according to the Endocrine Society guidelines as elevated age-adjusted serum IGF-1 levels together with failure of GH suppression below the accepted threshold following oral glucose tolerance testing or persistently elevated random GH levels. While exclusion criteria included being diabetic, pregnant, having a chronic illness, having severe chronic liver disease that is cancerous, having a history of metabolic bone disease, having an active mental illness, or having experienced heart or renal failure in the past.

2.1. Ethical approval

This research has been authorized by the Al-Mustansiriya University College of Science Ethics Committee in Iraq (1 Jan/ 2024, Ref: BCSMU/0124/0008C). In this study, the Department of Chemistry at Al-Mustansiriya University cooperated with the Specialized Center for Diabetes and Endocrinology in Baghdad, Al-Rusafa, Iraq, to get study samples after obtaining consent from all participants. Every study method and procedure matched the Declaration of Helsinki's ethical guidelines.

2.2. Biochemical analysis

The participants' blood samples were drawn in the morning after an overnight fast (10 hours) to account for diurnal variation. A volume of 5 mL was obtained from each individual. According to a study by Tanner et al. in 2008, most biochemical analytes remain stable even if centrifugation is delayed for up to 24 hours at temperatures of 15, 25, or 35 degrees Celsius. In this study, blood samples were centrifuged for 15 minutes at 3000 x g, and the separated serum was stored at -80 degrees Celsius for up to 3 months before biochemical analysis. Serum fasting glucose, calcium, and phosphorus levels were measured using an Aflo Automated Clinical Chemistry Analyzer (BioSystems S). A., Barcelona, Spain) following a 12-hour fast, according to the manufacturer's instructions. IGF-1

levels were measured by an enzyme-labeled chemiluminescent immunometric assay (Siemens, USA) according to the manufacturer's instructions, and are reported in nanograms per milliliter (ng/mL). Growth hormone (GH) levels were measured using a two-site chemiluminescent immunometric assay (Siemens, USA) with results presented in ng/mL. The serum 25-hydroxyvitamin D₃ [25(OH)D₃] level was measured by a 25(OH)D₃ competitive inhibition enzyme immunoassay (EIA) kit (Cloud-Clone Corp., USA). The levels of procollagen type 1 N-terminal propeptide (P1NP) were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Cloud-Clone Corp., USA).

2.3. The statistics of the analysis

The clinical and biochemical data were statistically analysed using IBM SPSS software (Version 22.0, USA, Armonk, NY, USA). Parametric analyses were performed after testing for normality using the Shapiro-Wilk test. For normally distributed continuous variables, results were reported as mean $\pm$ SD. An independent Student's t-test was employed after testing for variance homogeneity with Levene's test to detect statistically significant differences between the acromegaly patient groups and matched healthy control group. Pearson's

correlation analysis was used to investigate the type, direction, and magnitude of linear relationships among the measured biochemistry parameters. Receiver Operating Characteristic (ROC) curve analysis was set up to evaluate the diagnostic efficacy and clinical performance of the biomarkers evaluated. The clinical diagnosis (Active Acromegaly versus Healthy Controls) was used as the binary state variable. For each biomarker, the area under the curve (AUC) was calculated. The best diagnostic parameters with the highest values of the Youden index ($J = \text{Sensitivity} + \text{Specificity} - 1$) were defined as the optimal diagnostic cut-off points. In all statistical procedures, values of $\alpha < 0.05$ ($P < 0.05$) were considered significant, and exact P values were provided, based on the evidence of significance, not on a binary threshold [20].

3. Results

Each subject's biochemical data, along with its overall features, are presented in Table 1. No significant difference in age was observed between the acromegaly and control groups ($P = 0.28$). Moreover, there were significant differences in calcium, phosphorus, 25(OH)D₃, P1NP, FBG, IGF-1, and GH levels between the two study groups.

Table 1. Demographic characteristics and biochemical parameters of patients with acromegaly and healthy controls.

Parameters	Healthy control group (N=30)	Acromegaly group (N=60)	(p value)
Demographic			
Age (y)	45.10± 5.98	46.66±6.75	0.28
Disease duration (y)	—	8.86 ±5.32	—
Gender			
Male	16 (53.3%)	38 (63.3%)	0.36
Female	14 (46.7%)	22 (36.7%)	
Parameters of bone			
calcium (mg/dL)	8.45± 0.35	8.75± 0.59	0.012
phosphorus (mg/dL)	3.10± 0.33	3.75± 0.32	< 0.001
25(OH) D ₃ (ng/mL)	96.43± 24.13	19.16± 10.54	< 0.001
Serum P1NP (ng/mL)	5.92± 2.85	34.08± 4.48	< 0.001
Hormonal and metabolic parameters			
FBG (mg/dL)	85.48± 5.45	124.20±35.82	< 0.001
IGF-1 (ng/mL)	111.72± 9.85	585.53± 191.26	< 0.001
GH (ng/mL)	0.85± 0.32	4.69± 3.07	< 0.001

The data is displayed as Mean $\pm$ SD. For regularly distributed variables, the Independent Student's t-test was used to assess statistical significance. 25(OH) D₃:25-hydroxy vitamin D₃, P1NP:

procollagen type 1 N-terminal propeptide, GH: Growth Hormone, FBG: fasting blood glucose, IGF-1: Insulin-like Growth Factor 1. The analysis of Pearson's correlation test demonstrated an

important negative correlation between 25(OH) D₃ and calcium, besides a significant connection between age and P1NP, GH , P <0.05 in acromegaly patients (Table 2).

Table 2. Pearson correlation coefficient analysis among biochemical and clinical parameters in patients with acromegaly.

	Age (y)	Disease duration (y)	FBG (mg/dL)	GH (ng/mL)	IGF-1 (ng/mL)	P1NP (ng/mL)	25(OH)D ₃ (ng/mL)	calcium (mg/dL)	phosphorus (mg/dL)
Age (y)	1	0.20	0.37**	0.26*	0.06	-0.26*	0.17	0.02	0.16
Disease duration (y)	0.20	1	0.18	0.01	-0.01	-0.08	0.19	-0.16	-0.29*
FBG (mg/dL)	0.37**	0.18	1	-0.00	0.19	-0.13	0.15	-0.13	-0.07
GH (ng/mL)	0.26*	0.01	-0.00	1	0.64**	-0.03	-0.22	-0.26*	-0.03
IGF-1 (ng/mL)	0.06	-0.01	0.19	0.64**	1	-0.07	0.07	-0.38**	0.03
P1NP (ng/mL)	-0.26*	-0.08	-0.13	-0.03	-0.07	1	-0.12	0.05	0.09
25(OH) D ₃ (ng/mL)	0.17	0.19	0.15	-0.22	0.07	-0.12	1	-0.31*	-0.13
calcium (mg/dL)	0.02	-0.16	-0.13	-0.26*	-0.38**	0.05	-0.31*	1	0.38**
phosphorus (mg/dL)	0.16	-0.29*	-0.07	-0.03	0.03	0.09	-0.13	0.38**	1

FBG: fasting blood glucose, IGF-1: insulin-like growth factor 1, P1NP: procollagen type 1 N-terminal propeptide, 25(OH) D₃:25-hydroxy vitamin D₃, GH: growth hormone, **: refers to highly significant(p less than 0.01), * refers to significant(p less than 0.05)

Figure 1 of ROC for P1NP in acromegalic patients matched to control showed that it has an area under the curve equal to one (AUC = 1.00), with the highest value of sensitivity and specificity reaching 100%.

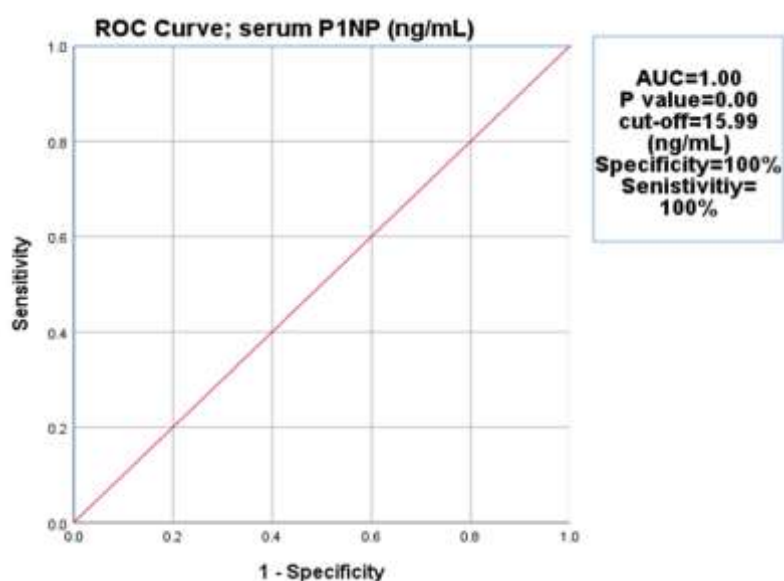


Figure 1. P1NP's ROC curve between two groups: A group of acromegalies and a group of healthy controls.

4. Discussion

It is believed that most cases of acromegaly are associated with abnormalities of the bones and joints [21]. Therefore, we designed this study to fully comprehend the changes in bone and mineral metabolism markers, including procollagen type 1 N-terminal propeptide (P1NP), calcium, and phosphorus, along with estimation vitamin D nutritional reserves in acromegaly, and the possibility of using P1NP as a surrogate marker for monitoring this disease. Remarkably, our findings demonstrated that acromegalic patients display a unique pattern of changes in biomarkers related to bone metabolism, characterized by increased levels of P1NP, calcium, and phosphorus, as well as decreased levels of vitamin D. Overly high blood P1NP levels are characteristic of acromegaly [22, 23]. Chen et al. [8] observed significant elevation of P1NP levels in the acromegaly group, since P1NP is a recognized biomarker for the formation of bones. The constant elevation of this marker across various registries validates its robustness, even though absolute cut-off borders may differ between contemporary and older cohorts due to assay heterogeneity and measurement methodologies. The exact molecular axis wherein GH/IGF-1 hypersecretion directly causes cellular osteoblast cleavage of type I procollagen, which is the mechanism releasing P1NP into the bloodstream, is reflected in this rise. This metabolic spike is strongly related to the nature of the illness, where increased levels of GH and IGF-1 promote the formation of new bone, resulting in higher rates of bone turnover and its indicators [23, 24]. Additionally, synchronous GH and IGF-1 excess is typically linked to both hyperphosphatemia and hypercalcemia in acromegaly patients, according to Sawicka-Gutaj et al. [12] and Shi et al. [25].

Intestinal absorption of calcium and renal tubular reabsorption of phosphate are pathologically stimulated by this ongoing hormonal surge. This significant change in mineral homeostasis indicates a state of uncoupled bone remodeling rather than a straightforward direct ratio effect or discrete tumor marker influences. Chronic GH and IGF-1 hypersecretion simultaneously promotes osteoblastogenesis and osteoclastogenesis in active acromegaly [21]. The delicate physiological balance between bone formation and resorption is upset by this uncoupled condition, which causes metabolic activity to shift toward a high-turnover bone state that profoundly changes the gastrointestinal and renal systems' ability to handle minerals. Conversely, acromegalic patients typically have low

vitamin D levels [26, 27]. Rather of general systemic inflammation or oxidative stress, the observed vitamin D deficit in these patients is mostly caused by a particular endocrine trifecta mechanism. First, the GH/IGF-1 axis hypersecretion increases renal 1- α -hydroxylase activity, which accelerates the conversion of nutritional 25(OH)D₃ into its active hormonal form, 1,25(OH)₂D₃. This causes the circulating nutritional 25(OH)D₃ storage pool recorded in baseline cross-sectional assays to be rapidly depleted [28]. Second, the GH/IGF-1 axis alters the delicate homeostatic ratio between bound total fractions and free bioavailable vitamin D in circulation by directly influencing the hepatic synthesis and circulating affinity of Vitamin D Binding Protein (DBP) [29]. Since vitamin D plays a fundamental role in preserving calcium and phosphorus homeostasis, controlling this metabolic depletion is still essential to avoiding the possible worsening of bone metabolic deterioration [30]. The age-related reduction in bone production shown in the general population correlates with the negative connection between P1NP and age in acromegaly patients [31, 32]. This results suggest that natural aging still has a harmful effect on bone metabolism, even in patients have acromegaly. Interestingly, there is an inverse relationship between phosphorus levels and the length of the illness; that is, phosphorus levels tend to decline as the illness progresses. This inverse relationship should be interpreted cautiously, though, as it may indicate the impact of lingering confounding variables, such as age-related decreases in renal phosphate reabsorption, gradual changes in tumor mass, or the start of later medical treatments.

According to Piskinpasa et al. [11], continued exposure to high GH and IGF-1 can cause disorders in the control of phosphate and other minerals, which may be the cause of the observed decrease in phosphorus levels over the period of the disease. This also helps to explain the well-known positive relationship between phosphorus and calcium levels in blood [33]. Additionally, the study revealed a negative correlation between GH and vitamin D and calcium. We recognize that these correlation coefficients' absolute values ($r = -0.26$ and $r = -0.29$) indicate modest clinical correlations, even if they are statistically significant ($P < 0.05$). Therefore, these findings are explicitly described as weak statistical trends or mild inverse relationships that suggest underlying multi-factorial homeostatic adjustments rather than a strict, direct cause-and-effect axis. This is consistent with the findings of Piskinpasa et al. [11], who observed that long-term mineral

regulation can be disrupted by persistent changes in GH/IGF-1 production without serving as a separate biological driver. Vasikaran et al. [34] discovered that bone turnover markers, such as CTX and P1NP, might be used to predict bone fractures. Although this validates our results, care must be taken when interpreting the flawless diagnostic performance shown in our ROC study (AUC = 1.00). The significant, non-overlapping metabolic difference between untreated acromegaly cases and healthy controls within this specific cohort is highlighted by this absolute gap. However, there is an inherent risk of model overfitting when evaluating this diagnostic limit within a single-center framework. Therefore, until verified by broader validation designs, P1NP should be described as a highly promising surrogate biomarker for reflecting skeletal turnover velocity and intra-cohort disease activity rather than an established universal diagnostic tool.

Lastly, it is important to recognize that our study arrangement has a number of limitations. Our geographical data distribution may not be as broadly generalizable as it may be because this study was carried out in a single-center setting with a very small sample size. Furthermore, long-term longitudinal monitoring of changes in bone markers after treatment was not possible because of the cross-sectional methodology. These scholarly limitations highlight the necessity of multi-center longitudinal designs in the future to confirm our results.

5. Conclusions

In conclusion, our initial results indicate that P1NP closely correlates with active disease states and may be a possible surrogate biomarker for tracking bone turnover dynamics in acromegaly, despite the constraints of our cross-sectional methodology. However, before routine clinical application, large-scale multi-center longitudinal studies are still strictly necessary to define its true utility and establish universal diagnostic thresholds due to the inherent risk of model overfitting within a single-center framework and the lack of an independent validation cohort.

Conflicts of Interest: Authors declare no conflict of interest regarding this work.

Funding: No fund was received for this work.

References

- [1] Turki, T.G.; Hashim, N.M. "Association between a High Level of Growth Hormone–Releasing Hormone (GHRH) and GHRH Genetic Polymorphism (rs566092278) with Acromegaly Cases". *Med J Babylon*, 22(2): 400–405, 2025.
- [2] Iglesias, P. "Acromegaly and Cardiovascular Disease: Associated Cardiovascular Risk Factors, Cardiovascular Prognosis, and Therapeutic Impact". *J Clin Med*, 14(6): 1906, 2025.
- [3] Fleseriu, M.; Biller, B.M.K.; Freda, P.U.; Gadelha, M.R.; Giustina, A.; Katznelson, L.; Molitch, M.E.; Samson, S.L.; Strasburger, C.J.; van der Lely, A.J.; Melmed, S. "A Pituitary Society update to acromegaly management guidelines". *Pituitary*, 24(1): 1–13, 2021.
- [4] Sorohan, M.C.; Baci, I.F.; Galoiu, S.A.; Niculescu, D.A.; Caragheorghopol, A.; Iordachescu, C.N.; Poiana, C. "Acromegaly Versus Hypogonadism: Bone Fragility and Evaluation". *Ann Endocrinol (Paris)*, 84(6): 719–726, 2023.
- [5] Malek, F.K.; Abbas, S.A.; Abed, B.A. "Measurement of Arginase Activity in Sera of Iraqi Acromegaly Patients with Diabetes". *Al-Mustansiriyah J Sci*, 35(1): 44–49, 2024.
- [6] Chiloiro, S.; Giampietro, A.; Gagliardi, I.; Bondanelli, M.; Veleno, M.; Ambrosio, M.R.; Zatelli, M.C.; et al. "Impact of the Diagnostic Delay of Acromegaly on Bone Health: Data from a Real Life and Long Term Follow-up Experience". *Pituitary*, 25(6): 831–841, 2022.
- [7] Melmed, S. "Acromegaly pathogenesis and treatment". *J Clin Invest*, 119(11): 3189–3202, 2009.
- [8] Chen, H.; Huang, H.; Wang, Y.; Zhang, Y.; Liu, M.; Lou, Y.; Zhang, Z.; et al. "Decreased Serum Wnt Antagonist Levels in Patients with Active Acromegaly". *Endocr Pract*, 28(5): 515–520, 2022.
- [9] Mazziotti, G.; Frara, S.; Giustina, A. "Pituitary Diseases and Bone". *Endocr Rev*, 39(4): 440–488, 2018.
- [10] Kim, T.Y.; Shoback, D.M.; Black, D.M.; Rogers, S.J.; Stewart, L.; Carter, J.T.; Posselt, A.M.; et al. "Increases in PYY and Uncoupling of Bone Turnover are Associated with Loss of Bone Mass After Gastric Bypass Surgery". *Bone*, 131: 115115, 2020.
- [11] Piskinpasa, M.E.; Piskinpasa, H. "Bone Biochemical Markers in Acromegaly: An Association with Disease Activity and Gonadal Status". *North Clin Istanbul*, 9(1): 74–81, 2022.

- [12] Sawicka-Gutaj, N.; Derwich-Rudowicz, A.; Biczysko, A.; Turchyn, S.; Ziolkowska, P.; Ziemnicka, K.; Gut, P.; et al. "Serum Phosphorus and Calcium as Biomarkers of Disease Status in Acromegaly". *Biomedicines*, 11(12): 3278, 2023.
- [13] Nuti, R.; Brandi, M.L.; Checchia, G.; Di Munno, O.; Dominguez, L.; Falaschi, P.; Fiore, C.E.; et al. "Guidelines for the Management of Osteoporosis and Fragility Fractures". *Intern Emerg Med*, 14(1): 85–102, 2019.
- [14] Cherian, K.E.; Kapoor, N.; Meeta, M.; Paul, T.V. "Dual-energy X-ray Absorptiometry Scanning in Practice, Technical Aspects, and Precision Testing". *J Midlife Health*, 12(4): 252–256, 2021.
- [15] Di Medio, L.; Brandi, M.L.; "Advances in Bone Turnover Markers". In *Advances in Clinical Chemistry*, 1st ed.; Makowski, G.S., Ed.; Elsevier: Cambridge, MA, USA, pp. 101–140, 2021.
- [16] Voulgaridou, G.; Papadopoulou, S.K.; Detopoulou, P.; Tsoumana, D.; Giagini, C.; Kondyli, F.S.; Lymperaki, E.; et al. "Vitamin D and Calcium in Osteoporosis, and the Role of Bone Turnover Markers: A Narrative Review of Recent Data from RCTs". *Diseases*, 11(1): 29, 2023.
- [17] Szulc, P.; Bauer, D.C.; Eastell, R. "Biochemical Markers of Bone Turnover in Osteoporosis". In: *Marcus and Feldman's Osteoporosis*, 5th ed.; Dempster, D.W.; Cauley, J.A.; Bouxsein, M.L.; Cosman, F., Eds.; Elsevier: 1545–1588, 2021.
- [18] Lorentzon, M.; Branco, J.; Brandi, M.L.; Bruyere, O.; Chapurlat, R.; Cooper, C.; Cortet, B.; et al. "Algorithm for the Use of Biochemical Markers of Bone Turnover in the Diagnosis, Assessment and Follow-up of Treatment for Osteoporosis". *Adv Ther*, 36(10): 2811–2824, 2019.
- [19] Bellissimo, M.P.; Roberts, J.L.; Jones, D.P.; Liu, K.H.; Taibl, K.R.; Uppal, K.; Weitzmann, M.N.; et al. "Metabolomic Associations with Serum Bone Turnover Markers". *Nutrients*, 12(10): 3161, 2020.
- [20] Kwak, S. "Are Only p-Values Less Than 0.05 Significant? A p-Value Greater Than 0.05 Is Also Significant!". *J Lipid Atheroscler*, 12(2): 89–95, 2023.
- [21] Giustina, A. "Acromegaly and Bone: An Update". *Endocrinol Metab (Seoul)*, 38(6): 655–666, 2023.
- [22] Ozer, F.F.; Dagdelen, S.; Erbas, T. "Relation of RANKL and OPG Levels with Bone Resorption in Patients with Acromegaly and Prolactinoma". *Horm Metab Res*, 50(7): 562–567, 2018.
- [23] Constantin, T.; Tangpricha, V.; Shah, R.; Oyesiku, N.M.; Ioachimescu, O.C.; Ritchie, J.; Ioachimescu, A.G. "Calcium and Bone Turnover Markers in Acromegaly: A Prospective, Controlled Study". *J Clin Endocrinol Metab*, 102(7): 2416–2424, 2017.
- [24] Takada, J.; Dinavahi, R.; Miyauchi, A.; Hamaya, E.; Hirama, T.; Libanati, C.; Nakamura, Y.; et al. "Relationship Between P1NP, a Biochemical Marker of Bone Turnover, and Bone Mineral Density in Patients Transitioned From Alendronate to Romosozumab or Teriparatide: A Post Hoc Analysis of the STRUCTURE Trial". *J Bone Miner Metab*, 38(3): 310–315, 2020.
- [25] Shi, S.; Zhang, L.; Yu, Y.; Wang, C.; Li, J. "Acromegaly and Non-parathyroid Hormone-dependent Hypercalcemia: A Case Report and Literature Review". *BMC Endocr Disord*, 21(1): 90, 2021.
- [26] Abdullah, A.H.; Mohaisn, I.K.; Nsaif, A.S.; Safaryan, A. "Studying the Impact of Vitamin D Deficiency in Iraqi Acromegalic Patients and its Relation with Some Biochemical Parameters". *Ann Trop Med Public Health*, 23(11): 231131, 2020.
- [27] Halupczok-Żyła, J.; Jawiarczyk-Przybyłowska, A.; Bolanowski, M. "Patients with Active Acromegaly are at High Risk of 25(OH)D Deficiency". *Frontiers in Endocrinology (Lausanne)*, 6: 89, 2015.
- [28] Kamenický, P.; Mazziotti, G.; Lombès, M.; Giustina, A.; Chanson, P. "Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications". *Endocr Rev*, 35(2): 234–81, 2014.
- [29] Bikle, D.D.; Schwartz, J. "Vitamin D Binding Protein, Total and Free Vitamin D Levels in Different Physiological and Pathophysiological Conditions". *Front Endocrinol (Lausanne)*, 10: 317, 2019.
- [30] Voulgaridou, G.; Papadopoulou, S.K.; Detopoulou, P.; Tsoumana, D.; Giagini, C.; Kondyli, F.S.; Lymperaki, E.; et al. "Vitamin D and Calcium in Osteoporosis, and the Role of Bone Turnover Markers: A Narrative Review of Recent Data from RCTs". *Diseases*, 11(1): 29, 2023.
- [31] Chubb, S.P.; Byrnes, E.; Manning, L.; Beilby, J.P.; Ebeling, P.R.; Vasikaran, S.D.; Golledge, J.; et al. "Reference Intervals for Bone Turnover Markers and their Association with Incident Hip Fractures in Older Men: The Health in

- Men Study". J Clin Endocrinol Metab, 100(1): 90–99, 2015.
- [32] Shao, J.; Zhou, S.S.; Qu, Y.; Liang, B.B.; Yu, Q.H.; Wu, J. "Correlation Between Bone Turnover and Metabolic Markers with Age and Gender: A Cross-sectional Study of Hospital Information System Data". BMC Musculoskelet Disord, 21: 603, 2020.
- [33] Shaker, J.; Deftos, L. "Calcium and Phosphate Homeostasis". Endotext [Internet], 2023.
- [34] Vasikaran, S.; Thambiah, S.C.; Tan, R.Z.; Loh, T.P. "The Use of Bone-Turnover Markers in Asia-Pacific Populations". Ann Lab Med, 44(2): 126–134, 2024.