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Diagnostic Utility of Vitamin D-Parathyroid Hormone Axis and Mineral Biomarkers in Osteoporotic Iraqi Men

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Abstract

Male osteoporosis is underdiagnosed. The vitamin D-parathyroid hormone (PTH) axis governs mineral homeostasis, but its diagnostic utility in Middle Eastern populations remains underexplored.

To evaluate alterations in calcium, phosphorus, vitamin D, and parathyroid hormone, and assess their diagnostic performance for osteoporosis in Iraqi men.

A case-control study analyzed 120 men (60 osteoporotic >50 years; 60 age-matched controls >50 years). Osteoporosis was diagnosed based on clinical criteria including DEXA T-score and/or fragility fracture history. Calcium and phosphorus were measured colorimetrically. 25-hydroxyvitamin D and intact parathyroid hormone were quantified via chemiluminescence immunoassay.

Osteoporotic patients had lower calcium (2.02±0.15 vs. 2.17±0.11 mmol/L, $p<0.0001$) and vitamin D (17.51±8.75 vs. 28.38±13.4 ng/mL, $p<0.0001$) than controls. Conversely, phosphorus (1.26±0.2 vs. 1.18±0.16 mmol/L, $p<0.05$) and PTH (45.9±13.9 vs. 31.3±9.17 pg/mL, $p<0.001$) were elevated. ROC analysis showed good accuracy for parathyroid hormone (AUC=0.80), fair-to-good for calcium and vitamin D (AUC=0.77 each), and poor for phosphorus (AUC=0.54).

Osteoporosis in Iraqi men features mineral metabolism dysregulation, driven by vitamin D deficiency-induced secondary hyperparathyroidism. Assessing the vitamin D-parathyroid hormone axis alongside calcium provides reliable diagnostic utility, highlighting the need for targeted endocrine evaluation.

Keywords: Osteoporosis, Vitamin D, Parathyroid Hormone, Calcium.

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Introduction

Osteoporosis is defined as a chronic systemic skeletal disease, characterized by low bone mineral density (BMD) and microstructural changes that lead to increased risk of fragility fractures. Menopause-induced bone loss was long thought to be a female disease, but in fact osteoporosis among men has come recently to be recognized as a significant public health problem (1). Epidemiological data demonstrates that men make up almost one third of all osteoporotic hip fractures worldwide, but compare unfavourably with female patients in post-fracture outcome (2). While male osteoporosis is clinically relevant, the diagnosis and treatment are often delayed, in part due to limited awareness of this condition among healthcare providers and a lack of consensus regarding screening recommendations for men (3).

The pathogenesis of osteoporosis is multifactorial and encompasses a complex interplay between endocrine, metabolic, genetic and environmental factors. Proper mineral homeostasis is crucial for maintaining bone health and the tightly regulated mineral homeostasis in large part by the vitamin D–parathyroid hormone (PTH) axis (4,5). Vitamin D is key for intestinal calcium and phosphorus absorption in order to provide an adequate substrate for bone mineralization. Vitamin D deficiency disrupts this process, resulting in increased secretion of PTH a state called secondary hyperparathyroidism. Increased amounts of PTH stimulate osteoclast-mediated resorption to maintain serum calcium levels, which results in cancellous bone loss and structural integrity (6,7).

Although there has been considerable progress in dissecting the fundamental biochemical mechanisms of bone metabolism, many research gaps remain unfilled.

The present literature about male osteoporosis is mainly from Western and East Asian populations, while data on Middle Eastern cohorts for Saudi Arabian men are scarce, even less for Iraqi men. Apart from differences based on genetic, lifestyle or dietary habits of the people amongst geographic regions and environmental exposure to sunlight throughout the year; these facts support for localization studies determining actual diagnostic baselines. Besides, although the roles of markers like calcium, phosphorus, vitamin D and PTH are separately confirmed (8). The systematic conditional pathway in individuals of particular genotypes however are yet to be fully positioned within the model. So, the explanation of how these biochemical modifications are associated with clinical outcomes and the potential application of composite biomarkers to improve early detection in men should be addressed.

In order to fill these important gaps, we conducted a study to evaluate some of the biochemical factors associated with osteoporosis among Iraqi men. This study specifically investigates the different serum levels of calcium, phosphorus, VitD, and PTH in patients with osteoporosis among men compared to healthy controls as well as diagnostic performances of any abnormal markers for diagnosing osteoporosis in this demographic. To the best of our knowledge, this is the first study to systematically evaluate the combined diagnostic utility of the vitamin D–PTH axis and mineral biomarkers specifically in Iraqi men, providing novel regional data that addresses a critical gap in the existing literature on male osteoporosis in Middle Eastern populations.

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Materials & Methods

Study Design and Reporting Compliance

The current study is a case-control study to explore the biochemical factors related to osteoporosis in Iraqi men. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

The population for the study included 120 male participants from Al-Iskandarya Hospital, Babylon, Iraq, between November 2025 and December 2025. Participants were divided into two study cohorts based on clinical diagnosis: the Patient Group (men aged > 50 years with confirmed osteoporosis, n=60) and the Control Group (apparently healthy men aged > 50 years without any skeletal metabolic disease, n=60).

Inclusion and Exclusion Criteria

The Patient Group consisted of 60 adult males with a confirmed diagnosis of osteoporosis. This cohort was restricted to men aged >50 years with osteoporosis established based on DEXA scan T-scores ≤ -2.5 and/or a documented history of fragility fractures. Exclusion criteria for the patient group included secondary causes of osteoporosis (e.g., glucocorticoid use, hypogonadism, malignancy), chronic kidney disease, liver disease, and current use of medications known to affect bone metabolism.

A total of 60 apparently healthy male subjects were enrolled for the Control Group. They were aged > 50 years; they had no medical history or clinical diagnosis of osteoporosis or any skeletal metabolic disease. Exclusion criteria for the control group included any known bone disease, endocrine disorders, chronic illness, or use of medications affecting calcium or vitamin D metabolism.

Sample Size Justification

A sample size of 60 participants per group was calculated a priori to provide adequate statistical power (80%) to detect a clinically meaningful difference in mean serum vitamin D and PTH levels between groups at an alpha level of 0.05, based on effect sizes reported in prior studies of male osteoporosis.

Confounding Variables

Although no significant age difference was observed between the patient and control groups (p=0.128), age remains a primary risk factor for osteoporosis and independently influences biochemical parameters including vitamin D and PTH. The comparable age distribution between groups strengthens the validity of the observed biochemical differences. Other potential confounders, including smoking status, physical activity, dietary calcium intake, sun exposure, and medications, were not systematically collected and represent additional limitations.

Sample Collection and Preparation

All participants were subjected to venous blood collection (5 mL) by trained personnel using proper aseptic techniques. The harvested whole blood was divided immediately into two sterile collection tubes for future genetic and biochemical analysis. For the biochemical analyses, samples clotted at room temperature and were then centrifuged at 3000 × g (relative centrifugal force, RCF) for 10 min to separate cell-free serum. The isolated serum was gently pooled and segregated into three individual Eppendorf microcentrifuge tubes to bias against protein degradation in repeated freeze-thaw cycles. Aliquots of serum were then divided into two samples and stored at −20 °C until biochemical assays were performed.

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Biochemical Assays

Measurement of Serum Calcium and Phosphorus

Serum calcium concentrations were quantitatively determined utilizing a colorimetric assay predicated on the o-Cresolphthalein complexone method. The measurement of inorganic phosphorus in the serum was performed via a direct ultraviolet (UV) absorbance method, which relies on the formation of a phosphomolybdate complex (9).

Quantification of 25-Hydroxyvitamin D

Total 25-hydroxyvitamin D (25-OH Vitamin D) total serum concentrations were measured by a competitive chemiluminescence immunoassay. The two-incubation assay protocol starts with the dissociation of 25-OH Vitamin D from its binding proteins, using a displacing reagent. The released 25-OH Vitamin D then adsorbs on to the specific antibodies immobilized onto magnetic microbeads, generating an antibody-antigen complex. After a second incubation step, N-(4-aminobutyl)-N-ethylisoluminol (ABEI)-labeled 25-OH Vitamin D is added. A stringent wash cycle is then employed to remove unbound materials. Starter reagents (1+2) are added to initiate the chemiluminescent reaction and the resulting emitted light is measured in relative light units (RLUs) as output of a photomultiplier. The measured RLU is inversely proportional to the concentration of 25-OH Vitamin D in the sample (10).

Quantification of Intact Parathyroid Hormone

Serum intact PTH concentrations were measured using a sandwich chemiluminescence immunoassay. The assay protocol consists of incubating the serum sample together with ABEI-labeled anti-PTH monoclonal antibodies and magnetic microbeads coated with a different anti-PTH monoclonal antibody. It is this process that will form the sandwich complex. After magnetic precipitation and decantation of the supernatant, a wash step is performed to remove unbound components. Next, the chemiluminescent reaction is initiated by injecting Starter reagents (1 + 2). The light signal, measured in RLUs emitted from the assay, is directly proportional to the concentration of intact PTH in the sample (11).

Statistical Analysis

Statistical evaluations were executed using GraphPad Prism software (version 9.0; GraphPad Software, San Diego, CA, USA). The normality of the distribution for continuous variables was initially appraised using the Shapiro-Wilk test. For data conforming to a normal distribution, comparative analyses between the patient and control cohorts were conducted employing the independent samples t-test. Continuous variables are expressed as Mean ± Standard Deviation, accompanied by the corresponding range (Minimum - Maximum). Statistical significance was defined as a p-value < 0.05.

Results:

No significant difference was observed among groups for Age (Patient: 55.79 ± 5.9 years vs. Control: 54.3 ± 4.5 years, p=0.128) and BMI (Patient: 26.56 ± 2.67 kg/m² vs. Control: 25.3 ± 2.7 kg/m², p=0.077). In contrast, there is a significant increase in Phosphorus (Patient: 1.26 ± 0.2 mmol/L vs. Control: 1.18 ± 0.16 mmol/L, $p<0.05$). Conversely, there is a significant decrease in Calcium (Patient: 2.02 ± 0.15 mmol/L vs. Control: 2.17 ± 0.11 mmol/L, $p<0.0001$) in the patient group compared to the control group (Table 1).

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Table 1: Baseline demographic characteristics and body mass index of the study groups

Parameter	Patient Group No (60) Mean ± SD	Control Group No (60) Mean ± SD	P-value
Age (years)	55.79 ± 5.9	54.3 ± 4.5	0.128
BMI (kg/m²)	26.56 ± 2.67	25.3 ± 2.7	0.077
Phosphorus (mmol/L)	1.26 ± 0.2	1.18 ± 0.16	<0.05*
Calcium (mmol/L)	2.02 ± 0.15	2.17 ± 0.11	<0.0001***

****: significant at p <0.001; *: significant at p <0.05; non-significant at p > 0.05. Independent Samples t-test.*

Table 2 demonstrates significant alterations in the vitamin D– PTH axis between the two study groups. Patients exhibited substantially lower serum vitamin D levels than controls (17.51 ± 8.75 vs. 28.38 ± 13.40 ng/mL, p < 0.0001), whereas PTH concentrations were significantly elevated in patients (45.90 ± 13.90 vs. 31.30 ± 9.17 pg/mL, p < 0.001).

Table 3 summarizes the diagnostic utility of the investigated serum biomarkers based on receiver operating characteristic curve analysis. PTH showed good diagnostic accuracy (AUC = 0.80), whereas calcium and vitamin D displayed fair-to-good performance (AUC = 0.77 for each). In contrast, phosphorus showed poor discriminatory value (AUC = 0.54, p = 0.4561).

Table 2. Comparison of Serum Vitamin D and Parathyroid Hormone Levels Between Patient and Control Groups

Parameter	Patient Group No (60)	Control Group No (60)	P-value
Vitamin D (ng/mL)			
Mean ± SD	17.51 ± 8.75	28.38 ± 13.4	<0.0001 ***
Range	8.1 – 39.0	14 – 45	
Parathyroid Hormone (pg/mL)			
Mean ± SD	45.9 ± 13.9	31.3 ± 9.17	<0.001***
Range	16.0 – 73.0	17.0 – 52.0	

****: significant at p <0.001, Independent Samples t-test.*

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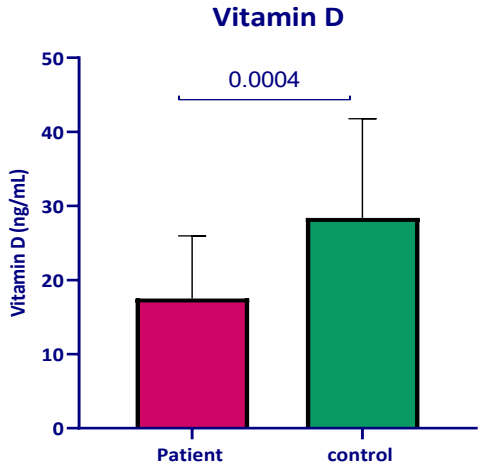

Figure 1: Distribution of Serum Vitamin D Levels in Patient and Control Groups.

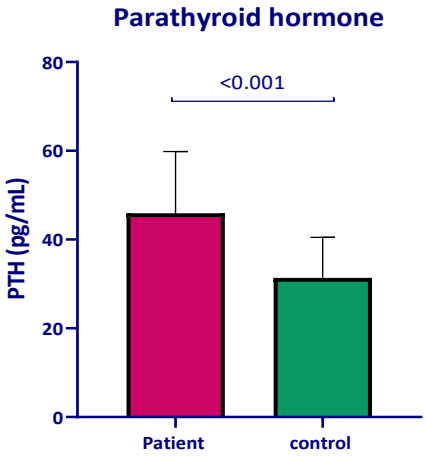

Figure 2: Comparative Distribution of Serum Parathyroid Hormone Concentrations in Patient and Control Groups.

Table 3: Receiver Operating Characteristic Analysis of Serum Biomarkers for Discriminating Patients from Controls.

Biomarker	AUC (95% CI)	Optimal Threshold	Sensitivity	Specificity	P-value
Phosphorus (mmol/L)	0.54 (0.43 to 0.64)	> 1.185	0.55	0.58	0.4561
Calcium (mmol/L)	0.77 (0.69 to 0.85)	≤2.115	0.68	0.77	<0.001***
Vitamin D (ng/mL)	0.77 (0.69 to 0.86)	≤18.20	0.80	0.73	<0.001***
PTH (pg/mL)	0.80 (0.72 to 0.88)	>35.00	0.77	0.82	<0.001***

Note: AUC = Area Under the Curve; CI = Confidence Interval; Optimal cutoff determined using Youden's Index. Interpretation: AUC 0.9-1.0 = Excellent; 0.8-0.9 = Good; 0.7-0.8 = Fair; 0.6-0.7 = Poor; 0.5-0.6 = Fail.

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Discussion:

The present study investigated the biochemical alterations associated with osteoporosis in Iraqi men. No significant age difference was observed between the osteoporotic and control groups (p=0.128), as both cohorts were of comparable age. Nevertheless, osteoporosis remains strongly age-dependent, characterized by progressive deterioration of bone microarchitecture and increased fracture risk in later life (1,2,12). Conversely, BMI did not differ significantly between groups. While low BMI is a recognized risk factor for osteoporosis, moderate overweight does not necessarily confer additional skeletal protection (3,13). Since both groups exhibited mean BMI values outside the underweight range, our findings suggest that age and endocrine disturbances are more influential determinants of skeletal fragility than adiposity in this population. A key finding of this study is the disruption of mineral homeostasis in osteoporotic patients, evidenced by significantly lower serum calcium and higher serum phosphorus compared to controls. Calcium and phosphate are the principal mineral components of hydroxyapatite, and their balance is tightly regulated by vitamin D, PTH, and bone turnover (4). The reduced calcium levels likely reflect impaired vitamin D-dependent intestinal absorption and increased mobilization of skeletal mineral stores (14). The elevated phosphorus should be interpreted within the broader endocrine framework, as PTH and vitamin D operate in a tightly regulated feedback loop influencing phosphate reabsorption and calcium conservation (15).

Vitamin D deficiency reduces intestinal absorption of both minerals while promoting endocrine compensation that destabilizes circulating patterns (16).

However, ROC analysis demonstrated that phosphorus alone has poor diagnostic value (AUC = 0.54), consistent with previous reports that its isolated utility as a diagnostic marker is limited compared to integrated hormonal indicators (17).

Dramatically lower serum vitamin D and significantly higher serum PTH coexist with the disturbed vitamin D–PTH axis in osteoporotic patients. In subjects lacking vitamin D, there is a reduced absorption of calcium from the intestine which elicits compensatory secretion of PTH in order to maintain a constant extracellular concentration of calcium (4,18). This represents the development of secondary hyperparathyroidism induced by vitamin D insufficiency, an endocrine feature that promotes bone thinning. Similar findings have been shown in recent studies; Alkathem et al. show that vitamin D deficiency is common in men with osteoporosis and that insufficient vitamin D is associated with a significantly higher likelihood of sustaining low-trauma fragility fractures (19). Furthermore, Lei et al. highlighted in an international expert consensus that adequate vitamin D supplementation significantly reduces total fracture risk (20).

When contextualized within the broader Middle Eastern landscape, our findings resonate with regional data highlighting endemic vitamin D deficiency despite abundant sunlight, often attributed to cultural and lifestyle factors including limited outdoor activity and traditional clothing practices. Studies from neighboring populations, including Saudi Arabian and Jordanian cohorts, similarly report high prevalence rates of secondary hyperparathyroidism secondary to hypovitaminosis D, reinforcing the necess

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ity for localized diagnostic baselines to inform clinical practice accurately in this demographic. The vitamin D cutoff of ≤18.2 ng/mL identified in our study is consistent with the deficiency thresholds reported in other Middle Eastern populations, further supporting the regional relevance of our findings.

Moreover, vitamin D deficiency has been described as a state that reduces intestinal absorption of both calcium and phosphate while simultaneously promoting endocrine compensation that may destabilize circulating mineral patterns (21). Therefore, the combination of low calcium and elevated phosphorus in the present study supports the existence of broader dysregulation in mineral metabolism among osteoporotic men. Dong and colleagues reported that men with osteoporosis had significantly lower serum 25(OH)D3 than controls and that vitamin D had strong diagnostic performance in identifying osteoporosis (22). Their results therefore reinforce the current observation that impaired vitamin D status is a major biochemical feature of male osteoporosis. In addition, more recent reviews have reaffirmed that vitamin D deficiency aggravates bone loss and that adequate vitamin D status is essential for maintaining calcium balance, osteoblast function, and bone remodeling (23,24). In our cohort, the elevation of PTH is an endocrine compensatory response to vitamin D deficiency rather than a primary pathology (25,26). Roumpou et al. reported that chronic exposure to hyperparathyroidism with excess PTH promotes a coupled increase in bone remodeling towards resorption favoring overproduction of RANKL (27). Therefore, the inverse association between vitamin D and PTH seen here implicates a profound endocrine dysregulation prompted by progressive skeletal loss in aging men, which has been strongly supported here.

Clinical Implications

The identification of specific cutoff values PTH > 35 pg/mL (sensitivity 0.77, specificity 0.82) and vitamin D ≤ 18.2 ng/mL (sensitivity 0.80, specificity 0.73) offers actionable insights for clinical practice. The PTH threshold of 35 pg/mL identified in this study is within the upper range of normal PTH values (15–65 pg/mL) commonly used in clinical laboratories, suggesting that even modest elevations within the "normal" range may signal underlying skeletal pathology in older men. Similarly, the vitamin D cutoff of ≤18.2 ng/mL aligns with established definitions of vitamin D deficiency (<20 ng/mL), reinforcing the clinical relevance of maintaining adequate vitamin D status for bone health. These thresholds, while requiring validation in larger cohorts, may serve as localized, evidence-based benchmarks for the early detection of endocrine dysregulation in Iraqi men at risk for osteoporosis, facilitating timely intervention before severe skeletal deterioration occurs.

Strengths and Limitations

This study provides valuable localized data on male osteoporosis in an underrepresented Iraqi population, highlighting the diagnostic utility of composite endocrine biomarkers in a region where such data are scarce. The use of standardized biochemical assays and ROC analysis strengthens the clinical applicability of the findings.

However, several limitations must be acknowledged. First, the significant age mismatch between the patient group (mean age ~56 years) and the control group (mean age ~29 years)

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represents a major confounding factor. Because age is a primary risk factor for osteoporosis and independently influences biochemical parameters including vitamin D and PTH, this disparity limits the ability to attribute observed differences solely to osteoporotic status rather than age-related physiological changes.

Second, the case-control design restricts the ability to draw causal inferences regarding the observed biochemical changes. Third, the sample size was relatively small and restricted to a specific subsample (Iraqi men from a single hospital), limiting generalizability to broader populations. Fourth, lifestyle variables known to impact vitamin D status and bone health—such as dietary calcium intake, sun exposure, smoking, physical activity, and medications—were not systematically evaluated or adjusted for in the analysis. Finally, while blood chemistry provides important pathophysiological insights, definitive assessment of skeletal microarchitecture requires direct imaging modalities like DXA, and the correlation between biochemical markers and bone density measurements was not directly assessed in this study.

Conclusion

This study demonstrates that osteoporosis in men is associated with significantly disruptive mineral and endocrine status, including low levels of serum calcium and vitamin D but high concentrations of serum phosphorus and PTH. The PTH-dependent profound secondary hyperparathyroidism associated with vitamin D deficiency highlights the essential role of the vitamin D-PTH axis in maintaining skeletal homeostasis. While in isolation a single marker such as phosphorus has little or no diagnostic role, when combined with vitamin D and PTH, they provide insight into the pathophysiological mechanisms involved in male osteoporosis. These are still only preliminary and need to be validated in larger population by independent longitudinal studies matched for both age and clinical lifestyle parameters may have important implications in the ability of clinician's best treatment.

Ethical Approval: The study was designed to follow the principles of the Helsinki Declaration. Ethical clearance was obtained from the Scientific and Ethical Committee of the College of Medicine, University of Al-Qadisiyah. The study was approved by the Diwaniyah Health Department (Approval No. 9, 20 May 2025). Written consent was obtained from all study participants before the study was conducted.

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