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RESEARCH ARTICLE

Association of Biochemical Indices with Skeletal Involvement in Primary Hyperparathyroidism

Primer Hiperparatiroidizmde Biyokimyasal İndekslerin İskelet Tutulumu ile İlişkisi

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ABSTRACT

Objective: Primary hyperparathyroidism (PHPT) is frequently associated with osteoporosis and cortical bone loss. This study aimed to investigate associations of biochemical parameters, adenoma size, the parathyroid function index (PFI), and the Wisconsin index (WIN) with osteoporosis and cortical skeletal involvement in patients with PHPT.

Materials and Methods: This retrospective study included 269 patients with PHPT. Participants were grouped by osteoporosis status. Demographic, biochemical, and densitometric data, along with PFI and WIN, were assessed. Among patients with osteoporosis, associations between distal one-third radius T-scores and biochemical parameters, composite indices, and adenoma size were examined. ROC analysis evaluated the ability of alkaline phosphatase (ALP), PTH, PFI, and WIN to distinguish osteoporosis.

Results: Osteoporosis was identified in 124 patients (46.1%). Patients with osteoporosis were older than those without osteoporosis ($p<0.001$). ALP levels were higher ($p<0.001$), whereas PTH levels showed a borderline increase ($p=0.050$). Distal one-third radius T-scores were inversely associated with serum calcium (Ca), PTH, ALP, PFI, and WIN (all $p\leq0.005$). The receiver operating characteristic (ROC) analysis showed that ALP had modest discriminative performance for osteoporosis [area under the curve (AUC)=0.674, $p<0.001$]. In contrast, PTH, PFI, and WIN showed no meaningful discriminative ability.

Conclusion: Osteoporosis was common in PHPT and associated with older age, higher ALP levels, and borderline-high PTH concentrations. PFI and WIN were associated with cortical bone loss but had limited utility for identifying osteoporosis, whereas ALP showed the highest, albeit modest, discriminatory performance among the evaluated parameters.

Keywords: Alkaline phosphatase, osteoporosis, parathyroid function index, primary hyperparathyroidism, Wisconsin index

ÖZET

Amaç: Primer hiperparatiroidizm (PHPT), sıklıkla osteoporoz ve kortikal kemik kaybı ile ilişkilidir. Bu çalışmada, PHPT'li hastalarda biyokimyasal parametreler, adenom boyutu, paratiroid fonksiyon indeksi (PFI) ve Wisconsin indeksi (WIN) ile osteoporoz ve kortikal iskelet tutulumu arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntemler: Bu retrospektif çalışmaya primer hiperparatiroidizm (PHPT) tanısı alan 269 hasta dahil edildi. Hastalar osteoporoz varlığına göre gruplandırıldı. Demografik, biyokimyasal ve dansitometrik veriler ile paratiroid fonksiyon indeksi (PFI) ve Wisconsin indeksi (WIN) değerlendirildi. Osteoporozu olan hastalarda distal üçte bir radius T-skorları ile biyokimyasal parametreler, kompozit indeksler ve adenom boyutu arasındaki ilişkiler incelendi. Alkalen fosfataz (ALP), parathormon (PTH), PFI ve WIN'in osteoporozu ayırt etme performansı ROC analizi ile değerlendirildi.

Bulgular: Osteoporoz 124 hastada (%46,1) saptandı. Osteoporozu olan hastalar, osteoporozu olmayanlara göre daha ileri yaşta idi ($p<0,001$). ALP düzeyleri osteoporoz grubunda anlamlı olarak daha yüksek bulunurken ($p<0,001$), PTH düzeyleri sınırda anlamlı bir artış gösterdi ($p = 0,050$). Distal üçte bir radius T-skorları ile serum kalsiyum (Ca), PTH, ALP, PFI ve WIN değerleri arasında anlamlı negatif korelasyonlar saptandı (tümü için $p\leq0,005$). Alıcı çalışma karakteristiği (ROC) analizinde, ALP'nin osteoporozu ayırt etme performansının orta düzeyde olduğu görüldü [eğri altındaki alan (AUC)=0,674; $p<0,001$]. Buna karşın, PTH, PFI ve WIN'in osteoporozu ayırt etmede anlamlı bir ayırt edici güce sahip olmadığı belirlendi.

Sonuç: PHPT'li hastalarda osteoporoz sık görülmekte olup ileri yaş, yüksek ALP düzeyleri ve sınırda yüksek PTH konsantrasyonlarıyla ilişkilidir. PFI ve WIN kortikal kemik kaybı ile ilişkili bulunmasına karşın, osteoporozun belirlenmesindeki ayırt edici değerleri sınırlıdır. Buna karşılık, ALP değerlendirilen parametreler arasında en yüksek ayırt edici performansı göstermiş olmakla birlikte, bu performans yalnızca sınırlı düzeydedir.

Anahtar Kelimeler: Alkalen fosfataz, osteoporoz, paratiroid fonksiyon indeksi, primer hiperparatiroidizm, Wisconsin indeksi

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INTRODUCTION

Parathyroid hormone (PTH) plays a central role in maintaining calcium (Ca) and phosphate balance. Under normal conditions, PTH secretion is regulated by Ca-sensing receptors (CaSRs) on parathyroid cells, which respond to fluctuations in circulating ionized Ca levels. In PHPT, this regulation is disrupted, leading to excessive PTH secretion despite hypercalcemia (1). Persistently elevated PTH levels promote bone resorption, stimulate renal 1α-hydroxylase activity to increase production of active vitamin D, and enhance intestinal Ca absorption. Moreover, increased renal tubular Ca reabsorption further contributes to elevated serum Ca concentrations (2). PHPT predominantly occurs in older individuals, particularly postmenopausal women, with epidemiological studies reporting a prevalence of approximately 0.84% in the general population (3). The disorder most commonly results from a hyperfunctioning parathyroid adenoma arising from monoclonal expansion of parathyroid cells and is frequently associated with decreased CaSR expression within parathyroid tissue (4). Skeletal involvement is a major clinical manifestation of PHPT. Although cortical bone loss is considered the hallmark skeletal feature of the disease, alterations in trabecular bone microarchitecture have also been documented (5). Consequently, bone deterioration in PHPT is not restricted to cortical-rich regions such as the distal one-third radius but may also affect trabecular sites, including the lumbar spine (5,6). Previous studies have reported osteoporosis and osteopenia in approximately 48.4% and 39.9% of patients with PHPT, respectively (7). Osteoporosis is characterized by impaired bone strength resulting from reduced bone mass and deterioration in bone quality, ultimately increasing fracture susceptibility. The clinical burden of osteoporosis extends beyond low bone mineral density because osteoporotic fractures are associated with substantial disability, healthcare utilization, and mortality. Worldwide estimates indicate that nearly nine million osteoporotic fractures occur annually, including fractures of the hip, forearm, and vertebrae (8). Among these fracture types, hip and vertebral fractures are associated with particularly adverse clinical outcomes and increased mortality risk (9).

Dual-energy X-ray absorptiometry (DXA) is the standard method for measuring bone mineral density and diagnosing osteoporosis. In PHPT, the distal one-third of the radius warrants particular attention because cortical bone deterioration is often more pronounced at this site than at the lumbar spine or hip (10,11). Although reduced BMD and osteoporosis are well-recognized manifestations of PHPT, the relationship between skeletal involvement and biochemical parameters remains incompletely understood. Serum Ca and PTH concentrations are considered indicators of biochemical disease severity; however, their associations with bone loss have yielded inconsistent results across previous studies (7). Similarly, 24-hour urinary Ca excretion (24-h urine Ca), a marker of hypercalciuria, has been associated with lower BMD, although its relationship to cortical bone loss remains unclear. Other biochemical markers of bone metabolism, including serum 25-hydroxyvitamin D [25(OH)D] and alkaline phosphatase (ALP), may also influence skeletal health; however, there is still no clear consensus regarding their relationship to osteoporosis in patients with PHPT (7,12). Furthermore, studies specifically evaluating the relationship between biochemical parameters and cortical bone loss at skeletal sites, such as the distal one-third of the radius, remain limited.

Recently, composite biochemical indices such as the parathyroid function index (PFI) and Wisconsin index (WIN), derived from routine biochemical parameters, have been proposed as practical markers of disease activity and severity in PHPT (13). However, data on their association with osteoporosis and cortical skeletal involvement remain scarce. Therefore, the present study aimed to investigate the association of serum Ca, P, PTH, 25(OH)D, ALP, 24-h urine Ca, PFI, WIN, and adenoma size with osteoporosis in patients with PHPT. Additionally, we aimed to evaluate the relationship between these parameters and distal one-third radius T-scores, which serve as indicators of cortical skeletal involvement.

MATERIALS AND METHODS

This retrospective study was conducted at a tertiary endocrine center and included patients with PHPT evaluated from July 2022 to March 2026. Eligible patients were identified using the institutional electronic database, and those with complete demographic, biochemical, imaging, and densitometric records were enrolled. Clinical, biochemical, and imaging variables were extracted from medical records, including corrected serum Ca (mg/dL), P (mg/dL), PTH (pg/mL), 25(OH)D (ng/mL), ALP (U/L), 24-h urine Ca (mg/day), DXA findings, and ultrasonographic adenoma diameter (mm). Bone mineral density was assessed using dual-energy X-ray absorptiometry (DXA). All measurements were performed on the same DXA scanner (STRATOS, Diagnostic Medical Systems [DMS], Montpellier, France) throughout the study period. Routine quality control and calibration procedures were performed consistently in accordance with the manufacturer's recommendations and institutional quality assurance protocols. Bone status was interpreted according to the International Society for Clinical Densitometry (ISCD) recommendations (10). Osteoporosis was defined as a T-score ≤−2.5 at any major skeletal site in postmenopausal women and in men aged ≥50 years. In premenopausal women and in men aged <50 years, Z-scores were used for diagnostic classification. Participants with a Z-score ≤−2.0 were classified as having bone mineral density below the expected range for age. They were included in the osteoporosis group for this study. Comparisons of biochemical parameters were performed between patients with and without osteoporosis. Correlation analyses were performed using distal one-third radius T-scores as continuous variables.

The PFI and WIN were calculated using the following formulas: PFI = [corrected serum Ca (mmol/L) × PTH (pmol/L)] / serum phosphorus (mmol/L), and WIN = corrected serum Ca (mmol/L) × PTH (pg/mL) (13). For PFI calculation, corrected serum Ca and P were expressed in mmol/L, and PTH in pmol/L. For WIN calculation, corrected serum Ca was expressed in

mmol/L and PTH in pg/mL.

The study was approved by the KTO Karatay University Non-Drug and Non-Medical Device Research Ethics Committee (meeting number: 08; meeting date: April 30, 2026; decision number: 2026/031). Because the study was retrospective, only anonymized data from existing patient records were analyzed.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous data were presented as mean ± standard deviation or as median (25th–75th percentile), depending on their distribution. Categorical variables were expressed as frequencies and percentages. Between-group comparisons were performed using Student's t-test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Relationships between distal one-third radius T-scores and clinical or biochemical variables, including adenoma size, were examined using Pearson's or Spearman's correlation analysis, as appropriate. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance of biochemical markers and composite indices for osteoporosis. The area under the curve (AUC), 95% confidence intervals (CI), sensitivity, specificity, and optimal cutoff values were calculated. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

A total of 269 patients with PHPT were included in the study, of whom 124 had osteoporosis and 145 did not. Patients in the osteoporosis group were significantly older than those without osteoporosis (60.18 ± 9.45 vs. 52.58 ± 9.33 years, p<0.001). The proportion of female patients was comparable between the two groups, with more than 80% in each group (83.9% vs. 84.1%, p=0.953). Among the female participants, seven in the osteoporosis group and twenty in the non-osteoporosis group were premenopausal; all remaining women were postmenopausal. The prevalence of nephrolithiasis was similar between patients with and without osteoporosis. Renal stones were identified in 19 of 124 patients (15.3%) in the osteoporosis group and in 22 of 145 patients (15.2%) in the non-osteoporosis group (p=0.973). Likewise, adenoma size did not differ significantly between the groups. The median adenoma diameter was 13 mm (10–19 mm) in patients with osteoporosis and 12 mm (9.25–16 mm) in those without osteoporosis (p=0.163). Detailed biochemical and densitometric characteristics of the study cohort are presented in Table 1.

Biochemical comparisons showed similar corrected serum Ca levels between the osteoporosis and non-osteoporosis groups (10.58 ± 0.66 vs. 10.50 ± 0.66 mg/dL, p=0.665). Serum P levels were also comparable between groups [2.70 (2.30–3.10) vs. 2.70 (2.50–3.12) mg/dL, p=0.522]. In contrast, creatinine (Cr) levels were significantly lower in patients with osteoporosis [0.63 (0.56–0.74) vs. 0.71 (0.62–0.78) mg/dL, p=0.004]. Patients with osteoporosis had significantly higher ALP levels than those without osteoporosis [113.50 (87.50–151.25) vs. 94.50

Table 1. Comparison of demographic, biochemical, and densitometric characteristics between PHPT patients with and without osteoporosis.

	Osteoporosis n =124	Non-osteoporosis n = 145	p
Age (years)	60.18 ± 9.45	52.58 ± 9.33	**<0.001**
Sex, n (%)			0.953
Female	104 (83.90%)	122 (84.10%)	
Male	20 (16.10%)	23 (15.90%)	
Nephrolithiasis, n (%)			0.973
Present	19 (15.30%)	22 (15.20%)	
Absent	105 (84.70%)	123 (84.80%)	
Adenoma diameter, mm	13 (10–19)	12 (9.25–16)	0.163
Ca, mg/dL	10.58 ± 0.66	10.50 ± 0.66	0.665
P, mg/dL	2.70 (2.30–3.10)	2.70 (2.50–3.12)	0.522
Cr, mg/dL	0.63 (0.56–0.74)	0.71 (0.62–0.78)	**0.004**
ALP, U/L	113.50 (87.50–151.25)	94.50 (76–108.50)	**<0.001**
PTH, pg/mL	125 (92–191.50)	112 (85.75–147.75)	0.050
25(OH)D, ng/mL	15.65 (10.00–22.63)	17.70 (11.85–22.28)	0.236
24-h urine Ca, mg/day	355.50 ± 145.98	339.50 ± 172.20	0.204
PFI	39.76 (26.26–66.28)	35.87 (24.51–53.35)	0.150
WIN	328.50 (230.60–519)	294.30 (217.20–397.20)	0.081
Lumbar spine T-score	-3.00 (-3.43 to -2.48)	-1.20 (-1.93 to -0.50)	**<0.001**
Femoral neck T-score	-1.61 ± 0.68	-0.61 ± 0.76	**<0.001**
One-third radius T-score	-2.90 (-3.63 to -2.30)	-0.85 (-1.50 to 0.10)	**<0.001**

Values are presented as mean ± standard deviation or median (25th–75th percentile), unless otherwise indicated. Comparisons between groups were performed using the independent-samples t-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. **Statistical significance was accepted as p < 0.05.** ALP: Alkaline phosphatase, Ca: Calcium, Cr: Creatinine, DXA: Dual-energy X-ray absorptiometry, mm: Millimeter, PFI: Parathyroid function index, P: Phosphorus, PTH: Parathyroid hormone, 25(OH)D: 25-hydroxyvitamin D, WIN: Wisconsin index.

(76–108.50) U/L, p<0.001]. PTH levels were also higher in the osteoporosis group, although the difference was borderline significant [125 (92–191.50) vs. 112 (85.75–147.75) pg/mL, p=0.050].

Serum 25(OH)D levels and 24-h urinary Ca excretion were comparable between the groups. The median 25(OH)D level was 15.65 ng/mL (10.00–22.63) in patients with osteoporosis and 17.70 ng/mL (11.85–22.28) in those without osteoporosis (p=0.236). Similarly, mean 24-h urinary Ca excretion was 355.50 ± 145.98 mg/day in the osteoporosis group and 339.50 ± 172.20 mg/day in the non-osteoporosis group (p = 0.204). The PFI and WIN values were higher in patients with osteoporosis; however, these differences were not statistically significant. The median PFI was 39.76 (26.26–66.28) in the osteoporosis group and 35.87 (24.51–53.35) in the non-osteoporosis group (p=0.150). Similarly, WIN values were 328.50 (230.60–519) and 294.30 (217.20–397.20) in the osteoporosis and non-osteoporosis groups, respectively (p=0.081). Bone mineral density parameters were significantly lower in patients with osteoporosis. Lumbar spine T-scores were −3.00 (−3.43 to −2.48) in the osteoporosis group and −1.20 (−1.93 to −0.50) in the non-osteoporosis group (p<0.001). Femoral neck T-scores were also significantly lower in patients with osteoporosis (−1.61 ± 0.68 vs. −0.61 ± 0.76, p<0.001). Likewise, one-third radius T-scores were significantly lower in the osteoporosis group [−2.90 (−3.63 to −2.30) vs. −0.85 (−1.50 to 0.10), p<0.001].

Correlation analysis among patients with osteoporosis showed significant negative correlations between one-third radius T-scores and several biochemical parameters, as presented in Table 2. One-third radius T-scores were negatively correlated with serum Ca levels (r=−0.253, p=0.005), PTH (r=−0.293, p=0.001), ALP (r=−0.279, p=0.002), PFI (r=−0.283, p=0.002), and WIN values (r=−0.306, p=0.001).

ROC curve analyses of biochemical parameters for discriminating osteoporosis in patients with PHPT are shown in Figure 1. As shown in Figure 1A, ALP demonstrated modest discriminatory performance for osteoporosis, with an AUC of 0.674 (95% CI: 0.607–0.741, p<0.001), whereas PTH showed no significant discriminatory ability (AUC=0.566, 95% CI: 0.495–0.637, p=0.069). In Figure 1B, neither PFI nor WIN demonstrated meaningful discriminatory ability for osteoporosis. The AUC values were 0.513 (95% CI: 0.442–0.584, p=0.716) for PFI and 0.519 (95% CI: 0.448–0.590, p=0.603) for WIN.

Table 2. Correlations of one-third radius T-scores with clinical and biochemical parameters in PHPT patients with osteoporosis

Variable	Correlation coefficient (r)	p value
Cr	−0.121	0.184
Ca	−0.253	**0.005**
P	0.061	0.513
25(OH)D	0.156	0.089
PTH	−0.293	**0.001**
ALP	−0.279	**0.002**
PFI	−0.283	**0.002**
WIN	−0.306	**0.001**
Adenoma diameter	−0.102	0.266

Values are presented as Pearson's or Spearman's correlation coefficients, as appropriate. Statistical significance was considered at p < 0.05, and statistically significant p-values are shown in bold. ALP: Alkaline phosphatase, Ca: Calcium, Cr: Creatinine, P: Phosphorus, PFI: Parathyroid function index, PTH: Parathyroid hormone, 25(OH)D: 25-hydroxyvitamin D, WIN: Wisconsin index.

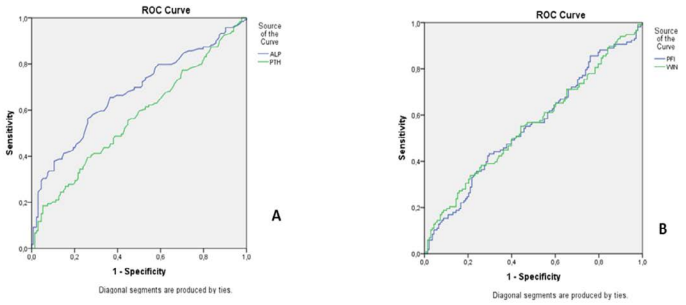

Figure 1. ROC curve analysis of biochemical parameters for discriminating osteoporosis in patients with PHPT
(A) ALP and PTH
ALP: AUC=0.674 (95% CI: 0.607-0.741), p<0.001
PTH: AUC=0.566 (95% CI: 0.495-0.637), p=0.069
(B) PFI and WIN
PFI: AUC=0.513 (95% CI: 0.442-0.584), p=0.716
WIN: AUC=0.519 (95% CI: 0.448-0.590), p=0.603

DISCUSSION

Previous studies have reported osteoporosis and osteopenia prevalence in patients with PHPT at approximately 48.4% and 39.9%, respectively (7). Consistent with the literature, osteoporosis was detected in 46.1% of patients with PHPT in the present study. PHPT is characterized by reduced bone mineral density and predominantly affects cortical bone; however, trabecular skeletal sites may also be adversely affected (5,7). In our study, patients with osteoporosis had significantly lower T-scores at the lumbar spine, femoral neck, and distal one-third radius, indicating involvement of both trabecular and cortical bone compartments. Although cortical bone involvement is considered the classic skeletal manifestation of PHPT, trabecular bone loss may also occur, particularly in patients with more severe or prolonged disease activity (5,6). Similar findings were reported by Kocabaş et al., who demonstrated that patients with lower baseline bone mineral density exhibited more pronounced skeletal involvement and evaluated skeletal recovery following parathyroidectomy in patients with PHPT (14). These findings further support the clinical importance of comprehensive skeletal assessment, including both trabecular and cortical skeletal sites, in patients with PHPT.

Furthermore, patients with osteoporosis exhibited significantly higher ALP levels and borderline higher PTH

levels than those without osteoporosis. Previous studies have demonstrated that elevated PTH levels in PHPT are associated with increased bone turnover and reduced bone mineral density, particularly at cortical skeletal sites. Bone turnover markers, including ALP, have been reported to correlate with disease severity and skeletal involvement in PHPT (15,16). In agreement with previous reports, patients with osteoporosis in our study had higher ALP levels and borderline higher PTH levels than those without osteoporosis. Moreover, ROC curve analysis showed that ALP had modest but statistically significant ability to discriminate osteoporosis in patients with PHPT (AUC=0.674), whereas PTH did not demonstrate significant discriminatory performance. However, the observed AUC indicates only modest discriminatory accuracy. Therefore, although ALP may serve as a useful adjunctive marker of skeletal involvement in PHPT, it should not be considered a reliable standalone predictor of osteoporosis and should be interpreted alongside clinical, biochemical, and densitometric findings.

Age is an established risk factor for skeletal deterioration, and the significantly older age of patients with osteoporosis in our cohort supports its contribution to bone involvement in PHPT (7). Vitamin D deficiency has been proposed to exacerbate the skeletal effects of PHPT by increasing PTH secretion and accelerating bone remodeling. Walker et al. demonstrated that lower 25(OH)D levels were associated with higher circulating PTH concentrations and greater deterioration of bone microarchitecture, suggesting a protective role of vitamin D in preserving skeletal health (17). Nevertheless, the association between serum 25(OH)D concentrations and osteoporosis in PHPT remains uncertain. Inoue et al. reported inverse relationships between 25(OH)D levels and markers of disease severity, including serum Ca and PTH, although these associations did not reach statistical significance (18). Similarly, our findings showed comparable 25(OH)D levels in patients with and without osteoporosis. Collectively, these observations indicate that vitamin D status alone may not be a major determinant of osteoporosis in PHPT. In contrast, age and disease-related biochemical alterations appear to have a greater impact on skeletal involvement.

Another finding of our study was significantly lower serum Cr levels in patients with osteoporosis. Previous studies have suggested that lower serum Cr concentrations may reflect reduced muscle mass, which has been associated with lower bone mineral density and an increased risk of osteoporosis, particularly in older individuals (19). The close relationship between muscle and bone health has led to the concept of the bone–muscle unit, in which reduced muscle mass may contribute to skeletal fragility and bone loss. In addition to biochemical parameters, several disease-related characteristics have been investigated as potential determinants of skeletal involvement in PHPT. Among these, adenoma size has been proposed as a potential indicator of disease severity, as larger adenomas are generally associated with higher serum Ca and PTH concentrations and a greater biochemical disease burden (20). Recently, Gezer et al. demonstrated a significant negative correlation between parathyroid adenoma volume and distal one-third radius bone mineral density, suggesting that larger adenomas may be associated with more pronounced cortical bone loss in patients with PHPT (21). In contrast, adenoma diameter did not differ significantly between patients with and without osteoporosis in our cohort. These findings suggest that adenoma size alone may not adequately reflect the extent of skeletal involvement or the risk of osteoporosis in PHPT.

The parathyroid function index (PFI) was originally developed as a biochemical tool to improve differentiation of PHPT from secondary hyperparathyroidism, particularly in patients with vitamin D deficiency and normocalcemic presentations. Guo et al. proposed the PFI formula based on the characteristic biochemical profile of PHPT, which typically includes elevated serum Ca and PTH levels and reduced serum P concentrations. In their study, PFI demonstrated high diagnostic sensitivity and specificity for distinguishing PHPT from vitamin D deficiency–related secondary hyperparathyroidism (22). Similarly, subsequent studies have suggested that PFI may serve as a simple and inexpensive diagnostic marker for identifying PHPT and differentiating it from other causes of elevated PTH levels (23). Therefore, PFI has primarily been studied as a diagnostic index of parathyroid functional activity rather than as a direct marker of skeletal involvement or the severity of osteoporosis. More recently, the potential role of PFI in predicting PHPT-related complications has attracted increasing interest. Baser et al. reported that a PFI of 36.43 predicted nephrolithiasis with 86% sensitivity and 68% specificity, suggesting that this index may reflect disease severity and complication risk; however, PFI was not identified as an independent predictor in multivariable analysis (13). In our cohort, although PFI values were numerically higher in patients with osteoporosis than in those without osteoporosis, the difference did not reach statistical significance. Nevertheless, within the osteoporosis group, PFI showed a significant negative correlation with one-third radius T-scores, indicating that higher PFI values are associated with more severe cortical bone loss. However, despite this correlation, PFI showed no meaningful discriminatory ability to identify osteoporosis in ROC analysis (AUC = 0.513, 95% CI: 0.442–0.584, $p = 0.716$). These findings suggest that PFI primarily reflects parathyroid functional activity and disease burden rather than osteoporosis risk. These findings are consistent with recent evidence indicating that PHPT is associated with systemic inflammatory and metabolic alterations that improve after parathyroidectomy, further supporting the concept that PHPT is a multisystem disorder and that biochemical markers may reflect overall disease burden beyond skeletal manifestations (24).

The Wisconsin Index (WIN), calculated as the product of serum Ca and PTH concentrations, was introduced by Mazeh et al. as a practical biochemical indicator of PHPT severity (20). Their findings showed that higher WIN values were linked to greater adenoma weight and increased biochemical disease activity, suggesting that WIN may reflect overall disease burden. Subsequent studies have examined WIN's utility in predicting

PHPT-related complications, particularly osteoporosis and nephrolithiasis. In a multicenter cross-sectional study, Baser et al. found a significant association between WIN and osteoporosis and proposed a cutoff of 283.29, which showed favorable diagnostic performance (13). In contrast, WIN values did not differ significantly between patients with and without osteoporosis in the present study. However, among individuals with osteoporosis, WIN showed a modest but significant inverse correlation with distal one-third radius T-scores (r=−0.306, p=0.001). This suggests that higher WIN values are associated with greater cortical bone loss. Given that the distal one-third radius consists predominantly of cortical bone and is particularly susceptible to the catabolic effects of excess PTH, this finding may have clinical relevance. Nevertheless, ROC analysis showed no meaningful discriminatory ability of WIN for identifying osteoporosis (AUC=0.519, 95% CI: 0.448–0.590, p=0.603). Therefore, although WIN may reflect certain aspects of skeletal involvement in PHPT, our results do not support its use as a reliable standalone marker for osteoporosis prediction.

Study Limitations

This study has several limitations. The retrospective, single-center design may reduce the external validity of the findings. In addition, most participants were women, reflecting the epidemiology of PHPT but potentially limiting extrapolation to male patients. Advanced techniques for evaluating bone quality, including high-resolution peripheral quantitative computed tomography and trabecular bone score analysis, were unavailable. Bone turnover markers other than ALP were not assessed. Furthermore, the observational design precludes causal inference regarding the relationship between biochemical variables and skeletal involvement. Nevertheless, the relatively large cohort and the concurrent assessment of conventional biochemical markers with PFI and WIN strengthen the study findings.

CONCLUSION

Osteoporosis was identified in 46.1% of patients with PHPT and was associated with older age, higher ALP levels, and borderline-higher PTH concentrations. Distal one-third radius T-scores showed significant negative correlations with serum Ca, PTH, ALP, PFI, and WIN, highlighting the close relationship between biochemical disease activity and cortical skeletal involvement. Among the evaluated parameters, ALP showed only modest discriminatory performance for osteoporosis, whereas PFI and WIN were associated with cortical bone loss but had no meaningful ability to identify osteoporosis.

DECLARATIONS

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