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Polycystic Ovary Syndrome Modifies the Association Between Parathyroid Hormone and Fasting-Derived Insulin Sensitivity: A Case–Control Study

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Abstract

Introduction: Polycystic ovary syndrome (PCOS), recently proposed to be renamed polyendocrine metabolic ovarian syndrome (PMOS), is associated with heterogeneous insulin resistance. Vitamin D status has been widely studied in PCOS, but parathyroid hormone (PTH), a calciotropic hormone with potential metabolic relevance, has received less attention. We investigated whether PTH was associated with fasting-derived insulin sensitivity independently of 25-hydroxyvitamin D [25(OH)D3] and whether this association differed by PCOS status.

Materials and Methods: In this BMI-matched case–control study, 33 women with PCOS and 30 healthy controls were enrolled. Serum PTH and 25(OH)D3 were measured. HOMA-IR and QUICKI were calculated from fasting glucose and insulin; QUICKI was the primary outcome. Multiple linear regression tested the PTH × PCOS interaction after adjustment for age, BMI, waist-to-hip ratio, and 25(OH)D3.

Results: Women with PCOS had higher PTH (53.43±20.07 vs 44.42±9.81 pg/mL, p=0.030), lower 25(OH)D3 (29.39±14.77 vs 36.72±6.90 ng/mL, p=0.016), higher HOMA-IR, and lower QUICKI than controls. PCOS modified the PTH–QUICKI association (interaction β=0.0109; 95% CI 0.0023–0.0196; p=0.014). In controls, higher PTH was associated with lower QUICKI (β per 10 pg/mL=-0.0106; 95% CI -0.0185 to -0.0027; p=0.009), whereas the corresponding slope in women with PCOS was β=0.0003 (95% CI -0.0034 to 0.0041; p=0.857). Sensitivity analyses supported the robustness of the interaction.

Conclusion: PCOS status modified the association between PTH and fasting-derived insulin sensitivity. The inverse PTH–QUICKI association observed in controls was non-significant in women with PCOS, suggesting altered calciotropic–metabolic coupling.

Key words: Parathyroid hormone; polycystic ovary syndrome; insulin resistance; calcifediol.

Introduction

Polycystic ovary syndrome (PCOS), recently proposed to be renamed polyendocrine metabolic ovarian syndrome (PMOS) through a global consensus process, is one of the most common endocrine disorders among reproductive-age women, with prevalence estimates varying according to diagnostic criteria (1, 2). Although traditionally defined by reproductive and androgenic features, PCOS is also characterised by a substantial metabolic phenotype, including insulin resistance, compensatory hyperinsulinaemia, impaired glucose regulation, and increased long-term cardiometabolic risk (3, 4). Identifying endocrine factors that contribute to metabolic heterogeneity in PCOS remains clinically and biologically relevant. Throughout this manuscript we use the established PCOS terminology, as the study was designed and participants were diagnosed according to existing PCOS criteria, while acknowledging the recently proposed PMOS reconceptualisation (1). Vitamin D status has been extensively studied in PCOS, with lower 25-hydroxyvitamin D [25(OH)D3] concentrations consistently associated with greater insulin resistance and adverse metabolic profiles (5–8). However, 25(OH)D3 reflects vitamin D nutritional status rather than the integrated endocrine response of the calcium–vitamin D axis. Parathyroid hormone (PTH), the principal calciotropic counter-regulatory hormone, rises in response to vitamin D insufficiency and hypocalcaemia and may therefore capture aspects of calcium–vitamin D axis dysregulation that circulating 25(OH)D3 alone does not reflect. Beyond its classical role in mineral homeostasis, PTH has been linked to pancreatic β-cell function, skeletal muscle physiology, and insulin sensitivity

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in non-PCOS populations (9–12), raising the question of whether it carries independent metabolic relevance in women with PCOS. Previous studies have reported higher PTH concentrations in women with PCOS compared with healthy controls (13, 14), but PTH has seldom been examined as a primary metabolic exposure in this population. Most available evidence has focused on 25(OH)D3 or vitamin D supplementation, using fasting-derived insulin resistance indices as metabolic outcomes (6–8), and few studies have simultaneously accounted for both PTH and 25(OH)D3 when examining insulin sensitivity. Whether the association between PTH and insulin sensitivity differs between women with and without PCOS has not been formally tested.

We conducted a BMI-matched case–control study in reproductive-age women to address this question. The primary aim was to test whether PCOS status modifies the association between circulating PTH and fasting-derived insulin sensitivity after adjustment for 25(OH)D3 and key anthropometric covariates. We hypothesized that the PTH–insulin sensitivity association would differ according to PCOS status, reflecting the altered endocrine-metabolic environment characteristic of the syndrome.

Materials and Methods

This BMI-matched case–control study was conducted at an outpatient obstetrics and gynaecology clinic of a tertiary training and research hospital in Turkey between February and July 2012. The study compared reproductive-age women with PCOS and BMI-matched healthy controls to evaluate whether PCOS status modified the association between circulating PTH and fasting-derived insulin sensitivity. The manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for observational studies (15).

Women aged 18-40 years were enrolled as PCOS cases or healthy controls. PCOS was diagnosed according to the Androgen Excess and PCOS Society criteria, which require hyperandrogenism together with ovarian dysfunction after exclusion of related disorders (16). Hyperandrogenism was defined as biochemical hyperandrogenism, based on elevated serum free testosterone, total testosterone, and/or DHEA-S above the assay-specific reference range used by the institutional laboratory, and/or clinical hyperandrogenism assessed by the modified Ferriman–Gallwey score (17). Ovarian dysfunction was defined as oligo-anovulation, indicated by menstrual cycles longer than 35 days, fewer than eight menstrual cycles per year, or amenorrhea lasting at least 90 days, and/or polycystic ovarian morphology on ultrasonography. All participants underwent pelvic ultrasonography. Polycystic ovarian morphology was defined according to the criteria in use during the study period as the presence of 12 or more follicles measuring 2–9 mm in diameter and/or ovarian volume greater than 10 mL in at least one ovary. Women with regular menstrual cycles, normal ovarian morphology, and no clinical or biochemical evidence of androgen excess were enrolled as controls. Disorders that could mimic PCOS or influence the study outcomes were excluded clinically and biochemically where appropriate. Exclusion criteria included hyperprolactinemia, thyroid dysfunction, non-classic congenital adrenal hyperplasia, Cushing syndrome, androgen-secreting tumors, diabetes mellitus, chronic hepatic, renal, or cardiovascular disease, hypertension, pregnancy or lactation, and other endocrine disorders affecting calcium or glucose metabolism. Women were also excluded if they had used oral contraceptives, systemic corticosteroids, or other medications affecting insulin sensitivity or calcium/vitamin D metabolism within 12 weeks of enrolment, or if they had artificial ultraviolet exposure within the same period. Controls were selected using BMI matching with a caliper of ±2 kg/m². The final available study population included 33 women with PCOS and 30 healthy controls. Anthropometric measurements were recorded, and BMI was calculated as weight in kilograms divided by height in meters squared. Waist-to-hip ratio was calculated from waist and hip circumferences. Fasting venous blood samples were collected in the early follicular phase, between 08:00 and 10:00 after at least 8 hours of fasting. Follicle-stimulating hormone, luteinizing hormone, estradiol, prolactin, sex hormone-binding globulin, total testosterone, dehydroepiandrosterone sulfate, and PTH were measured by chemiluminescent microparticle immunoassay. Free testosterone, 17-hydroxyprogesterone, and 25(OH)D3 were measured by enzyme-linked immunosorbent assay. Total calcium, phosphate, and alkaline phosphatase were measured using standard enzymatic methods. Fasting plasma glucose and fasting insulin were used to calculate HOMA-IR and QUICKI. HOMA-IR was calculated as fasting insulin (μU/mL) × fasting plasma glucose (mg/dL) / 405 (18). QUICKI was calculated as 1 / [log fasting insulin + log fasting plasma glucose] (19). QUICKI was selected as the primary

Table 1: Baseline characteristics of the study groups

Variable	PCOS (n=33)	Controls (n=30)	p
Age (years)	27.06 ± 5.63 (18.00-37.00)	30.43 ± 3.47 (22.00-34.00)	0.006
BMI (kg/m²)	24.36 ± 3.98 (18.21-36.05)	23.86 ± 3.19 (17.80-30.11)	0.591
Waist/hip ratio	0.80 ± 0.06 (0.70-0.91)	0.73 ± 0.05 (0.63-0.86)	<0.001
FGS	3.00 ± 2.17 (0.00-7.00)	0.63 ± 0.76 (0.00-2.00)	<0.001

Data are presented as mean ± SD (minimum–maximum). BMI, body mass index; FGS, Ferriman-Gallwey score.

Table 2: Metabolic parameters and insulin resistance indices

Variable	PCOS (n=33)	Controls (n=30)	p
FPG (mg/dL)	92.18 ± 9.96 (74.00-110.00)	84.13 ± 6.66 (71.00-97.00)	<0.001
FINS (μU/mL)	11.72 ± 4.21 (5.20-22.20)	9.25 ± 4.13 (4.20-27.20)	0.022
HDL-C (mg/dL)	47.67 ± 9.26 (31.00-69.00)	47.53 ± 6.45 (25.00-57.00)	0.947
LDL-C (mg/dL)	96.73 ± 18.42 (59.00-135.00)	96.27 ± 15.17 (70.00-139.00)	0.914
TG (mg/dL)	115.61 ± 57.63 (42.00-316.00)	106.23 ± 40.77 (70.00-274.00)	0.463
HOMA-IR	2.40 ± 0.91 (0.98-4.87)	1.75 ± 0.84 (0.74-5.31)	0.004
QUICKI	0.33 ± 0.02 (0.30-0.38)	0.35 ± 0.02 (0.30-0.40)	0.002

Data are presented as mean ± SD (minimum–maximum). FPG, fasting plasma glucose; FINS, fasting insulin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

metabolic outcome because it is a fasting-derived index of insulin sensitivity.

Ethical approval: The study was approved by the Sakarya University Medical Ethics Committee (Date: 01.02.2012; Meeting No: 2012/1; Reference No: B.30.2.SAÜ.0.20.05.04.050.01.04/57). Written informed consent was obtained from all participants. All procedures were performed in accordance with the Declaration of Helsinki.

Statistical analysis: The raw spreadsheet was checked for missing and implausible values before analysis. One PCOS participant had missing PTH and was therefore excluded from regression models that included PTH. Continuous variables are presented as mean ± standard deviation with minimum–maximum values. Between-group comparisons were performed using the independent-samples t test. QUICKI was the primary outcome, serum PTH was the primary exposure, and PCOS status was evaluated as an effect modifier. Before regression analyses, QUICKI and HOMA-IR distributions were inspected using histograms and normal probability plots and assessed with the Shapiro–Wilk test. QUICKI showed no significant deviation from normality in the overall sample; residuals from the primary QUICKI model also showed acceptable normality. HOMA-IR was right-skewed and was therefore log-transformed for sensitivity analysis.

Multiple linear regression was used to assess the association between PTH and QUICKI, including a PTH × PCOS interaction term. The model was adjusted for age, BMI, waist-to-hip ratio, and 25(OH)D3. PTH and 25(OH)D3 were scaled per 10 pg/mL and 10 ng/mL, respectively. The primary model included 62 participants with available PTH and covariate data, and coefficients are reported with 95% confidence intervals. Sensitivity analyses used log-transformed HOMA-IR as an alternative outcome, excluded participants with calcium >10.5 mg/dL, excluded influential observations defined by Cook's distance >4/n, and restricted the sample to the overlapping age range of the two groups (22–34 years). No formal a priori sample-size calculation was performed; the final sample size reflected eligible recruitment during the study period. Given the modest sample size and estimated post-hoc power of approximately 68% for the PTH × PCOS interaction term, the interaction analysis was considered exploratory and hypothesis-generating. A two-sided p value <0.05 was considered statistically significant. Analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

The final available dataset included 33 women with PCOS and 30 healthy controls. Baseline characteristics are shown in Table 1. Women with PCOS were younger than controls (27.06 ± 5.63 vs 30.43 ± 3.47 years, p=0.006). BMI was similar between groups (24.36 ± 3.98 vs 23.86 ± 3.19 kg/m², p=0.591), consistent with the BMI-matched design. Metabolic parameters and insulin resistance indices are presented in Table 2. Compared with controls, women with PCOS had higher fasting plasma glucose (92.18 ± 9.96 vs 84.13 ± 6.66 mg/dL, p<0.001), fasting insulin

Table 3: Calciotropic parameters

Variable	PCOS (n=33)	Controls (n=30)	p
25(OH)D3 (ng/mL)	29.39 ± 14.77 (3.24-82.00)	36.72 ± 6.90 (21.34-48.52)	0.016
PTH (pg/mL)	53.43 ± 20.07 (18.70-107.61)	44.42 ± 9.81 (25.60-63.50)	0.030
Calcium (mg/dL)	9.12 ± 0.82 (8.10-11.80)	8.87 ± 0.29 (8.20-9.80)	0.122
Phosphate (mg/dL)	3.69 ± 0.45 (2.10-4.60)	3.78 ± 0.29 (2.60-4.20)	0.343
ALP (U/L)	68.88 ± 26.74 (45.00-206.00)	53.31 ± 11.82 (36.00-92.00)	0.005

Data are presented as mean ± SD (minimum–maximum). PTH was available for 32 participants with PCOS and 30 controls; all other variables were available for 33 participants with PCOS and 30 controls. 25(OH)D3, 25-hydroxyvitamin D3; PTH, parathyroid hormone; ALP, alkaline phosphatase.

Table 4: Multiple linear regression for QUICKI including effect modification by PCOS status (n=62)

Predictor	β (95% CI)	p
PTH (per 10 pg/mL)	-0.0106 (-0.0185 to -0.0027)	0.009
PCOS vs control	-0.0597 (-0.1003 to -0.0192)	0.005
PTH × PCOS interaction	0.0109 (0.0023 to 0.0196)	0.014
25(OH)D3 (per 10 ng/mL)	0.0021 (-0.0025 to 0.0066)	0.371
Age (per year)	0.0003 (-0.0008 to 0.0014)	0.614
BMI (per kg/m²)	-0.0010 (-0.0028 to 0.0007)	0.226
Waist/hip ratio	-0.0456 (-0.1535 to 0.0623)	0.401

Coefficients are expressed per 10 pg/mL PTH and per 10 ng/mL 25(OH)D3. Model R^2=0.317; adjusted R^2=0.228. PTH, parathyroid hormone; PCOS, polycystic ovary syndrome; 25(OH)D3, 25-hydroxyvitamin D3; BMI, body mass index.

Table 5: Sensitivity analyses for the PTH × PCOS interaction

Analysis	Outcome	n	PTH × PCOS interaction β (95% CI)	p	R^2	Adjusted R^2
Primary model	QUICKI	62	0.0109 (0.0023 to 0.0196)	0.014	0.317	0.228
Excluding participants with calcium >10.5 mg/dL	QUICKI	61	0.0112 (0.0023 to 0.0200)	0.014	0.317	0.226
Excluding influential observations, Cook's distance >4/n	QUICKI	56	0.0094 (0.0015 to 0.0174)	0.021	0.379	0.289
Restricted to overlapping age range, 22–34 years	QUICKI	53	0.0103 (0.0011 to 0.0195)	0.029	0.343	0.240
Alternative metabolic outcome	log-HOMA-IR	62	−0.2096 (−0.3787 to −0.0406)	0.016	0.314	0.225

All models included PTH, PCOS status, the PTH × PCOS interaction term, 25(OH)D3, age, BMI, and waist-to-hip ratio, except for the age-restricted analysis, which used the same covariate structure within the overlapping age range. PTH and 25(OH)D3 were scaled per 10 pg/mL and 10 ng/mL, respectively. The interaction coefficient represents the difference in the PTH slope between women with PCOS and controls. In the log-HOMA-IR model, the direction of the coefficient is expected to be opposite to that in the QUICKI model because higher HOMA-IR indicates greater insulin resistance, whereas higher QUICKI indicates greater insulin sensitivity. PTH, parathyroid hormone; PCOS, polycystic ovary syndrome; QUICKI, quantitative insulin sensitivity check index; HOMA-IR, homeostatic model assessment of insulin resistance; BMI, body mass index; 25(OH)D3, 25-hydroxyvitamin D3.

(11.72 ± 4.21 vs 9.25 ± 4.13 μU/mL, p=0.022), and HOMA-IR (2.40 ± 0.91 vs 1.75 ± 0.84, p=0.004). QUICKI was lower in the PCOS group than in controls (0.33 ± 0.02 vs 0.35 ± 0.02, p=0.002). The reproductive hormone and androgen profile is summarised in Supplementary Table S1. LH was higher in women with PCOS than in controls (6.75 ± 3.40 vs 3.03 ± 1.22 mIU/mL, p<0.001), whereas FSH and estradiol did not differ significantly. Calciotropic

parameters are presented in Table 3. Women with PCOS had lower 25(OH)D3 concentrations than controls (29.39 ± 14.77 vs 36.72 ± 6.90 ng/mL, p=0.016) and higher PTH concentrations (53.43 ± 20.07 vs 44.42 ± 9.81 pg/mL, p=0.030). Total calcium and phosphate concentrations did not differ significantly between groups. ALP was higher in the PCOS group than in controls (68.88 ± 26.74 vs 53.31 ± 11.82 U/L, p=0.005). The multiple regression model for QUICKI is shown in Table 4. In controls, higher PTH was associated with lower QUICKI after adjustment for age, BMI, waist-to-hip ratio, and 25(OH)D3 (β per 10 pg/mL PTH=-0.0106; 95% CI -0.0185 to -0.0027; p=0.009). PCOS status significantly modified this association (PTH × PCOS interaction β=0.0109; 95% CI 0.0023 to 0.0196; p=0.014). Based on the interaction term, the estimated PTH–QUICKI slope among women with PCOS was close to null (β=0.0003; 95% CI -0.0034 to 0.0041; p=0.857). 25(OH)D3 was not associated with QUICKI in the adjusted model (β per 10 ng/mL=0.0021; 95% CI -0.0025 to 0.0066; p=0.371). The model explained 31.7% of the variance in QUICKI (adjusted R^2=0.228). The scatter plot of serum PTH versus QUICKI with within-group regression lines is shown in Fig. 1.

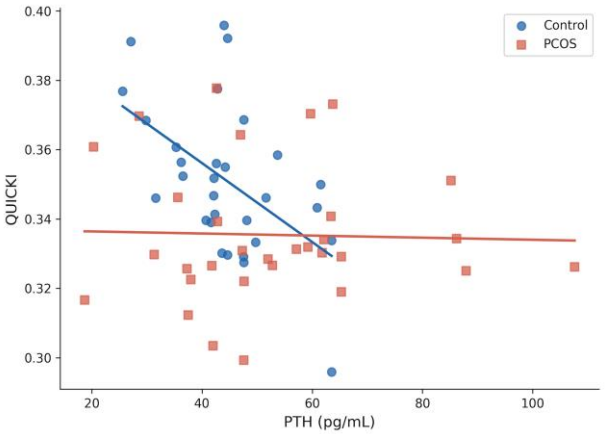


Fig. 1. Scatter plot of serum PTH versus QUICKI stratified by study group among participants with available PTH and QUICKI data (n=62).

Lines represent within-group ordinary least-squares regression fits. In controls, higher PTH was associated with lower QUICKI, whereas this association was attenuated in women with PCOS. PTH, parathyroid hormone; QUICKI, quantitative insulin sensitivity check index; PCOS, polycystic ovary syndrome.

Adjusted predicted QUICKI values across PTH concentrations from the interaction model are shown in Fig. 2. Sensitivity analyses are presented in Table 5. The PTH × PCOS interaction remained significant after excluding participants with calcium >10.5 mg/dL (interaction β=0.0112; 95% CI 0.0023 to 0.0200; p=0.014) and after excluding observations with Cook's distance >4/n (interaction β=0.0094; 95% CI 0.0015 to 0.0174; p=0.021). When log-HOMA-IR was used as an alternative metabolic outcome, the interaction was directionally consistent and statistically significant (interaction β=-0.2096; 95% CI -0.3787 to -0.0406; p=0.016). The interaction also remained significant when the analysis was restricted to the overlapping age range of the two groups, 22–34 years (interaction β=0.0103; 95% CI 0.0011 to 0.0195; p=0.029).

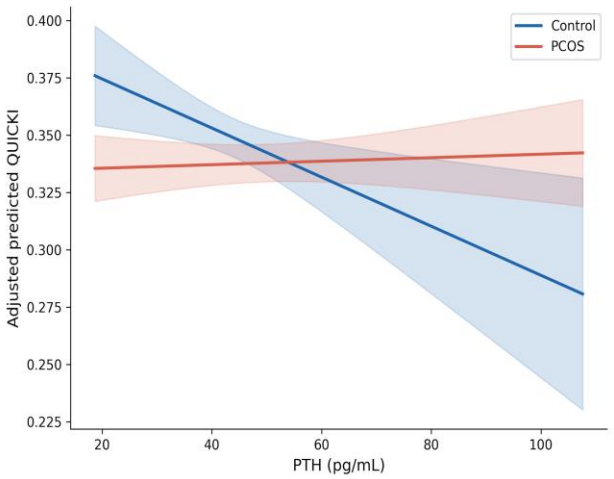


Fig. 2. Adjusted predicted QUICKI across PTH concentrations by study group derived from the interaction model (n=62).

Predictions are computed at mean covariate values for age, BMI, waist-to-hip ratio, and 25(OH)D3. Shaded areas represent 95% confidence bands. PTH, parathyroid hormone; QUICKI, quantitative insulin sensitivity check index; PCOS, polycystic ovary syndrome; 25(OH)D3, 25-hydroxyvitamin D3.

Discussion

In this BMI-matched case–control study of reproductive-age women, PCOS status modified the association between circulating PTH and fasting-derived insulin sensitivity. Among controls, higher PTH was associated with lower QUICKI after adjustment for age, BMI, waist-to-hip ratio, and 25(OH)D3. This association was not observed among women with PCOS. Sensitivity analyses supported the robustness of the interaction, including models excluding participants with high calcium values, excluding influential observations, restricting the sample to the overlapping age range, and using log-HOMA-IR as an alternative metabolic outcome. These findings suggest that the metabolic interpretation of PTH may differ according to PCOS status and that PCOS may alter the coupling between calciotropic physiology and fasting-derived insulin sensitivity. The control-group finding is consistent

with previous evidence linking higher PTH concentrations with dysglycaemia, insulin resistance, and lower insulin sensitivity in non-PCOS populations (11, 12). Metabolic abnormalities have also been reported in primary hyperparathyroidism, and some observational studies suggest cardiometabolic improvement after parathyroidectomy in selected cohorts (20-22). PTH may influence glucose metabolism through several mechanisms, including effects on intracellular calcium flux, pancreatic β-cell function, skeletal muscle, and insulin-responsive tissues (9, 10, 23). Although 25(OH)D3 has received substantial attention in PCOS, PTH may provide complementary information because it reflects the downstream endocrine response of the calcium–vitamin D axis rather than vitamin D status alone. Earlier studies have reported higher PTH concentrations in women with PCOS, but the role of PTH as a metabolic correlate in PCOS remains incompletely understood (13, 14). The present study extends this literature by evaluating PTH as the main exposure and by formally testing PCOS status as an effect modifier while accounting for 25(OH)D3. The finding that 25(OH)D3 was not independently associated with QUICKI in the adjusted model suggests that PTH may capture aspects of calcium–vitamin D axis dysregulation not fully reflected by 25(OH)D3 alone. The recent global consensus proposing the renaming of PCOS as polyendocrine metabolic ovarian syndrome (PMOS) reflects a broader reconceptualisation of the condition as a multisystem endocrine and metabolic disorder rather than a primarily reproductive one (1). This reframing is directly relevant to the present findings. If PCOS is understood as a state of endocrine-metabolic dysregulation extending beyond the hypothalamic–pituitary–ovarian axis, it is biologically plausible that relationships between calciotropic hormones and insulin sensitivity—such as the inverse PTH–QUICKI association observed in our control group—may differ in women with PCOS. The absence of a comparable PTH–QUICKI association in the PCOS group may therefore be consistent with altered hormonal crosstalk within the broader endocrine-metabolic phenotype that the PMOS terminology seeks to capture. Several mechanisms may explain why the inverse PTH–QUICKI association observed in controls was attenuated or absent in women with PCOS. PCOS is characterised by hyperandrogenism, altered insulin signalling, central adiposity, and low-grade inflammatory pathways, any of which may attenuate or obscure calcium-dependent contributions to insulin sensitivity (23, 24). In addition, adipose tissue distribution and vitamin D sequestration may differ between women with and without PCOS even when BMI is similar (24). These mechanisms remain speculative and should be examined in larger mechanistic studies. The findings should not be interpreted as supporting immediate clinical use of PTH for metabolic risk stratification in PCOS. Rather, they suggest that the relationship between calciotropic hormones and fasting-derived insulin sensitivity may be context-dependent. A uniform interpretation of PTH as a metabolic risk marker across women with and without PCOS may therefore be misleading. Future research should determine whether combined assessment of PTH and 25(OH)D3 has value for metabolic phenotyping in PCOS. This study has several strengths. The BMI-matched case–control design reduced confounding by overall adiposity, a major determinant of both insulin sensitivity and calciotropic biomarkers. PTH and 25(OH)D3 were measured concurrently, allowing evaluation of PTH after accounting for vitamin D status. The study also assessed both HOMA-IR and QUICKI, formally tested effect modification using an interaction term, and included sensitivity analyses addressing influential observations, high calcium values, and an alternative metabolic outcome. Nevertheless, the study addresses a biologically relevant endocrine-metabolic question and generates a testable hypothesis for future cohorts. The BMI-matched design and concurrent measurement of PTH and 25(OH)D3 help reduce two common sources of confounding in studies of calciotropic markers and insulin sensitivity. Future studies should validate these findings in larger, prospectively recruited cohorts using dynamic measures of insulin sensitivity and more detailed assessment of calcium–vitamin D physiology, body composition, diet, sun exposure, and PCOS phenotypes. Interventional studies may also help determine whether modification of elevated PTH or vitamin D deficiency affects insulin sensitivity differently in women with and without PCOS.

Study limitations: The single-centre design limits direct generalisability to populations with different genetic backgrounds, latitude-related sun exposure patterns, dietary calcium and vitamin D intakes, and healthcare settings. Several limitations should be considered. First, the sample size was modest, and the interaction analysis should be interpreted as exploratory and hypothesis-generating. Post-hoc power for the PTH × PCOS interaction was approximately 68%, below the conventional 80% threshold, further supporting cautious interpretation. Second, the dataset was collected in 2012 and analysed approximately

fourteen years later; therefore, the findings should be interpreted in light of temporal changes in assay platforms and calibration, laboratory reference ranges, and PCOS diagnostic frameworks. Third, the cross-sectional design precludes causal inference. Fourth, insulin sensitivity was assessed using fasting-derived surrogate indices rather than dynamic measures such as the euglycaemic clamp or oral glucose tolerance test-derived indices. Fifth, the use of Androgen Excess and PCOS Society criteria may limit generalisability to broader PCOS phenotypes, particularly non-hyperandrogenic phenotypes (16). Sixth, ALP was elevated in the PCOS group; as isoenzyme fractionation was unavailable, hepatic and bone contributions could not be distinguished. Finally, seasonal variation may have influenced 25(OH)D3 and PTH concentrations because samples were collected between February and July, and individual-level data were not available for adjustment.

Conclusions

PCOS status modified the association between PTH and fasting-derived insulin sensitivity in this BMI-matched case–control study. The inverse association between PTH and QUICKI observed in controls was attenuated in women with PCOS, suggesting that PCOS may alter calciotropic-metabolic coupling. Given the modest sample size and cross-sectional design, these findings should be considered exploratory and require confirmation in larger prospective studies using dynamic measures of insulin sensitivity.

Authors contributions: Author 1 contributed to conceptualization, methodology, investigation, data curation, formal analysis, and writing of the original draft. Author 2 contributed to methodology, supervision, interpretation of findings, and critical revision of the manuscript. Both authors read and approved the final manuscript.

Data availability statement: The datasets are available from the corresponding author on reasonable request, subject to institutional and ethical approvals.

Conflict of interest: The authors declare that they have no conflict of interest.

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Acknowledgements: The dataset used in this study was originally collected as part of a medical residency thesis completed in 2013 and was analysed in the present article using a distinct endocrine-metabolic research question and statistical framework. Full identifying details are provided in the title page.

Use of AI tools: ChatGPT based on GPT-4 architecture (OpenAI, San Francisco, CA, USA) was used to assist with language editing only. All content was reviewed and verified by the authors, who take full responsibility.

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