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SERUM SOLUBLE ENDOGLIN IN ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM: A CASE-CONTROL STUDY

RASTVORLJIVI ENDOGLIN U SERUMU KOD ASIMPTOMATSKOG PRIMARNOG HIPERPARATIREOIDIZMA: STUDIJA SLUČAJA I KONTROLNIH PACIJENATA

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Summary

Background: Primary hyperparathyroidism (PHPT) is associated with metabolic disorders, endothelial dysfunction, and increased cardiovascular risk. Soluble endoglin (sENG), an endothelium-derived biomarker, is a potential indicator of TGF-β-related vascular stress. This study aimed to compare serum sENG levels between patients with asymptomatic PHPT and healthy controls and to evaluate the association between sENG and metabolic parameters.
Methods: This cross-sectional study included 42 patients with biochemically confirmed asymptomatic PHPT and 39 age- and sex-matched healthy controls. Serum sENG levels and metabolic parameters were compared between groups. Welch t-test, chi-square test, correlation, and regression analyses were used to evaluate potential associations.
Results: Serum sENG levels were similar between the PHPT and control groups (1.40±1.13 vs 1.46±1.31 ng/mL, p=0.83). In the PHPT group, weak but not statistically significant positive associations were observed between sENG and body mass index, fasting glucose, insulin, and HOMA-IR. These associations were less pronounced in the control group. In linear regression analysis, body weight was identified as an independent determinant of sENG in the PHPT group (p=0.047). In the two-way ANOVA, no significant main or interaction effects were detected, and

Kratak sadržaj

Uvod: Primarni hiperparatireoidizam (PHPT) je povezan je metaboličkim poremećajima, endotelijalnom disfunkcijom i povećanim kardiovaskularnim rizikom. Rastvorljivi endoglin (sENG), biomarker porekla iz endotela, predstavlja potencijalni pokazatelj vaskularnog stresa povezanog sa TGF-β. Cilj ovog istraživanja je bio da uporedi serumske nivoe sENG kod pacijenata sa asimptomatskim PHPT i zdravih kontrolnih ispitanika, kao i da ispita povezanost između sENG i metaboličkih parametara.
Metode: U ovu studiju preseka uključena su 42 pacijenta sa biohemijski potvrđenim asimptomatskim PHPT i 39 zdravih kontrolanih pacijenata uparenih po starosti i polu. Upoređeni su serumski nivoi sENG i metabolički parametri između grupa. Za procenu potencijalnih povezanosti korišćeni su Welchov t-test, hi-kvadrat test, korelacione i regresione analize.
Rezultati: Serumski nivoi sENG su bili slični između PHPT i kontrolne grupe (1,40±1,13 naspram 1,46±1,31 ng/mL, p=0,83). U PHPT grupi uočene su slabe, ali statistički neznačajne pozitivne povezanosti između sENG i indeksa telesne mase, glikemije natašte, insulina i HOMA-IR. Ove povezanosti su bile manje izražene u kontrolnoj grupi. U linearnoj regresionoj analizi telesna masa je identifikovana kao nezavisan determinanta sENG u PHPT grupi (p=0,047). U dvosmernoj ANOVA analizi nisu utvrđeni značajni glavni niti interakcioni efekti, a granične

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List of abbreviations: PHPT, primary hyperparathyroidism; sENG, soluble endoglin; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; PTH, parathyroid hormone; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; ANOVA, analysis of variance; CI, confidence interval; TGF-β, transforming growth factor-beta; HbA1c, haemoglobin A1c; CD105, cluster of differentiation 105.

the borderline interactions observed for glucose and body mass index did not reach statistical significance.
Conclusion: Serum sENG levels did not differ significantly between patients with asymptomatic PHPT and controls. No statistically significant associations were observed between sENG and metabolic parameters. Although regression plots visually suggested directional patterns, these observations did not reach statistical significance. These findings should be interpreted with caution, and further studies with larger sample sizes are needed to clarify these associations.

Keywords: primary hyperparathyroidism, soluble endoglin, endothelial dysfunction, metabolic parameters, insulin resistance

interakcije uočene za glikemiju i indeks telesne mase nisu dostigle statistički značaj.
Zaključak: Serumski nivoi sENG se nisu značajno razlikovali između pacijenata sa asimptomatskim PHPT i kontrolnih pacijenata. Nisu utvrđene statistički značajne povezanosti između sENG i metaboličkih parametara. Iako su regresioni dijagrami vizuelno ukazivali na određene trendove, ti nalazi nisu dostigli statistički značaj. Ove rezultate treba tumačiti sa oprezom, a neophodna su i dalja istraživanja sa većim uzorcima radi razjašnjenja povezanosti.

Ključne reči: primarni hiperparatireoidizam, rastvorljivi endoglin, endotelijalna disfunkcija, metabolički parametri, insulinska rezistencija

Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of chronic hypercalcemia. It represents an important health problem, particularly in postmenopausal women (1). Recent studies suggest a potential association between PHPT and endothelial dysfunction, metabolic stress, and increased cardiovascular risk (2, 3). Although parathyroidectomy is clearly recommended as definitive treatment in symptomatic patients, the degree and clinical significance of subclinical endothelial involvement in asymptomatic PHPT have not yet been fully clarified (4). Therefore, it is important to investigate early vascular changes in asymptomatic PHPT using more sensitive biomarkers.

Endothelial dysfunction is one of the fundamental pathophysiological processes that occur in the early, potentially reversible stages of cardiovascular disease. In this process, endothelium-derived biomarkers play an important role in the early recognition of vascular stress (5). Endoglin (CD105) is a transmembrane glycoprotein that functions as a co-receptor for ligands of the transforming growth factor-β (TGF-β) superfamily and is highly expressed, particularly in endothelial cells. The circulating soluble form of endoglin, soluble endoglin (sENG), has emerged as a potential biomarker associated with endothelial stress, inflammation, and metabolic disorders (6, 7). Increased sENG levels have been reported in clinical conditions characterised by increased vascular and metabolic burden, such as myocardial infarction, diabetes mellitus, metabolic syndrome, and preeclampsia (8).

In PHPT, chronic excess of parathyroid hormone (PTH) is thought to modulate TGF-β signalling through mechanisms such as PTH1R–TβRII interaction and receptor internalisation, which may, in turn, indirectly affect vascular responses mediated by endoglin (CD105/sENG). However, data regarding sENG levels in patients with PHPT and the association of this biomarker with metabolic parameters are limited (9). Therefore, it remains unclear whether sENG represents a reliable indicator of subclinical endothelial dysfunction that may occur in the early stages of PHPT.

This study aimed to compare serum sENG levels between patients with asymptomatic PHPT and healthy controls and to evaluate the association between sENG levels and metabolic and biochemical parameters. In this way, the study sought to assess the association between metabolic burden and endothelial response during the asymptomatic stage of PHPT using sENG levels.

Materials and Methods

Study design and population

This cross-sectional study was conducted between March 2025 and August 2025. A total of 42 patients with biochemically confirmed PHPT and 39 healthy controls were included in the study. None of the patients with PHPT had undergone surgical intervention, and their clinical evaluations were performed at the Endocrinology and Metabolism Diseases Outpatient Clinic of Konya City Hospital.

The inclusion criteria were: aged 18–75 years; biochemically confirmed diagnosis of asymptomatic PHPT according to current guidelines (4); and no history of parathyroidectomy. Consecutively presenting patients who met these criteria were included. Symptomatic patients with nephrolithiasis or nephrocalcinosis, patients with fragility fracture or osteitis fibrosa cystica, those with clinical symptoms related to significant hypercalcemia, and those with evident target-organ involvement attributable to PHPT were excluded. Furthermore, to minimise potential confounding effects, individuals with coronary artery disease, essential hypertension, diabetes mellitus, hyperlipidaemia, obesity, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2), acute infection or inflammation, active malignancy, and those in the

pregnancy or lactation period were not included in the study. Patients diagnosed with secondary and tertiary hyperparathyroidism were also excluded.

The control group consisted of carefully selected healthy volunteers matched to the patient group for age and sex, with no known chronic, metabolic, or endocrine disease. All individuals in the control group had normal serum calcium levels, no clinical or biochemical suspicion of parathyroid disease, and were not taking any regular medication.

Demographic data for all participants, including age, sex, and body weight, were recorded. Height and weight measurements were performed using standard methods, and body mass index (BMI) was calculated as kilograms per square meter (kg/m^2). Venous blood samples were obtained from all participants after at least 8 hours of fasting.

Biochemical measurements

Data on biochemical parameters were obtained from analysis results obtained within the scope of routine clinical evaluation at the Central Laboratory of Konya City Hospital and recorded through the hospital automation system. Serum calcium and phosphorus levels were measured by the photometric method; alkaline phosphatase, total cholesterol, triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels by the colourimetric method; and fasting plasma glucose by the enzymatic method using the Cobas 8000 C automated biochemistry analyser (Roche Diagnostics, Mannheim, Germany).

Serum insulin levels were determined using the electrochemiluminescence immunoassay method with the Cobas e801 analyser (Roche Diagnostics, Mannheim, Germany). Insulin resistance was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index. The following formula was applied: HOMA-IR = [fasting insulin (μIU/mL) × fasting plasma glucose (mg/dL)] / 405.

Measurement of serum sENG

Serum sENG levels were determined by enzyme-linked immunosorbent assay (ELISA). After centrifugation, blood samples were stored in Eppendorf tubes at -80 °C until the day of analysis. sENG concentrations were measured using a commercial sandwich ELISA kit (E-EL-H6172, Elabscience Bionovation Inc., Wuhan, China) according to the manufacturer's instructions. The micro ELISA plate of the kit was pre-coated with antibodies specific to human endoglin, and the measurement was based on the sandwich ELISA principle. The kit's measurement range is 0.16–10 ng/mL, the analytical sensitivity is 0.09 ng/mL, and the intra- and inter-assay coefficients of variation are <10%. Optical density measurements were performed spectrophotometrically at 450 nm ± 2 nm, and sENG concentrations in the samples were calculated from the standard curve.

Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the KTO Karatay University Faculty of Medicine (approval date: January 30, 2025; approval number: 2025/044). In addition, institutional approval was granted by the Education Planning Board of Konya City Hospital (approval date: October 5, 2023; decision number: 10–44). Written informed consent was obtained from all participants before inclusion in the study.

Statistical methods

All statistical analyses were performed using R software (version 4.3.2). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as numbers and percentages. For comparisons between groups, the Welch t-test was used for continuous variables and the chi-square test for categorical variables. The associations between sENG and metabolic parameters were evaluated separately in the case and control groups using Pearson correlation analysis. Linear regression analysis was performed to examine the independent determinants of sENG. Two-way analysis of variance (ANOVA) was applied to evaluate interactions between group and metabolic parameters. Parametric test assumptions, including normality and homogeneity of variances, were assessed before analysis where appropriate. Statistical significance was accepted as $p<0.05$.

Results

Clinical and biochemical characteristics of the participants

A total of 81 participants were included in the study (42 patients with PHPT, 39 healthy controls). The PHPT and control groups were similar in terms of age, sex distribution, and BMI ($p>0.05$ for all comparisons).

Serum calcium and alkaline phosphatase levels were significantly higher in the PHPT group, whereas serum phosphorus levels were significantly lower ($p<0.001$ for all). Although insulin and HOMA-IR values were higher in the PHPT group

Table I Clinical and biochemical characteristics of PHPT and controls.

Variable	PHPT group n=42[1]	Control group n=39[1]	p-value[2]
Baseline demographic and anthropometric characteristics			
Age (years)	50.76±11.93	48.64±11.03	0.41
Sex (male/female)	6/36 (14.3/85.7%)	8/31 (20.5/79.5%)	0.46
Height (cm)	158.12±6.75	161.05±8.83	0.10
Weight (kg)	76.81±15.99	78.47±13.86	0.62
BMI (kg/m^2)	30.75±6.35	30.40±5.42	0.79
Metabolic indicators			
Glucose (mg/dL)	90.88±9.18	90.51±8.78	0.85
HOMA-IR	2.64±2.21	1.94±1.05	0.093
Insulin (μIU/mL)	11.47±8.56	8.57±4.67	0.082
HbA1c (%)	5.53±0.37	5.62±0.32	0.25
Urea (mg/dL)	12.56±3.89	12.00±3.04	0.47
Creatinine (mg/dL)	0.67±0.13	0.71±0.14	0.19
eGFR (mL/min/1.73 m^2)	101.68±16.24	100.79±12.78	0.79
Total cholesterol (mg/dL)	196.45±29.42	195.34±38.90	0.90
LDL cholesterol (mg/dL)	125.50±25.90	137.22±39.85	0.13
HDL cholesterol (mg/dL)	53.49±12.89	52.03±12.04	0.63
Triglyceride (mg/dL)	143.36±66.10	135.37±76.13	0.65
Bone-mineral metabolism			
Albumin (g/L)	45.76±2.77	45.05±2.05	0.19
Calcium (mg/dL)	10.95±0.63	9.25±0.41	<0.001
PTH (pg/mL)	131.73±55.01	—	—
Phosphorus (mg/dL)	2.80±0.43	3.25±0.36	0.001
25-hydroxyvitamin D (ng/mL)	15.21±7.25	17.28±11.08	0.36
24-hour urinary calcium Kalsiyum (mg/gün)	363.05±179.88	—	—
Alkaline phosphatase (U/L)	108.17±45.56	69.00±24.81	<0.001

[1]Continuous variables are presented as mean ± standard deviation and categorical variables as n (%). [2]Welch two-sample t-test and Pearson chi-square test were used for comparisons. Em dash (—) indicates parameters not measured in the control group or for which comparison could not be performed. $p<0.05$ was considered statistically significant.

Abbreviations: PHPT, primary hyperparathyroidism; sENG, soluble endoglin; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; PTH, parathyroid hormone.

compared with the control group, these differences were not statistically significant (p=0.082 and p=0.093, respectively). Lipid parameters did not differ significantly between the two groups. The demographic, anthropometric, glucose, lipid, and bone mineral metabolism parameters of the PHPT and control groups are presented in *Table I*.

Serum sENG levels

Serum sENG levels were similar between the PHPT and control groups (1.40±1.13 ng/mL vs 1.46±1.31 ng/mL; p=0.83). The distribution of sENG values in the PHPT and control groups is shown in the box plot graph presented in *Figure 1*.

Following the study process, one participant (46 years old, female) was diagnosed with breast cancer. This participant, who had the highest sENG level in the series (8.52 ng/mL), was excluded from the analyses due to a concomitant malignancy, per the exclusion criteria.

A sensitivity analysis was performed by excluding outlier observations from both groups, except for the case diagnosed with malignancy. The results obtained in this analysis were not statistically significant (p=0.91). Outlier observations were included in the main analyses.

Serum calcium and sENG levels

In the PHPT group, no statistically significant association was observed between serum calcium and sENG levels. Pearson correlation analysis showed a negligible association (r=0.01, p>0.05). Similarly, univariate linear regression analysis did not demonstrate a significant association (β=-0.23, 95% confidence interval ŠCIĆ: -0.80 to 0.34, p=0.43). In addition, subgroup analysis based on calcium levels (<11 vs ≥11 mg/dL) did not reveal a significant difference in sENG levels (p=0.68).

In the control group, the association between serum calcium and sENG levels was also weak and not statistically significant. Correlation analysis showed a low, non-significant positive association (r=0.18, p>0.05), and regression analysis confirmed the absence of a significant association (β=0.55, 95% CI: -0.50 to 1.60, p=0.29).

Overall, no statistically significant association was detected between serum calcium and sENG levels in either group.

Correlations between sENG and metabolic parameters

In the PHPT group, weak-to-moderate positive correlation coefficients were observed

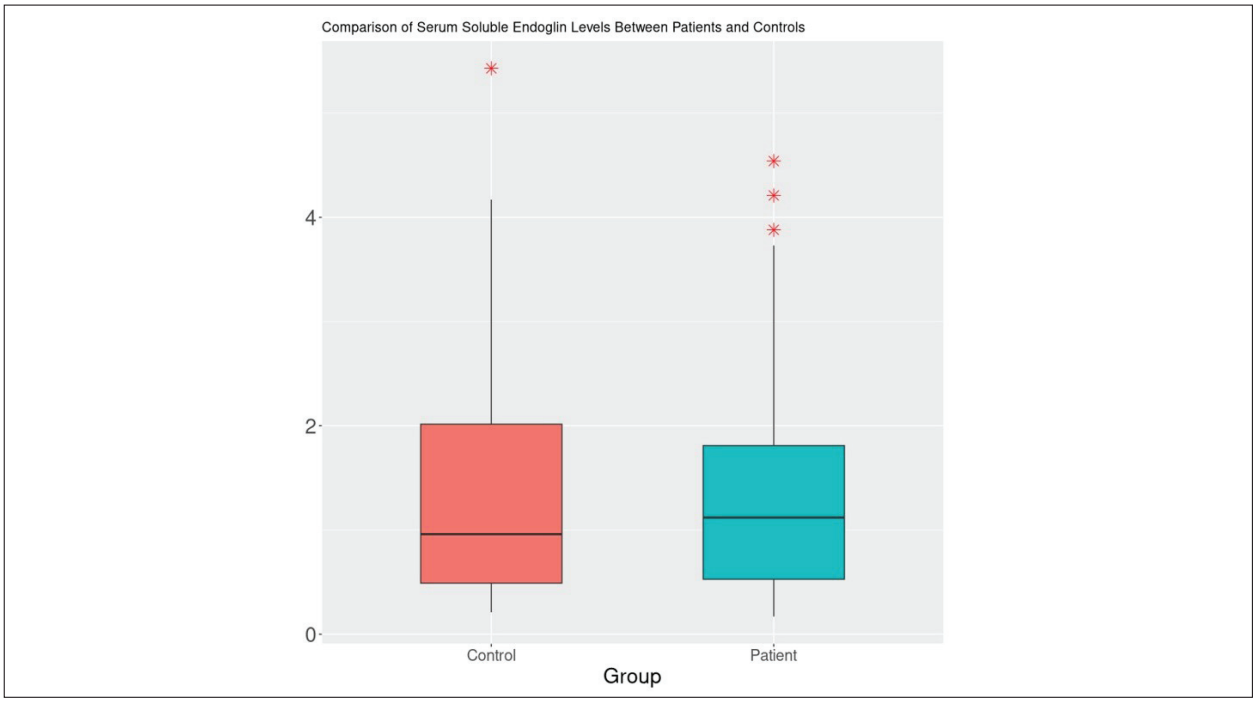

Figure 1 Boxplot representation of serum soluble endoglin (sENG) levels in the primary hyperparathyroidism (PHPT) and control groups.

The boxplot shows the comparison of serum sENG levels between patients with PHPT (n=42) and healthy controls (n=39). The boxes represent the median and interquartile range, the whiskers indicate the minimum and maximum values, and the red stars indicate outliers. No statistically significant difference was observed between the groups (Welch t-test, p=0.83).

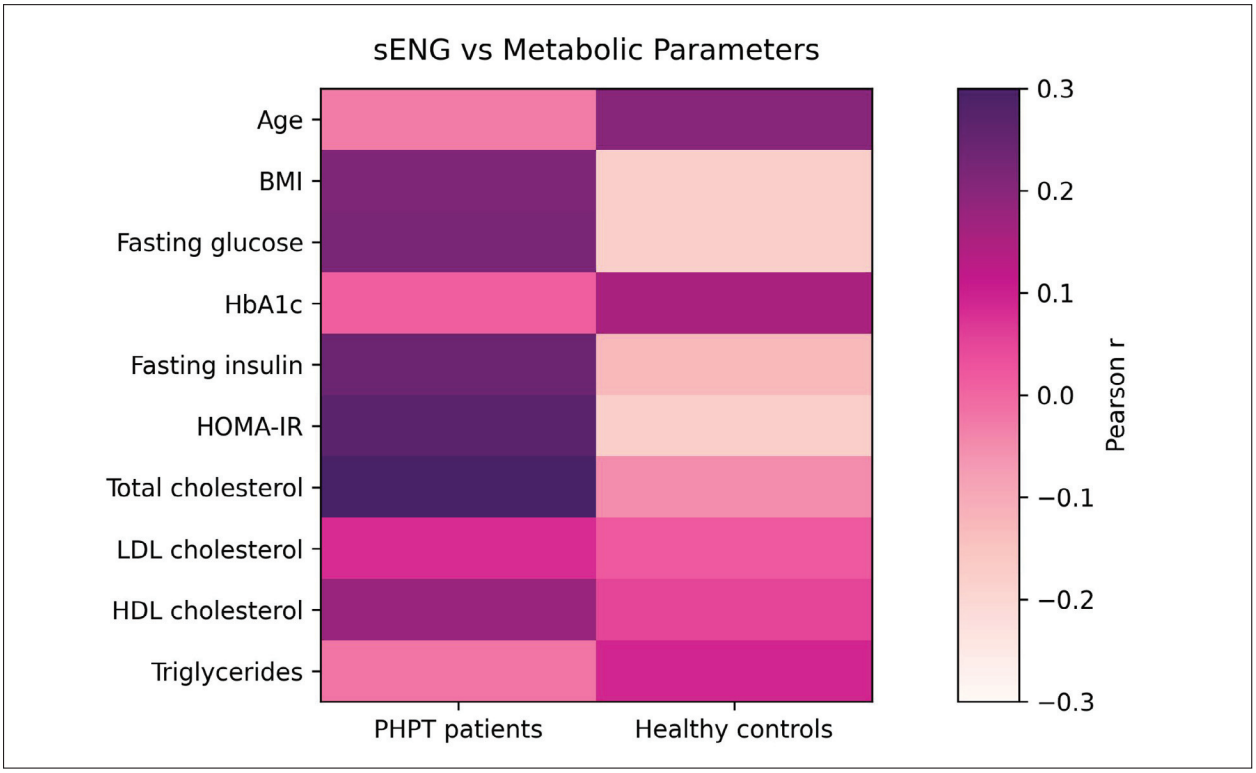

Figure 2 Pearson correlation heat map between soluble endoglin (sENG) levels and metabolic parameters in patients with primary hyperparathyroidism (PHPT) and healthy controls.

This heat map shows the Pearson correlation coefficients (r) between serum sENG levels and metabolic parameters in patients with PHPT and healthy controls. Colour intensity reflects the direction and relative strength of the correlations, with darker tones indicating stronger positive correlations and lighter tones indicating negative correlations.

No statistically significant correlations were detected in either group ($p > 0.05$ for all). In the PHPT group, correlation coefficients between sENG and body mass index, fasting glucose, HOMA-IR, and fasting insulin were numerically higher compared with the control group; however, none of these associations reached statistical significance.

between sENG levels and BMI ($r=0.21$), fasting glucose ($r=0.22$), insulin ($r=0.24$), and HOMA-IR ($r=0.27$). However, none of these correlations reached statistical significance ($p>0.05$ for all).

In the control group, correlations between sENG and metabolic parameters were weak and lacked a clear directional pattern. The visual distribution of correlations between sENG levels and metabolic parameters in the PHPT and control groups is shown in the Pearson correlation heat map presented in *Figure 2*.

Regression analyses

Clinical and biochemical variables affecting serum sENG levels in patients with PHPT and healthy controls were evaluated using univariate linear regression analyses. In analyses performed in the PHPT group, body weight was the only variable to show a positive, statistically significant association with sENG levels ($\beta=0.02$; 95% confidence interval [CI]: 0.00–0.04; $p=0.047$). None of the other demographic and metabolic parameters or PHPT-specific biochemical indicators (particularly PTH and serum calcium levels) showed a statistically significant association with sENG levels ($p>0.05$ for all).

In the regression analyses performed in the healthy control group, none of the evaluated variables, including age, sex, anthropometric measurements, glycaemic parameters, lipid profile, and indicators of kidney function, showed a significant association with serum sENG levels ($p>0.05$ for all).

Group × parameter interaction analyses (two-way ANOVA)

A two-way ANOVA was used to evaluate the effects of group (PHPT vs control), metabolic parameters, and their interactions on serum sENG levels. No statistically significant main effects of

Table II Two-way ANOVA of group and metabolic effects on sENG.

Variable	Group effect (p-value)	Parameter effect (p-value)	Interaction effect (p-value)
Glucose	0.079	0.201	0.081
HbA1c	0.489	0.965	0.487
Insulin	0.182	0.177	0.213
HOMA-IR	0.117	0.141	0.129
Body mass index	0.083	0.212	0.085
Total cholesterol	0.122	0.063	0.114
HDL cholesterol	0.645	0.266	0.622
LDL cholesterol	0.691	0.638	0.750
Triglyceride	0.658	0.881	0.670

The effects of group (primary hyperparathyroidism vs control), metabolic parameters, and their interaction (group × parameter) on sENG levels were evaluated using two-way ANOVA.
No statistically significant main or interaction effects were observed ($p>0.05$ for all).

Abbreviations: ANOVA, analysis of variance; sENG, soluble endoglin; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

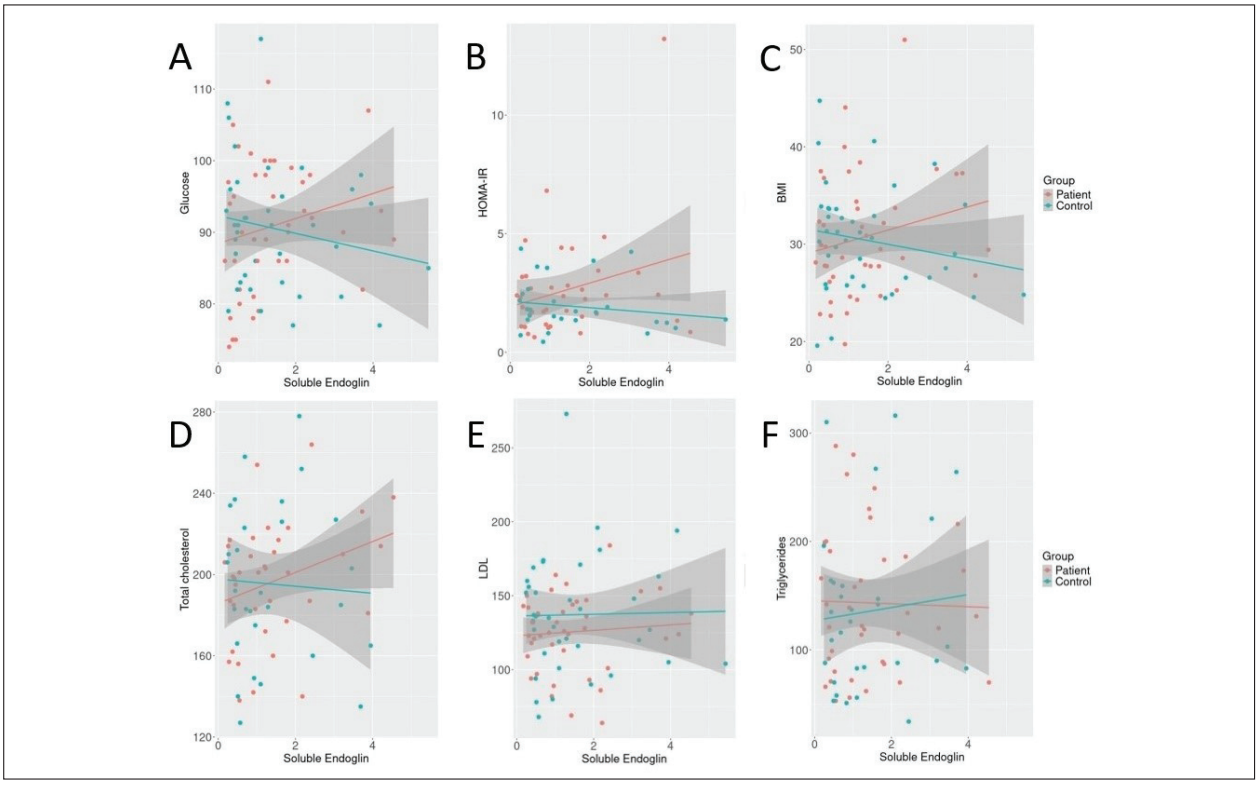

Figure 3 Interaction regression plots between soluble endoglin (sENG) and metabolic parameters.

(A) Fasting glucose, (B) HOMA-IR, (C) body mass index (BMI), (D) total cholesterol, (E) low-density lipoprotein (LDL) cholesterol, and (F) triglycerides.

In patients with primary hyperparathyroidism (PHPT), regression slopes between sENG and selected metabolic parameters (fasting glucose, HOMA-IR, BMI, and total cholesterol) showed differences in the direction of associations compared with healthy controls. These patterns were less consistent in the control group. No clear pattern was observed between sENG and LDL cholesterol or triglyceride levels. None of these associations reached statistical significance. The red lines represent the PHPT group, and the green lines represent the control group. Grey-shaded areas indicate the 95% confidence intervals.

group or metabolic parameters, or significant group × parameter interactions, were observed for the examined variables ($p > 0.05$ for all). Detailed results of the two-way ANOVA analyses are presented in *Table II*.

Among the analysed parameters, the p-values for the group × parameter interaction for glucose and BMI were 0.081 and 0.085, respectively, and did not reach statistical significance. The regression-based interaction plots (*Figure 3*) demonstrated differences in the direction of the associations between the PHPT and control groups, particularly for glucose, BMI, and total cholesterol.

Discussion

PHPT is associated not only with classical skeletal and renal effects but also with alterations in lipid and glucose metabolism, endothelial dysfunction, and increased cardiovascular risk. sENG, an endothelium-derived biomarker, has emerged as a potential indicator of TGF-β- related vascular stress and endothelial activation. However, circulating sENG levels and their relationship with metabolic parameters in PHPT have not yet been sufficiently clarified. Therefore, in the present study, serum sENG levels and their metabolic and endothelial associations were evaluated in 42 patients with a biochemically confirmed diagnosis of asymptomatic PHPT. The findings were compared with those of 39 normocalcaemic healthy controls, selected to minimise potential confounding factors and without a history of chronic disease or medication use.

In this study, when patients with asymptomatic PHPT were compared with normocalcaemic healthy controls with similar characteristics in terms of age, sex, BMI, and metabolic parameters, serum sENG levels were similar between the two groups. The observed differences in calcium, phosphorus, and alkaline phosphatase levels between the groups are consistent with the expected biochemical profile of PHPT and support the appropriateness of group selection. However, the similarity in sENG levels indicates that no measurable difference in this biomarker was detected in asymptomatic and mild PHPT cases.

Differences were also observed between the groups in terms of the direction of the associations between sENG and metabolic parameters. In the PHPT group, correlation coefficients between sENG and BMI, fasting glucose, insulin, and HOMA-IR were positive, whereas this pattern was not observed in the control group. However, none of these associations reached statistical significance, and no significant main effects or interactions were detected in the two-way ANOVA. These findings indicate that the association between metabolic parameters and sENG is not pronounced or measurable in asymptomatic PHPT cases. Given the lack of statistical support for the observed directional differences between groups, these findings should be interpreted with caution. Therefore, these associations should be confirmed in studies with larger sample sizes and including different clinical phenotypes.

Endothelial activation in PHPT has been investigated using various circulating markers, including interleukin-6, C-reactive protein, vascular cell adhesion molecule-1, von Willebrand factor, and soluble E-selectin. However, findings across studies have been heterogeneous, biochemical correlations have not been consistent, and a reliable and specific endothelial biomarker has not yet been established (10–12). The demonstration of increased CD105 expression in parathyroid proliferative lesions suggests that angiogenic and TGF-β–related pathways may be active in PHPT; however, it remains unclear whether these findings are reflected in circulating sENG levels (13, 14). In a pilot study by Gorbacheva et al., one of the few studies evaluating sENG levels in the PHPT population, sENG levels were reported to be lower than in healthy controls. The authors associated this paradoxical finding with sENG/TGF-β complex formation, decreased nitric oxide production, and endothelial dysfunction (9). These data suggest that the endothelial biomarker response in PHPT may not be linear and may vary with the disease's clinical heterogeneity.

In this context, the absence of a significant difference in sENG levels between the PHPT and control groups in the current study may be explained by several possible factors. First, the fact that the majority of the study sample had an asymptomatic and mildly hypercalcaemic phenotype may have limited the biochemical manifestation of endothelial stress. In addition, excluding comorbid conditions and medications that could increase metabolic burden yielded a relatively homogeneous sample with a low metabolic burden, which may have prevented endothelial stress from reaching a biochemically detectable level. However, the lack of PTH measurement in the control group and the presence of low vitamin D levels in both groups may be considered additional factors that could affect calcium-PTH balance and modulate biomarker levels. This may have contributed to the more limited biochemical differences observed between the groups. Given the heterogeneous nature of PHPT, it is expected that biomarker responses may be modulated by disease severity and the accompanying cardiometabolic burden (12, 15). Supporting this, improvements in vascular and endothelial parameters have been reported after parathyroidectomy in hypercalcaemic PHPT cases,

whereas a similar effect has not been demonstrated in normocalcaemic cases, suggesting that the vascular response may be phenotype-dependent (16). Furthermore, the relatively young mean age of our study group and the limited sample size may have made it difficult to detect potential differences.

The relationship between PHPT and body weight and composition are not clearly established in the literature. However, some studies have reported increased cardiovascular risk in patients with PHPT accompanied by higher body weight and BMI. Nevertheless, it remains unclear whether this relationship results directly from a PHPT-specific effect or from accompanying cardiometabolic disorders such as insulin resistance and dyslipidaemia (2, 17). Therefore, it is important to evaluate the potential effects of body composition and metabolic burden on endothelial response in PHPT. Although sENG is known to be associated with adiposity and metabolic stress, only a limited number of studies have evaluated its behaviour in the context of PHPT (9, 18). In this study, despite similar BMI values between the two groups, the observation of a positive correlation between sENG and BMI only in the PHPT group is noteworthy. Furthermore, the identification of body weight as an independent determinant of sENG levels in the linear regression analysis suggests a potential association that should be interpreted with caution. However, because the observed associations did not reach statistical significance and the sample size remained limited, it appears more appropriate to interpret these findings as hypothesis-generating.

In the literature, findings related to carbohydrate metabolism and insulin resistance in PHPT are heterogeneous. Some studies have reported increased insulin resistance and impaired glycaemic control in patients with PHPT, and partial improvements in insulin resistance and glucose metabolism have been observed after parathyroidectomy. In contrast, other studies have suggested that the association between PHPT and glucose metabolism is limited or does not result in clinically significant metabolic impairment (19–21). In this study, although insulin and HOMA-IR values were higher in the PHPT group, no statistically significant differences were observed between the groups in glucose metabolism-related parameters, including BMI, fasting glucose, and HbA1c. In addition, these parameters showed positive associations with sENG only in the PHPT group. Interaction analyses also revealed differences in the direction of the associations between the groups at similar glucose levels. However, the lack of statistical significance of these associations requires cautious interpretation of the findings. The exclusion of individuals with diabetes and of treatments that could affect glucose metabolism, together with the fact that glycaemic parameters were largely within the normal range in both groups, may have limited the statistical power to detect the observed differences. Therefore, studies including diverse clinical phenotypes and larger sample sizes are needed to elucidate the relationship between endothelial response and carbohydrate metabolism in PHPT.

The effects on lipid metabolism are also important in terms of the cardiometabolic profile of PHPT. The prevalence of dyslipidaemia in patients with PHPT has been reported to range from 30% to 49%, and some studies have reported increases in total cholesterol, LDL cholesterol, and triglycerides, accompanied by decreases in HDL cholesterol. However, this relationship is not consistent in the literature, and some studies have not found significant differences in lipid profiles between patients with PHPT and controls (3). Therefore, dyslipidaemia is considered one of the metabolic components that may contribute to the increased cardiovascular risk profile of PHPT, but may occur in a heterogeneous manner (22). In our study, no significant differences were observed between the case and control groups for LDL, HDL, total cholesterol, or triglycerides. Excluding individuals with a history of hyperlipidaemia or those on lipid-lowering therapy may have influenced this result and limited the detection of absolute lipid differences. Similarly, differences were observed between the groups in the direction of the associations between total cholesterol and sENG in the interaction analyses. However, these findings did not reach statistical significance and should be interpreted with caution. Further studies, including PHPT cohorts with a broader distribution of lipid profiles, are needed to understand these relationships better.

Endoglin (CD105) is a glycoprotein highly expressed in proliferating endothelial cells and plays an important role in angiogenesis and endothelial activation (23). Recent studies have demonstrated that sENG may be a potential biomarker associated with tumour invasiveness and angiogenesis in breast cancer and may also be related to prognosis (24, 25). In our study, during outlier analysis, the sENG level in a 46-year-old patient with PHPT was approximately 6 times the group median. It was subsequently learned that the patient had been diagnosed with metastatic breast cancer during follow-up. This case was not included in the main analyses. Although the primary aim of the study was not to evaluate the relationship between malignancy and sENG, this observation is consistent with the biological role of sENG related to angiogenesis and endothelial activation. However, this finding is not sufficient for a causal interpretation and may be considered an observation consistent with the literature.

Among the strengths of this study are the careful selection of patients with biochemically confirmed PHPT, the use of a healthy control group with normal calcium levels matched for age, sex, and BMI, and the exclusion of comorbidities and regular medication use that could affect metabolic parameters. In addition, measuring serum sENG levels using a sensitive, standard sandwich ELISA method and applying comprehensive statistical analyses strengthens the methodological rigour of the study. However, the study has several important limitations. First, the cross-sectional case-control design does not allow for causal inference. Considering the exploratory nature of the study and the relatively small sample size, it should be noted that the statistical power may be limited to detect subtle associations.

No formal adjustment for multiple comparisons was performed because the analyses were considered exploratory. Therefore, the results should be interpreted with caution. The single-centre design may limit the generalizability of the findings. The higher prevalence of PHPT in women and the resulting low number of male patients due to consecutive patient recruitment also represent an important limitation. In addition, the relatively younger mean age of the patient group compared with the general PHPT population and the wide age distribution may have affected the interpretation of the results. The fact that metabolic parameters remained largely within the normal range in both groups may have led to the evaluation of endoglin within a limited range of variation. The study's focus on asymptomatic and mildly hypercalcaemic PHPT phenotypes may limit the generalizability of its findings to more severe or symptomatic cases. The lack of evaluation of lifestyle factors, such as smoking, that may affect endothelial function, and the absence of postoperative comparisons are also important limitations of the study.

Although the significant differences observed in calcium, phosphorus, and alkaline phosphatase levels between the PHPT and control groups support the biochemical distinction between the study populations, the absence of PTH measurements in the control group due to lack of clinical indication represents an important methodological limitation and may have prevented the complete exclusion of normocalcaemic PHPT, a rare and diagnostically challenging variant of the disease. In addition, the low vitamin D levels observed in both groups should be considered a potential confounding factor that may affect calcium-PTH dynamics.

During data analysis, the outlier belonging to a patient with known malignancy was excluded. Apart from this case, although some outlier values were observed, they were included in the analyses because there was no clear clinical or methodological justification for their exclusion. Nevertheless, the potential effects of undiagnosed comorbid conditions in the overall cohort cannot be completely ruled out.

Future prospective studies with larger, multi-centre cohorts are needed to clarify the relationship between sENG, metabolic burden, and cardiovascular risk in PHPT, as well as its potential changes after parathyroidectomy. Analyses across different clinical phenotypes and risk profiles may further elucidate the role of sENG. In addition, combining sENG with functional and imaging-based vascular markers may improve understanding of its clinical relevance.

Conclusions

This study is one of the limited investigations evaluating serum sENG levels and their association with metabolic parameters in patients with PHPT. No significant difference in sENG levels was detected between patients with asymptomatic PHPT and healthy controls. Although the direction of the associations between sENG and BMI, glycaemic parameters, and lipid parameters differed, these findings did not reach statistical significance. Therefore, the clinical significance of sENG in PHPT remains uncertain and should be further evaluated in larger prospective studies including different risk groups.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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