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Serum Parathyroid Hormone Concentrations Are Increased in Women with Polycystic Ovary Syndrome

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Background: **The present study was designed to investigate the effects of polycystic ovary syndrome (PCOS) and of obesity on serum parathyroid hormone (PTH), 25-hydroxyvitamin D (25-OH-vitamin D), and 1,25-dihydroxyvitamin D [1,25-$(OH)_2$-vitamin D] concentrations and the possible associations of the above calciotropic hormones with the hormonal and metabolic characteristics of the syndrome.**

Methods: **We studied 58 obese [body mass index (BMI) >30 kg/m^2] women with PCOS, 64 overweight (BMI, 25–30 kg/m^2) women with the syndrome, 169 normal-weight (BMI <25 kg/m^2) women with PCOS, 29 obese controls (ovulatory women without clinical or biochemical hyperandrogenemia), 14 overweight controls, and 70 normal-weight controls. Blood samples were collected (at 0900 after an overnight fast) between the 3rd and 6th days of a menstrual cycle in the control groups and during a spontaneous bleeding episode in the PCOS groups. Circulating concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), testosterone, Δ4-androstenedione, 17α-hydroxyprogesterone, sex-hormone–binding globulin (SHBG), insulin, glucose, PTH, 25-OH-vitamin D, and 1,25-$(OH)_2$-vitamin D were measured.**

Results: **Both PCOS and increased body weight had a significant positive effect on serum PTH values. PTH concentrations were significantly correlated with age, BMI, glucose, PRL, SHBG, and testosterone. Only the correlations with testosterone and PRL were BMI-independent. The effect of PCOS on PTH concentrations remained significant after adjustment for BMI, but not after adjustment for testosterone concentration. Increased body weight also had a significant negative effect on 25-OH- and 1,25-$(OH)_2$-vitamin D concentrations, but no association with the syndrome was observed.**

Conclusions: **The results of the present study are in agreement with previous data supporting an association of increased PTH and decreased vitamin D metabolite concentrations with obesity. Moreover, the present findings indicate, for the first time, that PTH probably is also linked to PCOS-associated hyperandrogenism.**

The polycystic ovary syndrome (PCOS),[4] characterized by hyperandrogenic chronic anovulation, is probably the most common endocrine disorder in women of reproductive age *(1, 2)*. Insulin resistance and central obesity, prominent features of the syndrome, put patients at risk for long-term metabolic disorders, but also contribute to PCOS-associated hyperandrogenism *(3)*. Apparently, primary hypothalamic *(4)* and gonadal defects *(5)* play an

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[4] Nonstandard abbreviations: PCOS, polycystic ovary syndrome; PTH, parathyroid hormone; 25-OH-vitamin D, 25-hydroxyvitamin D; 1,25-$(OH)_2$-vitamin D, 1,25-dihydroxyvitamin D; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Δ4A, Δ4-androstenedione; DHEA-S, dehydroepiandrosterone sulfate; PRL, prolactin; 17α-OH-progesterone, 17α-hydroxyprogesterone; SHBG, sex-hormone–binding globulin; HoMA-IR, homeostasis model assessment of insulin resistance index; and GLM, general linear model.

important role in the complex pathogenesis of the syndrome as well.

Calcium homeostasis is closely related to obesity as well as the clinical aspects of the metabolic syndrome (syndrome X). Increased body fat is associated with alterations in vitamin D metabolism and parathyroid hormone (PTH) concentrations. Despite the fact that obese individuals have a larger total surface area to expose to sunlight, which would be expected to produce more vitamin D, it has been shown previously that 25-hydroxyvitamin D (25-OH-vitamin D) concentrations are decreased in obesity *(6–8)*. As a result of decreased bioavailability of vitamin D in obese individuals, PTH concentrations are significantly higher, independent of age, sex, and race *(7–11)*. It is possible that subcutaneous fat, which has been known to store vitamin D, sequesters larger amounts in obese persons *(6–8)*. Another possible explanation for the increased risk of relative vitamin D deficiency and, consequently, higher PTH concentrations in obesity is the fact that obese individuals, because of lower mobility, might have less exposure to solar ultraviolet radiation, which is indispensable for cutaneous synthesis of vitamin D *(12)*.

Altered calcium kinetics and cellular metabolism have also been directly associated with increased adiposity and syndrome X. In morbid obesity, in addition to increased PTH *(9)*, increased binding of calcium to plasma proteins has also been reported *(13)*. Moreover, PTH itself may promote weight gain because physiologic increases in PTH have been shown to increase intracellular calcium ion (Ca^{2+}) concentrations, which appear to promote triglyceride accumulation in adipose tissue by exerting coordinated control over lipogenesis and lipolysis *(14, 15)*.

The above mechanisms could account for the fact that high dietary intake of calcium and/or dairy products has recently been shown to reduce the risk for developing obesity and diabetes *(16–18)*. Indeed, Resnick *(19)* proposed a unifying "ionic hypothesis", in which the various metabolic abnormalities associated with syndrome X represent different tissue-specific manifestations of a cellular lesion characterized, in part, by increased steady-state intracellular Ca^{2+} concentrations. Consistent with this concept, correcting increases in intracellular Ca^{2+} leads to clinical improvements in blood pressure, insulin resistance, platelet aggregation, and left ventricular hypertrophy *(19)*.

In a brief report of a study involving 13 women with PCOS, PTH concentrations were significantly increased in some women with the syndrome *(20)*. Notably, in that study, PCOS-associated signs of hyperandrogenism were alleviated after administration of high doses of vitamin D, which has been known to suppress PTH production *(20)*. However, PTH concentrations in women with PCOS, a condition associated with obesity and the metabolic syndrome, have not been thoroughly studied. We therefore designed the present study to investigate (*a*) the effects of PCOS and obesity on serum PTH, 25-OH-vitamin D, and 1,25-dihydroxyvitamin D [1,25-$(OH)_2$-vitamin D] concentrations and (*b*) the possible associations of the above calciotropic hormones with the hormonal and metabolic characteristics of the syndrome.

Participants and Methods

PARTICIPANTS

We studied 291 women with PCOS (age range, 14–38 years). All were recruited from the outpatient endocrine infirmary of our clinic, with at least one of the following signs: oligomenorrhea, fertility problem, hirsutism, acne, and male-pattern alopecia. Diagnosis of PCOS was based on the presence of chronic anovulation (fewer than 6 cycles in 12 months) and hyperandrogenemia. Other common causes of hyperandrogenemia and/or anovulation (prolactinoma, congenital adrenal hyperplasia, Cushing syndrome, and virilizing ovarian or adrenal tumors) were excluded in accordance with the criteria proposed in 1990 by the NIH-National Institute of Child Health and Human Development *(21)*, and revised in 2003 by the Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group *(22)*.

We recruited 109 healthy women (age range, 18–38 years) as controls. All controls had normal ovulating cycles (menstrual cycle, 28 ± 2 days; blood progesterone >10 μg/L in 2 consecutive cycles), and no signs of hyperandrogenism. None of the women studied had galactorrhea or any systemic disease that affected their reproductive physiology or calcium homeostasis. All study groups were recruited between October and February 2004. No significant differences in sun exposure habits or daily calcium intake were reported by the participants. Participants were advised to avoid excessive consumption of dairy products for at least 1 week and to avoid sunlight exposure for 1 day before measurements. Furthermore, no woman reported use of any medication that could interfere with the normal function of the hypothalamic–pituitary–gonadal axis or calciotropic hormone concentrations during the last semester. Informed consent was obtained from all 400 women, and the study was approved by the Ethics Committee of the Institution.

The 400 women were divided into 6 groups based on body mass index (BMI) values and the diagnosis of PCOS: obese (BMI >30 kg/m^2) women with PCOS (n = 58); overweight (BMI, 25–30 kg/m^2) women with the syndrome (n = 64); normal-weight (BMI <25 kg/m^2) women with PCOS (n = 169); obese controls (n = 25); overweight controls (n = 14); and normal-weight controls (n = 70). Waist-to-hip ratios were available for 185 women with PCOS (40 obese, 39 overweight, and 106 normal-weight) and 67 controls (16 obese, 11 overweight, and 40 normal-weight).

HORMONE AND BIOCHEMICAL MEASUREMENTS AND CALCULATIONS

Blood samples were collected between the 3rd and 6th days of a menstrual cycle for the control groups and

during a spontaneous bleeding episode for the PCOS groups; blood was collected at 0900 after an overnight fast. In all women, basal serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, Δ4-androstenedione (Δ4A), and dehydroepiandrosterone sulfate (DHEA-S) were measured. Fasting concentrations of prolactin (PRL), 17α-hydroxyprogesterone (17α-OH-progesterone), sex-hormone–binding globulin (SHBG), glucose, insulin, and PTH were also measured. 25-OH-Vitamin D and 1,25-$(OH)_2$-vitamin D concentrations were also measured in 182 women with PCOS (38 obese, 49 overweight, and 95 normal-weight) and 46 controls (12 obese, 10 overweight, and 24 normal-weight). The homeostasis model assessment of insulin resistance index (HoMA-IR) was calculated according to the formula: [fasting insulin (mIU/L) × fasting glucose (mmol/L)]/22.5 *(23)*.

ASSAY METHODS

Plasma glucose concentrations were measured with the glucose oxidase technique on an automated analyzer (Roche/Hitachi 902; Roche Diagnostics). LH, FSH, PRL, androgens, 17α-OH-progesterone, 25-OH-vitamin D, 1,25-$(OH)_2$-vitamin D, and PTH were measured with RIA methods, and SHBG was measured with an IRMA. All of the assays were available commercially: FSH, LH, and PRL assays were from Nichols Institute Diagnostics; testosterone, Δ4A, DHEA-S, SHBG, and 17α-OH-progesterone assays were from Diagnostic Systems Laboratories; the PTH assay was from DiaSorin; and the 25-OH-vitamin D and 1,25-$(OH)_2$-vitamin D assays were from Biosource Europe S.A. Serum insulin concentrations were measured with an ELISA (Mercodia AB).

STATISTICAL ANALYSES

The Kolmogorov–Smirnov test was used to test the normality of distribution, and values that did not fit the gaussian distribution were log-transformed. General linear regression model (GLM)-based 2-way ANOVA was used to determine the independent effects of PCOS and body weight on PTH concentrations. Comparison of means and adjustments were also performed with univariate GLM. Bivariate correlation analysis (calculation of the Pearson coefficient after log-transformation) was used to assess the correlation of serum PTH concentration to each of the other variables. Independent relationships were assessed by partial correlation analysis. All analyses were performed with SPSS software (Ver. 11.5; SPSS, Inc.). Statistical significance was set at 5%.

Results

The anthropometric, hormonal, and metabolic features of the women studied and their statistical significance are summarized in Table 1. There was no significant difference in waist-to-hip ratio between women with PCOS and control women matched for BMI; the difference in age, however, was significant. All values were therefore ad-

Table 1. Clinical characteristics and basic hormone concentrations of the women studied.[a]

	Group							
	Obese		Overweight		Normal-Weight		*P*[b]	
	PCOS	Controls	PCOS	Controls	PCOS	Controls	PCOS	BMI
No. of women (total)	58	25	64	14	169	70		
Age, years	24.75 (0.84)	29.08 (1.19)	23.96 (0.74)	25.28 (1.71)	22.82 (0.37)	26.20 (0.73)	**<0.001**	**0.026**
BMI, kg/m^2	35.19 (0.63)	39.12 (1.39)	27.19 (0.18)	27.24 (0.35)	21.54 (0.14)	21.33 (0.22)		
WHR[c]	0.84 (0.015)	0.86 (0.020)	0.82 (0.015)	0.80 (0.015)	0.75 (0.004)	0.75 (0.004)	0.766	**<0.001**
No. of women for WHR	40	16	39	11	106	40		
LH, IU/L	6.56 (0.64)	5.72 (0.59)	6.14 (0.45)	4.42 (0.58)	9.46 (0.62)	6.28 (0.26)	**0.012**	**<0.001**
FSH,[d] IU/L	5.23 (0.22)	6.21 (0.34)	5.53 (0.22)	6.52 (0.13)	5.68 (0.14)	6.59 (0.25)	**0.003**	0.057
PRL, μg/L	13.53 (1.03)	11.37 (0.98)	14.52 (0.92)	14.72 (1.81)	16.28 (0.76)	13.06 (0.78)	0.190	0.410
Testosterone, ng/L	938.4 (35.6)	443.9 (16.7)	815.5 (23.3)	429.1 (26.6)	869.8 (19.6)	411.1 (10.5)	**<0.001**	**0.045**
Δ4A, μg/L	2.63 (0.13)	1.62 (0.07)	2.72 (0.07)	1.43 (0.08)	3.05 (0.07)	1.62 (0.05)	**<0.001**	0.074
DHEA-S,[d] mg/L	3.03 (0.17)	1.74 (0.11)	2.95 (0.12)	1.99 (0.13)	2.92 (0.08)	1.71 (0.06)	**<0.001**	0.477
17α-OH-progesterone, μg/L	1.06 (0.06)	0.71 (0.06)	1.26 (0.06)	0.74 (0.06)	1.23 (0.04)	0.73 (0.03)	**<0.001**	0.282
Glucose,[d] mg/L	962.2 (14.7)	1066. (22.1)	937.0 (17.3)	953.5 (34.6)	920.8 (25.3)	902.1 (14.1)	0.106	**<0.001**
Insulin, mIU/L	19.40 (2.38)	22.54 (2.36)	11.67 (0.91)	10.46 (1.47)	9.95 (0.96)	6.63 (0.34)	0.587	**<0.001**
SHBG,[e] nmol/L	27.13 (1.93)	31.32 (2.62)	32.11 (1.61)	45.14 (5.57)	38.61 (1.22)	64.82 (2.72)	**<0.001**	**<0.001**
HoMA-IR	4.63 (0.55)	5.89 (0.61)	2.76 (0.23)	2.51 (0.40)	2.25 (0.21)	1.48 (0.66)	0.356	**<0.001**

[a] Values are the mean (SE).

[b] Assessed by 2-way ANOVA. *P* adjusted for age in all comparisons except for age. Interaction term is nonsignificant ($P > 0.05$) unless otherwise indicated. Statistically significant values are in bold font.

[c] WHR, waist-to-hip ratio.

[d] Values were not log-transformed (1-sample Kolmogorov–Smirnov, $P > 0.05$).

[e] Significant interaction between PCOS and body weight ($P < 0.05$).

Table 2. Mean (SE) PTH, 25-OH-vitamin D, and 1,25-$(OH)_2$-vitamin D concentrations of the women studied.

	Group							
	Obese		Overweight		Normal-Weight		P^a	
	PCOS	Controls	PCOS	Controls	PCOS	Controls	PCOS	BMI
PTH, ng/L								
Measured value	27.88 (1.77)	27.67 (2.01)	24.55 (1.33)	17.45 (2.02)	24.34 (0.93)	19.61 (8.68)	**0.001**	**0.001**
Adjusted for age and BMI	23.84 (2.32)	21.13 (3.37)	23.95 (1.44)	16.68 (3.02)	26.38 (1.16)	21.08 (1.61)	**0.001**	0.223
Adjusted for age, BMI, and testosterone	23.32 (2.18)	22.06 (3.47)	23.76 (1.45)	17.61 (3.14)	26.02 (1.21)	22.05 (1.84)	0.063	0.339
25-OH-vitamin D, μg/L	22.80 (2.37)	18.58 (2.73)	31.37 (2.53)	25.43 (3.92)	31.24 (1.65)	21.19 (1.95)	0.122	**0.029**
1,25-$(OH)_2$-vitamin D,[b] ng/L	26.78 (1.74)	18.58 (2.73)	30.68 (1.60)	36.12 (3.88)	32.66 (0.79)	29.85 (1.57)	0.458	0.056
No. of women for vitamin D measurements	38	12	49	10	95	24		

[a] Assessed by 2-way ANOVA. *P* adjusted for age in all comparisons except for age. Interaction term is nonsignificant ($P > 0.05$) unless otherwise indicated. Statistically significant values are in bold font.

[b] Values were not log-transformed (1-sample Kolmogorov–Smirnov, $P > 0.05$).

justed for age and compared by means of univariate GLM-based analysis.

PCOS was associated with higher testosterone, Δ4A, DHEA-S, and 17α-OH-progesterone concentrations, and testosterone concentrations were also significantly increased with increased BMI. PCOS had a significant negative effect on FSH concentrations, whereas both decreased BMI and the syndrome were independently associated with significantly higher LH concentrations. Obesity had a strong positive effect on serum glucose and insulin concentrations as well as on HoMA-IR, whereas we found no independent association of the above variables with PCOS. SHBG concentrations were negatively affected by both obesity and the syndrome.

Women with PCOS (n = 291) had substantially higher PTH concentrations [mean (SE), 25.09 (0.71) ng/L] than did controls [21.18 (0.93) ng/L; n = 109; $P < 0.01$]. This difference remained significant after adjustment for age and BMI [25.29 (0.66) vs 20.51 (1.10) ng/L].

Both PCOS and increased body weight had a significant positive effect on serum PTH concentrations (Table 2). Specifically, obese women with PCOS had significantly higher PTH concentrations than did normal-weight women with the syndrome ($P = 0.04$), and obese controls had higher PTH concentrations than both overweight and normal-weight women of the control group ($P = 0.009$ and 0.008, respectively). We found no significant difference between overweight and normal-weight women with or without PCOS or between obese women with the syndrome and obese controls. Nevertheless, both overweight and normal-weight women with PCOS had significantly higher PTH concentrations than did their BMI-matched control groups ($P = 0.004$ and 0.002, respectively; Fig. 1A).

Calculation of the Pearson coefficient, after log-transformation, showed that circulating PTH was positively correlated with age ($r = 0.111$; $P = 0.026$), BMI ($r = 0.202$; $P < 0.001$), and glucose ($r = 0.11$; $P = 0.029$), PRL ($r = 0.149$; $P = 0.003$), and testosterone ($r = 0.151$, $P = 0.003$) concentrations and was negatively correlated with SHBG concentrations ($r = -0.125$; $P = 0.012$). However, partial correlation analysis indicated that only correlations to PRL ($r_{\text{partial corr}} = 0.179$; $P < 0.001$) and testosterone ($r_{\text{partial corr}} = 0.173$; $P = 0.001$; Fig. 2) concentrations were BMI-independent. The effect of PCOS on serum PTH concentrations (GLM analysis) remained significant after adjustment for BMI (Table 2 and Fig. 1B), but not after additional adjustment for testosterone concentrations, which rendered all differences borderline nonsignificant (Table 2 and Fig. 1C).

We found no significant difference between women with PCOS and controls regarding the concentrations of 25-OH-vitamin D and 1,25-$(OH)_2$-vitamin D (Table 2). Increased body weight had a significant negative effect on 25-OH-vitamin D concentrations ($P = 0.029$) and a borderline negative effect on 1,25-$(OH)_2$-vitamin D concentrations ($P = 0.056$). The concentrations of 25-OH-vitamin D were negatively correlated with BMI ($r = -0.194$; $P = 0.03$), PTH ($r = -0.142$; $P = 0.031$), insulin ($r = -0.146$; $P = 0.026$), and HoMA-IR ($r = -0.145$; $P = 0.027$) and positively with 1,25-$(OH)_2$-vitamin D concentrations ($r = 0.204$; $P = 0.013$). All of the above differences were BMI-dependent, except for the correlation with 1,25-$(OH)_2$-vitamin D ($r = -0.162$; $P < 0.02$).

Discussion

The present study was designed to investigate the effect of PCOS and obesity on serum PTH, 25-OH-vitamin D, and 1,25-$(OH)_2$-vitamin D concentrations. To the best of our knowledge, this is the first study in which calciotropic hormones in a sizeable sample of women with the syndrome were compared with those of ovulatory women without hyperandrogenism (controls) over a wide range of BMI values. Our results concerning the basic hormonal profiles of women with PCOS compared with controls are in accord with well-established evidence on the fundamental characteristics of the syndrome *(1, 24, 25)*.

Obese women with PCOS had significantly higher

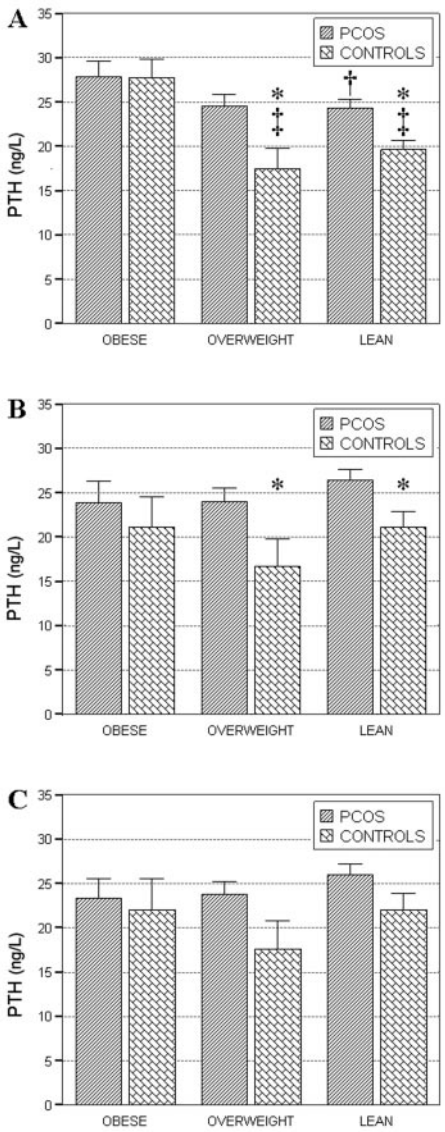

Fig. 1. Mean (SE) PTH concentrations of the women studied.

(*A*), unadjusted; (*B*), adjusted for age and BMI; (*C*), adjusted for age, BMI, and testosterone concentrations. ∗, $P < 0.005$ for difference between women with PCOS and BMI-matched controls; †, $P < 0.05$ and ‡, $P < 0.005$ vs obese women in the same category (with or without PCOS).

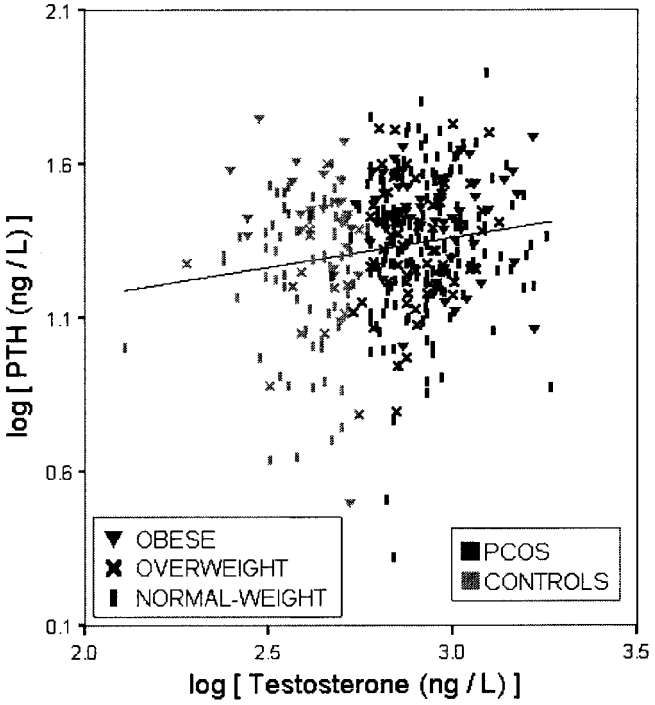

Fig. 2. Scatter-plot of serum PTH vs serum testosterone concentrations (log-transformed).

PTH concentrations than normal-weight women with the syndrome, whereas obese controls had higher concentrations than both overweight and normal-weight women of the control group. PTH concentrations did not differ significantly between overweight and normal-weight women with or without PCOS (Fig. 1A). However, the correlation with BMI was significant, and the above differences in PTH concentrations were rendered nonsignificant after adjustment for BMI (Table 2 and Fig. 1B). In other words, overall, obesity (BMI >30 kg/m^2) was found to be significantly associated with an increase in circulating PTH concentrations.

These findings are in agreement with previous reports of increased PTH concentrations in obese, compared with normal-weight, patients *(7–11, 26)*. Increased sequestration of vitamin D in adipose tissue has been proposed as a possible explanatory mechanism for these results *(6–8)*. Our findings are in agreement with previous reports of lower 25-OH-vitamin D concentrations in obese individuals. With regard to 1,25-$(OH)_2$-vitamin D, higher concentrations in obesity have been reported previously *(11)*. However, the results of a recent report *(7)*, which included a large number of obese individuals, are basically in agreement with our own. Finally, it should be noted that PTH itself might also be involved in the development of obesity. Indeed, intracellular Ca^{2+} seems to promote triglyceride storage and inhibit lipolysis *(14, 15)*, and PTH has been shown to increase intracellular Ca^{2+} concentrations *(14)*.

Intriguingly, in the present study, women with PCOS had significantly higher PTH concentrations than ovulatory women without hyperandrogenemia. This difference was attributed to significantly higher PTH concentrations in nonobese women with the syndrome compared with BMI-matched controls (Table 2; Fig. 1, A and B). This difference remained significant for both groups after adjustment for BMI (Fig. 1B). Apparently, when the effect of increased adiposity is not as strong, the syndrome contributes independently to increased serum PTH concentrations.

An interesting approach to the above findings would be that insulin resistance has been shown to be associated with decreased concentrations of vitamin D metabolites and increased PTH concentrations *(27, 28)*. In the present

study, however, we observed no significant correlations between insulin resistance and either PCOS or PTH concentrations. The observed association between 25-OH-vitamin D concentrations and HoMA-IR was BMI-dependent, apparently reflecting the effect of increased body weight on bioavailable vitamin D concentrations. It should be noted, however, that in the present study, insulin resistance was estimated by means of fasting glucose and insulin values and that such indices have been shown to correlate poorly with results derived from the "gold standard", i.e., the euglycemic hyperinsulinemic clamp *(29)*.

Another interesting finding, which has not been reported previously, was that serum PTH concentrations were positively correlated with circulating testosterone, independent of age and BMI (Fig. 2). Furthermore, additional adjustment of values for testosterone concentrations blunted the difference in PTH concentrations between women with PCOS and controls (Table 2 and Fig. 1C). It is therefore possible that increased PTH concentrations in PCOS are related to the associated hyperandrogenism, one of the critical traits of the syndrome *(1, 24, 25)*.

A significant correlation with PRL concentrations was also observed, in agreement with previous reports of a positive association between excess PTH concentrations and hyperprolactinemia *(30, 31)*. Any possible physiologic significance of this finding, as to whether it is somehow associated with hypothalamic–pituitary function in PCOS, remains to be investigated.

In the present study we observed an overall trend for increased concentrations of vitamin D metabolites in the syndrome. Apparently, increased PTH concentrations in the syndrome can not be attributed to relative deficits in bioavailable vitamin D, opposite to obesity-related mechanisms (Table 2). We postulate that direct associations between PTH and metabolic abnormalities of PCOS or increased androgen concentrations could be responsible for the observed differences, which, after all, were most evident in the nonobese groups (Fig. 1). It should be noted that, in a previous report, administration of high doses of vitamin D led to the attenuation of hyperandrogenism and menstrual disturbances in women with PCOS *(20)*. It is possible that vitamin D metabolite concentrations increase to compensate for insulin resistance *(28)*, but larger-scale investigations are definitely needed to clarify this issue.

In conclusion, the results of the present study are in agreement with previous data supporting an association of increased PTH concentrations with obesity *(26)*. Moreover, our findings indicate, for the first time, that PTH probably is also linked to PCOS-associated hyperandrogenemia by means of BMI-independent mechanisms. Notably, dietary measures that down-regulate PTH have been associated with reduced risk of developing obesity and diabetes *(14, 17)*. It is very possible that these results are mediated by the beneficiary effect of vitamin D on insulin sensitivity *(28)*. In this respect, modulation of vitamin D, calcium, and phosphate intake may, likewise, be beneficial against PCOS-associated metabolic and reproductive morbidity.

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