Elevated Circulating Levels of Betatrophin is Associated with Polycystic Ovary Syndrome

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Objectives: Betatrophin is newly identified hormone appreciated for its role as a potent inducer of beta cell proliferation in line with insulin resistance in mice. Polycystic ovary syndrome (PCOS) is an inflammatory-based metabolic disease associated with insulin resistance. However, no evidence was available whether betatrophin is involved in women with PCOS. The aim of the study was to ascertain whether betatrophin levels are altered in women with PCOS.

Methods: 164 women with PCOS and 164 age- and BMI- matched female controls without PCOS were recruited for this cross-sectional study. Circulating betatrophin levels were measured using ELISA; metabolic and hormonal parameters were also determined.

Results: Circulating betatrophin levels were significantly elevated in women with PCOS compared with controls (367.09 ± 55.78 vs. 295.65 ± 48.97 pg/ml, *P*<0.001). Betatrophin levels were positively correlated with insulin resistance marker HOMA-IR, free-testosterone, hs-CRP, atherogenic lipid profiles and BMI. In multivariate logistic regression analysis, the odds of subjects in the highest quartile (OR=2.51, 95% CI=1.31—4.81, *P*=0.006) of betatrophin having PCOS were significantly increased compared with subjects the lowest quartile betatrophin. Multivariate regression analyses showed that HOMA-IR, hs-CRP and free-testosterone were independent factors influencing serum betatrophin levels.

Table 1. Comparison of the demographic and laboratory characteristics of the subjects.

Variables	PCOS n=164	Controls n=164	P
Age, years	26.65 ± 3.31	26.82 ± 3.32	0.653
BMI, kg/m^2	26.66 ± 3.63	26.84 ± 3.77	0.662
Waist circumference, cm	89.05 ± 9.40	87.35 ± 9.01	0.095
SBP, mmHg	112.28 ± 10.24	110.15 ± 11.84	0.082
DBP, mmHg	71.32 ± 6.14	70.27 ± 7.14	0.160
Ferriman-Gallwey score	10.44 ± 1.97	4.37 ± 1.36	<0.001*
FBG, mg/dl	88.36 ± 5.91	84.98 ± 6.75	<0.001*
Insulin, µlU/ml	11.91 ± 3.11	8.18 ± 3.27	<0.001*
HOMA-IR	2.61 ± 0.73	1.72 ± 0.76	<0.001*
Total cholesterol, mg/dl	207.62 ± 41.03	192.07 ± 29.44	<0.001*
LDL-C, mg/dl	133.64 ± 37.28	122.84 ± 26.53	0.003*
HDL-C, mg/dl	50.19 ± 12.52	51.75 ± 11.18	0.236
Triglycerides, mg/dl	135.96 ± 42.79	87.64 ± 37.42	<0.001*
Non-HDL cholesterol, mg/dl	157.42 ± 40.22	140.31 ± 29.54	<0.001*
hs-CRP, mg/l	1.17 ± 0.61	0.65 ± 0.34	<0.001*
FSH, mIU/ml	6.35 ± 0.96	6.17 ± 1.18	0.127
LH, mIU/ml	9.59 ± 2.43	5.15 ± 1.39	<0.001*
Estradiol, pg/ml	44.74 ± 9.90	46.63 ± 9.17	0.074
Free-testosterone, ng/dl	53.33 ± 11.73	14.62 ± 3.30	<0.001*
Total-testosterone, ng/ml	0.42 ± 0.12	0.39 ± 0.11	0.080
DHEA-SO_4, µg/dl	144.00 ± 37.70	137.04 ± 41.80	0.114
Betatrophin, pg/ml	367.09 ± 55.78	295.65 ± 48.97	<0.001*

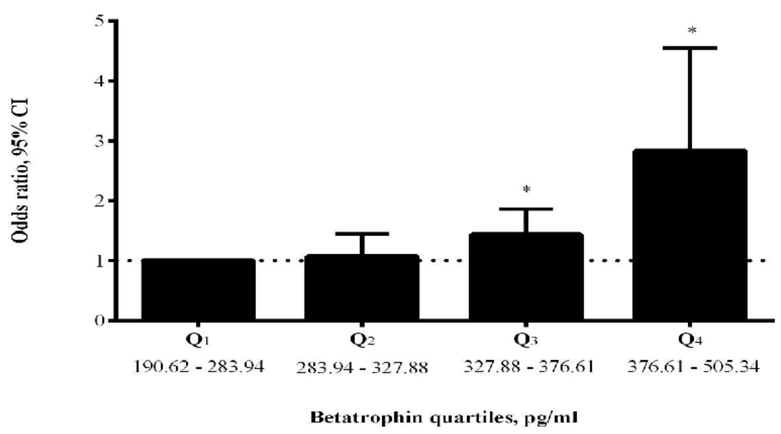
Table 2. Correlation coefficient between betatrophin levels and clinical parameters.

	Betatrophin			
	PCOS		Control	
	r	P	r	P
Age	0.127	0.168	0.079	0.321
BMI	0.143	0.039*	0.114	0.042*
Waist circumference	0.174	0.027*	0.135	0.038*
Systolic blood pressure	0.142	0.342	0.116	0.267
Diastolic blood pressure	0.138	0.264	0.154	0.325
Insulin	0.216	0.006*	0.145	0.021*
FBG	0.114	0.011*	0.110	0.036*
HOMA-IR	0.241	0.002*	0.128	0.025*
Free-testosterone	0.324	<0.001*	0.124	0.056
Total-testosterone	0.237	0.451	0.176	0.298
hs-CRP	0.335	<0.001*	0.113	0.006*
Total cholesterol	0.219	0.029*	0.196	0.035*
LDL-C	0.185	0.037*	0.121	0.041*
HDL-C	0.221	0.431	0.152	0.348
Triglycerides	0.341	0.031*	0.308	0.027*
Non-HDL cholesterol	0.317	0.035*	0.256	0.031*

Table 3. Evaluation of the effects of age, BMI, HOMA-IR, free-testosterone, LDL-C, triglycerides and hs-CRP on betatrophin using the multiple linear regression analysis (R^2=0.577).

	β	95% CI		P
		min	max	
Variables				
Age	0.189	-0.860	1.237	0.721
BMI	0.155	-0.372	0.683	0.563
HOMA-IR	0.944	0.317	1.572	0.003*
Free-testosterone	1.321	0.097	2.544	0.025*
LDL-C	0.401	-1.350	2.152	0.457
Triglycerides	0.623	-0.584	1.829	0.310
Hs-CRP	0.874	0.366	1.382	0.001*

Figure 1. Association of betatrophin with PCOS in adjusted models.



Conclusions: Betatrophin levels were increased in women with PCOS and were associated with insulin resistance, hs-CRP and free-testosterone in these patients. Elevated betatrophin levels were found to increase the odds of having PCOS. As betatrophin is mainly secreted from the liver, in the light of our results, hepato-ovarian axis may play a role in the development of PCOS. The physiologic and pathologic significance of our findings remain to be further elucidated.

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