HMGB1 is increased in adolescents with Polycystic Ovarian Syndrome (PCOS) and decreases after treatment with Myo-Inositol (MYO) in combination with Alpha-Lipoic Acid (ALA)

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BACKGROUND

Polycystic Ovarian Syndrome (PCOS) is one of the most common multisystem endocrine disorders among women of reproductive age, although it's aetiology remains unclear. PCOS is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology. Inflammation and insulin resistance (IR) characterize PCOS. High Mobility Group Box 1 (HMGB1) is a small protein which reflects both inflammation and insulin sensitivity and is increased in conditions of CFTR malfunction. We previously showed reduced CFTR gene expression in granulosa cells from polycystic ovaries. PCOS treatment is debated; as a first hypothesis it should adjust the pathophysiology, especially in adolescent girls in whom the endocrine system is not yet fully mature. Inositol derivatives and α-lipoic acid (ALA) are considered as a therapeutic option for positive effects on insulin sensitivity, androgen reduction and ovulation rhythm. We first described in cystic fibrosis (CF) and then in the PCOS an increase in HMGB1.

AIM

The aim of this study was to verify HMGB1 serum concentrations and metabolic changes in healthy and PCOS- affected adolescents and to verify any changes after treatment with MYO+ALA.

METHODS

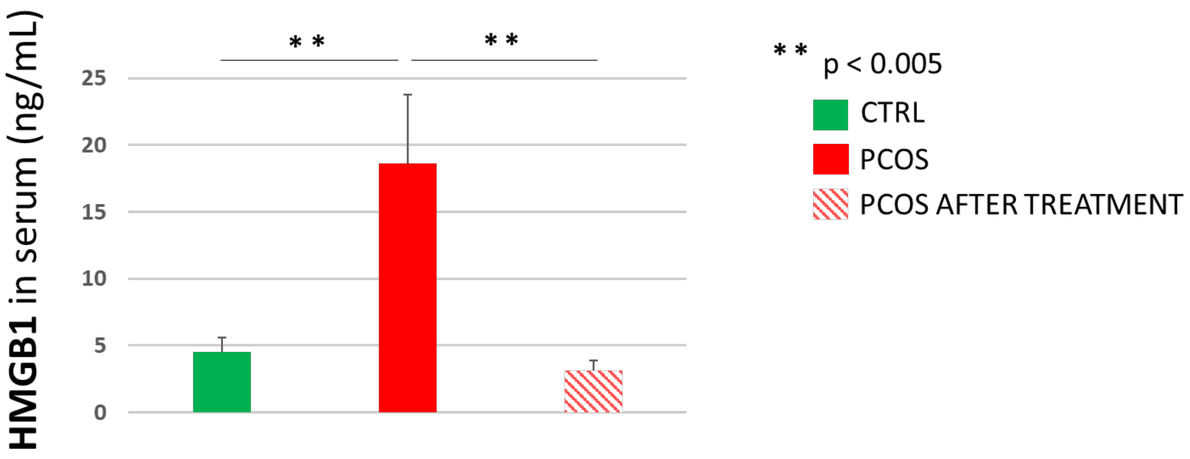
Twenty-five adolescents affected by PCOS (Rotterdam criteria) with a gynecological age of at least 2 years and 15 controls matched for age and BMI were enrolled (Table 1). At enrollment all subjects were screened for glycemia, insulin, hepatic and renal function, TSH, PRL, LH, FSH, E2, progesterone-17-OHP, delta-4-androstenedione, total testosterone, triglycerides, total and fractional cholesterol, IGF-I, uric acid. HOMA-IR and the TG/HDL-C ratio were calculated. Furthermore, the waist circumference (WC) and the WC/height ratio were measured. Ovarian and uterine volumes, number of follicles/ovary, uterus body/neck ratio, uterus volume were evaluated by pelvic ultrasound. Hirsutism was assessed using the Ferriman-Gallwey score. Acne was also evaluated. Patients were treated with MYO+ALA (2000 mg + 800 mg) for 3 months twice a day and for further 3 months, once a day. HMGB1 was assayed using a specific ELISA kit (HMGB1 ELISA, Tecan Trading AG). Statistical analysis was performed using SPSS v23.0.

Table 1 CLINICAL FEATURES OF SUBJECTS AT BASELINE

	CTRL (N=15)	PCOS (N=25)
CA (years)	18.18 ± 0.84	16.46 ± 0.57
BMI-SDS	0.4 ± 0.36	1.07 ± 0.24
Hyrsute (N)	-	19
Cycles (N)	Regular: 15	Regular: 14 Oligo: 6 Ameno: 5
Right Ovary (mL)	-	12.12 ± 1.02
Left Ovary (mL)	-	11.09 ± 0.91
TSH (uU/mL)	2.05 ± 0.45	1.78 ± 0.32
PRL (ng/mL)	19.01 ± 4.73	10.77 ± 1.58

Data are shown as mean ± SEM. PCOS: Polycystic Ovary Syndrome patients; CTRL: control subjects; CA: chronological age; BMI (Body Mass Index); N: number; Oligo: oligomenorrhoea; Ameno: amenorrohoea.

RESULTS



HMGB1 was increased in PCOS compared with controls (18.63 ± 5.12 vs 4.51 ± 1.10 ng/ml, p <0.005) and normalized after treatment (18.63 ± 5.12 vs 3.14 ± 0.74ng / ml, p <0.005).

METABOLIC FEATURES

	CTRL (N=15)	PCOS (N=25)	PCOS AFTER TREATMENT
FBG (mg/dL)	83.17 ± 2.46	85.40 ± 2.60	81.70 ± 2.97
Insulin (uU/mL)	10.99 ± 2.17	20.75 ± 3.00 *	12.55 ± 1.82 ¥
HOMA-IR (N)	2.29 ± 0.48	4.30 ± 0.55 *	3.12 ± 0.71 ¥
IGF-1 (ng/mL)	362.67 ± 32.84	477.00 ± 35.69 *	536.00 ± 89.80
Uric acid (mg/dL)	4.33 ± 0.03	5.21 ± 0.43	4.97 ± 0.44
Total cholesterol (mg/dL)	145.00 ± 15.05	152.78 ± 5.29 *	158.57 ± 9.51
TGL/HDL-C	1.51 ± 0.46	2.83 ± 0.59 *	2.63 ± 0.60

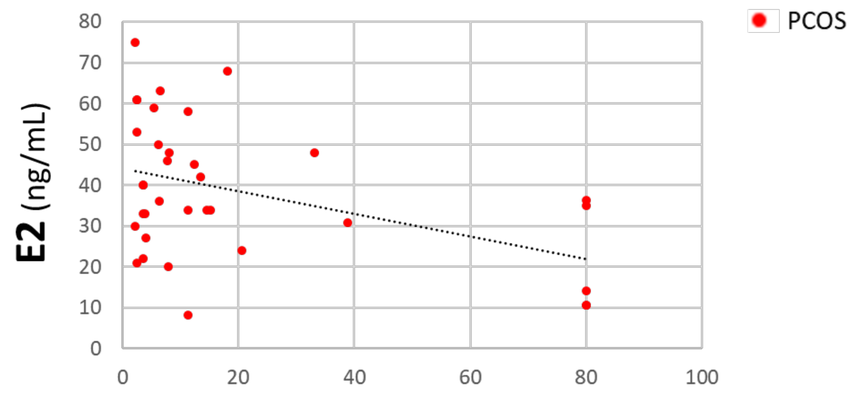
At baseline PCOS had higher insulin, HOMA, IGF-1, uric acid, total cholesterol, TGL/HDL-C than CTRL. HDL-C, LDL-C and TGL were similar. After treatment insulin and HOMA-IR significantly decreased.
(*p<0.05 PCOS vs CTRL; ¥ p<0.05 PCOS at baseline vs PCOS after treatment)

HORMONAL FEATURES

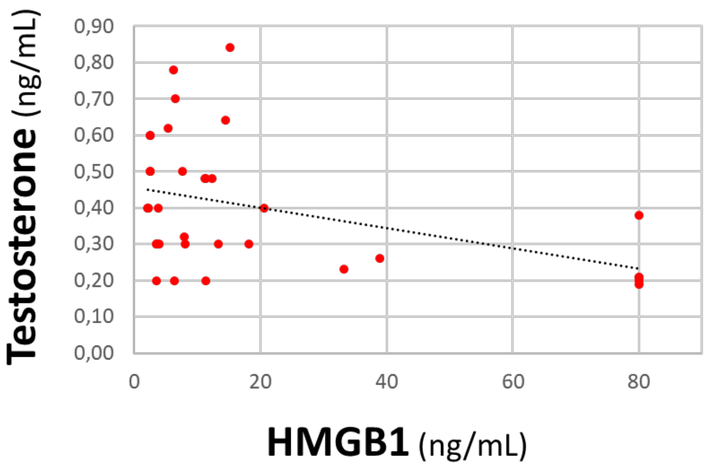
	CTRL (N=15)	PCOS (N=25)	PCOS AFTER TREATMENT
FSH (mU/mL)	4.35 ± 0.60	3.46 ± 0.31	4.16 ± 0.22
LH (mU/mL)	5.75 ± 1.25	6.25 ± 1.19	4.94 ± 0.76 ↓
E2 (pg/mL)	28.20 ± 5.90	42.13 ± 6.38	38.57 ± 5.44
P (ng/mL)	0.30 ± 0.00	0.29 ± 0.03	0.21 ± 0.03
17-OHP (ng/mL)	1.10 ± 0.32	0.94 ± 0.16	0.78 ± 0.11 ↓
D4A (mg/dL)	2.63 ± 0.45	3.11 ± 0.34	2.79 ± 0.41 ↓
T (ng/mL)	0.38 ± 0.05	0.42 ± 0.05	0.40 ± 0.04

LH, 17-OHP, and D4A decreased but not significantly after treatment.

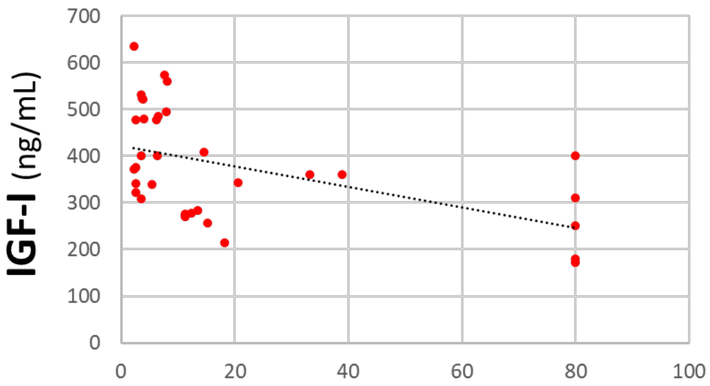
CORRELATION ANALYSES



HMGB1, in PCOS, was correlated with E2 (R: -0.40; P: 0.04).



HMGB1, in PCOS, was correlated with Total Testosterone (R: -0.41; P: 0.05).



HMGB1, in PCOS, was correlated with IGF-I (R: -0.48; P: 0.04). Furthermore HMGB1 was marginally correlated with TG/HDL (R: -0.43; P: 0.057).

CONCLUSIONS

These findings showed increased serum HMGB1 in PCOS adolescents. HMGB1 at baseline correlated with E2, Testosterone, and IGF-1 levels. Treatment with MYO+ALA for 6 months normalised HMGB1 concentrations. In addition, treatment decreased insulin and the HOMA-IR index. A decrease in LH, 17-OHP and D4A was also observed. Ovarian volume decreased but not significantly after treatment, and cycles improved. Hirsutism and acne were unchanged.

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