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BACKGROUND

Polycystic Ovarian Syndrome (PCOS) is one of the most common multisystem endocrine disorders among women of reproductive age, although its aetiology remains unclear. PCOS is characterised by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. High Mobility Group Box 1 (HMGB1) is a small protein which reflects both inflammation and insulin-sensitivity (Fig 1). Inflammation and insulin-resistance are features of PCOS. Interleukin-6 (IL-6) is involved in ovarian function and can contribute to insulin-resistance (Fig 1). Insulin-like Growth Factor Binding Protein-2 (IGFBP-2) behaves like an acute-phase protein being increased in chronic inflammation and involved in glucose metabolism regulation. IGFBP-2 overexpression has been shown to play a protective role against insulin-resistance (Fig 1). Insulin functions as a co-nadotropin modulating ovarian steroidogenesis and hyperinsulinism contributes to hyperandrogenism, a cause of arrest of follicular maturation present in PCOS.

OBJECTIVE

We aimed at assessing HMGB1, IGFBP-2, insulin and IL-6 concentrations and their relationships in follicular fluid (FF) from PCOS versus non-PCOS women.

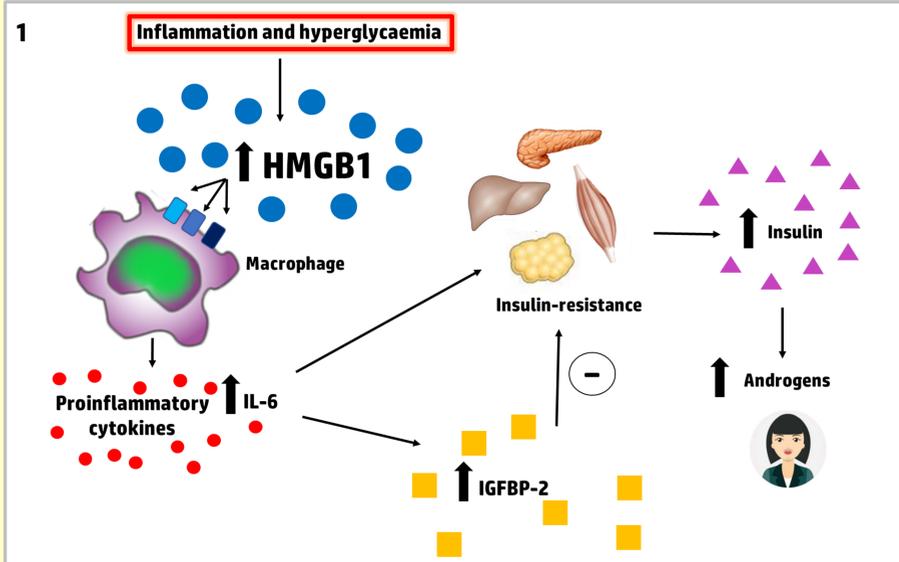


Table 1 CLINICAL FEATURES OF SUBJECTS

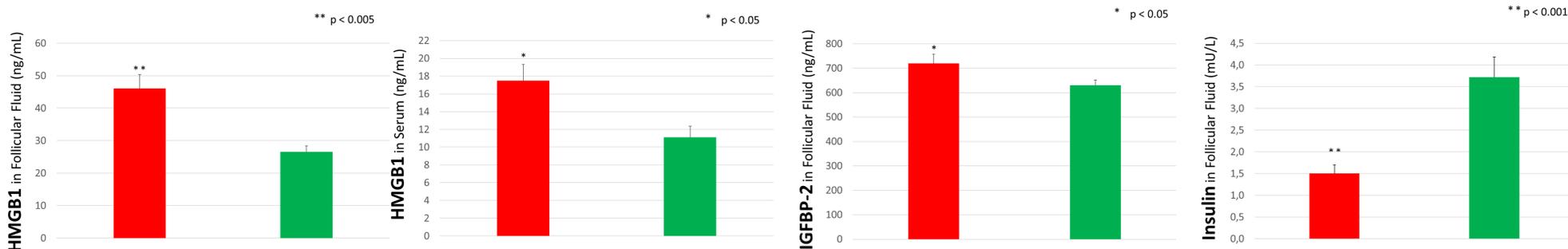
	CA (years)	BMI (kg/m ²)	Dominant Follicles (N)	E2 (pg/mL)	Hirsute (N)	Cycles (N)
PCOS (N=30)	34.43 ± 0.84	25.92 ± 0.99	4.77 ± 0.48	1894.10 ± 246.81*	12	Regular: 15 Oligo: 13 Ameno: 2
CTRL (N=36)	35.72 ± 0.55	24.08 ± 0.79	3.92 ± 0.45	1275.86 ± 129.27	-	Regular: 36

Data are mean ± SEM. PCOS: Polycystic ovarian syndrome patients; CTRL: controls; CA: chronological age; BMI: body mass index; N: number; E2: estradiol in serum; Oligo: oligomenorrhoea; Ameno: amenorrhoea; * p<0.05 PCOS vs CTRL.

METHODS

We enrolled 30 women with PCOS according to the Rotterdam Criteria, and 36 women fertile oocyte donors (Table 1), with tubarian or unknown infertility causes, with normal endocrine exams, regular menstrual-cycles, no hyperandrogenism, as controls (CTRL), all undergoing the same ovarian stimulation protocol for *in vitro* fertilization. HMGB1 both in FF and in serum, IGFBP-2, IL-6 and insulin in FF were assayed using specific ELISA kits (HMGB1 ELISA, Tecan Trading AG; IGFBP-2 ELISA, Mediagnost; Human IL6 Quantikine ELISA kit, R&D Systems, Inc.; Mercodia Ultrasensitive Insulin ELISA, Mercodia AB, respectively). Serum estradiol (E2) at oocyte retrieval was quantified. The N. of dominant follicles (>17 mm) at ultrasound was also recorded. Statistical analysis was performed using SPSS v.23.0.

RESULTS



HMGB1 in FF was higher in PCOS than in CTRL (46.09±4.25 vs 26.53±1.87 ng/mL; p=0.002)

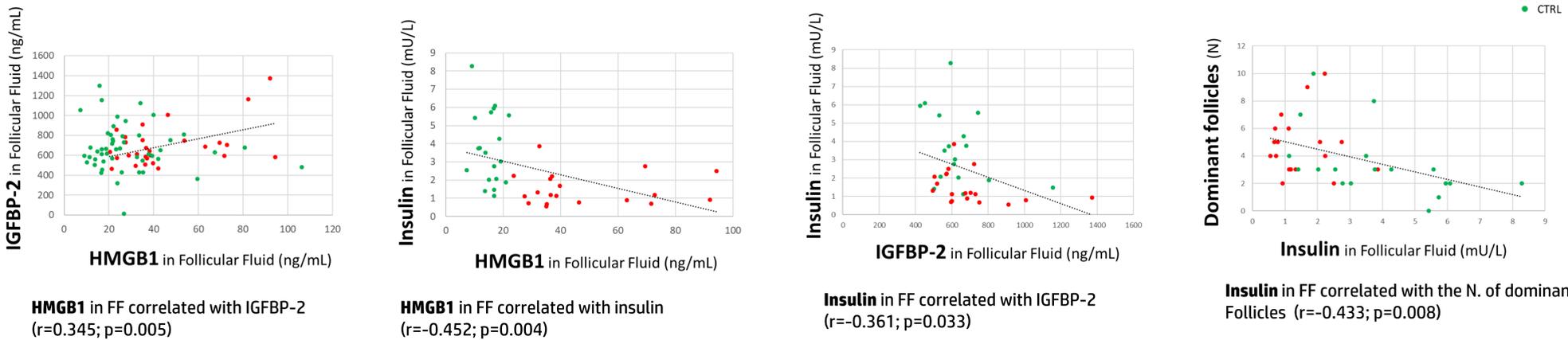
Serum **HMGB1** was confirmed higher in PCOS than in CTRL (17.47±1.84 vs 11.13±1.23 ng/mL; p=0.004)

IGFBP-2 in FF was higher in PCOS than in CTRL (719.15±37.99 vs 630.16±21.13 ng/mL; p=0.030)

Insulin in FF was lower in PCOS than in CTRL (1.50±0.20 vs 3.72±0.46 mU/L; p<0.001)

IL-6 in FF was similar in PCOS and in CTRL (11.52±1.92 vs 11.76±1.26 pg/mL; n.s.)

Serum and FF **HMGB1** concentrations did not correlate.



HMGB1 in FF correlated with **IGFBP-2** (r=0.345; p=0.005)

HMGB1 in FF correlated with **insulin** (r=-0.452; p=0.004)

Insulin in FF correlated with **IGFBP-2** (r=-0.361; p=0.033)

Insulin in FF correlated with the N. of dominant Follicles (r=-0.433; p=0.008)

CONCLUSIONS

HMGB1 both in FF and in serum and IGFBP-2 in FF were increased in PCOS, whereas insulin was decreased and IL-6 unchanged. IL-6 probably reflects other functions than inflammation; IL-6 was shown to promote uterine pre-implantation, embryo development, placental genesis and development (Bowen JM *et al.* 2003; Desai N *et al.* 1999). We speculate that HMGB1 and IGFBP-2 could reflect both inflammation and insulin concentrations. The low insulin and high HMGB1 and IGFBP-2 in FF from PCOS confirm that insulin-sensitivity is not well understood yet in the ovary.

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