DIFFERENTIAL REGULATION OF SERUM SEX HORMONE BINDING GLOBULIN IN POLYCYSTIC OVARIAN SYNDROME GIRLS IN RELATION TO WEIGHT.

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INTRODUCTION, AIMS AND OBJECTIVES:

It is thought that sex hormone binding globulin (SHBG) is involved in glucose homeostasis in addition to regulate the levels of sex hormones. Clinical studies associate reduced SHBG concentrations with insulin resistance (IR) suggesting SHBG as an early predictor for type 2 diabetes mellitus.

The aim of the study is to describe the relationship of SHBG with IR and hyperandrogenism markers in a group of adolescents affected with polycystic ovarian syndrome (PCOS), and how weight could affect these markers.

PATIENTS AND METHODS:

This was an observational, transversal, descriptive study in which we evaluated thirty-five women who fulfilled Rotterdam diagnostic criteria for PCOS. The inclusion criteria for this cohort were a) at least two years of evolution since menarche, b) have performed analytical hormone in early follicular phase of the menstrual cycle (after treatment with oral progesterone overload, Progevera® 10mg for 5 days, if amenorrhea). Exclusion criteria were a) history of thyroid disorders b) current treatment with oral contraceptives c) hyperprolactinemia (>30ng/ml) d) diabetes mellitus e) Cushing's syndrome f) androgen secreting tumor g) Congenital adrenal hyperplasia.
Glucose, insulin, SHBG, testosterone, LH and FSH were determined among other biochemical variables. Homeostasis model assessment-estimated insulin resistance (HOMA-IR) and free androgen index (FAI) were calculated **(Table 1).** Patients were divided into: normal weight (BMI<25kg/m^2) and overweight/obesity (BMI>25kg/m^2).

RESULTS:

- SHBG was significantly lower (22.1±11.8nmol/L vs. 35±16.9nmol/L, P=0.015) and HOMA-IR and insulin were significantly higher (5.4±2.8 vs. 2.3±0.63 P=0.001; 25.6±13.7mUI/mL vs. 12.8±5.3mUI/mL P=0.003) in girls with overweight/obesity respected to the normal weight group **(table 2).**
- In overweight girls, SHBG levels inversely correlated with BMI (r=-0.521, P=0.001), insulin (r=-0.476, P=0.011), HOMA-IR(r=-0.438, P=0.025) and FAI (r=-0.651, P<0.001), whereas in the normal-weight group SHBG inversely correlated with FAI (r=-0.736, P=<0.001), testosterone (r=-0.476, P=0.039) and hirsutism (r=-0.491, P=0.033) and positively with FSH (r=0.589, P=0.021) **(Table 3).**
- Stepwise regression analysis showed HOMA-IR as the only independent variable explaining 43% of SHBG variability (P = 0.011) in overweight/obesity girls, whereas in the normal weight group, FSH was the only independent predictor explaining 34.7% of changes in SHBG (P=0.021) **(Table 4).**

Table 1. Descriptive characteristics of the patients included in the study

	n: 35	Reference ranges
Age (years)	14.7 ± 1.61 (12-18)	
Body mass index (kg/m^2)	25.989± 6.9	18-25
Hirsutism (F-G)	10.8± 4.2	<8
Estradiol (pg/ml)	40.7± 28	12,5-166*
LH (mUI/L)	7.6 ± 4.8	2,4-12,6*
FSH (mUI/L)	4.5 ± 1.4	3,5-12,5*
SHBG (nmol/L)	29.2± 15.9	32,4-128
Testosterone (ng/dl)	44.4 ± 19.6	4,6-38,3
17-hydroxyprogesterone (ng/dL)	265± 147.5	19-182*
Androstendione (ng/dl)	357.05 ± 173.6	73-221
Dehydroepiandrosterone (ng/mL)	2824.7 ± 1139.8	715
Glucose (mmol/L)	4.6 ± 0.4	3,8-5,6
Insulin (mUI/mL)	19.2± 12.1	2,6-24,9
HOMA-IR	3.98± 2.6	0,5-5,5
HbA1c (%)	5.3 ± 0.32	4-5,7
Free androgen index (%)	8.0± 7.9	0,29-5,62

(Data are expressed as mean ± SD) * Follicular phase

Table 2. Anthropometric, clinical and laboratory data of the patients classified according to their BMI into two groups: normal weight or overweight and obese

	BMI<25kg/m2	BMI>25kg/m2	p
Age (years)	14.6 ± 1.8	14.8 ± 1.4	N.S.
Body mass index (kg/m^2)	21.4 ± 2.6	31.4 ± 6.4	<0.001
Hirsutism (F-G)	11.7 ± 4.3	9.8 ± 4.0	N.S.
Estradiol (pg/ml)	46.7 ± 38.5	35.4 ± 13.2	N.S.
LH (mUI/L)	6.6 ± 4.1	8.7 ± 5.5	N.S.
FSH (mUI/L)	4.2 ± 1.5	4.8 ± 1.3	N.S.
SHBG (nmol/L)	35.0± 16.9	22.1 ± 11.8	0.015
Testosterone (ng/dl)	44.3 ± 22.1	44.5 ± 16.7	N.S.
17-hydroxyprogesterone (ng/dL)	289.6 ± 163.7	231.6 ± 119.8	N.S.
Androstendione (ng/dl)	369.4 ± 204.3	343.2 ± 136.4	N.S.
Dehydroepiandrosterone (ng/mL)	2907.1 ± 1208.6	2726.8 ± 1083	N.S.
Glucose (mmol/L)	4.6 ± 0.39	4.7 ± 0.39	N.S.
Insulin (mUI/mL)	12.8 ± 5.3	25.6 ± 13.7	0.003
HOMA-IR	2.3± 0.63	5.4± 2.8	0.001
HbA1c (%)	5.17 ± 0.2	5.3 ± 0.37	N.S.
Free androgen index (%)	6.3 ± 5.7	10.1± 9.7	N.S.

Table 3. Significant correlations of SHBG

	n	Body mass index (kg/m^2)	Insulin (mUI/mL)	HOMA-IR	Free androgen index (%)	FSH (mUI/L)	Hirsutism (FG)	Testosterone (ng/dL)
All patients	35	-0.521	-0.476	-0.438	-0.651	0.263	-0.157	-0.239
		0.001	0.011	0.025	<0.001	NS	NS	NS
BMI<25kg/m2	19	-0.313	-0.049	0.247	-0.736	0.589	-0.491	-0.476
		NS	NS	NS	<0.001	0.021	0.033	0.039
BMI≥25kg/m2	16	-0.509	-0.682	-0.656	-0.639	0.075	0.097	0.232
		0.044	0.007	0.011	0.008	NS	NS	NS

Table 4. Linear regression with serum SHBG as the dependent variable

Patients with BMI ≤ 25kg/m^2 (R= 0.589, R^2= 0.347)

Predictors	β	p-value
FSH (mUI/mL)	7.562	0.021

Patients with BMI ≥ 25kg/m^2 (R= 0.656, R^2= 0.430)

Predictors	β	p-value
HOMA-IR	-0.522	0.011

CONCLUSIONS:

- ✓ In girls affected with PCOS, serum SHBG is subjected to different regulation according to the weight of the patients.
- ✓ In overweight/obese group, HOMA-IR is an independent factor which explains 43% of SHBG variability, however, in the normal weight group, FSH explained 34.7% of SHBG variability. So this study supports the hypothesis that SHBG could be an early marker of insulin resistance in the overweight/obesity group.

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