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Sex hormone–binding globulin and lipid profile in pubertal children

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Abstract

Men and women have different lipid profiles throughout life, related to changes in sex hormones; and this has been associated with sex-related differences in the prevalence of coronary heart disease. The influence of sex hormone changes during puberty on the lipid profile has been reported, but levels of sex hormone–binding globulin (SHBG) (the specific plasma binding protein of sex hormones) have not been evaluated even though its regulatory role might be crucial. The aim of this study was to analyze the relationship between sex hormones and SHBG and changes in plasma lipid levels during puberty. Our population-based sample included 370 healthy schoolchildren (175 male and 195 female), ranging from 12 to 15 years old. High-density lipoprotein cholesterol (HDL-C) levels were significantly lower in 15-year–olds than in younger boys, and apolipoprotein (apo) A-I levels steeply decreased across the studied age groups. Parallel to these changes, testosterone levels increased whereas SHBG decreased as age increases in boys. In girls, no significant differences were observed in these variables among the age groups. Testosterone and SHBG were highly correlated with anthropometric variables. Sex hormone–binding globulin was negatively associated with triglycerides (TG) in both sexes, remaining statistically significant after further adjustment for age and body mass index (BMI) in girls. Sex hormone–binding globulin was the only predictive variable for HDL-C and TG in multiple linear regression analysis, after adjustment by BMI, in both sexes, accounting for 10% of the variance of HDL-C in boys and for around 5% of the variance of TG in both sexes. In boys, testosterone and SHBG remained significantly correlated to apo A-I levels, even after adjusting for age and BMI, and were the most important predictive variables for apo A-I in multiple linear regression analysis. In conclusion, SHBG levels are related to a decrease in HDL-C and apo A-I levels during puberty in boys and to a decrease in TG levels during puberty in both sexes.

1. Introduction

Differences in plasma lipid levels seem to be related to the different onset and prevalence of coronary heart disease between men and women throughout life [1]. Thus, the effects of sex hormones and their regulatory action on lipid metabolism have been widely investigated [2-5]; and hormone levels have been associated with variations in lipid levels according to age and sex.

Pubertal development implies evident anthropometric, hormonal, and lipid changes that lead to different cardiovascular risk factors in both sexes. Plasma lipid levels remain similar during childhood, but important differences in the lipid profile between the sexes develop during puberty [6]. Most studies have reported a decrease in plasma cholesterol during adolescence in different populations [7-9]. Data in Spanish children showed that, between 12 and 15 years of age, high-density lipoprotein cholesterol (HDL-C) levels underwent an important decrease in boys while remaining unchanged in girls [10]. Some studies have analyzed the effects of sex hormone levels on plasma lipid levels in children, and the different trends in HDL-C levels by sex during puberty have been related to the rise of testosterone levels in boys [11,12]. However, all the studies have focused on total levels of sex hormones; and the role of sex hormone–binding globulin (SHBG) (the specific plasma binding protein of sex hormones) has not been evaluated in children. Sex hormone–binding globulin modulates the availability of biologically active free testosterone and estradiol and their metabolic clearance rate [13,14]; however, the regulation of SHBG itself is complex, involving the sex

Dedicated to Prof Manuel de Oya, as the warmest homage to his memory.

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hormones as well as nonsteroidal factors [15]. The regulatory role of SHBG might be crucial in the relationship between hormone levels and the modification of lipid profiles in children during puberty, an age at which important sex-related changes and differences in lipid levels start to become established. Thus, in our study, we analyzed, for the first time to our knowledge, the relationship between SHBG and plasma lipid levels in a population-based sample of 12- to 15-year–old Spanish children.

2. Participants and methods

2.1. Subjects

The sample population included 370 healthy school-children (175 male and 195 female) from the *Comunidad de Madrid*, ranging from 12 to 15 years old, who participated in the follow-up of a voluntary survey in Spain, "the Four Provinces Study," a large-scale cross-sectional study examining cardiovascular risk factors in 4 large metropolitan areas of the country [16].

2.2. Data collection and study variables

The study protocol was approved by the Ethics Committee of Clinical Investigation of the *Fundación Jiménez Díaz*. The investigation fulfils the principles contained in the Declaration of Helsinki and subsequent reviews, as well as the prevailing Spanish legislation on clinical research in human subjects. All parents had to give written consent for their children's inclusion in the study. A team consisting of one physician and several nurses was in charge of blood extractions and physical measurements. All children reported by their parents as having metabolic syndrome or endocrine, liver, or kidney disorders were excluded. Information on oral contraceptive consumption in girls was not collected.

2.3. Anthropometric variables

Measurements were taken with children wearing light clothing and barefoot. Weight was determined to the nearest 0.1 kg using a standardized electronic digital scale, and height was measured to the nearest 0.1 cm using a portable stadiometer. Body mass index (BMI; weight in kilograms divided by height in meters squared) was calculated from these parameters.

2.4. Biochemical data

Blood samples were obtained early in the morning after a 12-hour fasting period by venipuncture into Vacutainer tubes (Terumo, Leuven, Belgium). Samples were kept on ice and sent to the laboratory for analysis. Once centrifuged, fractions were separated and frozen at −70°C. Serum samples for laboratory analyses were blinded to the laboratory as to sex, age, and school. Cholesterol and triglycerides (TG) were measured enzymatically (Menarini Diagnostics, Firenze, Italy) with an RA-1000 Autoanalyzer (Technicon, Dublin, Ireland). The methods were calibrated by using a commercial

Table 1
Plasma lipid and hormone levels (mean ± SD) among Spanish pubertal children by age

	Boys				
	12 y (n = 41)	13 y (n = 30)	14 y (n = 57)	15 y (n = 47)	ANOVA
TC (mg/dL)	176.7 ± 26.3[a]	157.6 ± 21.7[b]	154.2 ± 21.1[b]	153.4 ± 22.8[b]	<.0001
LDL-C (mg/dL)	111.4 ± 25.2[a]	92.2 ± 18.8[b]	89.8 ± 20.8[b]	95.0 ± 21.5[b]	<.0001
Apo B (mg/dL)	69.2 ± 14.9	65.2 ± 10.9	63.8 ± 13.8	68.5 ± 15.2	NS
TG (mg/dL)	80.3 ± 32.2	89.3 ± 42.2	83.2 ± 36.0	91.3 ± 30.4	NS
HDL-C (mg/dL)	49.3 ± 10.2[a]	47.6 ± 11.6[a]	47.8 ± 11.2[a]	40.1 ± 9.5[b]	<.0001
Apo A-I (mg/dL)	150.7 ± 17.6[a]	141.8 ± 17.0[ab]	138.0 ± 15.3[b]	129.2 ± 15.9[c]	<.0001
Testosterone (ng/mL)	1.67 ± 1.30[a]	3.23 ± 2.43[b]	4.94 ± 3.18[c]	7.00 ± 2.80[d]	<.0001
Estradiol (pg/mL)	28.4 ± 6.2[ac]	27.3 ± 7.2[ab]	33.3 ± 12.7[cd]	33.6 ± 10.8[d]	.011
SHBG (nmol/L)	91.5 ± 58.3[a]	64.9 ± 25.1[ab]	56.9 ± 25.8[b]	44.0 ± 20.2[c]	<.0001
	Girls				
	12 y (n = 30)	13 y (n = 31)	14 y (n = 94)	15 y (n = 40)	ANOVA
TC (mg/dL)	177.2 ± 26.5[a]	169.5 ± 31.6[ab]	166.7 ± 25.1[ab]	159.3 ± 23.2[b]	.056
LDL-C (mg/dL)	112.3 ± 22.8[a]	100.2 ± 27.7[ab]	99.6 ± 23.3[ab]	97.3 ± 18.4[b]	.053
Apo B (mg/dL)	72.3 ± 10.4	71.1 ± 18.0	68.8 ± 15.4	66.4 ± 12.5	NS
TG (mg/dL)	83.3 ± 25.5	90.0 ± 34.7	80.9 ± 26.5	77.4 ± 16.4	NS
HDL-C (mg/dL)	48.2 ± 11.2	51.4 ± 13.9	50.9 ± 11.2	46.5 ± 12.8	NS
Apo A-I (mg/dL)	143.1 ± 16.3	140.1 ± 18.8	142.8 ± 16.9	139.3 ± 16.9	NS
Testosterone (ng/mL)	0.86 ± 0.35	0.85 ± 0.33	0.85 ± 0.34	0.95 ± 0.35	NS
Estradiol (pg/mL)	46.1 ± 19.0[a]	82.8 ± 67.9[b]	72.2 ± 46.6[b]	77.7 ± 53.8[b]	.028
SHBG (nmol/L)	60.7 ± 39.9	73.7 ± 29.8	74.2 ± 28.5	67.6 ± 24.9	NS

Different superscript letters ([abc]) present significant differences between the groups. Age group definitions: 12-year group, children between 11.5 and 12.4 years old; 13-year group, 12.5 to 13.4 years old; 14-year group, 13.5 to 14.4 years old; and 15-year group, 14.5 to 15.4 years old. TC indicates total cholesterol; NS, not significant.

lyophilized serum calibrator (Multicalibrator, Menarini Diagnostics). Two control sera, for normal (low control) and pathologic (high control) ranges, were used for accuracy and precision evaluation. High-density lipoprotein cholesterol was measured after precipitation of apolipoprotein (apo) B–containing lipoproteins with phosphotungstic acid and Mg (Roche Diagnostics, Madrid, Spain). Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula. Plasma apo A-I and apo B concentrations were measured by immunonephelometry (Dade Behring, Frankfurt, Germany) using N Apolipoprotein Standard Serum and Apolipoprotein Control Serum CHD (Dade Behring) for calibration and control, respectively. The interassay coefficients of variation were as follows: cholesterol, 1.4%; TG, 1.7%; apo A-I, 1.55%; and apo B, 4.8%. Testosterone and estradiol were determined by coated tube radioimmunoassay using commercial kits (DSL-4000 Active Testosterone and DSL-43100 Active Estradiol, respectively; Diagnostic Systems Laboratories, Webster, TX). Sex hormone–binding globulin was measured using an immunoradiometric assay kit (DSL-7400 Active SHBG, Diagnostic Systems Laboratories). The theoretical sensitivities of our testosterone, estradiol, and SHBG assays are 0.08 ng/mL, 11 pg/mL, and 3 nmol/L, respectively. The sensitivity of the testosterone assay is inadequate for the measurement of testosterone in females, as consistently admitted [17], and could be inadequate in a small percentage of children (around 10%) with testosterone levels less than this detection limit. With SHBG values greater than 14 nmol/L in both sexes, the analytical sensitivity of our SHBG assay largely exceeds the needs.

2.5. Statistical analysis

All statistical analyses were conducted using the statistical package SPSS v9.0 (SPSS, Chicago, IL). The results are expressed as mean ± standard deviation. Differences in the measurements by age in boys and girls were evaluated by analysis of variance (ANOVA). Post hoc analyses were carried out with Tukey test or Tamhane T2 test as required. Pearson correlation analyses were performed to evaluate the relationships between hormone levels and anthropometric variables and plasma lipid levels. Variables that showed departures from normality as assessed by the Kolmogorov-Smirnov test (hormone and TG levels in boys and estradiol and TG levels in girls) were logarithmically transformed before statistical analysis. Multiple linear regression models were used to analyze the relationships between sex hormones and lipids levels after forced adjustment for BMI.

3. Results

Table 1 shows lipid and hormonal profiles by age in the 175 boys and 195 girls included in our study. The average age of the children was 13.6 ± 1.1 years in boys and 13.7 ± 0.9 in girls. The prevalence of menarche was 83%, 87%, and 97% in 13-, 14-, and 15- year–old girls, respectively. Our study lacks information on oral contraceptive consumption; however, based on data for Spanish girls (Ministry of Health and Consumer Affairs), it is unlikely that a significant number of girls in our study were taking oral contraceptives. From the 10% of the 14- to 15-year–old Spanish girls having sexual relationships, only 11% of the 15-year–old girls seem to be taking oral contraceptives. In boys, TC and LDL-C levels were significantly higher in 12-year–olds than in older children. The HDL-C levels were significantly lower in 15-year–olds than in younger boys. The apo A-I levels in boys were significantly and progressively lower as the considered age increases (Fig. 1A). No significant differences in plasma

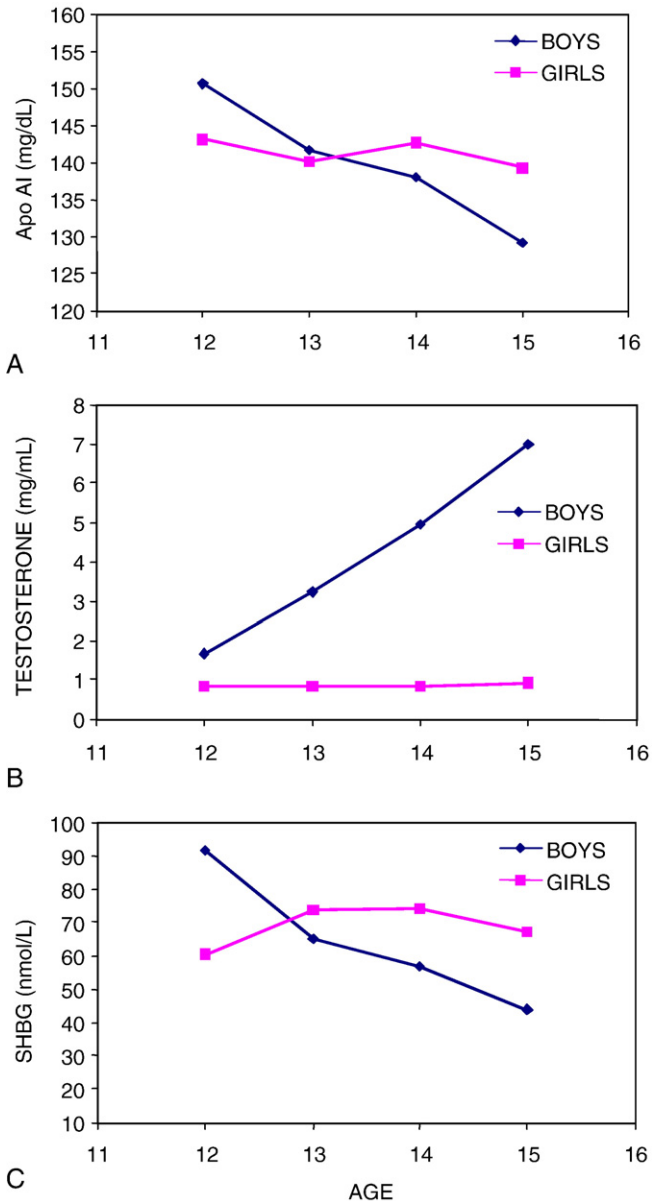

Fig. 1. Apolipoprotein A-I, testosterone, and SHBG levels in boys and girls by age. Age group definitions: 12-year group, children between 11.5 and 12.4 years old; 13-year group, 12.5 to 13.4 years old; 14-year group, 13.5 to 14.4 years old ; and 15-year group, 14.5 to 15.4 years old.

Table 2
Pearson correlations of sex hormones with anthropometric variables and plasma lipid levels

	Boys			Girls		
	Log testosterone	Log estradiol	Log SHBG	Testosterone	Log estradiol	SHBG
Weight	0.404†	0.191*	−0.667†	0.242†	0.006	−0.416†
Height	0.641†	0.271†	−0.583†	0.108	0.098	0.019
BMI	0.115	0.083	−0.516†	0.218†	−0.039	−0.467†
TC	−0.224†	−0.051	0.129	−0.041	−0.076	0.065
HDL-C	−0.241†	0.079	0.301†	−0.033	0.101	0.174*
Apo A-I	−0.431†	−0.045	0.350†	−0.066	0.060	0.128
Log TG	0.193*	−0.048	−0.236†	0.116	−0.002	−0.266†
LDL-C	−0.172*	−0.071	0.060	−0.057	−0.144	0.034
Apo B	0.039	−0.040	−0.106	0.094	−0.068	−0.011

* $P \leq .05$.
† $P \leq .01$.

lipid levels by age group have been observed in girls. In boys, mean testosterone levels were 4.56 ± 3.26 ng/mL; and in girls, estradiol levels were 71.2 ± 50.5 pg/mL. The SHBG levels were significantly lower in boys (61.6 ± 37.3 nmol/L) than in girls (70.8 ± 30.0 nmol/L). In boys, testosterone levels increased gradually and significantly (Fig. 1B); and SHBG levels decreased gradually and significantly (Fig. 1C) across the studied period. In girls, estradiol levels are higher in 13-year–olds than in 12-year–olds, but without differences between 13-, 14-, and 15-year–olds; and SHBG levels did not show significant differences across age groups.

Pearson correlations between hormones and anthropometric and lipid variables in boys and girls were evaluated (Table 2). Testosterone was positively associated with weight and height in boys and with weight and BMI in girls. Estradiol was significantly correlated with weight and height in boys, but not in girls. Sex hormone–binding globulin was highly negatively correlated with weight, height, and BMI in boys and with weight and BMI in girls. Weight and BMI were negatively correlated with HDL-C and apo A-I levels in both sexes and positively correlated with TG in boys (data not shown).

Partial correlation coefficients were computed adjusting for age and BMI (Table 3). In boys, after adjustment for age and BMI, testosterone levels—which had been significantly negatively correlated with TC, LDL-C, HDL-C, and apo A-I and positively correlated with TG in bivariate correlation analysis (Table 2)—remained negatively correlated with apo A-I and positively correlated with TG (Table 3). In bivariate analysis, SHBG was positively associated with HDL-C and apo A-I and negatively associated with TG in boys, whereas it was positively associated with HDL-C and negatively associated with TG in girls (Table 2). After adjusting for age and BMI, SHBG remained positively associated with apo A-I in boys and negatively associated with TG in girls (Table 3).

Stepwise multiple regression analyses were performed with HDL-C, apo A-I, and TG as dependent variables after adjustment for age and BMI. Independent variables included testosterone, estradiol, and SHBG. Sex hormone–binding globulin was the single predictive variable for HDL-C, accounting for 10% of the variance in HDL-C in boys and 3.2% in girls, after adjustment for BMI (Table 4). Sex hormone–binding globulin was also the only predictive variable for TG, accounting for 5.4% of its variance in boys and for 4.6% of the total variance in girls. In the regression model for apo A-I in boys, after adjusting for BMI, testosterone and SHBG account for 16.2% of the variance of plasma apo A-I levels in boys (Table 4).

4. Discussion

Important changes in plasma lipid levels related to sexual maturation occur during puberty. In our cross-

Table 3
Partial correlations between sex hormones and plasma lipid levels, adjusted for age and BMI

	Boys			Girls		
	Log testosterone	Log estradiol	Log SHBG	Testosterone	Log estradiol	SHBG
TC	−0.024	−0.008	0.047	−0.020	−0.065	0.082
HDL-C	−0.151	0.129	0.104	0.013	0.076	0.096
Apo A-I	−0.287†	0.048	0.169*	−0.012	0.070	0.058
Log TG	0.176*	−0.079	−0.050	0.091	0.015	−0.254†
LDL-C	−0.008	−0.078	0.121	−0.051	−0.122	0.089
Apo B	0.114	−0.034	0.049	0.095	−0.046	0.039

* $P \leq .05$.
‡ $P \leq .001$.

Table 4
Multiple linear regression models for HDL-C, apo A-I, and TG as dependent variables after adjustment for BMI

	HDL-C B (SE)	Apo A-I B (SE)	Log TG B (SE)
Boys			
Testosterone	−0.310 (0.294)	−1.314 (0.445)†	1.077 (0.976)
Estradiol	0.184 (0.088)	0.168 (0.135)	−0.387 (0.291)
SHBG	0.081 (0.026)†	0.118 (0.040)†	−0.178 (0.087)*
R^2 (%)	10.0	16.2	5.4
Girls			
Testosterone	−0.135 (2.760)	−1.552 (3.885)	1.700 (5.925)
Estradiol	0.016 (0.018)	0.008 (0.025)	−0.024 (0.039)
SHBG	0.067 (0.032)*	0.054 (0.046)	−0.182 (0.069)†
R^2	3.2	–	4.6

* $P < .05$.
† $P < .01$.

sectional study of pubertal children between 12 and 15 years old, we observed progressively lower HDL-C and apo A-I levels as the studied age increased in boys but not in girls, as previously described in Spanish populations [10] and others [9,18,19].

The relationship between sex hormone levels and these different sex-dependent changes in plasma lipid levels during puberty has been investigated, and the important decrease in HDL-C levels in boys has been linked to the increase in testosterone levels during puberty [11,12,20]. In our population, we actually observed a stronger correlation of testosterone with apo A-I than with HDL-C. In agreement with previous studies [21], the relationship between testosterone and HDL-C levels in the boys in our study seemed to be due to the effects of testosterone on apo A-I rather than the amount of cholesterol associated with these proteins.

However, to our knowledge, the relationship of SHBG with these changes in HDL-C levels during puberty has not been investigated previously. In our pubertal population, the progressive decrease in HDL-C and, in particular, apo A-I observed in boys but not in girls was also accompanied by a parallel decrease in SHBG levels in boys, whereas no changes were seen in girls. Boys included in our study were in a moment of important global changes, affecting both growth and hormonal levels; and a considerable increase in their body weight, greater than 15 kg, was accompanied by progressive changes in testosterone (increase) and SHBG (decrease) plasma concentrations with age [22]. In girls, however, estradiol levels rose from 12 to 13 years old but had no further significant increase. Weight in girls did not change across the studied period, and height was only slightly different between 12 years old and the rest of ages [22]. Changes in anthropometric variables may be affecting both hormone levels and lipid profile; thus, to check the relationship of sexual hormone and SHBG with lipid levels, multiple regression analysis adjusted by BMI was performed.

In our study, SHBG was identified as the only significant explanatory variable for HDL-C and TG levels, after adjustment by age and BMI, in both sexes, whereas both testosterone and SHBG were identified as the main predictive variables for apo A-I levels in boys. We observed a similar association between SHBG and TG levels in boys and in girls, with SHBG accounting for similar variance of TG levels in both sexes. However, we observed a stronger association between SHBG and HDL-C levels in boys than in girls that could be related to its effect on apo A-I levels noticed only in boys. Most cross-sectional studies in adults have reported SHBG to be a major determinant of TG and HDL-C, as the associations between these variables and SHBG are much stronger than their associations with the sex hormones themselves [5]. Sex hormone–binding globulin was found to be positively associated with HDL-C and negatively associated with TG in men [4,5,23-25] and in women [24,26-28], although a recent study in Japanese population has described this association in women but not in men [28], suggesting that the association may depend on the studied population. Other cross-sectional studies reported that even though SHBG correlated positively with HDL-C levels, adjustment for body weight weakened this association [29]. In our population, SHBG levels were inversely correlated with weight and BMI in both boys and girls; and although the correlation between SHBG and HDL-C weakened after adjusting for BMI, the correlation with apo A-I remained significant in boys, as did the correlation with TG in girls. No association was found between SHBG or sex hormones and LDL-C after adjustment by age and BMI.

Present observational study was not directed to establish the mechanism by which HDL-C decreases during puberty. Nevertheless, based on the known role of SHBG on sex-hormone transport and the strong correlations between SHBG and testosterone with HDL-C and apo A-I observed in boys during puberty, it is tempting to speculate that the increase in total testosterone and the decrease of SHBG, which facilitates the biodisposal of free testosterone, both contribute to reducing apo A-I and HDL-C concentration during puberty, possibly by increasing HDL particles catabolism [30]. The inverse relationship between SHBG and TG found in both sexes is intriguing, and the explanation is not evident. Further studies, possibly involving the measurements of changes in other proteins participating in lipoprotein metabolism, such us apo A-V and lipoprotein lipase, are required.

A limitation of our study is the sensitivity of the assay to determine testosterone in children with low levels of this variable. Unfortunately, the lack of information for children before the age of 12 years appears as another weakness in our study, in which, given its cross-sectional nature, it cannot be established which decrease occurred first—testosterone or SHBG—with the onset of puberty. Although the number of girls in our study taking oral contraceptives may be very low, the lack of information on oral contraceptive consumption appears as another limitation in our study.

In summary, in our pubertal population, SHBG levels are negatively associated with TG levels in boys and girls, and positively associated with HDL-C, being also related to apo A-I levels in boys. Sex hormone–binding globulin seems to play an important role on the decrease of HDL-C levels occurring during puberty in boys.

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