Relationship of dehydroepiandrosterone-sulphate with overweight and insulin sensitivity in 12-to-16-year-old Spanish children

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Running title: DHEA-S & insulin sensitivity in children

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Abstract

Aim: DHEA-S is the most abundant steroid hormone in human circulation. Although a relationship of DHEA-S with obesity-related diseases has been reported, the metabolic role of this hormone remains unclear, particularly in children. In our study, we have investigated the relationship of DHEA-S levels with anthropometric variables, insulin, HOMA, and free fatty acids in adolescents.

Subjects and methods: The study sample included 812 healthy 12-to-16-year-old children (383 boys and 429 girls). Plasma DHEA-S was determined by RIA, insulin concentrations by IRMA, and free fatty acids by using a commercial kit. Insulin resistance was estimated using the HOMA index.

Results: No significant differences in plasma DHEA-S levels were found between sexes. DHEA-S levels in overweight children were significantly higher than in normal-weight children. DHEA-S levels were significantly correlated with weight and BMI after adjusting for age. Significant positive correlations between DHEA-S and free fatty acids levels were found after adjusting for age and BMI, particularly in boys, but not between DHEA-S levels and insulin or HOMA in either gender.

Conclusions: DHEA-S levels in 12-to-16-year-old children are correlated with weight and BMI independently of age. We failed to find any association between DHEA-S and insulin levels, but we did find a significant correlation between DHEA-S and free fatty acids levels, suggesting that its association with free fatty acids may be related to the onset of the association of DHEA-S with insulin resistance.

Introduction

Dehydroepiandrosterone (DHEA) is the most abundant steroid hormone in human circulation, causing a wide variety of physiological effects. A relationship of DHEA and its sulphated form dehydroepiandrosterone sulfate (DHEA-S) with obesity and obesity-related alterations, including insulin resistance, has been suggested in adults [1].

DHEA-S concentrations are maintained at a minimum level between 1 and 6 years, after which they increase to reach adult levels by the end of the second decade of life [2]. Plasma insulin concentrations also increase with advancing puberty, with pubertal children being less insulin-sensitive than prepubertal children [3]. Research analyzing the relationship between DHEA-S levels and insulin in healthy children has yield contradictory results, with studies reporting a negative correlation between plasma DHEA-S concentrations and insulin sensitivity analyzing healthy prepubertal and pubertal children together [3], studies failing to find any significant associations between DHEA-S levels and insulin sensitivity in prepubertal children [4] or adolescents girls [5], and studies reporting this correlation during the transition from prepuberty to puberty, as well as during puberty [6].

In our study, we aimed to analyze the relationship between DHEA-S levels and anthropometric variables, glucose, insulin, HOMA, and free fatty acids (FFA) in a population-based sample of 12-to-16-year-old Spanish children.

Materials and Methods

Subjects: The sample group was made up of 812 healthy 12-to-16-year-old boys (383) and girls (429) who participated in a cross-sectional study designed to analyze cardiovascular risk factors in Spanish schoolchildren. The study protocol complied with the Helsinki Declaration guidelines and was approved by the Clinical Research Ethics Committee of the IIS-Fundación Jiménez Díaz. After full explanation of the purpose and procedures of the study, parents were required to provide written consent for their children to participate.

Anthropometric variables: Parents were asked to provide information regarding their children's general health and to report their birth weight as it appeared on their birth certificate. Height and weight measurements were taken with the children lightly dressed and barefoot, and body mass index (BMI) was computed based on these measurements. The children were classified as normal-weight or overweight according to the International Obesity Task Force BMI criteria for children.

Biochemical data: Fasting (12-hour) venous blood samples were obtained by venipuncture. DHEA-S was determined by radioimmunoassay (RIA) using a commercial kit: DSL-3500 DHEA-S (Diagnostic Systems Laboratories, Inc., Webster, USA)**.** Insulin concentrations were measured by IRMA using a commercial kit (BI-Insulin IRMA, Bio-Rad, Marnes la Coquette, France). Insulin resistance was estimated using the HOMA index and FFA levels were measured by using the Wako NEFA-C kit (Wako Industries, Osaka, Japan).

Statistical analysis: Statistical analyses were carried out using the SPSS software package, version 9.0 (SPSS Inc.). The Mann-Whitney test was used to compare DHEA-S mean values between boys and girls and between overweight and non-overweight children. Spearman correlation analyses were performed to evaluate the correlations between DHEA-S levels and anthropometric and biochemical variables.

Results

No significant differences in plasma DHEA-S levels were found between sexes. Plasma DHEA-S levels were significantly higher in overweight than in normal-weight boys (184.5 ± 128.0 µg/dl versus 151.0 ± 90.7 µg/dl, respectively) and were also significantly higher in overweight than in normal-weight girls (181.5 ± 112.3 µg/dl versus 145.8 ± 88.5) (table 1)

DHEA-S levels were positively and significantly correlated with weight and BMI in both girls and boys after adjusting for days of life (table 2). No significant correlations were found between birth weight and DHEA-S levels.

When analyzing the correlations between DHEA-S and insulin sensitivity-related variables after adjusting for age and BMI, we observed significant correlations between DHEA-S and FFA levels in both genders, with the correlation being higher in boys (table 2). In boys, DHEA-S was also negatively correlated with plasma glucose levels. No significant correlations were found between DHEA-S and insulin or HOMA in either gender.

Discussion

We have characterized DHEA-S levels in adolescents between the ages of 12 and 16 years, analyzing the association between DHEA-S and aspects related to insulin sensitivity. DHEA-S concentrations were slighter higher in boys, but without significant differences between genders. The data obtained from other populations of healthy adolescents studied in terms of sex-based differences in DHEA-S levels are scarce; the available literature either reports data on sick children or includes small sample sizes for the age range included in our study [2, 7].

Although a significant association between DHEA-S levels and obesity has been reported in some studies in children [8], other studies fail to find this relationship, and suggest that chronological age is a confounding variable in this association [9]. We have found significantly higher levels of DHEA-S in overweight children and a significant correlation between DHEA-S and weight and BMI after adjusting for age (days of life).

When analyzing the relationship of DHEA-S with insulin-related variables in our 12-to-16-year-old children, we failed to find any consistent association between DHEA-S concentrations and insulin, or HOMA, although a correlation between DHEA-S and glucose levels was present in boys. As in ours, the study of van Hoff et al failed to find any significant association between insulin and DHEA-S in healthy adolescent girls [5]. Other than this, the studies analyzing the association between DHEA-S and insulin or insulin resistance in healthy adolescents include small sample sizes for the age range similar to the age of children in our study [3, 4, 6] making difficult the comparison with our data. Even though our findings are independent of the age of the children, the lack of information on Tanner stage in our children appears as a limitation of our study, as we are unable to perform these analyses according to state of puberty.

However, an interesting finding in our study is the association between DHEA-S and FFA levels. As previously observed in rodents [10], recent studies in obese women have found that DHEA-S treatment modifies plasma fatty acid composition in both postmenopausal and premenopausal women [11]. In their study, de Heredia et al [10] suggest that FFA could be mediators in the insulin-sensitizing actions of DHEA-S.

In conclusion, in our study of 12-to-16-year-old children, we report that DHEA-S levels exhibit no differences between boys and girls, but are significantly associated with weight and BMI in both genders. A particularly noteworthy finding is that, although no significant associations between DHEA-S and insulin or HOMA have been established yet, DHEA-S is significantly correlated with FFA levels independently of age and BMI.

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Table 1: Plasma DHEA-S levels in normal-weight and overweight boys and girls.

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Boys	
Normal-weight (260)	Overweight (123)
151.0±90.7	184.5±128.0*
Girls	
Normal-weight (325)	Overweight (104)
145.8±88.5	181.5±112.3*

p: Test Mann-Whitney; *p≤0.01

Table 2: Correlations between DHEA-S and weight, BMI, insulin, HOMA, and FFA adjusted by age. (Correlation between DHEA-S and biochemical variables also adjusted according to BMI)

	DHEA-S (µg/dl)	
	Boys (n = 383)	Girls (n = 429)
Weight (kg)	**.157** **p = .002**	**.192** **p =.000**
BMI (kg/m^2)	**.168** **p = .001**	**.210** **p =.000**
Birth weight (kg)	-.072 p = .116	-.030 p =.637
Glucose (mg/dl)	-.111 p = .032	-.079 p =.110
Insulin (mIU/l)	-.073 p =.157	.083 p =.092
HOMA	-.084 p =.107	.075 p =.129
FFA (mEq/l)	**.208** **p =.000**	**.121** **p =.014**