Cardiovascular Risk Factors in Children and Adolescents with Congenital Adrenal Hyperplasia

Abstract

Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by impaired steroidogenesis. Glucocorticoid treatment with increased androgens may lead to cardiovascular and metabolic effects in these patients. In this study, we investigated the relationship between cardiovascular risk factors and androgen levels in children and adolescents with CAH due to 21 hydroxylase deficiency. **Materials and Methods:** A cross-sectional study of 78 patients (37 boys and 41 girls) with CAH aged 3–17 years. Anthropometric, body mass index (BMI), systolic (SBP), and diastolic (DBP) blood pressure were measured. Fasting blood glucose with plasma insulin and lipids were measured, and insulin resistance (HOMA-IR) calculated using the homeostasis assessment model. Furthermore, testosterone, Dehydroepiandrosterone sulfate (DHEAS), and 17-Hydroxyprogesterone (17OHP) were investigated. **Results:** The mean SBP and DBP were 112.01 ± 19.13 and 69.77 ± 7.56, respectively. The mean of HOMA-IR in patients was 2.25 ± 1.46. The frequency of patients with overweight and High HOMA index were, respectively, 33.3% and 29.3%. The correlation analysis between clinical characteristics and androgen serum levels showed that DBP and BMI had a significant positive correlation with 17OHP. The median regression analysis showed, only DBP in the adjusted model had a significant positive effect with 17OHP level ($P < 0.05$), and no significant relationship was observed for other characteristics. **Conclusion:** A significant association was found between BMI and DBP with serum concentrations of 17-OHP, suggesting that elevated 17-OHP can lead to an increased risk of cardiovascular disorders in children and adolescents with CAH.

Keywords: *17-hydroxyprogesterone, androgens, blood pressure, Cardiovascular System, congenital adrenal hyperplasia*

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Introduction

Congenital adrenal hyperplasia (CAH) is a rare inherited autosomal recessive disorder caused by enzymatic mutations leading to impair normal steroid synthesis.[1] Lack of the enzyme 21-hydroxylase is the most common cause of CAH (more than 90% of cases).[2,3] It is characterized by impaired aldosterone and cortisol production as well as excess androgen.[4] CAH caused by 21-hydroxylase deficiency is divided into classical and nonclassical types.[5] The world incidence of the classic form of this type of CAH estimated 1:12,000–1:15,000 live newborns.[6] Despite the lack of data on the incidence of CAH in Iran, it seems that due to high consanguineous marriages, Its prevalence has increased.[7]

Evidence suggests that patients with CAH often have cardiovascular risk factors such as obesity, weight gain, high blood pressure, dyslipidemia, and glucose homeostasis disorders, and insulin resistance.[8-10] Cardiovascular morbidity has been reported in patients with CAH.[11,12]

Patients with this disorder need treatment with glucocorticoid to suppress excessive production of ACTH and adrenal androgens and as a result, provide normal growth.[13,14] Furthermore, patients with salt-wasting form need treatment with mineralocorticoid to prevent the development of potentially lethal salt-losing crises. However, glucocorticoids and/or mineralocorticoids may increase cardiovascular risk in CAH patients.[9] Most studies have focused on the cardiovascular risk factors and metabolic outcomes 17OHP in Children and Adolescents with CAH, but to our knowledge, there are few data regarding the association between androgen serum

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levels and 17OHP concentrations and cardiovascular riskfactors in these patients. Therefore, in this study, we aimed to evaluate the cardiovascular risk factors associated with androgen levels in children and adolescents with CAH.

Materials and Methods

A cross-sectional study was conducted from 2018 to 2019 include 78 patients who were referred to pediatric endocrinology clinic of Isfahan endocrine and metabolism research center. Patients aged 3–17 years old. The inclusion criteria consisted of patients with CAH (21 hydroxylase deficiency) who have passed 3 years since diagnosis.

The diagnosis of CAH and subtype was confirmed in some patients by, clinical and biochemical data. In some cases, diagnosis confirmed by CYP21A2 mutation analysis. Patients with hyponatremia, hyperkalemia, increase plasma renin considered as salt-wasting, and patients without electrolyte imbalance were considered as simple virilizing (SV). Patients treated with hydrocortisone (10–20 mg/m^2/day in 2–3 divided doses). After recording the anthropometric indices (height (m), weight (Kg), and body mass index (BMI) (Kg/m^2), the patients were examined by an endocrinologist and their stage of puberty and blood pressure were determined. Pubertal status was determined by Tanner stages.[15] Patients were visited in endocrine clinic every 3 months. BP was measured after 5 min of rest, sitting mean systolic and diastolic blood pressure (SBP and DBP) was measured according to a standard nursing protocol by an automated oscillometric device from the right arm. We tried to minimize the factors that may affect blood pressure such as activity, anxiety also patients were asked not to eat for at least 30 min before measurement. The measurement of blood pressure was measured twice in case of BP >90th percentile by age and gender from both arms and legs.[16] Furthermore, lipid, glucose, insulin, testosterone, DHEAS, and 17-OHP levels were measured after 10–12 h of fasting.

Insulin resistance was determined by the homeostasis model assessment of insulin resistance (HOMA-IR) using the following formula described by Matthews *et al.*[17] HOMA-IR = (fasting Insulin [mU/ml] × fasting glucose [mg/dl]/405) and values higher than 2.7 was considered insulin resistance.[18] For all patients, Bone age was determined from an anteroposterior radiography of the left wrist using the Greulich and Pyle atlas.[19] Glucose and lipid metabolism were determined with indirect calorimetry methods.[20,21] DHEAS and testosterone were measured using a chemiluminescence immunoassay (Siemens Medical Solution Diagnostics, CA, USA). The level of 17-OHP was measured with ELISA (Enzyme-Linked Immunosorbent Assay) Kit.

Statistical analysis

Descriptive analysis was performed on demographic and clinical characteristics, such as number (percentage), maximum and minimum, mean (± standard deviation), and median (interquartile range [IQR]). All variables were checked for normal distribution using the Kolmogorov–Smirnov and Shapiro–Wilk test. Since the hypothesis of normality was not rejected for all characteristics, the nonparametric Spearman's rank correlation test was used to explore associations between clinical characteristics with androgen serum levels. Moreover, median regression was used to test the influence of the BMI, DBP, SBP, HOMA_index, TG (Triglyceride), CHOL (Cholesterol), and low-density lipoprotein (LDL) on the androgen serum levels (17OHP, testosterone, and DHEAS) in CAH Patients. $P < 0.05$ was considered as statistical significance. All statistical analyses were conducted using the software packages SPSS v. 24.0 (SPSS Inc., Chicago, USA).

Results

Descriptive analysis

The demographic and clinical characteristics of the study patients are presented in Table 1. A total of 78 patients with CAH, including 37 (47.4%) males and 41 (52.6%) females were included in the study. 51 cases (65.4%) had salt-wasting form of CAH and 27 (34.6%) cases had simple virilizing form of CAH. The mean age of the patients was 9.40 ± 4.09 years, with mean bone age 10.38 ± 4.25 years. Furthermore, the mean age at diagnosis was 1.99 ± 2.94 years. According to the WHO definitions, the mean BMI of patients was 20.54 ± 4.74 kg/m^2. The mean SBP and DBP were 112.01 ± 19.13 and 69.77 ± 7.56, respectively. The mean of HOMA-IR in patients was 2.25 ± 1.46.

The frequency of some risk factors in CAH patients are presented in Table 2, and accordingly, the frequency of patients with overweight and high HOMA index were, respectively, 33.3% and 29.3%.

Descriptive statistics on the androgen serum levels of CAH patients with 21-hydroxylase deficiency in this study are summarized in Table 3. According to these data, the median (IQR) levels of 17-OHP, testosterone, and DHEAS were 8.40 (21.83) ng/dl, 0.66 (2) ng/ml, and 79.00 (163.87 μ/dl), respectively.

Correlation analysis

The Spearman's rank correlation analysis between clinical characteristics (BMI, DBP, SBP, HOMA index, TG, CHOL, and LDL) and androgen serum levels (17OHP, Testosterone, and DHEAS) showed that DBP and BMI had a significant positive correlation (at the level of $P < 0.01$ and $P < 0.05$, respectively) with 17OHP [Table 4]. Other clinical characteristics showed no statistically

Table 1: General demographic and clinical characteristics of the patients

Characteristics	Cases (*n*=78), *n* (%)
Males, *n* (%)	37 (47.4)
Females, *n* (%)	41 (52.6)
Salt wasting, *n* (%)	51 (65.4)
Simple virilizing, *n* (%)	27 (34.6)
Chronological age (years)	9.40±4.09*
Bone age (years)	10.38±4.25
Age of diagnosis (years)	1.99±2.94
BMI (kg/m^2)	20.54±4.74
SDS of weight (kg)	2.25±3.09
SDS of height (m)	0.25±2.19
SBP (mmHg)	112.01±19.13
DBP (mmHg)	69.77±7.56
Fasting blood glucose (mg/dl)	85.13±10.06
HOMA index	2.25±1.46
TG (mg/dl)	94.43±46.70
Cholesterol (mg/dl)	155.15±31.96
LDL (mg/dl)	88.44±27.81
HDL (mg/dl)	51.28±12.02
Serum insulin level (mIU/L)	13.80±19.77
Sodium (meq/L)	137.24±5.04
Potassium (meq/L)	4.71±0.85

*Mean±SD. SD: Standard deviation, BMI: Body mass index, SDS: SD score, HOMA: Homeostasis model assessment, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TG: Triglycerides

Table 2: Frequency of clinical characteristics of the congenital adrenal hyperplasia patients enrolled in the study

Characteristics	Frequency, *n* (%)
Overweight	26 (33.3)
High SBP	15 (19.5)
High HOMA index	12 (29.3)
High TG (>100 mg/dL)	11 (14.1)
Low HDL	6 (18.2)
High DBP	5 (6.5)
High cholesterol (>200 mg/dL)	4 (12.1)
Obese	4 (5.1)
High LDL	2 (6.1)

SBP: Systolic blood pressure, HOMA: Homeostasis model assessment, TG: Triglycerides, HDL: High-density lipoprotein, DBP: Diastolic blood pressure, LDL: Low-density lipoprotein

significant correlation with androgen serum levels in CAH patients ($P > 0.05$).

Regression analysis

The median regression analysis is presented in Table 5. The results are reported as regression coefficient with standard error and *P* value in the crude and adjusted model for each characteristic. As the results show, only DBP in the adjusted model had a significant positive effect 17OHP level ($P < 0.05$) and no significant relationship was observed for other characteristics.

Discussion

In this study, we found a relationship between 17OHP and DBP in children and adolescents with CAH which has been less discussed in the previous studies. High blood pressure has been identified as one of the most important risk factors for cardiovascular disease.[22] Results of most studies that evaluating blood pressure in CAH patients, whether in children or adults, indicate that SBP and DBP is higher than normal range.[23-32] The results of our study showed high significant correlation ($P < 0.01$) between 17-OHP and DBP in CAH patients. On the other hand, after adjustment of age and sex, regression model also revealed the high positive significant relationship between 17-OHP and DBP in CAH patients ($P < 0.01$). To our knowledge, no studies to date have been reported the significant association between 17OHP and DBP.

In contrast, Roche *et al.*[26] found the blood pressure was not related to serum concentrations of 17-OHP in children and adolescents with CAH.

The prevalence of overweight has been reported as one of the cardiovascular risk factors in children with CAH in some studies.[25,29,33,34] According our study, 33. 3% of patients were overweight, which showed high prevalence of overweight among patients with CAH.[35] Similar to our results, Roche *et al.*[26] and Völkl *et al.*[33] reported the prevalence of overweight and obesity as a main risk factor in children and adolescents with CAH.

The results of our study showed significant correlation between concentrations of 17-OHP and BMI in CAH patients. In addition, regression analysis also confirmed the positive relationship between 17-OHP and BMI in CAH patients. This indicated that increased concentrations of

Table 3: Summary statistics for androgen serum levels in congenital adrenal hyperplasia patients with 21-hydroxylase deficiency

Androgens	Descriptive statistics						
	Mean±SD	Minimum	Maximum	Median	Quartile 1	Quartile 3	IQR
17OHP (ng/dl)	11.87±10.91	0.10	36.90	8.40	1.37	23.20	21.83
Testosterone (ng/ml)	1.81±3.32	0.02	18.00	0.66	0.20	2.20	2
DHEAS (µ/dl)	430.87±1373.17	0.10	7733.00	79.00	4.13	168.00	163.87

IQR: Interquartile range, SD: Standard deviation, 17OHP: 17-Hydroxyprogesterone, DHEAS: Dehydroepiandrosterone sulfate

Table 4: Correlations of clinical characteristics with 17-Hydroxyprogesterone, testosterone, and dehydroepiandrosterone sulfate

Variables	Androgens		
	17OHP (r, P)	Testosterone (r, P)	DHEAS (r, P)
BMI	0.229, <0.05*	−0.154, NS	−0.227, NS
DBP	0.297, <0.01**	−0.095, NS	−0.155, NS
SBP	0.188, NS	−0.037, NS	−0.104, NS
HOMA_index	−0.081, NS	−0.05, NS	0.202, NS
TG	−0.032, NS	−0.046, NS	−0.065, NS
Cholesterol	−0.168, NS	−0.074, NS	−0.16, NS
LDL	−0.226, NS	−0.165, NS	−0.145, NS
HDL	0.058, NS	0.035, NS	−0.001, NS

*Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level. 17OHP: 17-Hydroxyprogesterone, DHEAS: Dehydroepiandrosterone sulfate, BMI: Body mass index, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, HOMA: Homeostasis model assessment, TG: Triglycerides, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

17-OHP, which is known as index of CAH control, may contribute to an increased risk of cardiovascular factors.

In another study by Mendes-dos-Santos *et al.*,[6] children with CAH (2.1–10.2 years) had higher BMI and fat mass than healthy children. It should be noted that the fat in these patients was often visceral. Since androgens play an important role in lipid and glucose metabolism and consequently fat homeostasis,[36] imbalance of 17-OHP and androgens levels may likely be the cause of BMI increase in CAH patients.

A recent study showed that the obese and overweight group of children had significantly higher 17-OHP than the normal group.[37] Accordingly, it seems likely that control of 17OHP level may be one of the effective keys to decreasing obesity in CAH patients.

Although in our study, there was no statistical relationship between BMI with SBP or DBP, some studies have stated the possible relationship between them in CAH patients.[9,26,38] Nevertheless, in a study by Nebesio and Eugster,[30] who studied hypertension in children with CAH, found a rise in BMI was not a determining factor in blood pressure.

Conclusion

In our study, the significant association was found between BMI and DBP with serum concentrations of 17-OHP, suggesting that elevated 17-OHP can lead to an increased risk of cardiovascular disorders in children and adolescents with CAH.

Table 5: Relationship between clinical characteristics and androgen serum levels (17-hydroxyprogesterone, testosterone, and dehydroepiandrosterone sulfate) analyzed by median regression and linear regression

Clinical characteristics	17OHP				Testosterone				DHEAS			
	Crude model		Adjusted model		Crude model		Adjusted model†		Crude model		Adjusted model	
	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P
SBP	0.280 (0.199)	0.162	0.195 (0.115)	0.096	−0.5575 (0.716)	0.425	−0.042 (0.529)	0.937	0.001 (0.002)	0.451	0.001 (0.001)	0.145
DBP	0.198 (0.111)	0.079	0.309 (0.093)	0.001*	0.000 (0.354)	1.000	−0.599 (0.416)	0.155	0.000 (0.001)	1.000	−0.0004 (0.001)	0.680
FBS	0.052 (0.151)	0.730	0.149 (0.122)	0.230	−0.118 (0.465)	0.800	0.299 (0.462)	0.521	0.0004 (0.001)	0.764	0.001 (0.001)	0.583
HOMA index	0.000 (0.020)	1.000	0.002 (0.021)	0.908	−0.024 (0.062)	0.714	−0.027 (0.065)	0.682	0.0002 (0.0001)	0.264	0.0001 (0.0002)	0.382
TG	−0.424 (0.923)	0.648	−0.386 (0.810)	0.636	−0.424 (0.923)	0.648	−1.736 (2.734)	0.529	−0.001 (0.006)	0.924	−0.002 (0.007)	0.817
BMI	0.081 (0.050)	0.107	0.040 (0.038)	0.290	−0.190 (0.182)	0.298	0.026 (.154)	0.869	−0.0004 (0.000)	0.298	−0.001 (0.0003)	0.082
Cholesterol	−0.320 (0.436)	0.467	−0.121 (0.428)	0.778	0.401 (1.392)	0.775	0.115 (1.449)	0.937	0.001 (0.003)	0.698	−0.001 (0.003)	0.768
LDL	−0.587 (0.371)	0.121	−0.466 (0.376)	0.223	0.256 (1.117)	0.820	0.188 (1.152)	0.871	0.0003 (0.002)	0.886	−0.001 (0.002)	0.636
HDL	0.058 (0.166)	0.729	0.067 (0.173)	0.700	0.061 (0.531)	0.909	0.083 (0.594)	0.890	0.0004 (0.001)	0.725	0.0004 (0.001)	0.762

†Adjusted for age and sex, *Significant at the 0.05 level. SE: Standard error, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, FBS: Fasting blood sugar, HOMA: Homeostasis model assessment, TG: Triglyceride, BMI: Body mass index, LDL: Low density lipoprotein, HDL: High density lipoprotein, 17OHP: 17-Hydroxyprogesterone, DHEAS: Dehydroepiandrosterone sulfate

Conflicts of interest

There are no conflicts of interest.

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