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Original article

Growth and Metabolic Syndrome (MetS) Criteria in Young Children with Classic Congenital Adrenal Hyperplasia (CAH) Treated with Corticosteroids (CS)

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Abstract. *Background:* Treatment of children with congenital adrenal hyperplasia (CAH) with corticosteroids (CS) may increase the risk for developing different components of metabolic syndrome (MetS). *Aim:* We assessed the occurrence of cardiometabolic risk factors in children with CAH on treatment with CS since early infancy. *Methods:* Data of 30 children with CAH were analyzed retrospectively. They have received hydrocortisone (HC; n = 11) or prednisolone (P; n= 19) and fludrocortisone (0.1- 0.15 mg once daily) since early infancy. The different cardiometabolic criteria including blood pressure (BP), fasting glucose, low-density lipoprotein (LDL), and serum cholesterol concentrations were studied and compared with the data for 66 age-matched obese children. *Results:* Children with CAH on treatment for > 5 years had a high rate of obesity and overweight (60%) and short stature (23.3%), respectively. They had higher occurrences of abnormal cardio-metabolic components including high LDL and triglyceride and BP as well as increased carotid intima-media thickness (CIMT). Females had higher body mass index (BMI) and BP compared to males. The less controlled group was older and had faster linear growth compared to the controls. In the CAH group, BP and CIMT were correlated significantly with BMI-SDS and weight-standard deviation score (Wt-SDS). Neither the level of 17-hydroxy-Progesterone (17-OHP), nor the HC dose was correlated with BP, CIMT or BMI. *Conclusion:* These findings suggest the role played by excessive weight gain on the increased cardiometabolic risk factors in children with CAH on treatment with CS. (www.actabiomedica.it)

Key words: Congenital adrenal hyperplasia (CAH), children, cardiometabolic risk factors, blood pressure, metabolic syndrome.

Introduction

Glucocorticoids have been used for half a century for treating patients with congenital adrenal hyperplasia (CAH) to prevent adrenal crisis and virilization and to allow normal linear growth and development. Hydrocortisone in two or three daily divided doses represents the therapy of choice in growing patients with classic CAH because of its lower risk for growth suppression compared with the longer-acting steroid preparations. The standard dose is typically in the range of 10–20 mg/m^2/day. However, patients with CAH, due to severe 21-hydroxylase deficiency (21-OHP-D), need an increased dose of glucocorticoids during periods of stress (1).

There are various diagnostic methods for metabolic syndrome (MetS) in children and adolescents. According

to the International Diabetes Federation (IDF), MetS is diagnosed if children, aged between 10–16 years, have central adiposity (≥ 90th percentile) and two of the followings: triglycerides (TG) ≥ 150 mg/dl, HDL-C < 40 mg/dL, systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥ 85 mmHg, fasting plasma glucose (FG) ≥ 100 mg/dL (2). Based on the WHO criteria, MetS is diagnosed when three or more of the following features are found: body mass index (BMI): > 95th percentile, hyperinsulinemia or impaired fasting glucose or impaired glucose tolerance, BP > 95th percentile, TG > 105/136 mg/dL (1.2/1.5 mmol/L) for children aged < 10 and > 10 years, respectively, and HDL-C< 35 mg/dL (0.9 mmol/L) (3).

Previous studies have suggested that young adults with classical CAH have an increased prevalence of the different components of metabolic syndrome including obesity, hypertension, elevated fasting blood glucose, and dyslipidemia. However, the reported incidence of MetS in children and adolescents with CAH is relatively sporadic (4-8).

Both, the elevated androgens (despite attempts at the optimization of glucocorticoid dosing) as well as the supraphysiologic glucocorticoid doses, which are required to suppress excess ACTH signaling to the adrenal gland, are suggested to contribute to cardiometabolic disease (9,10).

Therefore, there is a need for following children with classical CAH from diagnosis at infancy through early childhood and adolescence to better depict the natural history of MetS and its components, along with markers of cardiovascular risk (11). In addition, studying the possible relationship between hormonal control and treatment-related factors on the one hand and these cardiometabolic abnormalities, on the other hand, is important for a better understanding of their contribution in the pathogenesis of MetS that could ultimately lead to the improvement of treatment and prevention of MetS during adulthood.

Substantially, the aims of the study were: (a) to assess the occurrence of cardiometabolic risk factors in children with CAH on treatment with CS since early infancy and to compare them with another high-risk group of obese children with body mass index - SDS (BMI-SDS) > 2; (b) to compare cardiometabolic abnormalities in children with CAH on treatment with two different forms of glucocorticoids (CS: hydrocortisone versus prednisone); and lastly (c) to compare the occurrence of markers of cardiovascular risk in children with CAH on treatment with CS according to their gender and hormonal control, based on the level of 17-Idrossi-Progesterone (17-OHP).

Patients and methods

Data of 30 children with CAH treated with CS were analyzed retrospectively. They received hydrocortisone (HC; n =11 patients) or prednisolone (P; n= 19 patients) and fludrocortisone (0.1- 0.15 mg OD) since early infancy. The mean HC dose was 22.5 ± 7 mg/m^2. The growth data [height (Ht), Ht-SDS, weight, BMI, BMI-SDS, and BP were recorded during each clinic visit along the duration of treatment. The markers of cardiovascular risk abnormal cardiometabolic criteria included impaired fasting glucose (IFG), high low-density lipoprotein (LDL) and cholesterol, reduced high-density lipoprotein cholesterol (HDL-cholesterol) levels, and high blood pressure for age and sex over the period of treatment.

The occurrence of steroid-associated cardiometabolic abnormalities in children with CAH on treatment with CS since early infancy was compared with another high-risk age-matched group of obese children with BMI-SDS > 2 (n = 66 subjects).

The cardiometabolic abnormalities in children with CAH on treatment with two different forms of glucocorticoids (HC versus P) were compared. In addition, the cardiometabolic abnormalities were compared in males versus females and in those with good hormonal control (based on the assessment of 17-OHP level) versus those less controlled. 17-OHP was categorized as suppressed if the values were below 3 nmol/L, controlled if the values were between 3- 6 nmol/L, and less controlled if > 6 nmol/L.

MetS was defined using the modified National Cholesterol Education Program Adult Treatment Panel III devised by the American Heart Association and National Heart, Lung, and Blood Institute. For children 4 years and older, MetS was defined using Weiss et al. criteria (12). MetS was diagnosed in patients who presented 3 or more of the following criteria:

fasting blood glucose ≥100 mg/dL, BP >95th percentile, TGL > 95th percentile, HDL < 5th percentile, or BMI ≥ 95th percentile. National Health and Nutrition Examination Survey (NHANES) data (2015-2016) were used to interpret lipids in relation to age, race, and sex-specific norms for pediatrics (13).

High-resolution B-mode ultrasonography was performed to measure the carotid intima-media thickness (CIMT) and to evaluate the color Doppler flow characteristics of the carotid arteries. A CIMT value of more than 0.9 mm or over the 75th percentile was considered abnormal (14). CIMT data were compared to those for 30 normal age-matched children.

Statistical analysis

Data are reported as mean ± SD, or as frequencies and percentages. Student t-test was used to compare the different variables between the studied groups when the data were normally distributed and Wilcoxon rank sum test when the data were not normally distributed. Significance was accepted when P: < 0.05. Linear regression equation was used to investigate correlations between the different variables.

Ethics

The study complied with the Declaration of Helsinki and was approved by the Ethical Committee of Alexandria University, College of Medicine, approved the study (MS: 0105553- 21-6-2018). Written informed consent was obtained from the parent/guardian for all patients and controls included in the study.

Results

Comparison between the CAH group treated for an average of 5 years with CS and age-matched obese children showed that short stature (Ht-SDS < -2) and high LDL occurred more significantly in the CAH group. As opposed, impaired fasting glucose and low HDL occurred more frequently in the obese group. Hypertension was detected in 2/30 (6.7%) of the CAH group vs 12.1% in the obese group (Table 1).

Children who received P, once daily dose (n = 22) were compared to those on two divided doses of HC (n = 8). Both groups were taking fludrocortisone for 5 years or more. Those on HC were taking 15.2 ± 3.7 mg /m2 daily and those on P were taking 21.0 ± 5.2 mg/m^2 HC equivalent dose.

After 5 years of treatment with P or HC the Ht-SDS, BMI, and BP did not differ significantly between the two groups. Six out of the 22 children on P therapy had short stature (Ht-SDS <-2) versus 1 out of the 8 children on HC. Fasting glucose, insulin, and homeostasis model of assessment IR (HOMA-IR) values did not differ between the two groups. However, high

Table 1. Metabolic risk factors among CAH children on CS therapy for > 5 years vs obese children.

Variables	CAH on corticosteroids for >5 yr.	Obese 5-10 yr.	P value
Number of subjects	30	66	
Age (years)	6.7 ± 2.3	7.8 ± 2.5 (*)	0.043
Overweight and obese (%)	60%	100% (*)	< 0.0001
Short stature Ht-SDS <-2	23.3% (*)	6%	0.013
IFG > 5.6 mmol/L	0%	16.7% (*)	0.017
LDL > 2.7 mmol/L	26.7% (*)	7.5%	0.011
HDL < 1.03 mmol/L	3.3%	21.2%	0.17
TG >1.7 mmol/L	16.6%	7.5%	0.17
Cholesterol > 4.5 mmol/L	10%	21.2%	0.18
HOMA IR > 2.5	6.6%	45% (*)	0.01
Hypertension (BP > 95th centile for age and sex)	6.6%	12.1%	0.41

Legend: (*) difference statistically significant.

cholesterol was detected in 3/22 of those treated with P and low HDL was detected in 1/22 of those treated with P but in none of the HC-treated group. LDL was significantly higher in the P-treated group versus the HC group. Obesity and overweight occurred both in the P (32% and 27.3%, respectively) and in HC groups (12.5 % and 50%, respectively). Hypertension was detected in 1 patient on P and another patient on HC treatment. However, the difference between the two groups was not statistically significant (Table 2). The CIMT values (mean: 0.52 ± 0.07 mm) were significantly higher in the CAH group versus normal age-matched control children (0.044 ± 0.004, P: <0.001).

Comparison between the growth and metabolic data of males (n =11) and females (n =19) with CAH showed that the dose of steroid to achieve control did not differ among the two groups. Females had slightly higher BMI compared to males. 5 /11 males were overweight and 1/11 obese, while 5/19 females were overweight and 7/19 were obese. Blood pressure (especially diastolic BP) was higher in females versus males (P: 0.0096). One girl had both systolic and diastolic high BP. Ht-SDS did not differ between the 2 genders. 2/11 boys and 4/19 girls had Ht-SDS < -2. The components of the lipogram, fasting glucose, fasting insulin, and HOMA-IR did not differ among the two groups. High cholesterol was detected in 2/11 boys and 3/19 girls. High triglycerides were detected in 1/11 boys and 4/19 girls.

The comparison between the growth and metabolic data of the hormonally controlled group (n =19, 2/19 had Tanner's stage 2 for pubic hair) with the less controlled group (5/11 had Tanner's stage 2 for pubic hair and 1/11 had Tanner's stage 3, based on the level of 17-OHP (a level of 17-OHP between 3 to 6 nmol/L was considered controlled while a level of 17-OHP > 6 nmol/L was considered less controlled) are presented in table 3. The pubic hair, assessed with Tanner's stage, was more advanced in the latter group (P= 0.26).

High BP was detected in 1/19 of the controlled group but none of the less controlled group. HC dose was significantly higher in the less controlled group. The components of the lipogram, fasting glucose, fasting insulin and HOMA-IR did not differ among the two groups.

The systolic and diastolic BP were correlated significantly with BMI and Wt-SDS but not with the

Table 2. Anthropometric and biochemical data in children with CAH: Comparison between those taking prednisone (P) vs hydrocortisone (HC).

Prednisone n = 22	**Age (years)**	**HC eq. mg/m^2**	**Systolic mmHg**	**Diastolic mmHg**	**Ht-SDS**	**BMI kg/m^2**	**17-OHP ng/mL**
Mean	6.4	21.0 (*)	98.4	62.8	-0.67	18.7	2.99
SD	2.6	5.2	6.7	4.1	1.60	5.0	3.19
Hydrocortisone n =8							
Mean	7.4	15.2	96.5	61.2	-0.32	18.9	2.56
SD	3.0	3.7	12.5	7.7	1.2	3.3	2.51
P value	0.35	<0.01	0.64	0.33	0.93	0.95	0.66
Prednisone n = 22	**Cholesterol mmol/L**	**TG mmol/L**	**HDL mmol/L**	**LDL mmol/L**	**Fasting Insulin μU/mL**	**FPG mg/dL**	**HOMA-IR**
Mean	162.0	74.0	55.1	91.3	6.5	73.9	1.16
SD	30.1	24.9	10.7	26.3	5.9	11.1	0.82
Hydrocortisone n =8							
Mean	144.5	69.1	53.5	72.8	6.2	73.7	1.13
SD	19.0	25.8	4.9	19.1	2.5	6.7	0.47
P value	0.11	0.61	0.67	0.06	0.85	1.00	0.84

Legend: **(*)** 1 mg of prednisone is approximately equivalent to 4 mg of hydrocortisone

Table 3. Anthropometric and biochemical data of children with CAH: Controlled versus less controlled.

	Age years	HC dose in mg	SBP mmHg	DBP mmHg	Wt- SDS	Ht-SDS	BMI kg/m^2	17-OHP ng/mL
Controlled n =19								
Mean	5.9	21.1	97.0	62.2	0.37	-0.61	17.8	1.9
SD	1.9	6.5	9.4	5.5	1.2	1.4	2.6	0.7
Less controlled n = 11								
Mean	7.9	27.1	99.4	62.8	0.40	-0.52	20.40	8.2
SD	3.3	6.4	7.1	5.0	1.80	1.60	3.48	2.5
P value	0.042	0.03	0.57	0.61	0.96	0.89	0.041	<0.001

Table 4. Correlations between anthropometric and metabolic variables in children with CAH.

	Age yr	HC dose/m2	SBP	DBP	WtSDS	HtSDS	BMI	Tanner	17OHP	Cholesterol	TG	HDL	LDL	F insulin	FBG	HOMA-IR
Age yr	1.00															
HC dose/m2	0.26	1.00														
SBP	0.48	-0.14	1.00													
DBP	0.40	-0.07	0.73	1.00												
WtSDS	0.52	0.07	0.41	0.31	1.00											
HtSDS	0.09	0.22	0.22	0.14	0.56	1.00										
BMI	0.79	0.02	0.43	0.33	0.64	0.01	1.00									
Tanner	0.80	0.10	0.49	0.36	0.52	0.22	0.63	1.00								
17OHP	0.24	0.07	0.05	0.00	0.01	0.13	0.09	0.43	1.00							
Cholesterol	0.15	-0.23	0.18	0.14	0.13	0.17	0.00	0.29	0.06	1.00						
TG	-0.08	0.10	-0.27	-0.16	-0.02	0.39	-0.23	-0.24	-0.22	0.23	1.00					
HDL	0.30	-0.03	0.09	0.14	-0.14	-0.28	0.14	0.41	0.14	0.47	-0.29	1.00				
LDL	0.03	-0.29	0.17	0.19	0.10	0.15	-0.07	0.16	0.10	0.93	0.23	0.25	1.00			
F insulin	0.03	0.07	-0.02	-0.03	0.05	0.27	-0.12	0.05	0.18	-0.04	0.02	-0.08	-0.17	1.00		
FBG	0.06	-0.03	0.19	0.14	0.22	0.32	0.03	0.06	0.01	-0.02	0.22	-0.14	-0.02	-0.23	1.00	
HOMA-IR	0.02	0.26	0.04	0.00	0.08	0.47	-0.15	0.03	0.22	-0.06	0.18	-0.18	-0.19	0.91	0.15	1.00

level of 17-OHP nor with the HC dose. Ht-SDS was correlated significantly with fasting insulin level and HOMA-IR but not with HC dose or 17-OHP level (Table 4). Mean CIMT was correlated to the limit of significance with Wt-SDS (r = 0.35, P = 0.05) (Figure 1) and BMI (r = 0.37, P = 0.047). 17-OHP concentration was not correlated with blood pressure, CIMT or BMI. HOMA-IR was positively correlated with HC dose (Figure 2).

Discussion

Our children with classic CAH on CS treatment for > 5 years had a high rate of obesity and overweight (60%) and short stature (23.3%). In addition, some of them had a higher occurrence of metabolic findings including hypertension, high LDL, and triglyceride levels. Sarafoglou et al. (15) noticed the occurrence of early onset obesity in children with CAH and the occurrence of adiposity rebound (AR) as early as 3.3 years of age. Takishima et al. (16) observed that AR in CAH patients occurred before the age of 4 years. In support of our findings, Bhullar et al. (17) found that CAH patients (n =46) had earlier hypertension at 3.4 ± 1.3 years, and obese CAH patients had earlier hypertension than lean patients. In their study, earlier AR predicted higher BMI-SDS during childhood, as well as increased central obesity and total body fat in adolescence.

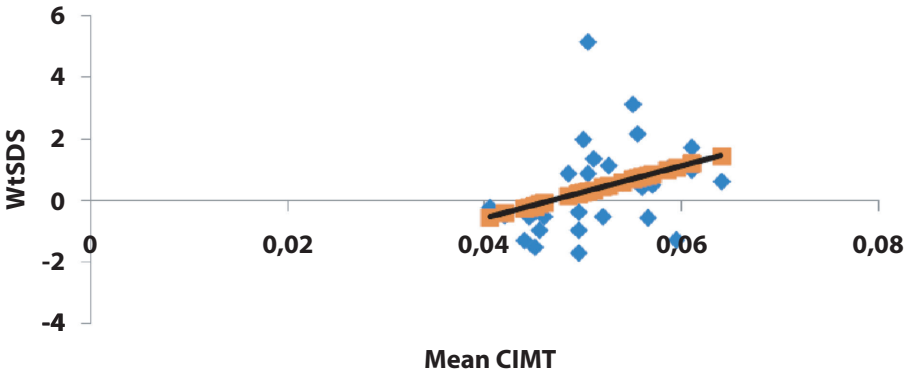

Figure 1. Correlation between carotid intimal-media thickness (CIMT) and weight- SDS (Wt-SDS) (r:0.35, P:0.05).

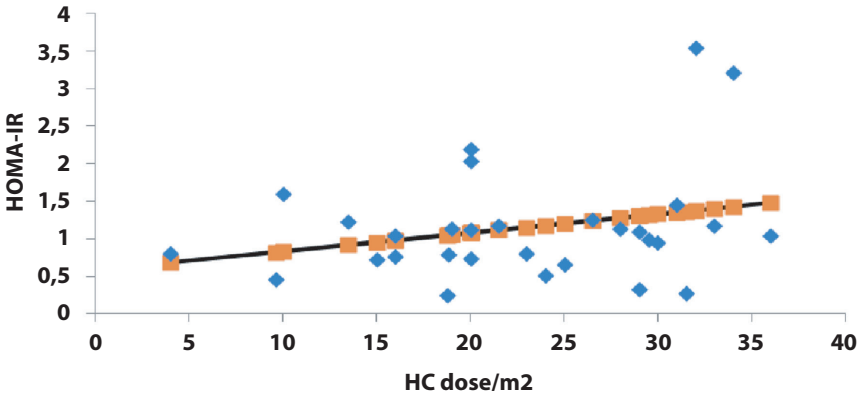

Figure 2. Correlation between hydrocortisone dose (mg/m^2) and homeostasis model assessment of insulin resistance (HOMA-IR) (r:0.26, P: 0.045).

In our patients with CAH, blood pressure (both SBP and DBP) was correlated significantly with BMI and Wt-SDS. In addition, the mean CIMT correlated to the limit of significance with Wt-SDS. Akyürek et al. (18) studied 25 children and adolescents (5-15 years) with CAH. In 24% (n=6) of CAH patients, 24-h ambulatory BP monitoring showed hypertension. Twenty percent (n=5) had nocturnal hypertension. CIMT was higher in patients with nocturnal hypertension.

An increased BMI, waist to height ratio, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), VAT: SAT ratio, HOMA-IR, and higher systolic blood pressure (SBP) has been reported in adolescents with CAH compared to controls (7,19,20). In our study 2/30 of our young children with CAH had high HOMA-IR, and both were obese. However, our patients were young, and it was noted that the prevalence of insulin resistance (IR) in youth with CAH increased with age.

Collectively, these findings pointed out the relation between increased weight and increased cardiometabolic risk factors in these children. This is not surprising, since it is known that high cortisol levels can lead to increased appetite, fat accumulation (truncal), and altered lipid and glucose metabolism (21,22).

In previous studies, IR has been related to HC dose and BMI-SDS. In our study, there was a positive correlation between the HC dose and HOMA-IR (Figure 2). Some authors suggest that lower HC doses could lead to a reduction of IR. Corticosteroids can increase IR through many mechanisms including increased hepatic steatosis, increased lipolysis, and free fatty acids, decreased adiponectin, and decreased insulin signaling in muscles (23,24). Moreover,

Hashemi et al. (25) reported that 17-OHP serum concentrations were positively correlated with DBP and BMI in adolescent patients with CAH. However, in our study 17-OHP concentration was not correlated with blood pressure, CIMT, or BMI.

Compared to obese children without CAH, our children with CAH had a higher prevalence of elevated LDL levels. This can be explained by the effect of corticosteroids (HC and P) on worsening lipid profiles. High cholesterol and high LDL were found in 3/22 and 1/22 of patients taking P but none of the patients on HC therapy. This suggested that P may have a negative effect on lipid profile compared to HC. Documented changes in human lipid profiles on varying doses of P included elevated VLDL, TG, and LDL cholesterol, and increased or decreased HDL cholesterol (26,27).

Interestingly, our female patients with classic CAH on CS treatment for > 5 years had a high rate of obesity, higher BMI, and slightly higher BP compared to males (P: 0.0096). In support of our findings, sexual dimorphism has been observed in adolescents with CAH (12-18 years) with high blood pressure observed to be more prevalent in females compared to males with CAH (28).

In women, it has been shown that androgen excess plays an important role in favoring the growth of visceral fat. Moreover, there is evidence that the combination of androgen excess and obesity may favor the development of MetS and type 2 diabetes (29). In our study, BMI was significantly higher in the less controlled group (with a higher 17O-HP level). Changes in the hormonal milieu during puberty can lead to inadequate suppression of adrenal androgens with increased levels at a time when adherence to medical therapy presents a challenge (30). A single daily dose of P was comparable to twice daily HC doses in achieving control of children with CAH, assessed by 17- OHP levels. Increased occurrence of overweight and obesity was significant in both groups. No dysglycemia occurred in both groups.

The comparison of growth and metabolic data of the hormonally controlled versus the less controlled group showed that the less controlled children were older, had more advanced pubertal development (Tanner's stage pubic hair), accelerated growth, higher BMI-SDS, and were taking higher doses of HC. Ht-SDS was > 2 SDS in 2/11 of the less controlled group (high androgen effect) but in none of the controlled group.

Our study confirmed the higher occurrence of obesity and different metabolic components in young children with CAH on CS therapy. BMI and Wt-SDS were correlated with CIMT and SBP and DBP suggesting an important role of increased weight in the potential development of cardiometabolic risk factors. Neither the level of 17-OHP nor the dose of HC was correlated with BP or CIMT.

In conclusion, young children with CAH must be monitored closely for abnormal growth (weight and height) as well as for the occurrence of abnormal cardiometabolic risk factors. There is a necessity for studying patients with classical CAH from the diagnosis through older adulthood to better characterize the natural history of the metabolic syndrome and its components in relation to the development of cardiovascular abnormalities. This could eventually lead to the prevention of metabolic syndrome and cardiovascular diseases in adulthood. To ensure the continuation of care, clear communication between pediatric and adult endocrinologists is needed during the transition period.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Trapp CM, Speiser PW, Oberfield SE. Congenital adrenal hyperplasia: an update in children. Curr Opin Endocrinol Diabetes Obes. 2011;18:166-70.
2. Alberti KGM, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. Lancet 2005;366:1059–62.
3. Organization WH: Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. World Health Organization; 1999
4. Torky A, Sinaii N, Jha S, Desai J, El-Maouche D, Mallappa A, Merke DP. Cardiovascular Disease Risk Factors and Metabolic Morbidity in a Longitudinal Study of Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab 2021;106:e5247-e57.
5. Subbarayan A, Dattani MT, Peters CJ, Hindmarsh PC. Cardiovascular Risk Factors in Children and Adolescents with Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency. Clin Endocrinol 2014; 80:471–7.

6. Bonfig W, Roehl FW, Riedl S, et al. Blood Pressure in a Large Cohort of Children and Adolescents With Classic Adrenal Hyperplasia (CAH) Due to 21-Hydroxylase Deficiency. Am J Hypertens 2016; 29:266–72.
7. Marra AM, Improda N, Capalbo D, et al. Cardiovascular Abnormalities and Impaired Exercise Performance in Adolescents With Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab 2015; 100:644–52.
8. Akyürek N, Atabek ME, Eklioğlu BS, Alp H. Ambulatory Blood Pressure and Subclinical Cardiovascular Disease in Patients With Congenital Adrenal Hyperplasia: A Preliminary Report. J Clin Res Pediatr Endocrinol 2015;7:13–8.
9. Improda N, Barbieri F, Ciccarelli GP, Capalbo D, Salerno M. Cardiovascular Health in Children and Adolescents With Congenital Adrenal Hyperplasia Due to 21-Hydroxilase Deficiency. Front Endocrinol 2019; 10:212.
10. Falhammar H, Frisen L, Hirschberg AL, et al.. Increased Cardiovascular and Metabolic Morbidity in Patients With 21-Hydroxylase Deficiency: A Swedish Population-Based National Cohort Study. J Clin Endocrinol Metab 2015; 100:3520–8.
11. Kim MS, Fraga NR, Minaeian N, Geffner ME. Components of Metabolic Syndrome in Youth With Classical Congenital Adrenal Hyperplasia. Front Endocrinol (Lausanne) 2022;13:848274
12. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 2004;350:2362-74.
13. Hickman TB, Briefel RR, Carroll MD, et al. Distributions, and trends of serum lipid levels among United States children and adolescents ages 4-19 years: data from the Third National Health and Nutrition Examination Survey. Prev Med 1998;27:879-90
14. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008; 21:93-111
15. Sarafoglou K, Forlenza GP, Yaw Addo O, et al. Obesity in Children With Congenital Adrenal Hyperplasia in the Minnesota Cohort: Importance of Adjusting Body Mass Index for Height- Age. Clin Endocrinol 2017; 86:708–16.
16. Takishima S, Nakajima K, Nomura R, et al. Lower Body Weight and BMI at Birth Were Associated With Early Adiposity Rebound in 21-Hydroxylase Deficiency Patients. Endocr J 2016; 63:983–90
17. Bhullar G, Tanawattanacharoen VK, Yeh MY, et al. Early Adiposity Rebound Predicts Obesity and Adiposity in Youth With Congenital Adrenal Hyperplasia. Horm Res Paediatr 2020; 93:609–15.
18. Akyürek N, Atabek ME, Eklioğlu BS, Alp H. Ambulatory Blood Pressure and Subclinical Cardiovascular Disease in Patients With Congenital Adrenal Hyperplasia: A Preliminary Report. J Clin Res Pediatr Endocrinol 2015;7:13–8.
19. Kim MS, Ryabets-Lienhard A, Dao-Tran A, et al. Increased Abdominal Adiposity in Adolescents and Young Adults With Classical Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency. J Clin Endocrinol Metab 2015;100:E1153–59.
20. Vijayan R, Bhavani N, Pavithran PV, et al. Metabolic Profile, Cardiovascular Risk Factors and Health-Related Quality of Life in Children, Adolescents and Young Adults With Congenital Adrenal Hyperplasia. J Pediatr Endocrinol Metab 2019; 32:871–7.
21. Fardet L, Feve B. Systemic glucocorticoid therapy: a review of its metabolic and cardiovascular adverse events. Drugs 2014;74:1731–45.
22. Peckett AJ, Wright DC, Riddell MC. The effects of glucocorticoids on adipose tissue lipid metabolism. Metabolism 2011;60:1500–10.
23. Gomes LG, Mendonca BB, Bachega TASS. Long-Term Cardio-Metabolic Outcomes in Patients With Classical Congenital Adrenal Hyperplasia: Is the Risk Real? Curr Opin Endocrinol Diabetes Obes 2020;27:155–61.
24. Mooij CF, van Herwaarden AE, Sweep FCGJ, et al. Cardiovascular and Metabolic Risk in Pediatric Patients with Congenital Adrenal Hyperplasia Due to 21 Hydroxylase Deficiency. J Pediatr Endocrinol Metab 2017; 30: 957–66.
25. Hashemi Dehkordi E, Khaheshi S, Mostofizadeh N, Hashemipour M. Cardiovascular Risk Factors in Children and Adolescents With Congenital Adrenal Hyperplasia. Adv Biomed Res 2021; 10:19.
26. Quinkler M, Ekman B, Marelli C, Uddin S, Zelissen P, Murray RD; EU-AIR Investigators. Prednisolone is associated with a worse lipid profile than hydrocortisone in patients with adrenal insufficiency. Endocr Connect 2017;6:1-8.
27. Ross IL, Marais AD. The influence of glucocorticoids on lipid and lipoprotein metabolism and atherosclerosis. S Afr Med J 2014;104:671-4.
28. Bonfig W, Roehl FW, Riedl S, et al. Blood Pressure in a Large Cohort of Children and Adolescents with Classic Adrenal Hyperplasia (CAH) Due to 21-Hydroxylase Deficiency. Am J Hypertens 2016; 29:266–72
29. Pasquali R, Oriolo C. Obesity and Androgens in Women. Front Horm Res 2019;53:120-34.
30. Merke DP, Poppas DP. Management of adolescents with congenital adrenal hyperplasia. Lancet Diabetes Endocrinol 2013;1:341-52.

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