Cardiology in the Young

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Periaortic fat thickness and cardiovascular risk factors in children with congenital adrenal hyperplasia

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Abstract

Objective: Children with congenital adrenal hyperplasia are considered to be at an elevated risk for cardiovascular morbidity and mortality. The objective of this study was to evaluate the association between periaortic fat thickness and the cardiometabolic profile in children diagnosed with congenital adrenal hyperplasia. *Method:* A total of 20 children and adolescents with congenital adrenal hyperplasia and 20 healthy control subjects were enrolled in the study. We investigated metabolic and anthropometric parameters, comparing these values to those of the control group. Periaortic fat thickness was assessed using an echocardiographic method that has not previously been applied to paediatric patients with congenital adrenal hyperplasia. *Results:* The subjects in the congenital adrenal hyperplasia group were significantly shorter than the control subjects ($p = 0.021$) and exhibited a higher body mass index ($p = 0.044$) and diastolic blood pressure ($p = 0.046$). No significant differences were observed between the congenital adrenal hyperplasia group and control subjects concerning age, weight, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels. Additionally, dyslipidemia was identified in 5% ($N = 1$) of the congenital adrenal hyperplasia group. The mean fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance, and fasting glucose-to-fasting insulin ratio were similar between the congenital adrenal hyperplasia group and the control subjects. However, 15% ($n = 3$) of the congenital adrenal hyperplasia group had insulin resistance. Two children with congenital adrenal hyperplasia (10%) were diagnosed with hypertension.

Periaortic fat thickness was significantly greater in the congenital adrenal hyperplasia group compared to the control group ($p = 0.000$), with measurements of 0.2039 ± 0.045 mm in the congenital adrenal hyperplasia group and 0.1304 ± 0.022 mm in the control group. In children with congenital adrenal hyperplasia, periaortic fat thickness exhibited a negative correlation with high-density lipoprotein cholesterol ($r = -0.549$, $p = 0.034$) and a positive correlation with the dose of hydrocortisone ($r = 0.688$, $p = 0.001$). *Conclusion:* Our results provide further evidence of subclinical cardiovascular disease in children with congenital adrenal hyperplasia. It is crucial to regularly assess cardiometabolic risk in children with congenital adrenal hyperplasia. The measurement of periaortic fat thickness in this population may serve as a valuable tool for identifying individuals at high risk for developing early atherosclerosis.

Introduction

Congenital adrenal hyperplasia is a group of autosomal recessive disorders characterised by deficiencies in cortisol biosynthesis. More than 95% of congenital adrenal hyperplasia cases are due to 21-hydroxylase deficiency.[1] Increasing evidences suggests that individuals with congenital adrenal hyperplasia have higher cardiometabolic risk, though the exact mechanisms remain unclear. Factors such as obesity, insulin resistance, hypertension, dyslipidemia,[2,3,4] hyperandrogenism, and the administration of supraphysiological doses of glucocorticoids and mineralocorticoids, as well as adrenal medullary hypofunction, have been implicated in the cardiometabolic risk associated with congenital adrenal hyperplasia.[5,6,7] These factors may contribute to endothelial dysfunction and make these patients prone to developing atherosclerosis and cardiovascular diseases at an early age.[8]

Periaortic adiposity is a critical indicator of atherosclerosis, with its pathogenesis believed to exert localised effects on blood vessels.[9] The present study aims to evaluate the relationship between periaortic adipose thickness and metabolic parameters in children with congenital adrenal hyperplasia. The significance of our study is applying of this measurement technique for the first time in children with congenital adrenal hyperplasia.

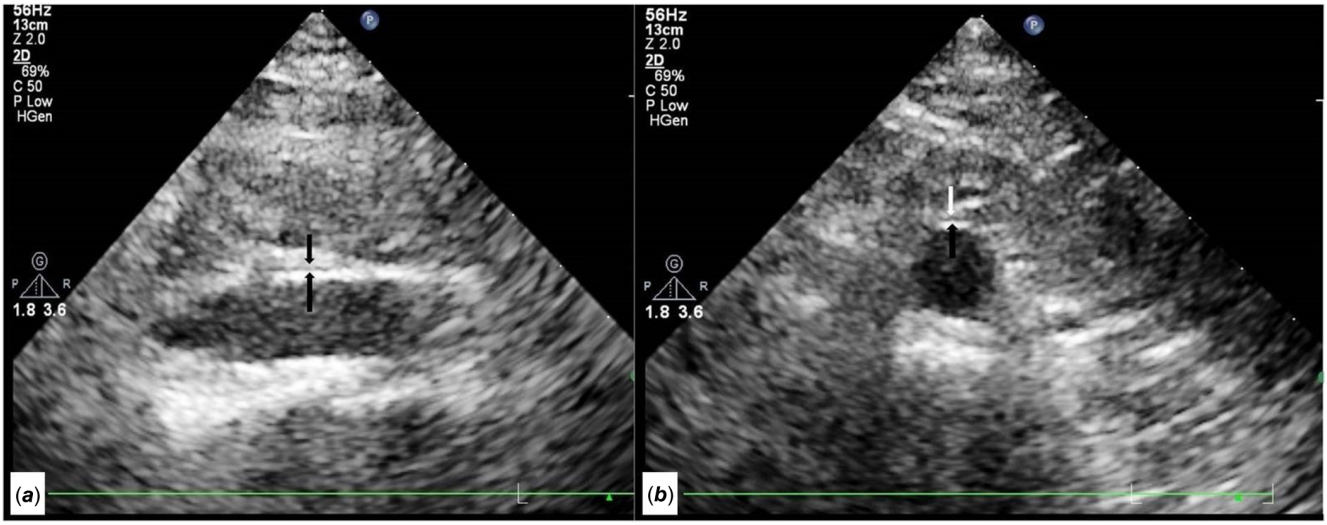

Figure 1. (***a***) Longitudinal (sagittal) and (***b***) transverse sections of periaortic adipose tissue and adventitia views on transthoracic echocardiography.

Materials and method

Study population

This study was performed retrospectively between August 2010 and August 2012 at the Necmettin Erbakan Üniversity Konya, Turkey. The study was approved by the local ethics committee. Approval number is 2024/5009. The study population comprised only Turkish subjects. We included 20 children and adolescents (11 females, 9 males), aged between 5 and 15 years, with salt-wasting 21-hydroxylase deficiency who were already being followed by the Pediatric Endocrinology Outpatient Clinic. All patients had salt-wasting form of congenital adrenal hyperplasia and they had been diagnosed in the neonatal period.

All patients received replacement therapy in the form of oral hydrocortisone (15–18 mg/m^2 body surface area/day) given twice, and 9 α-fludrocortisone (100–150 μg/m^2 body surface area/day) given once or twice daily.

The adequacy of steroid therapy is monitored by regular assessment of clinical and laboratory data in accordance with current guidelines.[10]

Twenty age- and sex-matched children and adolescents, admitted to the outpatient clinics of the Departments of Pediatric Endocrinology, were enrolled into the study as a control group. The control group had no chronic or endocrinologic disease, and their weight and height percentiles were normal.

All subjects were examined by the same physician. Body weight and height were measured by standard methods and devices. Body mass index was calculated by the equation: body weight (kg)/ height (m^2).

Obesity was defined as a body mass index greater than the 95th percentile for age and gender.[11]

Biochemical evaluation

Fasting blood samples were collected from all patients and controls in the morning, between 08:00 and 09:00 h, following an overnight fast. Venous blood samples were obtained for the assessment of serum glucose and lipid metabolism parameters. Serum levels of glucose, insulin, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were analysed in our biochemistry laboratory using standard methodologies. According to the International Diabetes Federation's criteria for adolescents, a triglyceride level exceeding 150 mg/dL was considered elevated, while a high-density lipoprotein cholesterol level below 40 mg/dL was categorised as low.[12]

The homeostasis model assessment of insulin resistance and the fasting glucose/fasting insulin ratio were calculated as estimates of insulin resistance. The fasting glucose/fasting insulin ratio was computed as fasting insulin concentration (μU/mL) divided by fasting glucose concentration (mg/dL). The homeostasis model assessment of insulin resistance was calculated using the formula: (fasting insulin concentration (μU/mL) × fasting glucose concentration (mmol/L))/22.5.[13] Insulin resistance was defined as the homeostasis model assessment of insulin resistance value exceeding 3.16.[14]

Blood pressure measurements

Clinic blood pressure was measured three times at one-minute intervals using a mercury sphygmomanometer, following a minimum resting period of 10 mins. The clinic blood pressure was calculated as the mean of the three measurements. Hypertension was defined as clinic blood pressure ≥ the 95th percentile for age, sex, and height.[15]

Echocardiography

Echocardiographic studies were carried out with a Philips Hewlett-Packard Sonos5500, using 12 MHz flat probes. Measurement of perivascular adipose tissue was done with conventional methods from the adventitia layer of the abdominal aorta and the adventitial layer of the aorta adjacent to the form of the measurement of the linear echogenic line. Periaortic adipose tissue cannot be directly distinguished with echocardiographic and ultrasonographic images in deep tissue. Therefore, it should be measured with adventitia (Figure 1). Measurements were taken in both the axial and sagittal planes in the supine position at the L1-2 level (just above the umbilicus), proximal to the iliac bifurcation. Evaluation was firstly done by a paediatric cardiologist and radiologist and repeated three times. Because this was the first use of echocardiography for periaortic fat measurement, reliability tests

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Table 1. Clinical characteristics of study population

	Cah patients (n:20)	Control group (n:20)	p
Age	9.2 ± 4.2	11.5 ± 2.75	0.068
Weight (kg)	40.2 ± 20.7	42.8 ± 14.5	0.665
Height (cm)	127.6 ± 31.3	148.1 ± 16.8	0.021
Body mass index (kg/m^2)	21.9 ± 4.5	18.6 ± 3.1	0.044
Total cholesterol (mg/dL)	166.26 ± 2.3	160.7 ± 25.4	0.532
Triglycerides (mg/dL)	106.5 ± 70.7	102.9 ± 55.1	0.875
LDL-cholesterol (mg/dL)	94.39 ± 20.06	94.3 ± 22.5	0.991
HDL-cholesterol (mg/dL)	50.1 ± 13.8	47.7 ± 13.0	0.611
Fasting glucose (mg/dL)	83.5 ± 0.64	84.1 ± 8.1	0.787
Fasting insulin (μU/mL)	12.07 ± 10.7	9.07 ± 3.8	0.320
FGIR	10.8 ± 7.01	10.91 ± 5.5	0.991
HOMA-IR	2.6 ± 2.2	3.13 ± 3.03	0.632

*p < 0.05 accepted as significant. LDL-cholesterol: low density lipoprotein cholesterol; HDL-cholesterol: high-density lipoprotein cholesterol; FGIR: fasting glucose-to-insulin ratio; HOMA-IR: homeostasis model assessment for insulin resistance.

were performed. Subsequently, measurements were performed three times by a paediatric cardiologist and values were averaged.

Statistics

The Kolmogorov–Smirnov test was employed to assess data normality. Results are presented as mean ± standard deviation. Differences among groups were analysed using the Student's *t*-test and chi-square tests. All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS/Windows Version 16.0, SPSS Inc., Chicago, IL, USA). The consistency of periaortic fat thickness measurements was evaluated through intraclass correlation coefficients with 95% confidence intervals. A *p*-value of <0.05 was considered statistically significant.

Results

A total of 40 children consented to participate in the study (20 congenital adrenal hyperplasia, 20 control subjects). The groups were matched for age, gender, and body size. The characteristics of the study population are summarised in Table 1.

Subjects in the congenital adrenal hyperplasia group were significantly shorter than those in the control group ($p = 0.021$) and exhibited a higher body mass index ($p = 0.044$). Obesity was identified in 10% of children with congenital adrenal hyperplasia. No significant differences were noted between the congenital adrenal hyperplasia and control groups concerning age, weight, high-density lipoprotein cholesterol, and low high-density lipoprotein cholesterol levels. Dyslipidemia was identified in 5% ($N = 1$) of the congenital adrenal hyperplasia patients.

Mean fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance, and the fasting glucose/fasting insulin ratio were similar between the congenital adrenal hyperplasia and control groups. However, 15% ($N = 3$) of the congenital adrenal hyperplasia subjects had insulin resistance. The mean duration of follow-up for children with congenital adrenal hyperplasia was 8.2 ± 2.4 years, with a mean hydrocortisone dose of 16.41 ± 1,81 mg/m^2 and fludrocortisone dose of 120 ± 24 μg/m^2.

Table 2. Cardiovascular parameters of study population

	Cah patients group	Control group	p
Clinic mean Systolic blood pressure (mmHg)	105.25 ± 11.9	103.8 ± 10.4	0.743
Clinic mean Diastolic blood pressure (mmHg)	68.16 ± 11.19	59.26 ± 10.56	0.046
Periaortic fat thickness (mm)	0.2039 ± 0.045	0.1304 ± 0.022	0.000

*p < 0.05 accepted as significant.

Table 3. Significant correlations between Periaortic fat thickness and other cardiovascular risk factors in children with Cah patients

	p	r
HDL-cholesterol (mg/dL)	0.034	−0.549
Hydrocortisone dose	0.001	0.688

HDL-cholesterol: high-density lipoprotein cholesterol.

Cardiovascular parameters of the study population are presented in Table 2. The congenital adrenal hyperplasia group demonstrated significantly higher diastolic blood pressure ($p = 0.046$), with 10% of children diagnosed as hypertensive. Periaortic fat thickness was significantly greater in the congenital adrenal hyperplasia group compared to the control group ($p = 0.000$), with measurements of 0.2039 ± 0.045 mm in the congenital adrenal hyperplasia group and 0.1304 ± 0.022 mm in the control subjects. Table 3 shows the significant correlations between periaortic fat thickness and other cardiovascular risk factors in children with congenital adrenal hyperplasia, indicating a negative correlation with high-density lipoprotein cholesterol ($r = -0.549$, $p = 0.034$) and a positive correlation with hydrocortisone dosage ($r = 0.688$, $p = 0.001$).

Discussion

The population with congenital adrenal hyperplasia is prone to developing early cardiovascular risk factors, including hypertension, insulin resistance, obesity, and hyperlipidaemia. Consequently, these individuals have an increased risk of cardiovascular disease.[16]

Childhood hypertension is a well-known risk factor for cardiovascular health in later life.[17] Limited data exist regarding blood pressure in congenital adrenal hyperplasia patients, with reported prevalence rates of hypertension varying from 2–5% to 20–66%.[5,18–24] Some studies have indicated normal blood pressure in congenital adrenal hyperplasia patients.[25–27] Potential predisposing factors for hypertension may include altered adrenal medullary function, glucocorticoid and mineralocorticoid treatment, and androgen excess.[28–29] However, the relationship between hypertension and glucocorticoid and mineralocorticoid dosages is not well established. Additionally, there is insufficient evidence to support a direct association with hyperandrogenism.[30]

In our study, we observed that 10% of children with congenital adrenal hyperplasia were hypertensive, with significantly elevated diastolic blood pressure compared to the control group. The

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hydrocortisone dosage in our cohort was within recommended guidelines.[10] Therefore, blood pressure should be measured at each clinic visit.

Glucose homoeostasis is altered in congenital adrenal hyperplasia patients. Several studies have demonstrated a tendency towards insulin resistance in children and adolescents with congenital adrenal hyperplasia, as assessed by increased homeostasis model assessment of insulin resistance.[24,32–36] A meta-analysis found no significant differences in fasting blood glucose, fasting insulin, or glucose response following a glucose load.[37] This is consistent with our findings, as we identified insulin resistance in 15% of children with congenital adrenal hyperplasia. The mean fasting glucose and fasting insulin levels were similar between the congenital adrenal hyperplasia and the control group.

Dyslipidemia may occur as a consequence of increased body fat. Several studies have reported negligible rates of dyslipidemia among patients with congenital adrenal hyperplasia.[33,35] This appears to be in line with our findings that routine lipid profile assessments may not be necessary. However, further research is warranted to better address this issue.

In numerous studies, an increased prevalence of obesity has been documented in children with congenital adrenal hyperplasia.[23,38–39] In our cohort, 10% of children with congenital adrenal hyperplasia were classified as obese, and their body mass index was significantly elevated compared to the control group. Obesity has potentially negative effects on cardiac and metabolic health. Routine evaluations for cardiac and metabolic diseases are recommended for patients with congenital adrenal hyperplasia. Furthermore, early lifestyle counselling should be done.[40]

Patients with congenital adrenal hyperplasia are prone to increased visceral adipose tissue, which is a risk factor for cardiovascular diseases.[36] There is a significant association between specific adipose tissues and cardiovascular diseases. Perivascular fat tissue, which is considered to be a visceral fat, secretes proinflammatory substances and has a local pathogenic effect on blood vessels.[41]

Periaortic fat tissue is a subtype of perivascular fat surrounding aorta and may serve as a marker of perivascular fat in whole of the body, including small blood vessels.[42,43]

Studies have demonstrated that periaortic fat tissue exhibits paracrine signalling and communicates with the aortic wall.[44] An increase in the volume of periaortic fat tissue correlates with enhanced inflammatory effects on vascular structures.[45] Compared to other measures of adiposity, periaortic fat tissue has demonstrated a stronger association with cardiometabolic risk profiles and subclinical atherosclerosis.[46]

There are few studies that focus on periaortic fat tissue. The measurement techniques employed in these studies, such as CT and MRI, are often impractical for routine clinical application.

In the present study, we measured this critical atherosclerosis indicator, periaortic fat tissue, for the first time in children with congenital adrenal hyperplasia using conventional echocardiographic techniques. Our findings indicate that periaortic fat tissue is significantly higher in children with congenital adrenal hyperplasia. Moreover, periaortic fat thickness was negatively correlated with high-density lipoprotein cholesterol, suggesting its important role in determining cardiometabolic risk.

One of the potential contributing factors to increased cardiometabolic risk in patients with congenital adrenal hyperplasia is the administration of supraphysiological doses of glucocorticoids and mineralocorticoids.[5,6] In our study, periaortic fat tissue was positively correlated with the dose of hydrocortisone. Therefore, it is essential to administer doses that are close to physiological levels in order to minimise these potential risk factors.

The main limitation of this study is its limited size and the challenges associated with assessing the impact of steroid treatment. Data regarding the type of steroids used and their cumulative lifetime dosages were not available; therefore, we used the current steroid dosage for our analyses.

Nonetheless, our results suggest that children with congenital adrenal hyperplasia are prone to dyslipidemia, hypertension, insulin resistance, elevated body mass index, and increased periaortic fat tissue; collectively suggesting an elevated cardiovascular risk. Consequently, these patients should be monitored and treated according to guidelines for hypertension, overweight, metabolic syndrome, and hyperlipidaemia to prevent cardiovascular disease.

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