

# Metabolic profile and cardiovascular risk factors in adult patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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## ABSTRACT

**Background:** In congenital adrenal hyperplasia (CAH), long-term glucocorticoid treatment coupled with increased androgens may lead to undesirable metabolic effects. The aim of our report was to determine the prevalence of metabolic abnormalities and cardiovascular risk factors in a population of adult patients with CAH due to 21 hydroxylase deficiency. **Materials and Methods:** Twenty-six patients (11 males and 15 females, mean age  $\pm$  SD=27.4 $\pm$ 8.2 years) were recruited. Anthropometry, body composition, metabolic parameters and cardiovascular risk factors were studied. **Results:** Obesity (overweight included) was noted in 16 patients (61.5%), with android distribution in all cases. Bioelectrical impedance showed increased body fat mass in 12 patients (46.1%). Lipid profile alterations and carbohydrate metabolism disorders were detected in seven (26.9%) and five (19.2%) patients respectively. Moderate hepatic cytolysis, associated with hepatic steatosis, was found in one patient. Seven patients (27%) had insulin resistance. Ambulatory blood pressure monitoring showed abnormalities in six patients (23%). Increased carotid intima media thickness was found in 14 patients (53.8%). **Conclusion:** Adult CAH patients tend to have altered metabolic parameters and a higher prevalence of cardiovascular risk factors. Lifelong follow-up, lifestyle modifications, and attempts to adjust and reduce the glucocorticoid doses seem important.

**Key words:** Cardiovascular risk, metabolic profile, body composition, congenital adrenal hyperplasia, 21-hydroxylase deficiency

## INTRODUCTION

Congenital adrenal hyperplasia (CAH) describes a group of inherited autosomal recessive disorders affecting adrenal steroid synthesis. The most frequent CAH variant, accounting for 95% of all affected patients, is 21-hydroxylase deficiency (21-OHD) and caused by inactivating mutations in the 21-hydroxylase gene (CYP21A2).<sup>[1]</sup> The impaired cortisol secretion causes ACTH levels to rise and stimulate adrenocortical hormone secretion, resulting in adrenal

hyperplasia, and increased production of androgens and steroid precursors before the enzymatic defect. Two distinct phenotypes are recognized in CAH due to 21-OHD: classical CAH, the most severe form comprises both salt-wasting (SW) and simple virilizing (SV) forms, with a worldwide incidence of 1:15000 live births, and the nonclassical (NC) form which may be asymptomatic or associated with signs of postnatal or even adult onset androgen excess. Most patients are compound heterozygotes having different mutations of the CYP21 gene on each allele.<sup>[1]</sup> The clinical expression of CAH is reported to be correlated with the less severely mutated allele.<sup>[2]</sup> Treatment of CAH consists of glucocorticoids and, when necessary, mineralocorticoids to prevent adrenal crises and to suppress the abnormal secretion of androgens and steroid precursors from the adrenal cortex.<sup>[3]</sup> In addition to impaired adrenocortical function, classic CAH is characterized by compromised adrenomedullary function. The latter is owing to developmental defects in the formation of adrenal medulla,

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10.4103/2230-8210.102995

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leading to a reduction in epinephrine and metanephrine stores.<sup>[4]</sup>

Lifelong glucocorticoid replacement therapy is required in CAH patients to reduce adrenal androgen excess.<sup>[5]</sup> The therapeutic spectrum of glucocorticoids is narrow and supraphysiological doses, often needed to control the hyperandrogenism, are potentially harmful and result in the development of an iatrogenic Cushing's syndrome.<sup>[6]</sup> Abnormalities in lipid and glucose metabolism, as well as increased body mass index (BMI), body fat mass, insulin, leptin and blood pressure levels have been reported in patients with 21-OHD, with potential long-term complications in later life.<sup>[7,8]</sup>

The aim of the present work was to determine the prevalence of metabolic abnormalities and cardiovascular risk factors in a population of adult patients with CAH due to 21-OHD.

## MATERIALS AND METHODS

### Patients

We included 26 patients (11 males and 15 females, mean age $\pm$ SD=27.4 $\pm$ 8.2 years, range=16.5-48 years) who were followed at the department of endocrinology in Mahdia and Sfax, in Tunisia. This sample includes all patients

with CAH due to 21-OHD, aged more than 16 years and regularly followed at these two clinics since 1982.

Patients or their parents were informed about the purpose of the study. Clinical and hormonal data of recruited patients are presented in Table 1. Data concerning presentation, diagnosis, medical and surgical treatment, and other relevant information were reviewed. All individuals had CAH with 21-OHD. The diagnosis of CAH was based on clinical and biochemical criteria (i.e. elevated levels of 17-hydroxyprogesterone (17-OHP) and androstenedione, ACTH stimulation test). None of the patients was treated in utero with dexamethasone.

Ten patients (six males, four females) had the SW form of CAH, and they had been diagnosed in their first year of life. Eight patients (five males, three females, age at diagnosis: Between birth and six years) were diagnosed as classical SV patients. In the other eight patients (women only in this group), the NC form was diagnosed during between 15 and 44 years of age. All patients had been treated from the time of diagnosis. Twenty-one patients, 16 with the classical form and five with the NC form, were started on a regimen of hydrocortisone (HC), given two or three times daily, while the remaining five patients (three with the NC form and two with the classic SV form) were treated with dexamethasone

**Table 1: Clinical and hormonal data of the included patients**

Patient No./ Sex/Age (yr)/ phenotype	Height (cm) (Standard Deviation)	Weight (kg)	BMI (kg/m <sup>2</sup> )	Treatment regimen, drug molecules and daily doses	Follow-up duration (yr)	17-OHP (ng/mL)	ACTH (pg/mL)	$\Delta$ 4-A (ng/mL)	Supine PR (ng/L)
1/M/21/SW	155 (-3)	48.7	20.3	HC: 13.8 mg/m <sup>2</sup> FC: 75 $\mu$ g	21	50	537	2.3	23
2/M/18/SW	160 (-1.6)	57.3	22.4	HC: 18.2 mg/m <sup>2</sup> FC: 50 $\mu$ g	18	60	74	4.6	13
3/M/23/SW	186 (+2)	80	23.1	HC: 15.6 mg/m <sup>2</sup> FC: 50 $\mu$ g	23	21.3	295	3.1	18
4/M/16.5/SW	158 (-2.6)	85.1	34.1	HC: 16 mg/m <sup>2</sup> FC: 100 $\mu$ g	16.5	12	77	2.9	18
5/M/22.5/SW	166 (-1.3)	83	30.1	HC: 15.9 mg/m <sup>2</sup> FC: 75 $\mu$ g	22.5	60	150.8	14.7	16.5
6/M/22.5/SW	163 (-1.8)	72.5	27.3	HC: 13.5 mg/m <sup>2</sup> FC: 50 $\mu$ g	22.5	9	233	2.9	9
7/M/31/SV	162 (-2)	67.7	25.8	HC: 12.8 mg/m <sup>2</sup> FC: 50 $\mu$ g	28	25.5	68	6.7	14.7
8/M/17.5/SV	178 (+0.6)	106.1	33.5	DEX: 0.5 mg	11.5	18.9	57	1.6	10
9/M/18/SV	164 (-1.6)	68.8	25.6	DEX: 0.5 mg	11.5	1.64	6.5	2.1	12
10/M/28/SV	156 (-3)	69.8	28.7	HC: 18.2 mg/m <sup>2</sup> FC: 50 $\mu$ g	22	1.8	368	2.7	14.5
11/M/47.5/SV	143 (-5.1)	57.4	28.1	HC: 18.7 mg/m <sup>2</sup>	41.5	9.8	42	2.1	9
12/F/21/SV	163(0)	58.4	22	HC: 16.2 mg/m <sup>2</sup> FC: 100 $\mu$ g	18	7	59	1.6	12.8
13/F/26/SV	150 (-1.4)	52.8	23.5	HC: 23.8 mg/m <sup>2</sup> FC: 75 $\mu$ g	26	23.9	39	2.5	32
14/F/25/SW	168 (+1)	57.8	20.5	HC: 12.8 mg/m <sup>2</sup> FC: 75 $\mu$ g	25	8.1	25	1.9	12
15/F/23.5/SW	149 (-2.5)	55.7	25.1	HC: 16.4 mg/m <sup>2</sup> FC: 75 $\mu$ g	23.5	9.5	41	4.7	2.7
16/F/22/SW	166 (+0.5)	72.7	26.4	HC: 13.1 mg/m <sup>2</sup> FC: 50 $\mu$ g	22	3.3	32	3.9	9.7
17/F/27/SW	164 (+0.2)	68	25.3	HC: 29.8 mg/m <sup>2</sup> FC: 100 $\mu$ g	27	77	320	15.2	44
18/F/33/SV	155 (-1.4)	75.4	31.4	HC: 22.3 mg/m <sup>2</sup> FC: 50 $\mu$ g	33	70	166.6	4.7	12
19/F/28/NC	157 (-1)	55	22.3	HC: 13.2 mg/m <sup>2</sup>	3	14	13	24	-
20/F/26/NC	163 (0)	58.4	22	HC: 14.7 mg/m <sup>2</sup>	5	3.7	32.8	3.9	-
21/F/30.5/NC	150 (-2.4)	52.8	23.5	DEX: 0.5 mg	9	6.9	235.4	5.3	-
22/F/48/NC	154 (-1.6)	71.6	30.2	HC: 13.7 mg/m <sup>2</sup>	4	17.6	58	12.6	-
23/F/36/NC	156 (-1.2)	73.2	30.1	HC: 21.5 mg/m <sup>2</sup>	15	12.8	78	2.6	-
24/F/36/NC	141 (-4)	69.1	34.8	DEX: 0.5 mg	13	53.6	31	1.8	-
25/F/34/NC	148 (-2.8)	67.9	31	HC: 17.1 mg/m <sup>2</sup>	4	1.1	7.6	1.7	-
26/F/32/NC	163 (+0)	61.3	23.1	DEX: 0.5 mg	17	6.9	29.5	4.4	-

SW: Salt wasting, SV: Simple virilizing, NC: Non-classical, HC: Hydrocortisone, FC: Fludrocortisone, DEX: Dexamethasone,  $\Delta$ 4-A:  $\Delta$ 4-androstenedione, PR: Plasma renin  
BMI: Body mass index, 17-OHP: 17-hydroxyprogesterone, ACTH: Adrenocorticotropic hormone

(once daily). Salt wasters were treated with  $27.9 \pm 9.6 \text{ mg/m}^2$  per day of HC the first two years of life, and the doses were decreased to  $17.6 \pm 6.6 \text{ mg/m}^2$  per day during childhood. Daily doses of HC in patients with classical and NC form were respectively  $17.3 \pm 4.6 \text{ mg/m}^2$  and  $16.04 \pm 3.4 \text{ mg/m}^2$  during adulthood. For dexamethasone, the prescribed doses ranged from 0.25 to 0.75 mg per day. Fifteen patients (10 with the SW form and five with the SV form) additionally received  $9\alpha$ -fludrocortisone (FC; twice daily).

The adequacy of therapy was monitored periodically on the basis of clinical and laboratory data, in accordance with current guidelines.<sup>[9]</sup> Adequate hormonal control of CAH was defined if serum androgen levels were within the normal range and 17-OHP concentration in serum was 2.0-10 ng/mL (6-30 nmol/L). The mean duration of the follow-up period was  $18.5 \pm 9.3$  (range 3 to 41.5) years. Good compliance with glucocorticoid treatment was noted in 14 patients (53.8%). Seven patients (five with the SW form and two with the SV form) had experienced a salt-wasting adrenal crisis in the neonatal period. The onset of puberty (defined by onset of breast development in females and increased testicular Volumes in males) was  $10.8 \pm 1.4$  years for girl and  $11.2 \pm 1.2$  years for boys. Menarche occurred spontaneously in all patients, at an average age of  $12.8 \pm 1.1$  years.

One female patient with the NC form (patient *n*<sup>o</sup>23) had a history of previously diagnosed congenital hypothyroidism. She was started on L-thyroxine  $10 \mu\text{g/kg}$  per day at the age of six months, but she was irregular in follow-up and was not compliant with treatment.

One patient with the SW form (patient *n*<sup>o</sup>4) developed hypertension at eight year of age and responded well to Nifedipine. Detailed investigations (renal Doppler ultrasound, adrenal CT scan, urinary metanephrine, 11-deoxycortisol and aldosterone concentrations) failed to detect any cause for secondary hypertension, and a diagnosis of essential hypertension was made.

## Methods

From January 2009 to November 2010, patients were prospectively studied as outpatients.

### *Clinical characteristics and body composition*

Height, weight, and waist circumference were evaluated using standard methods. Blood pressure, supine and standing, was registered and signs of hypo/hypercortisolism and hyperandrogenism were recorded. Body mass index (BMI) was calculated as  $\text{weight}/(\text{height})^2$  ( $\text{kg/m}^2$ ). Fat mass (kg) and body fat percent (BF%) were assessed with bioelectrical impedance equipment (TANITA, TBF-300, France). The measurements were performed in a standing

position, with electrodes in contact with soles and heels of both feet. The equation for BF% used by this model of Tanita was developed by Brožek:  $\text{BF}\% = (4.57/\text{body density} - 4.142) * 100$ .<sup>[10]</sup>

### *Endocrinological and metabolic investigations*

Blood samples were collected in the morning after an overnight fast for measurements of serum lipids [total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C)], liver enzymes [serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT)], electrolytes, plasma glucose, hormones [insulin, leptin, testosterone,  $\Delta 4$ -androstenedione ( $\Delta 4$ -A), 17-OHP, renin, plasma ACTH]. Samples were centrifuged and separated immediately after collection and were stored at  $-20^\circ\text{C}$  until assayed.

### *Biochemical assays*

Plasma glucose was measured using a glucose oxidase method on a glucose analyzer and TC, TG, and HDL-C by enzymatic methods. Fasting serum insulin levels were measured by enzyme linked immunosorbent assay (ELISA) using the insulin ELISA kit (biocompare, Catalog Number YK060; intraassay and interassay coefficients of variation <10%). Serum leptin levels were determined by ELISA technique using Leptin-EASIA KAP2281 kit (DIA source ImmunoAssays S.A. B-1400 Nivelles, Belgium), with a sensitivity of 0.5 ng/mL.

### *Metabolic assessment*

A 75g oral glucose tolerance test (OGTT) was done in all patients and was evaluated using the criteria of the World Health Organization (WHO).<sup>[11]</sup>

Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedwald's formula in individuals with triglycerides <400 mg/dL. The following situations were defined as dyslipidemia: TC >200 mg/dL, LDL-C > 135 mg/dL, TG >150 mg/dL, and/or HDL-C <35 mg/dL for males or <40 mg/dL for females.<sup>[12]</sup>

Insulin resistance (IR) was estimated using the homeostasis model assessment (HOMA) method as previously described:  $\text{IR} = \text{insulin} (\mu\text{U/mL}) \times \text{glucose} (\text{mmol/L}) / 22.5$ .<sup>[13]</sup> A HOMA-index  $\geq 2.77$  has been suggested to indicate insulin resistance.<sup>[14]</sup> The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria were used to define the metabolic syndrome.<sup>[15]</sup>

### *Cardiovascular risk profile assessment*

Ambulatory 24hrs blood pressure profiles (ABPM) was performed in all patients. The following blood pressure

(BP) characteristics were measured: Mean 24hrs systolic and diastolic, daytime systolic and diastolic, and nighttime systolic and diastolic. Daytime BP less than or equal to 140/90mmHg and the night time blood pressure less than or equal to 125/80mmHg were considered to be normal.<sup>[16,17]</sup> Patients were defined as dippers when nighttime systolic BP fall was  $\geq 10\%$ , and non-dippers when nighttime systolic BP fall was  $< 10\%$ .<sup>[18]</sup>

Carotid Intima-Media Thickness (CIMT) was assessed in all patients using high-resolution B-mode ultrasound with a 10-MHz linear transducer. Measurements were performed in the posterior wall of both common carotid arteries (CCA), at three angles. The average of the mean CIMT values of the three segments was calculated to determine the mean right and left CIMT per patient.<sup>[19]</sup> In the current study, the mean CIMT was compared with reference values from the Multi-Ethnic Study of Atherosclerosis.<sup>[20]</sup> Patients were thereby stratified as having normal CIMT (CIMT  $< 75$ th percentile) or increased CIMT (CIMT  $\geq 75$ th percentile in at least one CCA).<sup>[20]</sup>

## RESULTS

### Clinical characteristics and body composition

Mean female height was  $158.8 \pm 7.6$  cm (range, 141-168) and mean male height was  $163.1 \pm 11.4$  cm (range, 143- 186). Twenty-one patients (nine males and 12 females, 80.7%) had a final height below the target height. Mean BMI was  $26.5 \pm 4.3$  kg/m<sup>2</sup> (range, 20.3-34.8). Mean office systolic and diastolic blood pressures were  $124 \pm 17$  and  $87 \pm 11$  mmHg respectively (range, 100-150 and 40-100 respectively), and there was no significant change in values on standing up. Except of patient *n*<sup>o</sup>4 with prior diagnosis of hypertension, no one has been diagnosed with office hypertension. No patient had signs of hypercortisolism. Bioelectrical impedance showed increased body fat mass in 12 patients (46.1%) including nine (SW/SV: 5/4) with the classical form and three with the NC form.

### Metabolic profile

10 patients (three males and seven females, 38.4%) had normal BMI; eight patients (five males and three females, 30.7%) were overweight, while eight patients (three males and five females, 30.7%) were obese, with android distribution in all cases. Among all overweight and obese patients, 12 had the classic form (SW/SV: 6/6) and four had the NC form.

Lipid profile alterations (at least one abnormal lipid fraction) were detected in seven patients (one male and six females, 26.9%) including one with the SV form (patient *n*<sup>o</sup>8) and six with the NC form. Reduced HDL-C

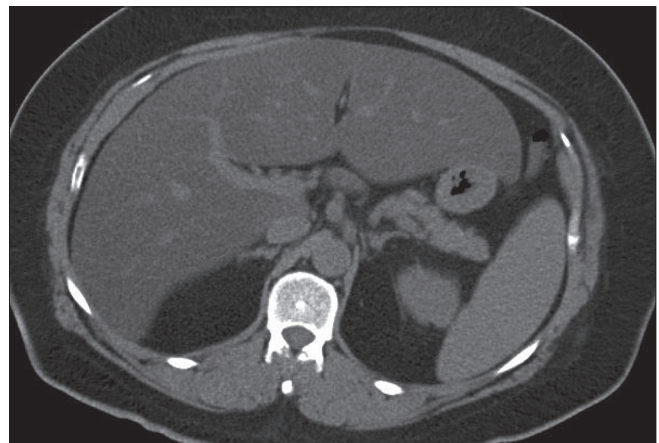
constituted the highest abnormality (five patients; one male and four females) followed by hypertriglyceridemia in three patients (patient *n*<sup>o</sup>19, 23 and 24), hypercholesterolemia in two patients (patient *n*<sup>o</sup>22 and 25) and elevated LDL-C in 1 patient (patient *n*<sup>o</sup>25).

Insulin resistance (HOMA-IR ranging from 2.79 to 4.27) was documented in seven patients (three males and four females, 27%) including one with the SW form (patient *n*<sup>o</sup>4), three with the SV form (patient *n*<sup>o</sup>8, 9 and 18) and three with the NC form (patient *n*<sup>o</sup>22, 23 and 25). Hyperleptinemia was detected in three patients (patient *n*<sup>o</sup>2, 15 and 19, 11.5%). Moderate hepatic cytolysis was found in patient *n*<sup>o</sup>8 (ASAT: 103 UI/L, ALAT: 223 UI/L). This patient had also hepatic steatosis found on abdominal CT scan that showed abnormal low signal intensity of the liver, hypointense relative to the spleen [Figure 1].

During OGTT, 21 patients (80.7%) had normal glucose tolerance, while carbohydrate metabolism disorders were detected in five patients (19.2%). Four patients (patients *n*<sup>o</sup>8, 22, 24 and 25) were identified as having glucose intolerance and one patient (patient *n*<sup>o</sup>22) had diabetes (Blood glucose 120 min: 11.05 mmol/L). The metabolic syndrome as defined by the NCEP ATP III criteria was documented in patient *n*<sup>o</sup>23, who had diabetes, obesity, low HDL-C, and hypertriglyceridemia. Table 2 shows metabolic parameters according to clinical phenotype of CAH.

### Cardiovascular risk profile

ABPM showed mild daytime systolic hypertension (150 mmHg) in one patient with the SW form (patient *n*<sup>o</sup>5). Indeed, five patients (two males and three females,

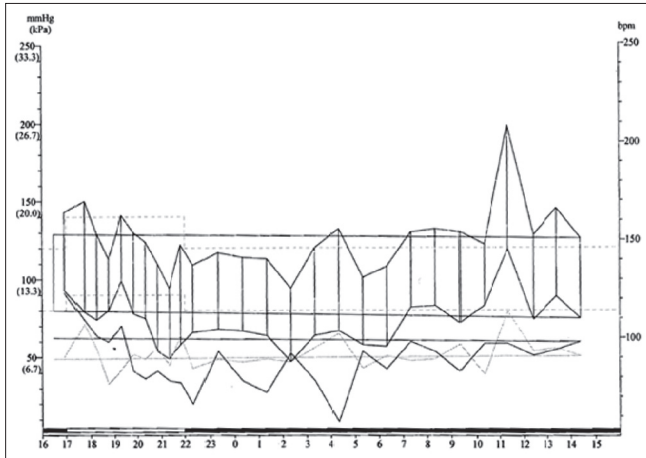


**Figure 1:** Abdominal CT scan image of patient *n*<sup>o</sup>8, with the classical simple virilizing form of congenital adrenal hyperplasia. This image illustrates low density of the hepatic parenchyma (relative to splenic parenchyma) indicating diffuse steatosis



19.23%) were classified as nondippers [Figure 2]. Among these patients, one had the SW form, two had the SV form and two had the NC form.

Comparison with reference values revealed normal CIMT in 12 patients (46.1%). In the remaining 14 patients (five males and nine females, 53.8%), an increased CIMT value, up to 1.1 mm, was observed in at least one CCA. These patients were classified as follow: four with the SW form, four with the SV form and six with the NC form. Table 3



**Figure 2:** Ambulatory blood pressure monitoring illustrating a nondipper pattern in patient n°8 with the simple virilizing form of congenital adrenal hyperplasia

illustrates cardiovascular parameters according to clinical phenotype of CAH.

## DISCUSSION

We studied cardiovascular and metabolic risk profiles in a cohort of CAH adult patients due to 21-OHD. Our report illustrates some indications of increased cardiovascular and metabolic risk in this population, consistent with the previous studies.<sup>[7,8,21]</sup>

In our study, seven patients (27%) were overweight, and eight patients (30.7%) were obese, with android distribution in all cases. BMI was found to be elevated in most<sup>[5,22,23]</sup> but not all reports<sup>[24]</sup> on CAH patients. Moreover, higher body fat mass has been reported, using different methods such as skin-fold thickness, whole-body dual-energy x-ray absorption (DXA) scan, and bioelectrical impedance analysis.<sup>[21,25,26]</sup> This last method was used in our study and showed elevated body fat mass in 46.1% of patients. The causes of the excessive increase in body weight and fat mass are unclear, but several factors may contribute. Overtreatment with glucocorticoids may lead to a Cushingoid syndrome with central obesity, resulting from redistribution of fat from peripheral to central depots.<sup>[7,8,26]</sup> Furthermore, adrenomedullary dysfunction with decreased secretion of epinephrine may play a role in the development of obesity. Catecholamines, like epinephrine, contribute to

**Table 2: Metabolic profile of patients according to clinical phenotype of congenital adrenal hyperplasia**

	SW patients (n=10)	SV patients (n=8)	NC patients (n=8)	All patients (n=26)
BMI (kg/m <sup>2</sup> )	25.4±4.3	27.3±3.8	27.1±4.9	26.5±4.3
Body fat percentage	21.6±10.3	25.7±8.3	27.9±12.5	24.8±10.6
Fasting blood glucose (mmol/L)	4.49±0.3	4.62±0.6	5.46±2.5	4.82±0.52
75-g OGTT 120 min glucose (mmol/L)	5.94±0.9	6.22±1.56	7.14±1.56	6.39±1.41
Total cholesterol (mg/dL)	154±8	164±15	187±38	166±26
HDL cholesterol (mg/dL)	47±6	43±6	47±7	46±6
Triglycerides (mg/dL)	89±28	93±24	98±3	91±27
LDL cholesterol (mg/dL)	89±10	102±13	120±30	101±27
Fasting insulin (μUI/mL)	8.8±0.9	11.2±7.2	9.05±3.2	9.6±4.3
HOMA-IR	1.77±0.6	2.43±1.6	2.29±1.2	2.1±1.1
Serum leptin (ng/mL)	6.34±5.4	8.57±2.2	7.41±5.6	7.51±4.7

BMI: body mass index, SW: Salt wasting, SV: Simple virilizing, NC: Non-classical, OGTT: oral glucose tolerance test, HOMA-IR: homeostasis model assessment-insulin resistance

**Table 3: Prevalence of cardiovascular risk factors in our patients according to clinical phenotype of congenital adrenal hyperplasia**

	SW patients (n=10)	SV patients (n=8)	NC patients (n=8)	All patients (n=26)
24-hour systolic blood pressure (mmHg)	115.8±9.7	114.6±7.2	114.1±9.4	114.9±8.9
24-hour diastolic blood pressure (mmHg)	71±7.4	72.4±1.1	70.5±4.5	71.2±4.8
Daytime systolic blood pressure (mmHg)	119±12	118.4±9	116±8, 8	117.9±10.2
Daytime diastolic blood pressure (mmHg)	73.12±7.6	72.8±2.1	73.5±5.3	73.15±5.4
Night-time systolic blood pressure (mmHg)	107.75±8.1	108.8±10.3	106.5±7.4	107.6±8.45
Night-time diastolic blood pressure (mmHg)	62.75±5.8	67.8±4.7	64.8±5.7	64.7±5.4
Right-CIMT (mm)	0.49±0.07	0.51±0.03	0.6±0.24	0.55±0.2
Left-CIMT (mm)	0.51±0.08	0.48±0.1	0.65±0.23	0.53±0.2

SW: Salt wasting; SV: Simple virilizing, NC: Non-classical, CIMT: carotid intima-media thickness

lipolysis and inhibit insulin secretion, thereby preventing an increase in fat mass. Other possible explanations for the increased fat mass could be hypogonadism in men and hyperandrogenism in women.<sup>[7,8,21]</sup>

Literature data suggest that both classic and non-classic CAH patients exhibit higher fasting serum insulin and a higher insulin resistance, as determined by HOMA model.<sup>[27-29]</sup> This appeared to be in line with our findings, since we have found elevated HOMA-IR in 27% of our patients. In addition, elevated serum leptin levels were reported in CAH patients.<sup>[29]</sup> Recently, Völkl *et al* found decreased soluble leptin receptor (sOB-R) associated with normal serum leptin concentrations. They hypothesized that this specific change in the leptin axis may contribute to the increased risk of overweight and obesity.<sup>[30]</sup> In our cohort, only three patients showed hyperleptinemia. So, this finding highlights the importance of measurement of sOB-R in our population.

It has been suggested that high insulin combined with increase leptin concentrations in CAH patients might be due to both overproduction of androgens and treatment with supraphysiological doses of glucocorticoids. The chronic adrenomedullary hypofunction might also promote such metabolic abnormalities as a result of the absence of inhibition receptor  $\beta$ 3-mediated catecholamine effects on insulin and leptin secretion.<sup>[7,8,21]</sup>

Both hyperleptinemia and hyperinsulinism may alter the activity of enzymes participating in adrenal steroidogenesis and may result in a further increase in androgen production and onset of metabolic syndrome.<sup>[21]</sup> The later was present in only one patient in our study.

Carbohydrate metabolism disorders were detected in five of our participants (19.2%), including four patients with glucose intolerance and one patient with diabetes. In literature, no study has demonstrated an increased frequency of type two diabetes in CAH patients. However, female patients seem to be at increased risk of gestational diabetes mellitus which is a well-known predictor of future type 2 diabetes.<sup>[22,31]</sup>

To date, only six studies report on lipid profiles in CAH patients.<sup>[7,32]</sup> Most of them did not show unfavorable changes. Our results, showing lipid profile alterations in 26.9% of patients, disagree thus with literature findings. Normality of lipid profiles in most studies seems to be surprising, because obesity and insulin resistance, both common in CAH patients, are known to be associated with dyslipidemia. A possible explanation is that lipid profiles were mainly evaluated in younger CAH patients.<sup>[7]</sup> Nevertheless, the recent study, reported by Zimmermann

*et al*, suscites particular interest. In fact, it was able to demonstrate that, despite apparently normal routinely assessed lipid parameters, CAH patients could have discrete alterations in lipid metabolism characterized by an elevation in concentrations of cholesterol in the small-dense low-density lipoproteins subfractions (sd-LDL). Such alterations might be an additional metabolic risk predisposing to an accelerated atherogenesis.<sup>[32]</sup>

One of our patients showed moderate hepatic cytolysis, associated with hepatic steatosis. Falhammer *et al*, demonstrated that obese and non-obese female patients with CAH showed higher liver function tests (LFT) compared with controls. LFT were positively correlated to BMI, body fat and waist circumference. The authors concluded that not only central obesity but also glucocorticoids might influence LFT. Elevated liver enzymes could represent markers for increased future metabolic risk and could further predict the metabolic risk of CAH individuals. However, the prevalence of hepatic steatosis was not determined in this study.<sup>[33]</sup>

There is minimal data on hypertension in CAH patients.<sup>[7,8]</sup> Overall, there is tendency towards an increased prevalence of hypertension. In a previous study including 91 children and adolescents with classic CAH, essential hypertension (hypertension of unknown etiology) was noted in five of them, possibly due to intrinsic dysregulation inherent to CAH.<sup>[34]</sup> In our study, one patient with the SW form was diagnosed as having essential hypertension after careful investigations. Moreover, altered 24-h blood pressure profiles with elevated systolic levels have been reported. These blood pressure alterations, found in 23% of our patients, seem to be associated with BMI, and not affected by mineralocorticoid or glucocorticoid replacement dose.<sup>[35-37]</sup> Interestingly, non-dipper blood pressure pattern, characterized by the absence of physiologic nocturnal nadir in systolic blood pressure, has been described in CAH patients.<sup>[34-37]</sup> Its prevalence was 19, 23% in our patients. Nondipper status has been shown to be an additional risk factor for the development of adverse cardiovascular events.<sup>[38]</sup>

Our study provides evidence showing a high rate of Increased CIMT in CAH patients. This finding is in line with an Italian study,<sup>[39]</sup> which demonstrates reduced insulin sensitivity and increased intima-media thickness (IMT), independently of cumulative glucocorticoid doses and androgen levels.<sup>[40]</sup> IMT is considered as a measure of subclinical atherosclerosis and a predictor of myocardial infarction and stroke, independently of traditional risk factors for atherosclerosis.<sup>[40]</sup>

Inflammation plays an important role in the initiation and progression of atherosclerosis and the development of atherosclerotic events.<sup>[41]</sup> Inflammatory markers, such as adiponectin, tumor necrosis factor alpha, interleukin-6 and high sensitivity C-reactive protein, have been shown to predict future cardiovascular events in individuals with and without established cardiovascular disease.<sup>[41]</sup> These markers have not yet been studied in CAH patients.<sup>[7,8]</sup>

The present study has potential limitations. The small sample and the involvement of few individuals >30 years old did not allow us to establish statistical correlations. In addition, our study cohort appears to be heterogenous since we have included patients with both classic and non-classic forms of the disease. As consequence, it is not surprising to find more higher degrees of obesity, abnormal lipids, and carotid intima-media thickness in the non-classic CAH patients, as this group have received the most potent steroid dexamethasone in the doses almost equal to or higher than the doses used for the classical CAH patients. Despite these limitations, our study was able to assess simultaneously several cardiometabolic risk factors in CAH patients. Further studies with larger cohorts of patients are required in order to better evaluate the risk of atherosclerotic vascular disease in CAH patients, and to discuss the range of pharmacological interventions in this population.

## CONCLUSION

The present study illustrates high prevalence of some metabolic abnormalities and established risk factors for cardiovascular disease in CAH adult patients. This unfavorable cardiometabolic profile may be due to either the existence of hyperandrogenism in untreated or undertreated patients or to the supra-physiological doses of glucocorticoids used to suppress androgen levels to normal values. Lifelong followup, early lifestyle modifications, and attempts to adjust the glucocorticoid doses may reduce cardiovascular risk in this group of patients.

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**Cite this article as:** Mnif MF, Kamoun M, Mnif F, Charfi N, Naceur BB, Kallel N, *et al.* Metabolic profile and cardiovascular risk factors in adult patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Indian J Endocr Metab* 2012;16:939-46.

**Source of Support:** Nil, **Conflict of Interest:** No.