Lipid Profile in Congenital Adrenal Hyperplasia

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Glucocorticoids have been reported to exert a marked effect on lipoprotein metabolism. Several studies have shown a potential risk of hyperlipidemia in patients under long-term glucocorticoid therapy. Current management of patients with congenital adrenal hyperplasia (CAH) includes the use of glucocorticoids to attenuate the increased production of undesirable adrenal hormones. A case-control study was designed to compare the serum lipid profiles of 14 patients with CAH under glucocorticoid therapy and 14 normal controls and to determine the characteristics of the profiles. A total of 9 patients (64.3%) had serum total cholesterol (TC) greater than 4.4 mmol/L (170 mg/dL), compared with 6 individuals in the control group (42.3%). Nine patients with CAH (64.3%) had serum triglycerides (TGs) more than 1.0 mmol/L (90 mg/dL), compared with only 2 in the control group (14.3%). Similarly, the mean serum TG was higher in the CAH group versus the controls, 1.33 mmol/L (118 mg/dL) versus 0.75 mmol/L (67 mg/dL), respectively. Serum low-density lipoprotein, (LDL-C) and high-density, lipoprotein (HDL-C) cholesterol were determined in 13 children with CAH and in the 14 controls. Nine CAH patients (69.2%) and 8 controls (57%) had LDL-C greater than 2.8 mmol/L (<110 mg/dL). For HDL-C, 2 children with CAH (15.4%) and 4 controls (28.6%) had levels less than 0.9 mmol/L (35 mg/dL). There were no significant differences for the cholesterol index, 0.24 for the controls and 0.22 for the CAH group. In the CAH group, the mean serum TG level and the percentage of individuals with TGs greater than 1.0 mmol/L were statistically significant compared with the controls. The mean serum TC and LDL-C, as well as the percentage of subjects with levels over the cutoff point, although slightly higher in the CAH group, were of no statistical significance. The results of this pilot study suggest that long-term glucocorticoid therapy in patients with CAH may induce abnormalities in the serum lipid profile characterized mainly by an increment in serum TGs.

GLUCOCORTICOIDS have been implicated in the development of several abnormalities of lipoprotein metabolism. The long-term administration of glucocorticoids has been associated with elevated serum levels of total cholesterol (TC) and triglyceride (TG) in animal models and humans.[1-3] Experiments in healthy subjects have shown significant changes in the lipid profile as early as 14 days after administration of pharmacological doses of glucocorticoids.[4,5]

The mechanism of glucocorticoid-induced hyperlipidemia has been associated with a compensatory hyperinsulinism as a result of glucocorticoid-induced insulin resistance. Hyperinsulinism increases the production rate of lipoproteins, including the very–low-density lipoprotein cholesterol (VLDL-C) subfraction. In addition, a defective removal of plasma lipoproteins leads to a subsequent increase in the concentration of TG-rich lipoproteins, TC, and low-density lipoprotein cholesterol (LDL-C).[1,6,7]

The clinical evidence of lipid disorders in patients undergoing glucocorticoid therapy is striking. Increments in serum lipid levels have been reported in patients with asthma,[8] renal transplant,[9,10] heart transplant,[11] and rheumatic disease.[1,2]

The current therapeutic approach for children with congenital adrenal hyperplasia (CAH) is based on lifelong administration of glucocorticoids not only to replace the cortisol they lack but also to suppress the hypothalamic-pituitary-adrenal axis to attenuate the increased production of undesirable adrenal hormones. Although there are no data on the incidence of atherosclerotic vascular disease in adults with CAH, the long-term risk for atherosclerotic vascular disease may be presumably increased in children with induced hyperlipidemia.[12]

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SUBJECTS AND METHODS

Study Population

The patients and controls involved in this case-control study belonged to a homogeneous Hispanic population. All were recruited from the pediatric endocrine clinic (CAH patients) and the well-child clinic (controls) of the Instituto de los Seguros Sociales in Medellin, Colombia. The CAH group included 14 prepubertal children (4 boys and 10 girls) between 13 months and 10 years of age. The control group included 14 normal prepubertal children (8 boys and 6 girls) between 21 months and 9 years of age. Prepubertal stage was determined by physical examination using the Tanner classification. For boys, a testicular volume less than 3 cc (measured with an orchidometer) and the absence of pubic hair, and for girls, the absence of breast development and/or pubic hair, were indicative of a prepubertal stage.

Individuals with a family history of hypercholesterolemia, hypertriglyceridemia, or secondary hyperlipidemia, or who were receiving medications known to induce changes in the serum lipid profile were excluded from the study. Also, those presenting with obesity or a recent history of major trauma or febrile illness were excluded, as these events can induce abnormalities in lipid metabolism.

All children with CAH were on treatment with prednisone, the available oral glucocorticoid in Colombia, at a dose equivalent to 10 to 20 mg/m^2/d hydrocortisone. The diagnosis of CAH was made based on the level of 17-hydroxyprogesterone (17-OHP). All patients with CAH had 21-hydroxylase deficiency and were on glucocorticoid treatment since infancy. Only patients who had good compliance with the glucocorticoid regimen were included. Good compliance was assessed by an appropriate growth rate, normal levels of the biochemical markers total testosterone, androstenedione, and plasma renin activity (PRA), and bone age within 2 SD of the chronological age. Although 3 patients had a bone age between 2 and 3 SD, they were included in the study considering that 1 year before the study their bone age did not advance abnormally (Table 1).

The determination of cutoff points for TC and LDL-C, 4.4 mmol/L (170 mg/dL) and 2.8 mmol/L (110 mg/dL), respectively, was made

Table 1. Hormonal Status and Bone Age at the Time of Study: CAH Group

Patient No.	Sex	CA	BA	Testosterone (ng/dL)	Androstenedione (ng/dL)
1	F	18 mo	2 yr*	4.1	8
2	F	13 mo	18 mo*	2.3	12
3	F	19 mo	2 yr*	3.3	9
5	F	2 yr 4 mo	3 yr*	8.0	15
6	F	2 yr 10 mo	2 yr 9 mo*	5.0	8
7	M	3 yr 2 mo	3 yr 6 mo*	9.0	16
8	F	4 yr 7 mo	6 yr 6 mo†	8.0	20
9	M	5 yr 3 mo	6 yr*	9.0	16
10	F	6 yr	6 yr 6 mo*	2.0	11
11	F	6 yr 8 mo	10 yr†	3.8	10
12	M	8 yr	8 yr 3 mo*	2.3	12
13	M	8 yr 3 mo	10 yr 6 mo†	7.0	11
14	F	10 yr 6 mo	11 yr 6 mo*	4.0	10

NOTE. All patients were evaluated for at least 1 year prior to the study and had prepubertal levels of sex steroids (normal: total testosterone, prepubertal, <3-10 ng/mL; androstenedione, prepubertal, 8-50 ng/dL).

Abbreviations: CA, chronological age; BA, bone age; F, female; M, male.

*BA <2 SD.

†BA 2-3 SD.

following the recommendations of the National Cholesterol Education Program (NCEP) and the Committee on Nutrition of the American Academy of Pediatrics.[13,14] For TG, a cutoff of 1.0 mmol/L (90 mg/dL)[15] was implemented, and for high-density lipoprotein cholesterol (HDL-C), the cutoff was 0.9 mmol/L (35 mg/dL).[15] Finally, a HDL-C/TC ratio greater than 0.20 was used as a cutoff point.[15]

Laboratory Techniques

After a 12-hour fast, the serum lipid profile including TC, TG, LDL-C, and HDL-C was determined for each individual in both groups. All samples were processed in the same laboratory (Mayo Medical Laboratories, Rochester, MN) and were analyzed in the same assay. The guidelines of the NCEP Working Group on lipoprotein measurement were followed.[16] TC and TG were determined by enzymatic methods. HDL-C was determined by chemical precipitation of non-HDL-C fractions. LDL-C was quantified indirectly using the Friedewald equation, LDL-C = TC − HDL-C − (TG/5).

Statistics

The results are presented as a percentage and the mean ± SD. To determine if the mean values of the 2 data sets were significantly different, the unpaired Student's *t* test was used with a computer program (SigmaPlot for Windows, SPSS, Chicago, IL, 1995). A *P* value less than .05 was considered statistically significant. To establish statistical significance for data presented as a percentage, the χ^2 test was implemented, with a *P* value less than .01 statistically significant.

RESULTS

Figure 1 depicts the percentage of patients and normal controls with abnormal serum levels of lipids. Nine patients with CAH (64.3%) had serum TC greater than 4.4 mmol/L (170 mg/dL), compared with 6 individuals (42.3%) in the control group. Nine children with CAH (64.3%) had TG greater than 1.0 mmol/L (90 mg/dL), compared with 2 controls (14.3%). For LDL-C, 9 CAH patients (69.2%) of 13 in whom LDL-C levels were determined and 8 controls (57%) had LDL-C greater than 2.85 mmol/L (110 mg/dL). Two of 13 CAH patients (15.4%) and 4 controls (28.6%) had HDL-C less than 0.9 mmol/L (35 mg/dL), but the difference was not statistically significant. The percentage of CAH patients with TC and LDL-C over the cutoff point, although slightly higher compared with the controls, was not statistically significant. For serum TG, the difference between the 2 groups was statistically significant ($\chi^2 = 7.32$ (1 *df*) $P < .01$). The mean serum TC and LDL-C in the CAH group were mildly elevated compared with the controls but were without statistical significance, 4.6 ± 0.18 mmol/L (177 ± 7 mg/dL) versus 4.3 ± 0.12 mmol/L (165 ± 5 mg/dL) and 3.0 ± 0.16 mmol/L (113 ± 6 mg/dL) versus 2.9 ± 0.12 mmol/L (112 ± 6 mg/dL), respectively. For serum TG, the mean value in the CAH group was higher and statistically significant compared with the controls, 1.32 ± 0.15 mmol/L (118 ± 15 mg/dL) versus 0.75 ± 0.07 mmol/L (67 ± 7 mg/dL), respectively ($P = .043$). The mean serum HDL-C was similar for both groups, 1.0 ± 0.05 mmol/L (39 ± 6 mg/dL). The HDL-C/TC ratio for the control group was 0.24, compared with 0.22 for the CAH group, values which are above the fifth percentile.

DISCUSSION

No previous known studies have reported the potential effects of glucocorticoid therapy on the lipid profile of patients with CAH. The results of this pilot study coincide with previous reports of lipid abnormalities induced by glucocorticoid therapy in patients with conditions such as asthma,[8] rheumatoid disorders,[1,2] and heart and kidney transplants.[9-11] We must acknowledge that the sample size of this study is small; however, the

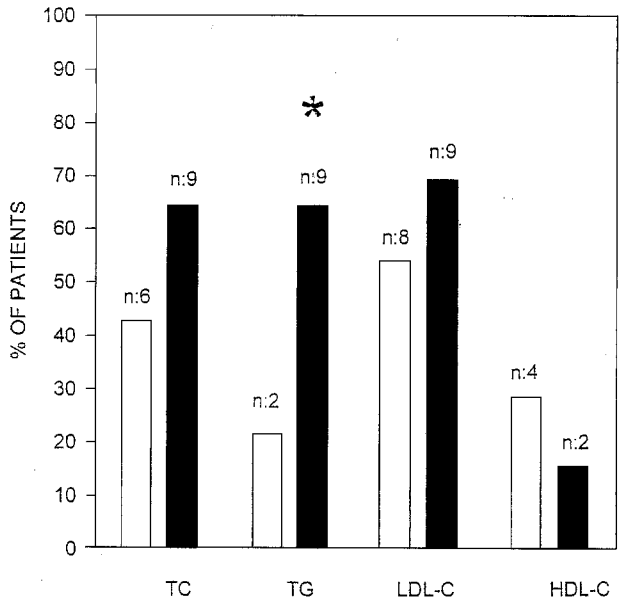

Fig 1. Percentage of individuals with TC >4.4 mmol/L (170 mg/dL), LDL-C >2.8 mmol/L (110 mg/dL), HDL-C < 0.9 mmol/L (35 mg/dL), and serum TG > 1.0 mmol/L (90 mg/dL). (□) Control group; (■) CAH group. Although the percentage of CAH patients with serum TC and LDL-C over the cutoff point was slightly higher compared with the control group, only the percentage of patients with elevated serum TG was statistically significant (*$P < .01$). Statistical significance was determined using the χ^2 test.

statistical analysis showed significance for some differences in the lipid profile among both groups. Considering that serum lipid levels in prepubertal individuals show no significant age- or sex-related dependence,[15] the control group was not matched for age and gender with the CAH patients. Similarly, all subjects in both groups were prepubertal, which eliminates potential changes in the serum lipid profile associated with the production of sex steroids. For the same reason, an exclusion criterion for patients in the CAH group was the presence of pubertal levels of total testosterone or androstenedione, which could account for abnormalities in the lipid profile. 17-OHP levels were not measured, considering its questionable clinical usefulness in the follow-up evaluation of patients with CAH compared with androstenedione or PRA. Its shorter half-life, diurnal variation, and response to stress, plus the fact that it is frequently elevated in patients with CAH regardless of their degree of clinical control, may limit its usefulness.

Although there are no reports on the specific effects of 17-OHP on lipid metabolism, we cannot exclude the possibility that the eventually high levels of 17-OHP in the group with CAH contributed to the observed difference in the lipid profile between the groups. This possible confounding factor was untested in the present study. Although exercise is another confounding variable that can induce changes in lipid metabolism mainly by reducing the serum level of LDL-C,[17] this variable was not controlled in the present study because of the difficulty in objectively measuring the degree of physical activity in children of a young age. Although our patients were receiving prednisone instead of hydrocortisone, which is considered the glucocorticoid of choice for the treatment of CAH in the United States, the results obtained in our study can be extrapolated considering that the dose of prednisone administered to our patients was equivalent to the standard dose of hydrocortisone most commonly prescribed in the United States. In addition, the degree of glucocorticoid-induced hyperlipidemia is similar for the different types of glucocorticoids compared at equivalent doses.

In our study, a greater number of individuals with abnormally elevated levels of TC, TG, and LDL-C were found in the group receiving glucocorticoids, but only the difference for serum TG was statistically significant. However, when the cutoff point for TC is increased to 4.8 mmol/L (190 mg/dL, 85th percentile) as previously suggested,[18] none of the controls show values above this level, in contrast to 36% of the CAH patients. In addition, the mean concentration of TG was higher in the patient group compared with the controls, which has been reported in patients on glucocorticoid therapy.[1,8,9] Although the number of controls with HDL-C below the fifth percentile was slightly higher compared with the CAH patients, the difference was of no statistical significance. The mean serum level of HDL-C and the HDL-C/TC ratio were similar for both groups. Although the therapeutic dose of prednisone in our patients was an equivalent of a dose of 10 to 20 mg hydrocortisone/m^2, most patients were on 15 mg/m^2; therefore, no dose-response data were sought.

Changes in the lipid profile as a result of administration of glucocorticoids have been reported as early as the first month of steroid treatment in normal controls.[4,5] The fact that our patients were receiving the recommended dose of glucocorticoids makes the results of this study worrisome. Long-term use of glucocorticoids could lead to significant atherosclerosis as a result of the induced hyperlipidemia.[12] There are several reasons for concern about the appropriate diagnosis of hyperlipidemia and its treatment. The most important is the causal relationship between hyperlipidemia and atherosclerotic vascular disease (coronary heart disease, cerebrovascular accident, visceral atherosclerosis, and peripheral vascular disease). Clinical and epidemiological studies have demonstrated a strong causative correlation between elevated TC and LDL-C levels and an increased risk of cardiovascular morbidity and mortality.[19,20] Universal screening for hyperlipidemia in children has remained controversial,[13,18] but screening for high-risk populations has been advocated by the NCEP and the American Academy of Pediatrics.[13,14] If glucocorticoid therapy proves to increase the risk of hyperlipidemia in children with CAH, routine screening might be indicated in this population and other pediatric groups on therapeutic regimens with glucocorticoids, considering the potential association of dyslipidemia and atherosclerosis in children and young adults.[12]

Although this is a pilot study and the sample size was small, these results suggest that glucocorticoid therapy in patients with CAH may induce abnormalities in the serum lipid profile that should be considered in the clinical assessment of these patients. A larger study is necessary to confirm these preliminary results.

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