Acta Paediatrica Hungarica, 29 (3—4), pp 395—403 (1988—1989)

Steroid metabolism in obese children II. Steroid excretion of obese and normal weight children

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Received 10 December 1986

Comparative studies on adrenal function have been performed in 56 children, 31 obese and 25 of normal weight. Their body weight fell within the range between 80 and 215% of the ideal weight (100%). Nine steroids resp. steroid groups were measured by gas chromatography. The participants were grouped by degree of fatness, sex and presence of absence of puberty (Tanner I or higher than I).

The urinary steroid excretion rate was corrected for weight. Altered steroid metabolism was found in obese children as compared with the normal groups: not only the excretion of cortisol metabolites was increased but also that of androgen metabolites and pregnenediol, metabolite of pregnanolone. There is a trend for increased excretion of all steroid groups, in certain cases this attains the level of statistical significance.

Wide variability was observed in the steroid excretion of obese children, in about one third of them there was hypersecretion of some components of the steroid spectrum. This phenomenon was more frequently encountered in boys. Extension of the normal range of steroid excretion rates of obese children seems to be justified.

Altered endocrine functions accompanying obesity have been long known. A large number of studies on adrenocortical function of obese individuals has been conducted to establish a solid base for differential diagnosis between simple overweight and hyperandrogenism and Cushing's syndrome occurring in obese persons. In obesity normal plasma cortisol, plasma free cortisol and urinary free cortisol excretion is the rule as shown by many authors summarised by Glass et al [6]. Others have reported on increased cortisol production rates and cortisol metabolite excretion [3, 7, 12, 20]. Again other workers think that the cortisol metabolite excretion rate is normal if corrected for creatinine excretion [18, 19].

Less and contradictory information is available on adrenal production and renal excretion of androgens. Increased 17-ketosteroid excretion was observed by Cohen [2] in four obese children between 6 and 12 years of age and by Simkin [17] in 62 obese adults, while Poisnick et al [15] have reported on moderately depressed 17-ketosteroid excretion found 54 obese women. Gray et al [7] found increased values for androsterone (A), ethio-

cholanolone (E) and 11-keto-(A + E) excretion by gas chromatographic separation in 15 obese girls and 8 boys, aged 9 to 20 years but the degree of increment did not attain the level of significance. Kiss and Fehér [11] performed measurements in 47 obese children and found normal 17-ketosteroid and ketosteroid fraction excretion in all age groups. A high DHA production rate and urinary excretion rate, accompanied by normal DHA-sulfate values were observed by Fehér and Halmy [4] in three obese women.

This study has been aimed at the urinary excretion of metabolites of cortisol, androgens and intermediary steroids in obese children, a spectrum was established by using gas chromatography. Experience described in the first part of this paper prompted us to relate the excretion rates to weight.

Material and Methods

Urine collection

A 24-hour specimen was collected by 31 obese children, 17 girls and 14 boys. 14 girls, whose steroid excretion has already been described in another context [10] and 11 boys, both of normal body weight served as controls. The following subgroups were set up:

Prepubertal: girls: obese: 4
non-obese: 8

boys: obese: 4
non-obese: 5

Pubertal: girls: obese: 13
non-obese: 6

boys: obese: 10
non-obese: 6

Anthropometric data

These are described in the first part of the paper.

Procedure

Preparation and gas chromatographic analysis of the urine samples were carried out as indicated in Part I, urine extracts obtained by acid hydrolysis and simultaneous toluene extraction were acetylated before chromatography on two columns of different packing to obtain adequate specificity.

Statistical analysis

Student's *t*-test; the threshold for statistical significance was set at $P \leq 0.05$.

Results

In Figure 1 the excretion rates of obese and non-obese children are compared. The excreted steroids are grouped in nine groups. Means, SEM values and P values are also indicated to demonstrate the differences between obese and normal weight children. There is a trend for increased excretion rates, even corrected for weight, in three groups: prepubertal girls and boys, pubertal boys. A contrary tendency was, however, encountered in pubertal girls. The differences are relatively large in the prepubertal children, especially for cortisol metabolites and allo-tetrahydrocorticosterone (aTHB). Statistical significance could only be shown in a few groups.

$C_{21}O_5$ stands for the sum of cortisol metabolites. The above mentioned trends can be seen for both compound groups, in fact, a significant difference

was found between obese and non-obese prepubertal boys. In some obese children extremely high cortisol metabolite excretion occurred in spite of the absence of any endocrine abnormality demonstrated in obese children.

Combined values of androsterone (A) and ethiocholanolone (E) were calculated and shown in the figure while

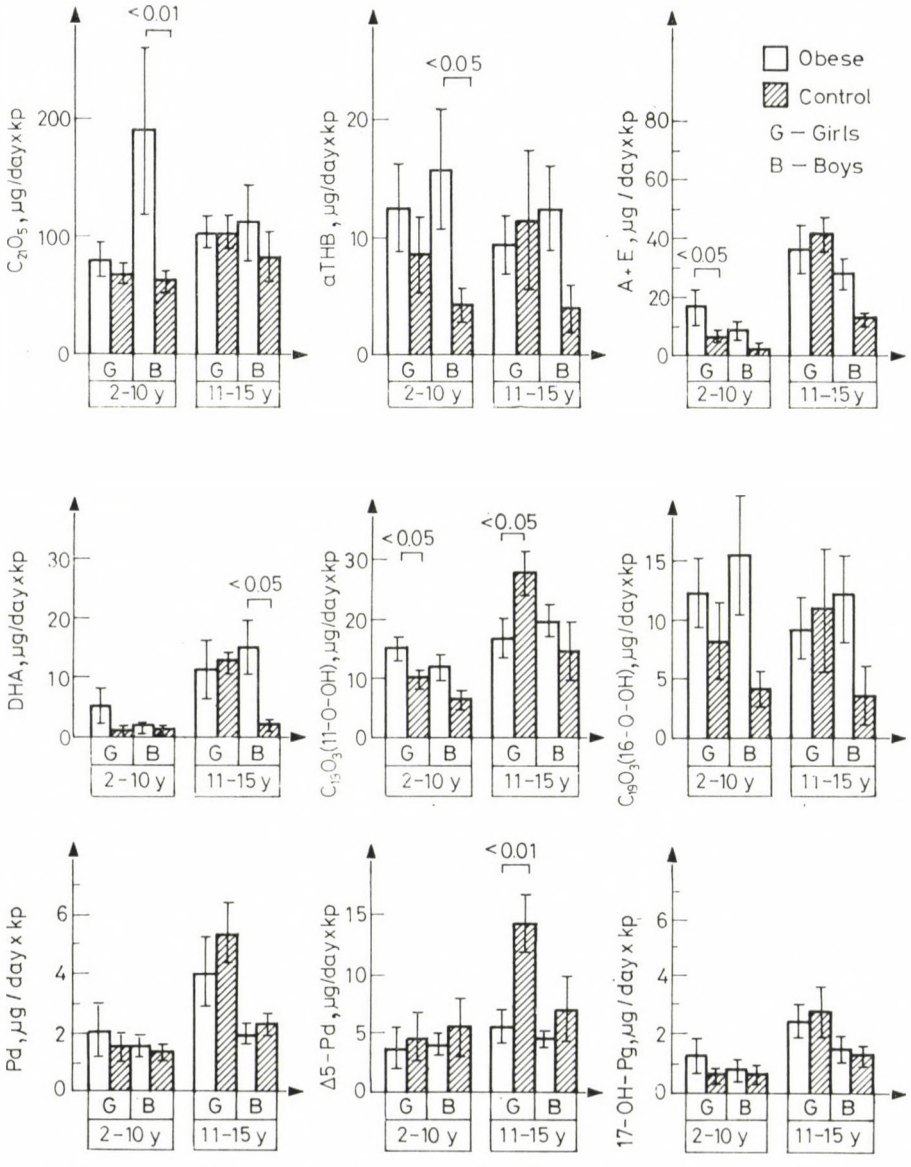

FIG. 1. Means and SEM values of urinary steroid excretion of obese and non-obese children, N = 60

TABLE I

Hyperexcretion of individual steroids in obese children, percentual incidence of hyperexcretion broken down by sex, degree of hyperexcretion, by sex and age. Obese 1: value below mean + 2SD of controls, Obese 2: value exceeding mean + 2SD of controls

Steroid		Prepubertal					
		Girls			Boys		
		controls	obese 1	obese 2	controls	obese 1	obese 2
	N	8	4	—	5	—	4
$C_{21}O_5$	mean	64.0	90.9	—	60.3	—	190.6
	SD	±23.0	±32.1	—	±22.2	—	±69.1
	N	8	4	—	5	1	3
aTHB	mean	4.5	11.3	—	4.2	8.1	18.5
	SD	±9.9	±7.8	—	±3.2	—	±10.9
	N	8	3	1	5	2	2
A + E	mean	7.4	10.7	40.1	3.3	4.4	13.1
	SD	±6.4	±3.9	—	±1.1	±1.1	±8.1
	N	8	2	2	5	2	2
DHA	mean	1.2	2.4	11.9	1.0	0.7	2.2
	SD	±0.9	±0.4	±9.4	±0.4	±0.4	±0.2
$C_{19}O_3$ (11-O-OH)	N	8	3	1	5	3	1
	mean	10.9	14.7	21.9	7.2	9.9	16.7
	SD	±5.7	±1.6	—	±3.6	±1.7	—
$C_{19}O_3$ (16-O-OH)	N	8	4	—	5	2	2
	mean	5.0	2.6	—	1.6	1.7	5.6
	SD	±3.8	±1.3	—	±1.2	±2.2	±0.3
	N	8	4	—	5	4	—
Pd	mean	1.6	1.7	—	1.4	1.5	—
	SD	±1.2	±1.4	—	±0.6	±0.6	—
	N	8	4	—	5	4	—
Δ5-Pd	mean	5.0	3.6	—	5.9	4.4	—
	SD	±4.8	±1.5	—	±5.6	±3.4	—
	N	8	3	1	5	3	1
17-OH-Pg	mean	0.7	0.8	3.2	0.7	0.1	1.8
	SD	±0.6	±0.5	—	±0.8	±0.03	—

Steroid		Pubertal					
		Girls			Boys		
		controls	obese 1	obese 2	controls	obese 1	obese 2
	N	6	12	1	6	8	2
$C_{21}O_5$	mean	103.1	93.9	198.6	70.5	77.5	255.7

TABLE I (continued)

	SD	±31.0	±40.0	—	±44.4	±47.1	±81.3
	N	6	13	—	6	7	3
aTHB	mean	11.4	10.9	—	3.8	7.1	25.1
	SD	±13.7	±10.6	—	±3.9	±3.4	±15.4
	N	6	12	1	6	4	6
A + E	mean	42.1	29.8	120.1	18.1	13.4	38.3
	SD	±14.4	±19.5	—	±1.7	±5.5	±12.1
	N	6	11	2	6	1	9
DHA	mean	13.4	5.4	44.6	1.9	3.0	20.3
	SD	±2.6	±3.2	±34.8	±0.8	—	±21.5
$C_{19}O_3$ (11-O-OH)	N	6	12	1	6	10	—
	mean	18.8	14.9	69.2	15.8	20.1	—
	SD	±11.0	±8.1	—	±12.4	±8.7	—
$C_{19}O_3$ (16-O-OH)	N	6	12	1	6	5	5
	mean	7.8	6.7	36.7	2.5	2.5	14.0
	SD	±9.6	±5.2	—	±2.1	±1.3	±10.4
	N	6	10	3	6	10	—
Pd	mean	5.4	2.3	10.5	2.3	1.9	—
	SD	±2.3	±1.2	±2.9	±0.9	±0.9	—
	N	6	13	—	6	10	—
Δ5-Pd	mean	8.9	5.7	—	7.4	4.4	—
	SD	±6.4	±3.8	—	±6.2	±2.1	—
	N	6	13	—	6	10	1
17-OH-Pg	mean	2.9	2.5	—	1.3	1.3	3.7
	SD	±1.8	±2.0	—	±0.9	±1.1	—

Steroid		$\frac{N_{obese}}{N_{obese\ 1}} \times 100$		$\frac{\text{mean value}_{obeses}}{\text{mean value}_{controls}}$			
				Girls		Boys	
		Girls	Boys	Prep	Pub.	Prep.	Pub.
	N						
$C_{21}O_5$	mean	6%	43%	—	1.9	3.5	3.6
	SD						
	N						
aTHB	mean	—	43%	—	—	4.5	6.6
	SD						
	N						
A + E	mean	11%	57%	6.3	2.9	4.0	2.1
	SD						
	N						
DHA	mean	22%	79%	9.9	3.3	2.2	10.7
	SD						

TABLE I (continued)

$C_{19}O_3$ (11-O-OH)	N						
	mean	11%	7%	2.0	3.7	2.3	—
	SD						
$C_{19}O_3$ (16-O-OH)	N						
	mean	6%	50%	—	4.7	3.5	6.0
	SD						
Pd	N						
	mean	17%	—	—	1.9	—	—
	SD						
Δ5-Pd	N						
	mean	—	—	—	—	—	—
	SD						
17-OH-Pg	N						
	mean	6%	14%	4.6	—	2.8	2.9
	SD						
	mean	8.8%	32.6%	2.5	2.1	2.5	3.5
	SD	±7.3	±28.3	±3.6	±1.8	±1.6	±3.6

DHA values are demonstrated apart. A significant difference was observed for A + E in prepubertal girls and for DHA in pubertal boys.

The sum of 11-keto (A + E) and 11-hydroxy (A + E) was termed as $C_{19}O_3$(11-O-OH). For this value a significant difference between obese and non-obese was encountered in both girl groups, prepubertal and pubertal. It is noteworthy that the obese had lower excretion rates.

In the group of $C_{21}O_2$ steroids Pd stands for pregnandiol and Δ5-Pd for pregnenediol. No difference was found with pregnanediol while low excretion of pregnenediol was seen in obese children of all groups, the difference is significant in girls after onset of puberty.

No significant differences were observed with 17-hydroxy-pregnanolone (17-OH-Pg), within the $C_{21}O_3$ steroids.

The ratio of $C_{19}O_2$ steroids to $C_{21}O_5$ steroids, which exhibits a value increasing during puberty and is an indicator of the ontogenesis of the zona reticularis in girls [10] showed a different pattern in boys and girls. In girls, the high value was encountered in the prepubertal group while in boys, in the pubertal group.

During physiological puberty, the quotient of 11-keto resp. 11-hydroxy-$C_{19}O_3$ steroids and $C_{19}O_2$ steroids decreases. In our experience, the value of the quotient was lower in obese children of any group and reached the adult value earlier than in the controls. In obese pubertal boys the value of the DHA/A + E quotient was significantly higher than in controls.

The steroid excretion of the obese children was not homogeneous. In some children a normal pattern was found while in certain children values exceeding the normal values many times could be observed. The steroid

metabolite values were therefore regrouped according to whether they fell within (obese 1) or above the mean ± ± 2 SD (obese 2). Table I shows these subgroups, their mean and SD values. The percentage of cases with high values was calculated for boys and girls separately, and the degree of excess was calculated for both sexes and Tanner groups separately.

Discussion

In accordance with a number of authors [2, 7, 15, 17] we found minor alterations of the endocrine functions of obese children as compared with normal individuals.

In the 56 children, grouped by Tanner's stages of puberty, sex and weight, nine steroids resp. steroid groups were investigated. There was a general tendency for increased excretion in obese children but the difference only rarely attained the degree of statistical significance. This is partly due to the wide scatter indicating to a marked inter-individual variability in the obese groups: both extremely high and low values did here occur. Similar large inter-individual variation has been described by Migeon et al [12] and O'Connel et al [14]. Prezio et al [16] feel that hyperexcretion may be expected in about one third of obese children.

In girls having entered puberty, however, none of the steroid components showed a higher excretion rate in obese individuals than in controls. The weight excess was most pronounced just in this group, correction for weight results in lower values, this points to the fact that the excess of steroid excretion is smaller than the weight excess.

Δ5-Pd excretion exhibits a pattern different from that of all other steroids investigated: it was lower in obese children, invariably for all groups. DHA is stored in fat [4] as is progesterone [9]. Δ5-Pd is a metabolite of pregnenolone, its decreased urinary output may be due to storage of pregnenolone in fat.

On the other hand, the cortisol metabolites and aTHB show an increased mean value in all but one groups of obese children: pubertal girls being the exception. Such a concomitant increase of corticoid and aTHB excretion has already been seen by us in children between 2 and 15 years exposed to surgical stress [8]. The finding of increased cortisol metabolites and aTHB in obese may be ascribed to emotional stress due to obesity. This idea has already been put forward by other authors as well [1, 20]. This increased excretion of cortisol metabolites accompanied by normal plasma cortisol indicates accelerated cortisol metabolism [20], midly increased ACTH output is needed for the maintenance of the unchanged plasma cortisol level [6], the continuous moderate stress acts in the same direction.

During the maturation process of adrenal function, development of the zona reticularis is accompanied by an increased quotient of $C_{19}O_2$ steroids per cortisol metabolites and a decrease in the value of the quotient of $C_{19}O_3$(11-O-OH) metabolites per $C_{19}O_2$ steroids. In our experience, these

changes supervene in obese children earlier than in normal weight children, pointing to a premature onset of the development of the zona reticularis, the adrenarche. Earlier onset of menarche has been described in obese girls [2, 6]. Genazzani et al [5] have reported on accelerated maturation of adrenal functions in prepubertal obese girls. The significantly higher DHA value, found in pubertal boys, reflects testicular testosterone production.

Two distinct patterns of urinary steroids occur in obese children. First, the spectrum is identical with that of normal children both in respect of quantities and ratios. In the second type there is a significantly increased steroid excretion, exceeding the mean plus 2 SD limit, in fact individual steroid excretion values may be extremely high without coexistent endocrine disease. Such peaks were observed both for cortisol metabolites and androgens. Our findings are supported by those of Migeon et al [12], Dunkelman et al [3] and Simkin [17]. Hyperexcretion occurs in boys more frequently (30%) than in girls (10%). Molnár et al [13] observed that hyperlipidaemia is more frequent within obese boys than obese girls. The different distribution of abnormal steroid excretion within the two sexes again speaks for biochemical and hormonal abnormalities occurring more frequently in boys than in girls.

On the basis of our data extension of the normal range of excretion values of obese children seems reasonable.

Acknowledgment

We are very deeply indebted to Professor D.N.Kirk, (Steroid Reference Collection, London) for the reference steroids and to Mrs Márta Szécsényi and Miss Krisztina Nemes for their invaluable technical assistance.

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