Urate Changes in Lean and Obese Boys During Pubertal Development

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Uric acid metabolism is not uniform throughout puberty. Serum urate increases progressively in obese boys as puberty advances, but it increases significantly only at the end of puberty in lean subjects. Urate filtered per unit of body weight increases in all subjects at the end of puberty when fractional excretion is diminished. Urate clearance decreases at the beginning of puberty in obese boys and at the end of puberty in lean subjects. Urate excretion corrected for body weight and the urinary uric acid to creatinine ratio do not change over the course of pubertal development in both lean and obese boys. These results suggest the following hypotheses: (1) renal retention of urate may represent the first mechanism by which uricemia is enhanced at puberty; (2) the kidney may finely modulate serum uric acid concentration through different mechanisms of urate handling, presumably occurring at different tubular sites; and (3) obesity may evoke sooner the urate changes that in lean boys are observed at the end of puberty.

ALTHOUGH uric acid metabolism in humans is not uniform throughout life, the developmental aspects of urate homeostasis in childhood and adolescence and its clinical relevance remain to be fully explored.

In a previous report, parameters of uric acid metabolism obtained in lean and obese girls before and during pubertal development were discussed.[1] This study presents data on serum uric acid concentration and renal handling of urate assessed in lean and obese boys.

SUBJECTS AND METHODS

Uric acid metabolism was evaluated in lean and obese boys before and during pubertal development. The lean group consisted of 60 consecutive healthy children admitted to the hospital because of nonemergency surgery (mostly for minor ocular disorders, phimosis, and hernias), referred to the endocrine unit because of parental concern regarding growth and/or the rate of pubertal development (which were in the normal range), or seen as outpatients for routine control. The obese group consisted of 66 consecutive boys attending the endocrine unit because of overweight. All these subjects were divided into subclasses according to stage of pubertal development (group A, prepubertal children; group B, Tanner stage II to III; and group C, Tanner stage IV to V).[2] Characteristics of the study population are summarized in Table 1.

Obesity was defined as a weight for height greater than 120% of the ideal.[3] It has been expressed as the body mass index.

Subjects studied as inpatients were given a standard hospital diet. Families of outpatients had been instructed to eliminate foods high in purine content. No subjects were taking medication. Informed consent was obtained from the guardians before performing the biochemical investigation. The study was approved by the Ethics Committee of the hospital.

Urate changes were evaluated by assessing serum uric acid concentration, urate filtration, urate clearance, and urinary excretion. Since both metabolic acidosis and extracellular fluid volume depletion may affect uric acid excretion, urine testing for ketones and sodium content was performed. Subjects with ketosis or a urinary sodium content less than 20 mmol/L (suggesting volume depletion) were excluded.

The following parameters were assessed. (1) For determination of serum uric acid concentration, a blood specimen for serum urate was drawn in the morning after an overnight fast at the end of urine collection. (2) Urate filtration (mmol/24 h and μmol/kg/24 h) was assessed from serum urate concentration and glomerular filtration rate, using the clearance of endogenous creatinine evaluated over a 24-hour period as a measure of glomerular filtration.[4] Filtered urate was calculated as follows: filtered urate (μmol/24 h) = serum urate (μmol/mL) × creatinine clearance (mL/min) × 1,440 minutes. (3) A 24-hour urine specimen was collected for determination of urate clearance (mL/min and mL/kg/min), urate excretion (μmol/24 h and μmol/kg/24 h), and urate to creatinine ratio. (4) Fractional excretion of urate was calculated using the formula FE% = (UUA × SCr/SUA × UCr) × 100, where UUA is urinary uric acid concentration, SUA is serum uric acid concentration, UCr is urine creatinine concentration, and SCr is serum creatinine concentration.

Uric acid values were determined in serum and urine using a spectroscopic uricase method (Uric Acid Test, MPD; Sclavo, Siena, Italy). Creatinine levels were measured in serum and urine using the Jaffé method (Creatinine; Merck, Darmstadt, Germany).

Results are expressed as the mean ± SD. Comparisons were made using a nonparametric technique (Mann-Whitney U),[5] and correlations by means of the Spearman rank correlation coefficient.[6]

RESULTS

Table 1 summarizes characteristics of the study population. Tables 2 and 3 show the mean values of urate parameters as assessed in lean and obese boys at different stages of pubertal development.

The mean value of serum uric acid gradually increases in lean subjects as puberty advances, but a statistically increased level occurs only during the late stage of pubertal development (group C). The calculated total amount of uric acid filtered at the glomerulus is significantly enhanced at each stage of puberty. Nevertheless, when this parameter is corrected for body weight, only children from group C show significantly increased levels. Urate clearance and fractional excretion decline during the late pubertal stage. Urate excretion per unit of body weight and the urinary uric acid to creatinine ratio do not change significantly among all groups. Serum uric acid concentration correlates directly with filtered urate per unit of body weight in the lean group as a whole ($r = .696, P < .01$), and inversely with fractional excretion ($r = -.394, P < .01$). Serum uric acid correlates

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Table 1. Characteristics of the Study Population

Characteristic	Group A	Group B	Group C
Age (mo)			
Lean boys	90 ± 25 (14)	146 ± 21 (37)	175 ± 17 (9)
Obese boys	86 ± 18 (19)	141 ± 19 (39)	181 ± 13 (8)
BMI (kg/m²)			
Lean boys	15.87 ± 1.53 (14)	16.25 ± 1.92 (37)	17.81 ± 2.14 (9)
Obese boys	23.51 ± 2.30 (19)	26.23 ± 3.05 (39)	31.23 ± 3.46 (8)
	$P < .0001$	$P < .0001$	$P < .0001$

NOTE. Group A, prepubertal boys; group B, Tanner stage II to III; group C, Tanner stage IV to V. Number of subjects is shown in parentheses.

Abbreviation: BMI, body mass index.

directly with urinary uric acid corrected for creatinine excretion ($r = .507$, $P < .01$). No correlation is found between serum uric acid concentration and urate excretion corrected for body weight ($r = .108$, NS) or between serum urate and urate clearance per unit of body weight ($r = .090$, NS). A direct correlation is also observed between filtered and excreted urate ($r = .534$, $P < .01$).

Serum uric acid increases significantly at each stage of pubertal development in the obese population. However, as occurs in lean subjects, a larger relative filtration takes place only at the end of puberty, when a minor fraction of filtered urate is excreted. Urate clearance per unit of body weight decreases significantly at the beginning of puberty (group B). Both uric acid excretion per unit of body weight and the urate to creatinine ratio do not differ statistically among the three groups of obese children. A direct correlation between serum uric acid and filtered urate per unit of body weight ($r = .739$, $P < .01$) and an inverse correlation between serum urate and fractional excretion ($r = -.431$, $P < .01$) can be observed in the obese group as a whole. The calculated amount of filtered uric acid is directly correlated with renal excretion ($r = .669$, $P < .01$). No correlation is found between serum uric acid and urate clearance per unit of body weight ($r = -.159$, NS), urate excretion per unit of body weight ($r = .041$, NS), and urate to creatinine ratio ($r = .092$, NS).

Table 2. Uric Acid Parameters Assessed in Lean Boys

Parameter	Group A (n = 14)	Group B (n = 37)	Group C (n = 9)
Serum urate concentration (μmol/L)	145 ± 41	157 ± 46	278 ± 32
		A & B v C, $P < .0001$	
Urate filtration			
mmol/24 h	13 ± 4	19 ± 6	48 ± 21
	A v B & B v C, $P = .0001$		A v C, $P < .0001$
μmol/kg/24 h	577 ± 160	583 ± 190	1,023 ± 428
	A v C, $P = .002$		B v C, $P = .001$
Urate clearance			
mL/min	3.60 ± 2.23	4.31 ± 1.88	2.83 ± 1.84
		B v C, $P = .02$	
mL/min/kg	0.13 ± 0.06	0.13 ± 0.06	0.05 ± 0.03
	A v C, $P = .002$		B v C, $P = .0008$
Urate excretion			
μmol/24 h	720 ± 446	910 ± 363	1,136 ± 767
μmol/kg/24 h	28 ± 12	28 ± 12	24 ± 14
% filtered urate	5.35 ± 3.01	5.25 ± 2.48	2.59 ± 1.79
	A v C, $P = .01$		B v C, $P = .002$
Urate to creatinine ratio (μmol/μmol)	0.12 ± 0.06	0.12 ± 0.06	0.09 ± 0.06

NOTE. Group A, prepubertal boys; group B, Tanner stage II to III; group C, Tanner stage IV to V.

Table 3. Uric Acid Parameters Assessed in Obese Boys

Parameter	Group A (n = 19)	Group B (n = 39)	Group C (n = 8)
Serum urate concentration (μmol/L)	164 ± 36	207 ± 58	324 ± 60
	A v B, $P = .004$	A v C, $P < .0001$	B v C, $P = .0002$
Urate filtration			
mmol/24 h	18 ± 6	32 ± 16	64 ± 13
	A v B, $P = .0002$	A v C, $P < .0001$	B v C, $P = .0001$
μmol/kg/24 h	499 ± 160	523 ± 196	708 ± 125
	A v C, $P = .005$		B v C, $P = .009$
Urate clearance			
mL/min	3.35 ± 1.32	4.10 ± 2.04	4.08 ± 1.51
mL/min/kg	0.09 ± 0.03	0.06 ± 0.03	0.04 ± 0.02
	A v B, $P = .03$		A v C, $P = .003$
Urate excretion			
μmol/24 h	821 ± 422	1,166 ± 583	1,856 ± 583
	A v B, $P = .01$	A v C, $P < .0001$	B v C, $P = .006$
μmol/kg/24 h	22 ± 11	20 ± 9	20 ± 6
% filtered urate	4.70 ± 2.07	4.18 ± 2.13	2.87 ± 1.44
		A v C, $P = .03$	
Urate to creatinine ratio (μmol/μmol)	0.13 ± 0.05	0.12 ± 0.06	0.12 ± 0.04

NOTE. Group A, prepubertal boys; group B, Tanner stage II to III; group C, Tanner stage IV to V.

In this study, a comparison between lean and obese boys at the same stage of pubertal development shows significant differences only between subjects in group B (early puberty). Serum uric acid concentration and daily filtration rate are higher in obese children ($P = .0002$ and $P < .0001$, respectively). Total urate excretion is increased in obese boys ($P = .04$). Urate clearance per unit of body weight, urate excretion per unit of body weight, and fractional excretion are decreased ($P < .0001$, $P = .0008$, and $P = .05$, respectively). Filtered urate per unit of body weight and the mean urinary uric acid to creatinine ratio are similar.

DISCUSSION

The results presented in this cross-sectional study suggest that striking changes in uric acid metabolism take place in both lean and obese boys during pubertal development.

In lean subjects, serum urate and filtered urate per unit of body weight are significantly increased toward the end of puberty, when urate clearance per unit of body weight and fractional excretion are decreased. By contrast, serum uric acid concentration appears to be significantly increased in the obese population at each stage of pubertal development, and urate clearance per unit of body weight is simultaneously significantly decreased. Overall, in both lean and obese boys, increased serum urate concentration occurs in parallel with decreased urate clearance and decreased fractional excretion. This phenomenon suggests

that renal retention of urate may represent the earliest mechanism by which uricemia is enhanced at puberty.

In lean boys, striking alterations in uric acid metabolism occur at the end of puberty, whereas in obese boys, they occur at the beginning of pubertal development. Urate clearance per unit of body weight is diminished in obese children of group B (early puberty) compared with obese prepubertal children, whereas this parameter is similar among lean children of groups A and B. In addition, fractional excretion of urate is decreased in obese children of group B compared with their lean counterparts, despite an increased serum uric acid concentration, an increased amount of total urate filtered at the glomerulus, and a similar amount of filtered urate per unit of body weight. An early increase in renal function resulting in decreased fractional excretion of urate has been previously observed in obese girls.[1] Data obtained in boys further support the hypothesis that obesity may prematurely evoke changes in urate metabolism that in lean subjects may be observed later.

The role of the kidney in determining serum urate level appears to be complex. This study provides evidence that pubertal development is associated with renal urate retention in both lean and obese boys, as indicated by decreased renal clearance of uric acid and decreased fractional excretion.

Renal retention of urate may be potentially caused by decreased filtration, increased tubular reabsorption, or decreased tubular secretion. Previous studies have shown that serum uric acid is nearly completely filtered by the glomerulus membrane, since insignificant binding of urate to plasma proteins is present at body temperature.[7] This study shows that the calculated total and relative filtrations are increased significantly at the end of puberty in both lean and obese boys. As a consequence, a decreased filtration should be ruled out as a cause of urate retention.

Decreased excretion of urate is then presumed to reflect changes in renal tubular transport, resulting in increased reabsorption, decreased secretion, or both. The tubular phases that may modulate uric acid excretion have been evaluated in the past by means of pharmacologic tests and are described as follows. The amount of urate filtered at the glomerulus is almost completely reabsorbed in the proximal tubule by a high-capacity system. Tubular secretion of urate occurs further distally, and subsequently, reabsorption of secreted urate occurs at a postsecretory site.[8] Nevertheless, although several observations have provided support for the four-component model of uric acid excretion, the exact mechanism and sites of tubular urate transport remain to be fully elucidated.

This investigation shows that the tubular handling of urate may be finely modulated. Urate clearance per unit of body weight and fractional excretion of urate decrease significantly throughout puberty in both lean and obese boys. By contrast, urate excretion corrected for body weight does not change significantly over the course of pubertal development, despite an increased filtration rate occurring at the end of puberty. In addition, the urinary uric acid to creatinine ratio appears to be similar in all subjects independently of body fat and pubertal development. All these data show evidence of different mechanisms of renal urate handling presumably occurring at different tubular sites. Further studies are needed to obtain information about the mechanisms that may account for the above patterns of urate excretion. Indeed, taking into account these results, it appears likely that the most important regulatory system responding to homeostatic needs may reside within the kidney's apparatus for urate secretion and its subsequent reabsorption.

It is worth noting that all boys, independently of body mass index and degree of pubertal development, show similar values for the urinary uric acid to creatinine ratio. This feature seems to link uric acid metabolism to the lean body mass, particularly skeletal mass. An interrelation between uric acid homeostasis and muscle has been previously observed in different physiologic and pathologic conditions.[9-13] A striking development of skeletal mass occurs in boys just during late adolescence, when increased insulin resistance, a condition associated with increased uricemia,[12] is also observed. Further studies are needed for understanding the nature and physiological relevance of such an association.

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