Growth hormone response to a standardised exercise test in relation to puberty and stature

S A GREENE, T TORRESANI, AND A PRADER

Department of Pediatrics, University of Zurich, Zurich, Switzerland

SUMMARY Growth hormone (GH) was measured before and 10 minutes after a standardised bicycle exercise test (duration 15 minutes) in 37 short children (group 1: mean (SD) age 12.8 (3.5) years; mean (SD) bone age 10.4 (3.6) years; mean (SD) height standard deviation score (SDS) -2.8 (0.7)), 16 tall children (group 2: mean age 12.9 (2.8) years; mean bone age 13.9 (1.4) years; mean height SDS 3.0 (0.8)), and 30 normal children (group 3: mean age 13.3 (3.2) years; mean bone age 12.8 (3.4) years; mean height SDS -0.4 (0.8)). Results of GH are expressed as mean (SEM).

The pre-exercise GH was similar in the three groups (group 1, 8.0 (2.3) mU/l, group 2, 8.5 (2.5) mU/l, and group 3, 8.3 (2.3) mU/l). There was a significant rise in GH after exercise in all three groups. GH after exercise was higher in group 2 (35.1 (2.5) mU/l) compared with groups 1 and 3 (17.8 (3.0) and (20.8 (3.2) mU/l). Post-exercise GH was <10 mU/l in 29 children (34% total; 49% group 1, 6% group 2, and 34% group 3). There was a positive relation between post-exercise GH and both bone age and pubic hair stage. Multiple regression analysis revealed that relevant predictors of a rise in GH with exercise were different for the sexes in these children with varying stature: for boys, bone age and pubic hair stage; for girls, height and height SDS. All the tall girls were in puberty. No statistical relation was observed between post-exercise GH and cardiovascular response to exercise, time of day of exercise, time of eating before exercise, and plasma insulin or insulin to glucose ratio at time of exercise. We conclude that the GH response to the physiological stimulus of exercise is higher in puberty compared with childhood. Therefore, although children may be suspected of having GH deficiency after a failure of GH to increase after exercise, a non-response may be a normal finding in prepubertal children, independent of stature.

The growth hormone (GH) response to the physiological stimulus of exercise is advocated as part of the investigation of growth disorders in children.^{1–8} As in pharmacological and other physiological tests of GH secretion, however, the stimulus of exercise may fail to induce a significant rise in plasma GH concentration.⁹ Studies investigating the factors that influence GH response to exercise have concentrated on the standardisation of the exercise test and the degree of work performed by the subject. Even with attention to these details, there is still a high percentage of children with no rise in GH with exercise—that is, a false no response. We therefore investigated factors that influence the GH response to exercise by measuring GH before and after a standardised exercise test in short and tall children and compared this response with that seen in children of normal stature.

Patients and methods

Eighty three children (49 boys and 34 girls) were investigated. Group 1 consisted of 37 short children (27 boys and 10 girls) with constitutional growth delay, defined as height <3 rd centile with a height velocity at the 50th centile for age (according to data from the Zurich longitudinal growth study). (Prader A, Issler C, Molinari L, Largo R. Body measurements, growth measurements and bone age of healthy children, Unpublished data.) Group 2 consisted of 16 tall children (eight boys and eight girls) whose height was >97 th centile. Group 3 consisted of 30 children of normal stature (14 boys and 16 girls) whose height was between the 3rd and 97th centiles; 20 were friends or siblings of children in groups 1 and 2, and 10 were children under investigation for other endocrine problems but in

Table 1 *Chronological age, bone age, and height standard deviation score (SDS) in group 1 (short children), group 2 (tall children), and group 3 (children of normal stature). Values are mean (SD)*

	Chronological age (yrs)	Bone age (yrs)	Height SDS
Group 1 (n=37)	12.8 (3.5)	10.6 (3.8)	-2.6 (0.8)
Group 2 (n=16)	12.9 (2.8)	14.1 (1.6)	3.2 (0.9)
Group 3 (n=30)	14.4 (2.7)	12.8 (3.4)	-0.5 (0.8)

whom growth was normal. Informed consent was obtained from the children and their parents before the test. Puberty in each child was assessed according to Tanner.¹⁰ Mean chronological age, bone age (Greulich and Pyle¹¹), and height standard deviation score (SDS) for each group is shown in Table 1.

Each child performed a 15 minute standardised incremental workload test using a bicycle ergometer (Puch Tunturi). In the first five minutes of the test the child exercised at a constant work load of 1 watt/kg, in the second five minutes at 1.5 watts/kg, and in the final five minutes at 2 watts/kg. At the end of the exercise period the pulse rate was counted. All children completed the exercise test. The youngest child was 5.3 years of age and the shortest child 100.2 cm in height.

Blood samples were taken from 75 of the children (90%) before the exercise test and from all of the children 25 minutes after the start of the exercise. Group 1 had blood taken at more frequent intervals: 0, 5, 10, 15, 25, 45, and 60 minutes from the start of exercise. From each blood sample blood glucose (mmol/l), plasma insulin (pmol/l), and plasma growth hormone (mU/l) were measured according to our laboratory methods.¹²

Statistical differences comparing pre- with post-exercise GH were calculated by a paired Wilcoxon test. Statistical differences of post-exercise GH within the three groups were calculated by the non-parametric ranked analysis of variance according to Kruskal and Wallis. Statistical differences in prepubertal post-exercise GH compared with pubertal values were calculated by a Mann-Whitney test. Calculation of relevant predictors of the post-exercise GH response was performed by multiple regression analysis.¹³

Results

The plasma concentration of GH pre- and post-exercise is given in Table 2. Results are expressed as mean (SEM).

Pre-exercise GH was similar in all three groups. There was a significant increase in GH with exercise

Table 2 *Growth hormone (mU/l) before and 10 minutes after exercise (15 minutes' duration) in group 1 (short children), group 2 (tall children), and group 3 (children of normal stature). Values are mean (SEM)*

	Pre-exercise	Post-exercise
Group 1	8.0 (2.3)	17.8 (3.0)
Group 2	8.5 (2.5)	35.1 (2.5)
Group 3	8.3 (2.2)	20.8 (3.2)

in all three groups (Δ GH: group 1, 9.8 (2.7) mU/l, group 2, 26.6 (2.5) mU/l, and group 3, 12.5 (2.7) mU/l; $p < 0.001$). This rise in GH with exercise remained significant on separation of the groups by sex, with the exception of short girls (group 1 girls). Post-exercise GH was significantly higher in group 2 compared with groups 1 and 3 ($p < 0.005$). Separation of the groups by sex revealed no significant differences in boys in post-exercise GH (group 1, 19.0 (3.6) mU/l, group 2, 27.1 (3.1) mU/l, group 3, 22.9 (4.7) mU/l) but a significantly higher GH in tall girls (group 1, 14.5 (5.7) mU/l, group 2, 43.0 (8.9) mU/l, and group 3, 18.9 (4.5) mU/l; $p < 0.025$).

In the seven children from group 1 who had blood taken more often during and after exercise GH peaked between 15 and 25 minutes. At 0 minutes mean GH measured 3.9 mU/l, at 5 minutes 5.0 mU/l, at 10 minutes 9.7 mU/l, at 15 minutes 16.0 mU/l, at 25 minutes 16.0 mU/l, at 45 minutes 10.0 mU/l, and at 60 minutes 3.3 mU/l, respectively.

Post-exercise GH was < 10 mU/l in 29 children (34% total; 49% group 1, 6% group 2 and 34% group 3). No significant relations were observed between post-exercise GH and time of day of exercise, time of last meal in relation to exercise test, plasma insulin or insulin to blood glucose ratio, or cardiovascular response to exercise. All children had a pulse rate above 160 beats/min at the end of the exercise, with 85% having a pulse rate > 200 .

There was a positive relation between post-exercise GH and both bone age ($p < 0.05$) and pubic hair stage ($p < 0.05$); this was also present on separation of the groups by sex (Figs. 1 and 2). Post-exercise GH was significantly higher with advancing bone age and in post-puberty compared with prepuberty: GH at bone age < 10 years was 13.8 (2.8) mU/l and at bone age > 10 years was 25.3 (2.7) mU/l ($p < 0.01$); GH at pubic hair stage P1 was 12.8 (2.2) mU/l and at P3-5 was 31.4 (3.4) mU/l ($p < 0.05$). Multiple regression analysis revealed that the relevant predictors of a rise in GH with exercise was different for the sexes: for boys, the predictors were bone age and pubic hair stage ($p < 0.001$); for girls, the predictors were height and height SDS

Fig. 1 The post-exercise growth hormone response (10 minutes after a 15 minute exercise period) related to bone age in group 1 (short children) ($\blacktriangle$), group 2 (tall children) ($\bigcirc$), and group 3 (children of normal stature) ($\blacksquare$).

Fig. 2 The post-exercise growth hormone response (10 minutes after a 15 minute exercise period) related to pubic hair stage according to Tanner¹⁰ in children of varying stature. Data for boys and girls combined.

($p < 0.001$). All the tall girls and five of the eight boys were in advanced puberty.

Discussion

The post-exercise GH concentration after a standardised exercise test showed considerable variation in children with differing stature. One third of the children had a 'false no response' result, with post-exercise GH < 10 mU/l. Failure to detect a rise in GH after the exercise could be accounted for by the use of a single blood test taken 10 minutes after the exercise, which may miss a rise in GH. Previous studies have shown this, however, to be the time of the peak response of GH to exercise,^{1 14 15} and this was confirmed in the seven children from group 1 who had blood samples taken at more frequent intervals.

The degree of physical work performed during the exercise test is a factor known to influence the GH response to exercise. Prolonged mild exercise and severe maximum exercise have both been shown to be poor stimuli of GH; a submaximal workload test, exercising to roughly 70% of maximum oxygen capacity, with the exercise period limited to between 10–20 minutes, seems optimal in inducing a rise in GH.¹ In this study the exercise period was 15 minutes and a rise in the pulse rate to > 160 beats/min suggests that an oxygen uptake in the order of 70% was achieved,¹⁶ even in the face of the expected variation in physical fitness of the children.

No relation was observed between the post-exercise GH response and time of day at which the exercise was performed (all tests being performed between 0800 and 1700h) and in the timing of the meal previous to the exercise. Insulin and blood glucose concentrations at the time of the exercise also had no relation to the GH response.

The development of puberty influenced the GH response to exercise. The older the bone age and the further the stage of pubic hair development the higher the post-exercise GH concentration. The relevant predictors of GH response were different in the groups of children when separated by sex: multiple regression analysis confirmed bone age and pubic hair stage as the relevant predictor in boys but suggested that stature was the relevant predictor in girls. Height, age, bone age, and pubic hair stages themselves were correlated with the pubertal growth spurt, and this would seem to account for the higher GH in tall children in comparison with other children. The apparent excessive GH response in tall girls, however, is not completely explained. It is interesting to note that tall girls in puberty have been reported as showing a 'paradoxical' GH response to oral glucose¹⁷ and thyrotrophin releas-

ing hormone.¹⁸ It remains to be seen if a high GH response to physiological and pharmacological testing indicates a pathological cause of tall stature in tall girls or if they are being investigated at the point of puberty where GH response would be expected to be maximal.

Age related changes in the spontaneous secretory rate and pattern of GH have been reported previously. Changes have been seen in response to pharmacological testing, as well as in the physiological tests of sleep and exercise.¹⁹⁻²² Twenty four hour measurements of GH have shown a change in secretory pattern from prepuberty to adolescence.²³ Enhancement of GH secretion to pharmacological tests by either testosterone²⁴ or exercise is higher in puberty compared with childhood. Therefore, although children may be suspected of having GH deficiency after a failure of GH to increase with exercise, a non-response may be a normal finding in prepubertal children, independent of stature.

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References

- Buckler JMH. Exercise as a screening test for growth hormone release. *Acta Endocrinol (Copenh)* 1972;**69**:219-29.
- Keenan BS, Killmer LB, Sode J. Growth hormone response to exercise. *Pediatrics* 1972;**50**:760-4.
- Lacey KA, Hewison A, Parkin JM. Exercise as a screening test. *Arch Dis Child* 1973;**48**:508-12.
- Johansen AJ. A single growth hormone determination to rule out growth hormone deficiency. *Pediatrics* 1977;**59**:467-8.
- Johnsonbaugh RE, Bybee DE, Georges LP. Exercise tolerance test: single sample screening technique to rule out growth hormone deficiency. *JAMA* 1978;**240**:664-6.
- Milner RDG, Burns EC. Investigations of suspected growth hormone deficiency. *Arch Dis Child* 1982;**57**:944-7.
- Nicoll AG, Smail PG, Forsyth CG. Exercise test for growth hormone deficiency. *Arch Dis Child* 1984;**59**:1177-8.
- Lazaro CdeS, Parkin JM, Turner SJ. Treadmill exercise test in short children. *Arch Dis Child* 1984;**59**:1179-81.
- Butenandt O. The exercise test for growth hormone secretion. *Pediatric and Adolescent Endocrinology* 1983;**12**:53-60.
- Tanner JM. *Growth at adolescence*. Oxford: Blackwell Scientific Publications, 1962.
- Greulich WW, Pyle SI. *Radiological atlas of skeletal development of the hand and wrist*. California: Stanford University Press, 1959.
- Bucher H, Zapf J, Torresani T, Prader A, Froesch R, Illig R. Insulin-like growth factors I and II, prolactin, and insulin in 19 growth hormone deficient children with excessive, normal, or decreased longitudinal growth after operation for craniopharyngioma. *N Eng J Med* 1983;**309**:1142-6.
- Armitage P. *Statistical methods in medical research*. Oxford: Blackwell Scientific Publications, 1971.
- Hartley LH, Mason JW, Hogan RP, et al. Multiple hormone responses to graded exercise in relation to physical training. *J Appl Physiol* 1972;**33**:602-6.
- Sutton J, Lazarus L. Growth hormone in exercise: comparison of physiological and pharmacological stimuli. *J Appl Physiol* 1976;**41**:523-7.
- Astrand P-O, Rodahl K. *Textbook of work physiology*. New York: McGraw-Hill, 1977.
- Eiholzer U, Torresani T, Bucher H, Prader A, Illig R. Paradoxical rise of growth hormone after oral glucose load in tall girls: a physiological finding in puberty? *Pediatr Res* 1985;**19**:633.
- Evain-Brion D, Garnier P, Schimpff RM, Chaussain JL, Job JC. Growth hormone response to thyrotropin-releasing hormone and oral glucose loading tests in tall girls and adolescents. *J Clin Endocrinol Metab* 1983;**56**:429-32.
- Sperling MA, Kenny FM, Drash A. Arginine growth hormone induced response in children: effects of age and puberty. *J Pediatr* 1970;**77**:462-7.
- Bierich JR, Potthof K. Spontaneous secretion of growth hormone in children with constitutional growth delay and adolescence with early normal puberty. *Monatsschr Kinderheilkd* 1979;**127**:561-5.
- Berich J, Brugmann G, Schippert R. Die Spontansekretion des Wachstumshormons im Nachtlichen Tiefschlaf. *Monatsschr Kinderheilkd* 1985;**133**:342-6.
- Okada Y, Hikata, Ishtobi K, Wada M, Santo Y, Haranada Y. Human growth hormone secretion after exercise and oral glucose administration in patients with short stature. *J Clin Endocrinol Metab* 1972;**34**:1055-8.
- Finkelstein JW, Roffwang HP, Boyar RM, Kream K, Hellman L. Age related change in the twenty-four hour spontaneous secretion of growth hormone. *J Clin Endocrinol Metab* 1972;**35**:665-70.
- Illig R, Bucher H. Testosterone priming of growth hormone release. *Pediatric and Adolescent Endocrinology* 1983;**12**:75-85.
- Lippe B, Wong S, Kaplan SA. Simultaneous assessment of growth hormone and ACTH reserve in children pre-treated with diethylstilbesterol. *J Clin Endocrinol Metab* 1971;**33**:949-56.

Correspondence to Dr S A Greene, Evelina Children's Hospital, 12th Floor, Guy's Tower, London Bridge, London SE1 9RT.

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