

Original Article

Favorable Impacts of Growth Hormone (GH) Replacement Therapy on Atherogenic Risks in Japanese Children with GH Deficiency

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Abstract. Growth hormone (GH) affects body composition and atherogenic risk factors. Severe hyperlipidemia may develop in GH-deficient adults as a consequence of continuous GH deficiency. We investigated changes in lipid profiles in 158 Japanese children (103 boys and 55 girls) with GH deficiency who had been enrolled in the Pfizer International Growth Database Japan during 3 yr of GH replacement therapy to evaluate whether GH treatment has beneficial effects on atherogenic risk factors. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and atherogenic index were evaluated before treatment and then once a year during treatment. The mean baseline TC was within the normal range in both boys and girls. Seventeen (16.5%) of the 103 boys and 18 (32.7%) of the 55 girls, however, had a TC level over 200 mg/dl before treatment. The mean TC level showed a significant decrease in girls. In a separate analysis, patients of both sexes with a TC level > 200 mg/dl showed significantly decreased TC. LDL decreased significantly only in girls, while HDL showed no change in either sex. The atherogenic index decreased significantly in girls. GH replacement therapy in children with GH deficiency had beneficial effects on lipid metabolism and atherogenic risk in both sexes. Early GH treatment would produce lipid metabolism benefits in these patients.

Key words: growth hormone replacement therapy, atherogenic risk, GH deficiency

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Introduction

Many studies have documented increased atherogenic risk in adults with growth hormone (GH) deficiency, as reflected by visceral obesity, hyperlipidemia, increased intima-media thickness, increased frequency of atherogenic

plaques in the carotid arteries and vascular endothelial dysfunction (1–6). These changes may start to develop in childhood and progress with age in GH-deficient patients, resulting in increased morbidity and mortality from cardiovascular disease in adults with GH deficiency (7, 8). The high mortality rate in GH-deficient patients becomes similar to the level of the normal population after GH replacement therapy (8).

Recently, analysis of a nationwide autopsy database in Japan also revealed that cerebrovascular disease rates were higher in patients with hypopituitarism than in age- and gender-matched control populations (9). There are, however, few reports on lipid profiles in Japanese children with GH deficiency (10–13).

In this study, we investigated changes in lipid profiles and atherogenic risk in GH-deficient children during GH treatment to evaluate whether GH replacement therapy has beneficial effects on risk factors for cardiovascular disease.

Patients and Methods

In total, 158 Japanese children with GH deficiency (103 boys 3.4 to 16.4 yr of age; 55 girls 4.7 to 12.5 yr of age) who had been enrolled in the Pfizer International Growth Database (KIGS) Japan were studied during 3 yr of GH treatment, with a weekly dose of 0.175 mg/kg of body weight. GH deficiency had been diagnosed in all patients based on a peak GH level of less than 10 ng/ml, as determined with a conventional kit (recombinant GH was not the standard) in at least two provocative tests. All patients were euthyroid and prepubertal, and none had any signs of puberty during the entire study period. Patients were excluded from the study if they had reported receiving GH treatment and/or gonadal steroid replacement within the past years. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and atherogenic index (TC/HDL ratio) (10) were evaluated

before treatment and then annually during the 3 yr of GH treatment.

Responses to GH treatment were assessed using ANOVA for repeated measures. When the *F* value was significant ($p < 0.05$), pairs of treatment time periods were compared using Dunnett's *t* test. Results are presented as means \pm SD. A *p* value less than 0.05 was considered to be statistically significant.

Ethical committee approval was obtained for each site. All participants gave written informed consent.

Results

At the start of GH treatment, the mean TC levels were within the normal ranges, 172.7 ± 32.6 in boys and 182.2 ± 33.2 in girls (Table 1). Seventeen of the 103 boys (16.5%) and 18 of the 55 girls (32.7%), however, had TC levels greater than 200 mg/dl (Fig. 1). This rate was higher than that in a study of Hisayama school-aged children in whom no more than 5–10% had TC above 200 mg/dl (14).

During treatment, the mean TC levels tended to decrease in both sexes, though to a statistically significant extent only in girls ($p < 0.01$) (Table 1). In a separate analysis, both boys and girls with TC levels over 200 mg/dl showed significantly decreased TC after the initiation of GH therapy ($p < 0.01$) (Fig. 1). On the other hand, those with TC levels under 200 mg/dl showed no changes in TC during the study period. LDLC decreased significantly only in girls ($p < 0.05$), while HDL showed no change in either sex. The atherogenic index decreased significantly only in girls with TC levels over 200 mg/dl (Table 1).

Discussion

Risk factors for cardiovascular disease, or a predisposition to the development of such factors, may be present in adolescence and even early childhood, and dyslipidemia is one of the major

Table 1 Change in lipid profile and atherogenic index

Item	Sex	Patient No.	Baseline	Yr 1	Yr 2	Yr 3
TC (mg/dl)	Male	103	172.7 ± 32.6	169.9 ± 30.0	168.6 ± 26.0	167.3 ± 27.0
	Female	55	182.2 ± 33.2	178.8 ± 32.8	171.2 ± 35.0**	170.5 ± 29.2**
≥ 200 mg/dl	Male	17	228.3 ± 24.4	206.6 ± 24.0**	199.3 ± 27.8**	200.8 ± 25.8**
	Female	18	220.7 ± 17.6	213.0 ± 26.2	205.1 ± 31.5*	198.6 ± 25.2**
< 200 mg/dl	Male	86	161.7 ± 20.6	162.6 ± 25.4	162.5 ± 20.9	160.7 ± 22.0
	Female	37	163.5 ± 20.0	162.1 ± 20.6	154.8 ± 22.7*	156.8 ± 19.7
LDLC (mg/dl)	Male	13	88.5 ± 29.9	89.1 ± 27.8	87.5 ± 23.3	79.8 ± 16.1
	Female	5	106.6 ± 31.8	96.2 ± 30.9	99.4 ± 24.1	85.8 ± 28.2*
HDL (mg/dl)	Male	13	57.7 ± 10.3	62.8 ± 13.9	62.8 ± 16.1	56.8 ± 11.8
	Female	5	65.0 ± 20.5	65.0 ± 23.8	68.6 ± 18.3	65.4 ± 21.7
Atherogenic index	Male	11	3.15 ± 0.65	3.14 ± 0.75	2.92 ± 0.74	2.97 ± 0.64
	Female	5	3.21 ± 1.27	2.99 ± 1.05	2.91 ± 0.87	2.89 ± 0.80

* and **: p<0.05 and p<0.01 (ANOVA), respectively. TC: Total cholesterol, LDLC: Low-density lipoprotein cholesterol, HDLC: High-density lipoprotein cholesterol.

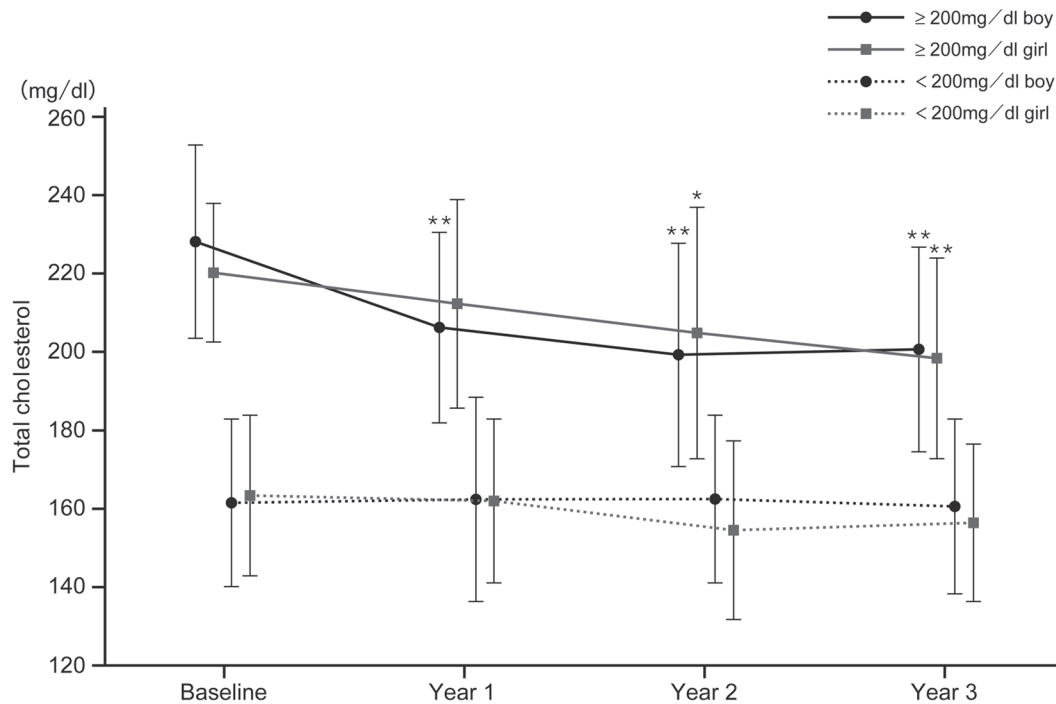


Fig. 1 Change in total cholesterol (TC) compared by baseline TC and sex. * and **: p<0.05 and p<0.01 vs. baseline by analysis of covariance, respectively.

risk factors in GH-deficient patients (15). Many studies have documented increased atherogenic risk, as reflected by visceral obesity and hyperlipidemia, in adults with GH deficiency (7,

8).

Criteria for normal cholesterol levels differ among populations (16). According to the new criteria for normal serum lipid levels in Japanese

children reported in a nationwide study, acceptable TC levels were less than 190 mg/dl, borderline levels were 190–219 mg/dl and high levels exceeded 220 mg/dl (17). On the other hand, the cut-off points for TC levels in children and adolescents suggested by the American Academy of Pediatrics are as follows: acceptable levels are below 170 mg/dl, borderline levels are 170–199 and elevated levels exceed 200 mg/dl (15). According to these criteria, we employed a TC level of at least 200 mg/dl as an indicator of hypercholesterolemia in children with GH deficiency.

At the start of GH treatment, the mean TC levels were within the normal ranges in both boys and girls. This study, however, clearly demonstrated the rate of hypercholesterolemia, i.e., a TC level over 200 mg/dl, before GH treatment in children with GH deficiency to be much higher than that in the normal population: 16.5% in boys and 32.7% in girls with GH deficiency vs. 5–10% in Hisayama school-aged controls (14). The rate of hypercholesterolemia (a TC level over 200 mg/dl) at the start of GH treatment was also reportedly as high as 18% in a long-term study of GH treatment effects on lipid metabolism in Japanese children with GH deficiency (11).

Japanese adults with GH deficiency also reportedly had increased risks of cardio- and cerebrovascular morbidity and mortality as compared with the normal population (18, 19). Severe hyperlipidemia may develop in GH-deficient adults, following a milder state during childhood, as a consequence of continuous GH deficiency. These metabolic abnormalities may result in increased morbidity and mortality from arteriosclerotic diseases (7, 8, 20–22).

During GH treatment in our study, the mean TC levels tended to decrease in both boys and girls, though to a statistically significant extent only in girls. LDLC decreased significantly only in girls, while HDLC showed no changes in either sex. In an additional analysis, however, both boys and girls with TC levels over 200 mg/dl

showed significantly decreased TC, while those with a TC level under 200 mg/dl showed no changes during GH therapy. The atherogenic index decreased significantly only in girls with TC levels over 200 mg/dl. These results indicate that GH replacement therapy has beneficial effects on atherogenic risks with a considerable gender difference, i.e., more beneficial effects on atherogenic risk were seen in girls than in boys. These results are in contrast to those of a previous report on Japanese children with GH deficiency indicating that atherogenic risk factors improved during GH treatment and worsened after discontinuation of GH especially in boys, whereas the changes were somewhat equivocal in girls (11, 23). In addition, previous studies of adults with GH deficiency indicated that men are more responsive to GH treatment than women (24, 25). In our study, large baseline differences in TC levels between boys and girls, as reflected by the prevalence of hypercholesterolemia, i.e., a TC level over 200 mg/dl, being twice as common in girls, may be one of the reasons for GH being more effective in reducing atherogenic risks in girls. In fact, those with a TC level over 200 mg/dl showed no gender difference in TC reduction during GH therapy. It will be necessary to evaluate the severity of GH deficiency in future studies.

GH functions as a major metabolic hormone by optimizing body composition and lipid metabolism. GH suppresses the accumulation of triglyceride in fat tissue by inhibiting lipoprotein lipase activity (26) and stimulates lipolysis by activating hormone sensitive lipase in fat cells (27). GH also regulates lipoprotein metabolism by enhancing clearance of low-density lipoprotein (LDL) through the expression of hepatic LDL receptors (28).

Cardiovascular mortality is increased in adults with hypopituitarism, and women are disproportionately affected, with etiologies of GH deficiency (8, 20–22) and untreated gonadotropin deficiency (22). The impact of gender on mortality rate is clear, but the underlying reasons remain

obscure. The higher mortality rate in women may simply reflect that GH deficiency removed the natural survival advantage of women, who live longer than men in the general population. Further studies concerning gender and pubertal factors are needed to elucidate the influences of GH on atherogenic risk factors in boys and girls with similar severities of GH deficiency.

In conclusion, this study clearly demonstrated that risks of premature arteriosclerosis are already developing even in childhood in those with GH deficiency. GH replacement therapy has beneficial effects on lipid metabolism and atherogenic risk in these patients. Early GH treatment, in addition to promoting growth, would thus produce lipid metabolism benefits in these patients.

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