Metabolic Co-Morbidities Revealed in Patients with Childhood-Onset Adult GH Deficiency after Cessation of GH Replacement Therapy for Short Stature

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Abstract. GH therapy was approved in 2006 for treatment of adult growth hormone deficiency (GHD) in Japan. Until then, GH was used only to treat short stature in children with GHD and the treatment was stopped when the final height was reached. In the present study, we investigated metabolic co-morbidities experienced by adults with childhood-onset (CO) GHD after the cessation of GH. Forty-two patients with COGHD (M/F 22/20, age at follow up when the retrospective analysis was carried out: 18–52 yr) treated with GH in childhood were studied. We reviewed the medical records of these patients to determine the metabolic co-morbidities that developed after cessation of GH. The median age was 19 yrs (range: 14–38) at cessation of GH, and the following co-morbidities were observed: hypertriglyceridemia in 15 (41%) patients, non-alcoholic fatty liver disease (NAFLD) in 11 (29%) patients, hypercholesterolemia in 10 (26%) patients, diabetes mellitus (DM) in 4 (10%) patients, and hypertension in 1 (2.4%) patient. The median BMI when these complications became overt was 23.5 kg/m^2 for those with hypertriglyceridemia, 26.0 kg/m^2 for those with NAFLD, 20.9 kg/m^2 for those with hypercholesterolemia, and 27.2 kg/m^2 for those with DM. More than two co-morbidities were experienced by 32% of men and 30% of women. In conclusion, adults with COGHD after the cessation of GH have multiple metabolic co-morbidities. Lifelong GH replacement might be important for improving the overall metabolic profiles in these patients.

Key words: Hypertriglyceridemia, NAFLD, Hypercholesterolemia, DM, Hypertension

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TRADITIONAL clinical practice in children with growth hormone deficiency (GHD) is to discontinue GH treatment in adolescence after attainment of final height. However, GH has multiple beneficial effects not only on linear growth but also on the maintenance of normal body composition and metabolism throughout adult life. In some patients with severe childhood-onset (CO) GHD, the disease persists in adulthood. The metabolic abnormalities include abdominal adiposity, dyslipoproteinaemia, and insulin resistance;

glucose intolerance and increased prevalence of hypertension are common features in adults with untreated severe GHD [1]. Furthermore, epidemiological studies indicate that adults with hypopituitarism in whom all pituitary hormone deficits except GH are replaced have reduced life expectancy due to cardiovascular or cerebrovascular diseases compared with the general population [1]. GH replacement therapy in adults with GHD has been available in many countries over the past decades. More recently, the importance of continuing GH therapy into adulthood in patients with persistent COGHD has been recognized for completing maturation of body mass components and preventing abnormal metabolic profiles [2, 3]. However, in Japan, GH therapy has been approved for severe adult GHD only since 2006. Until that time, GH was used only to treat short stature in children with GHD and

the treatment was stopped when the final height was reached. In the present study, we investigated the metabolic consequences of stopping GH treatment in adolescence in patients with childhood-onset adult GHD.

Patients and methods

Forty-two patients with childhood-onset adult GHD who were treated with GH in their childhood (22 men, 20 women; mean age at follow up when the retrospective analysis was carried out, $33 \pm$ SEM 1.4 yr, range 18–52 yr) were studied. One of the following GH stimulation tests was used to confirm that peak GH response was less than 3 ng/ml: the insulin-induced hypoglycemic test (n = 36), L-dopa test (n = 1), glucagon-propranolol test (n = 1), GRH test (n = 1), arginine test (n = 1), and GHRP-2 test (n = 2) [4]. The L-dopa and GRH tests identified patients with three and four pituitary hormone deficits including GH deficit, respectively, and serum IGF-I levels of these patients were 73 and 34 ng/ml, respectively. As a result, adult GHD was diagnosed. The causes of COGHD were hypopituitarism due to birth trauma associated with neonatal asphyxia and/or breech presentation (n = 20), suprasellar germinoma (n = 11), craniopharyngioma (n = 7), Rathke's cleft cyst (n = 1), tuberculous meningitis (n = 1), ependymoma (n = 1), and Chiari malformation (n = 1). In addition to GHD, all patients had multiple pituitary hormone deficiencies in various combinations as shown in Table 1 and 90% (38/42) of the patients had more than three pituitary hormonal deficiencies. None of the patients had been treated with GH after reaching final height. Appropriate hormonal replacement therapy other than GH was prescribed in all subjects except 3 women and a man who did not receive sex hormone replacement either because of age (being older than 50 yrs; n = 1), complications (spina bifida n = 1 and liver dysfunction n = 1), or circumstance (just before the start of sex hormone replacement; n = 1), and the patients were in stable condition. In 17 women with gonadotropin deficiency who were receiving sex hormone replacement therapy, the route of estrogen replacement was oral in 14 and transdermal in 3.

The medical charts of these patients were reviewed and co-morbidities (including impaired glucose and lipid metabolism, hypertension, liver dysfunction, and diabetes mellitus) that developed after the cessation of

Table 1. Pituitary hormone deficiency in adults with COGHD.

Hormone deficiency		
Gonadotropin	40/42	(95%)
Thyrotropin	36/42	(86%)
Corticotropin	27/42	(64%)
Prolactin	6/42	(14%)
Vasopressin	18/42	(43%)
No. of deficient pituitary hormones	n	
1*	0	
2	4	
3	10	
4	14	
5	10	
6	4	
Total	42	

*: isolated GH deficiency

GH were recorded. The median observation period was 14 yrs (range: 2–28 yrs). The biochemical blood tests were performed three or four times a year. Hypercholesterolemia was considered if serum cholesterol levels were higher than 220 mg/dl and HDL-hypocholesterolemia was considered if serum HDL-cholesterol levels were less than 42 mg/dl for men and less than 50 mg/dl for women. Hypertriglyceridemia was considered if serum triglyceride levels were greater than 150 mg/dl. The diagnosis of non-alcoholic fatty liver disease (NAFLD) was based on the finding of elevated serum transaminase with findings of fatty liver by abdominal ultrasound and history of alcohol consumption less than 200 ml per day. Measurements of aspartate transaminase (AST) and alanine transaminase (ALT) were performed using standard hospital laboratory techniques and the reference ranges of AST and ALT were 13–33 U/I and 6–30 U/I, respectively. The diagnosis of diabetes mellitus (DM) was based on the finding of elevated fasting or non-fasting plasma glucose levels (≥200 mg/dl more than 2 times) and HbA1c.

The median age of the 42 patients in our study at the cessation of GH was 19 yrs (range: 14–38). The body mass index (BMI) at the time of the cessation (n = 40 patients) was 23.2 kg/m^2 for men (n = 21, range: 18.3–29.9) and 22.0 kg/m^2 for women (n = 19, range: 15.8–27.1). There was no significant gender difference in BMI (P = 0.07). Some of the patients already had the complications at start of study, *i.e.*, of the 42 patients,

Table 2. Complications that developed after the discontinuation of GH: The age and BMI of patients at the onset of complications

	N	Age (y.o.)	BMI (kg/m^2)
Hypertriglyceridemia	15	27 (16–37)	23.5 (16.2–26.5)
NAFLD*	11	30 (16–44)	26.0 (20.8–33.1)
Hypercholesterolemia	10	27 (16–31)	20.9 (17.2–26.5)
Diabetes mellitus	4	26 (20–32)	27.2 (24.3–28.2)
Hypertension	1	35	30.3

* NAFLD: non-alcoholic fatty liver disease

Fig. 1. Rate of hypertriglyceridemia development increased with time after the discontinuation of GH. The dark gray area indicates the number of the patients who already had hypertriglyceridemia at start of study.

eight had decreased HDL-cholesterol levels, five had hypertriglyceridemia, four had NAFLD, three had hypercholesterolemia, and one had DM during GH therapy for short stature in childhood.
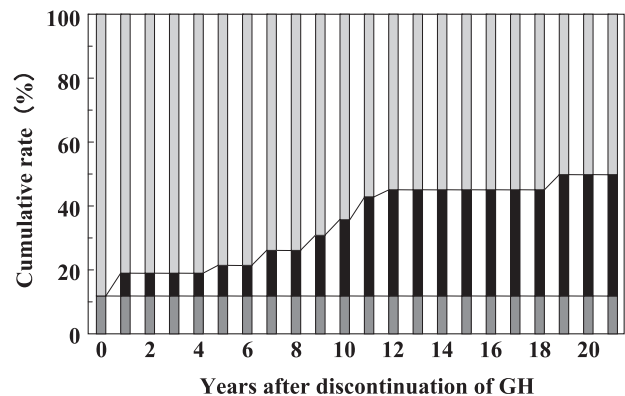
Hormonal assays

Serum GH concentration was measured using a commercially available immunoradiometric assay kit (Eiken Chemical Co., Ltd., Tokyo, Japan). Serum IGF-I levels were measured by immunoradiometric assay kit (Daiichi Radioisotope Laboratories, Tokyo, Japan).

Statistics

The Mann-Whitney *U* test was used to compare the BMI in men and women at the cessation of GH. The paired *t* test was used to assess the differences in BMI at the cessation of GH and the time when the complications became overt. All statistical analyses were performed using StatViewR 5.0 (SAS Institute Inc., Cary, NC, USA), with statistical significance established at p<0.05.

Results

Table 2 shows the co-morbidities that developed after the discontinuation of GH. Hypertriglyceridemia was observed in 15 patients at the median age of 27 yrs (range: 16–37), began to appear one year after the discontinuation of GH, and was found in 41% (15/37, five had hypertriglyceridemia at start of study) of patients 21 yrs after discontinuation (Fig. 1). The median BMI (recorded in 12 of 15 patients) was significantly higher at the onset of hypertriglyceridemia (23.5 kg/m^2, range: 16.2–26.5) than at the cessation of

GH (20.6 kg/m^2, range: 15.8–27.4, P<0.05).

NAFLD was observed in 11 patients (median age of 30 yrs; range: 16–44), began to appear one year after the cessation of GH, and was found in 29% (11/38, four had NAFLD at start of study) of patients 21 yrs after discontinuation (Fig. 2). The BMI (recorded in 10 of 11 patients) tended to be higher at the onset of NAFLD (26.0 kg/m^2, range: 20.8–33.1) than at the cessation of GH (22.4 kg/m^2, range: 16.1–27.4, P = 0.05).

Hypercholesterolemia was observed in 10 patients (median age, 27 yrs; range: 16–31), began to appear one year after the discontinuation of GH, and was found in 26% (10/39, three had hypercholesterolemia at start of study) 21 yrs after discontinuation (Fig. 3). The BMI (recorded in 9 of 10 patients) did not significantly differ at the onset of hypercholesterolemia (20.9 kg/m^2, range: 17.2–26.5) from that at the cessation of GH (20.6 kg/m^2, range: 15.8–27.4, P = 0.11).

Serum HDL cholesterol levels were measured over time in 39 patients. Decreased level of HDL cholesterol was observed in 8 patients during GH therapy for short stature in childhood and newly found in 17 out of the remaining 31 patients (55%) after GH discontinuation.
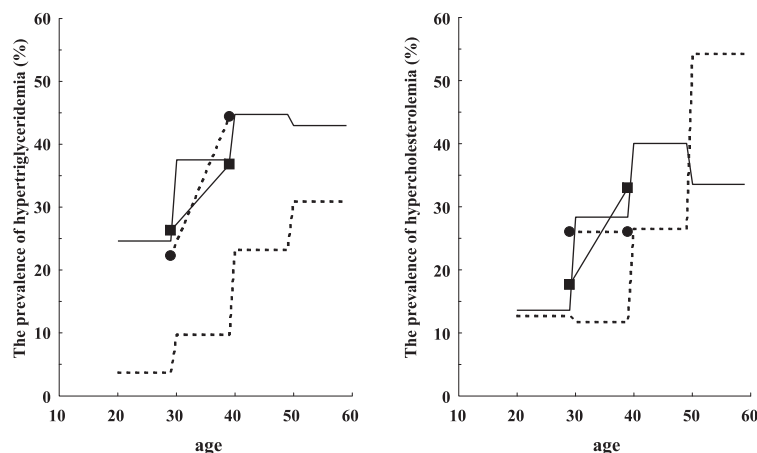
In this study, the prevalence of hypertriglyceridemia, NAFLD, and hypercholesterolemia at 10 yrs after the cessation of GH (median age of patients, 29 yrs old) was 26.3%/22.2% (male/female), 22%/10% (M/F), and 17.6%/26% (M/F), respectively. The prevalence of each co-morbidity at 20 yrs after the cessation of GH (median age, 39 yrs old) was 36.8%/44.4% (M/F), 33%/25% (M/F), and 33%/26% (M/F),
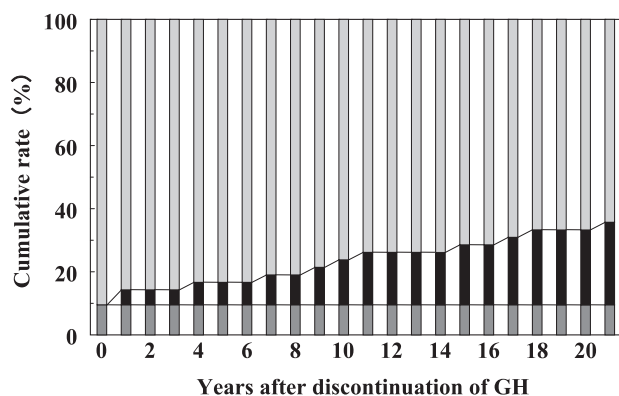
Fig. 2. Rate of NAFLD development increased with time after the discontinuation of GH. The dark gray area indicates the number of the patients who already had NAFLD at start of study.
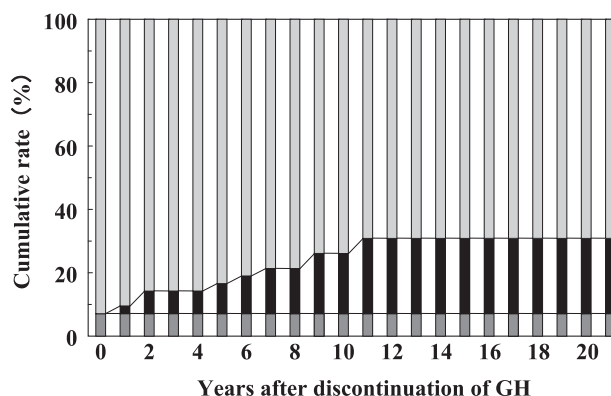
Fig. 3. Rate of hypercholesterolemia development increased with time after the discontinuation of GH. The dark gray area indicates the number of the patients who already had hypercholesterolemia at start of study.

Fig. 4. A comparison of the prevalence of hypertriglyceridemia and hypercholesterolemia between patients with GHD and the Japanese general population. The prevalence of dyslipidemia 10 and 20 yrs after the discontinuation of GH was plotted for two median ages, 29 and 39 yrs old. Solid line, the prevalence in men; dotted line, the prevalence in women; closed square, men with GHD; closed circle, women with GHD. The prevalence in the general population was quoted from ref. 5.

respectively. The prevalence of abnormal lipid metabolism was plotted at the median age of the GHD patients and compared with those in the Japanese general population [5] (Fig. 4). It appears that the prevalence of hypertriglyceridemia in women with GHD might be higher than that of the general population.

DM was observed in four patients (median age, 26 yrs; range: 20–32), began to appear three yrs after the discontinuation of GH, and was found in 10% (4/41, one had DM at start of study) of patients 21 yrs after discontinuation. The median BMI (recorded in four patients) at the onset of DM (27.2 kg/m², range: 24.3–28.2) was not significantly different from that at the cessation of GH (23.4 kg/m², range: 20.0–27.4,

P = 0.12).

The BMI of the one patient (age, 35 yrs) who developed hypertension was 30.3 kg/m² at onset of the disease (Table 2).

Next, we determined how many of the five metabolic co-morbidities (DM, hypertriglyceridemia, hypercholesterolemia, NAFLD, and hypertension) developed in each of the 42 adults with COGHD. No complications occurred in 40% of men and 35% of women. One co-morbidity occurred in 14% of men and 30% of women and two occurred in 17% of men and 30% of women. Moreover, three male patients had more than three co-morbidities. Unlike men, no women had more than three co-morbidities.

Discussion

GH plays an important role in the maintenance of normal body composition and metabolism in adult life and long-term GH deficiency during adulthood may cause several metabolic complications related to premature atherosclerosis [6]. The aim of the present study was to investigate the effect of discontinuing GH replacement on the development of metabolic co-morbidities in adults with childhood-onset GH deficiency. Mauras *et al.* reported that GH-deficient adolescents had normal lipid and carbohydrate metabolism and body composition two yrs after discontinuation of GH. They concluded that GH treatment could be discontinued for at least 2 yrs in many GH-deficient adolescents who were in good metabolic balance at the time of GH discontinuation [7]. On the other hand, all the metabolic co-morbidities in our study started to appear after one year, except for DM, which became overt in a few patients after three yrs.

Serum triglyceride levels can be normal or increased in adults with GH deficiency [8]. The serum triglyceride concentration is generally unaffected by GH replacement therapy [9]. In this study, 41% of the patients had hypertriglyceridemia within 21 yrs after the discontinuation of GH, and BMI was significantly higher at the onset of hypertriglyceridemia than at the cessation of GH. Moreover, the median age when hypertriglyceridemia began to appear was less than 30 yrs old. These data suggested that the association of obesity and cessation of GH might contribute to hypertriglyceridemia at a younger age in our patients.

On the other hand, a number of studies demonstrated total and LDL cholesterol was higher in adults with GH deficiency than age-matched controls [10]. Johansson *et al.* reported that serum levels of LDL cholesterol tended to be higher in young adults with GH deficiency than in control subjects during a two-year period after GH cessation [11]. In agreement with their study, we found that hypercholesterolemia appears as early as one year after cessation. Rudling *et al.*, investigating the effect of GH on lipid profile in 1992 [12, 13], observed GH up-regulated hepatic LDL receptors that increased the clearance of LDL-cholesterol by the liver. They also demonstrated that the administration of GH could decrease serum cholesterol levels in humans. In this study, at the time that hypercholesterolemia occurred, the median BMI was less than 25 kg/m^2, suggesting that hypercholester-

olemia might occur directly from a lack of GH activity rather than indirectly from obesity mediated by GH hyposecretion.

In Japan, dyslipidemia is a relatively common finding and the prevalence of hypercholesterolemia and hypertriglyceridemia in the general population among men and women in their twenties is, respectively, 13.6% (men) and 12.6% (women) and 24.6% (men) and 3.7% (women). Their prevalence among men and women in their thirties is, respectively, 28.4% (men) and 11.7% (women) and 37.5% (men) and 9.7% (women) [5]. These data indicate that lifestyle factors including dietary background might contribute to the high prevalence of dyslipidemia in Japanese. In this study, although we could not directly compare the dyslipidemia prevalence in adults with COGHD with this prevalence in adults in the general population, we could conclude that not only dietary factors and aging but also GH deficiency may play a role in the occurrence of abnormal lipid profiles especially in women with childhood-onset adult GH deficiency. The accumulation of abdominal fat or decrease in physical activity due to impaired exercise performance associated with GH deficiency might also contribute to dyslipidemia and predispose patients to premature atherosclerosis. Furthermore, most patients in this study had multiple pituitary hormone deficiencies and the majority of women with gonadotropin deficiency were receiving oral estrogen replacement. As several reports indicate hormone replacement therapy itself plays some role in the development of metabolic disorders including dyslipidemia [14, 15], the possibility cannot be ruled out that hormone replacement therapy contributes to the development of dyslipidemia.

According to the report on the prevalence of serum HDL-cholesterol levels in the Japanese general population, the prevalence of HDL hypocholesterolemia (less than 40 mg/dl for men and less than 50 mg/ml for women) was 11–15% in men and 7–14% in women aged between 20 and 59 yrs [5]. By comparison, 55% of our patients had decreased HDL, indicating the prevalence of decreased HDL in GHD patients was high. These data suggested that lack of GH itself might be an important risk factor for decreased HDL.

Liver dysfunction with hyperlipidemia or non-alcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) are frequently observed in adult patients with GH deficiency. Kaji *et al.* reported that fatty liver was the third most common complication

(after hypercholesterolemia and hypertriglyceridemia) in adults with GH deficiency in Japan [16]. In this study, 29% of the patients had NAFLD within 21 yrs after the discontinuation of GH. The prevalence of NAFLD at 10 and 20 yrs after the cessation of GH (the median ages, 29 and 39 yrs old, respectively) was 22%/10% (M/F) and 33%/25% (M/F). Kojima *et al.* reported that the prevalence of fatty liver was about 25–27% among Japanese males aged between 30 and 60 yrs and increased gradually with age to a peak of 23% in females in their sixties, which was 3.4 times the prevalence in females in their thirties [17]. By comparison, we found the prevalence of NAFLD in female patients with GHD appears to be higher for the same age groups. Possibly, the higher prevalence of hypertriglyceridemia in women with GHD might contribute to the earlier occurrence of NAFLD. In our study, the median BMI at the onset of NAFLD was more than 25.0 kg/m^2, suggesting that increased body fat mass might also contribute to the occurrence of NAFLD in GH-deficient patients. From the high prevalence of NAFLD in our patients, it is speculated that GH deficiency is a risk factor for NAFLD/NASH, and NAFLD may be regarded as one of the important complications in patients with adult GH deficiency. Recently, Takahashi *et al.* reported a case of adult GH deficiency associated with NASH [18]. In this patient, NASH was dramatically improved by GH replacement, and the authors presumed that the replacement of GH could reverse NASH associated with adult GH deficiency. Further studies are required to confirm that continuing GH replacement into adulthood can prevent the onset of NAFLD in patients with childhood-onset adult GHD.

Fasting plasma glucose and insulin concentrations are normal in lean adults with GH deficiency [1]. However, adults with GH deficiency tend to be obese and have increased central adiposity. A hyperinsulinemic-euglycemic clamp study by Johansson *et al.* confirmed that patients with adult GH deficiency are insulin resistant [19]. Beshyah *et al.* reported a higher prevalence of abnormal glucose tolerance (44%) and diabetes (11%) in GH-deficient patients (mean age, 48 yrs) [20]. They also found that patients with impaired glucose tolerance were older than those with normal glucose tolerance. In this study, 10% of the patients developed DM after the cessation of GH, and though prevalence of DM in our study was similar to that reported by Beshyah *et al.*, the median age of

our study population was much younger. The median BMI was more than 25 kg/m^2 in four patients at the onset of DM, but not significantly higher than the median BMI at the cessation of GH. Notably, Japanese are much less likely to be obese than Caucasians and are more likely than Caucasians to develop metabolic disorders including type II diabetes at lower obesity levels [21]. Therefore, we conclude that GH deficiency might contribute to impaired glucose tolerance by increasing body fat mass at a younger age.

Sanmarti *et al.* reported that the prevalence of hypertension was higher in GH-deficient patients (22%) than in the general population in Spain [22]. In our series, hypertension was observed only in one male patient. The differences in patients' age (52 yrs) and BMI (more than 30 kg/m^2 in 34% of the subjects) might be one reason for the different prevalence of hypertension between the Spanish study and our study.

In 2006, Itoh *et al.* reported metabolic disorders in 49 Japanese patients with adult-onset GH deficiency without GH replacement. In their study, mean age and duration of GHD were, respectively, 53.8 yrs and 16 ± 10 yrs, and the prevalence of hypertriglyceridemia, NAFLD, hypercholesteremia and DM was 37, 43, 45, and 8%, respectively [23]. In our study, the median age of our patients 16 yrs after the cessation of GH was 35 yrs old, which was 19 yrs younger than found in Itoh's study. Furthermore, at that time, the prevalence of hypertriglyceridemia, NAFLD, hypercholesterolemia, and DM was 35, 21, 26, and 10%, respectively, suggesting that the prevalence of NAFLD and hypercholesterolemia was lower in our study. As the changes in prevalence of metabolic disorders over time after the diagnosis of GHD were not shown in Itoh's study, we could not compare our results with theirs directly. Thus, the impact of aging might be stronger than the impact of duration of GHD on the occurrence of NAFLD and hypercholesterolemia.

In this study, men more than women experienced multiple metabolic co-morbidities. The median BMI at the cessation of GH in men (23.2) and women (22.0) was not significantly different. In general, it is presumed that estrogen is vasculoprotective and that male gender augments the risk of coronary artery disease. Therefore, male gender itself may have played a role in increasing the number of co-morbidities that developed per person. In this study, 90% (36/40) of the patients with gonadotropin deficiency were receiving sex hormone replacement therapy, although it was

not clear whether the replacement of sex hormones affected the severity and number of metabolic co-morbidities in our patients. Concerning the number of overlapped metabolic co-morbidities in one person in the Japanese general population, an analysis using Japanese criteria for metabolic syndrome, in a report by the Ministry of Health, Labour and Welfare, found the prevalence of Japanese men who had one, two, and three metabolic risk factors (dyslipidemia, elevated blood pressure, or glucose intolerance) increased with age from 31% (20–29 year age group) to 53% (50–59 year age group), from 4% (20–29) to 23% (50–59), and from 0.8% (20–29) to 7% (50–59), respectively. The prevalence of Japanese women who had one, two, and three of these component factors increased from 5% (20–29 year age group) to 46% (50–59 year age group), from 0% (20–29) to 18% (50–59), and from 0% (20–29) to 4% (50–59), respectively [5]. Thus, a maximum of 7% of individuals (both men and women) between the ages of 20 and 59 yrs had three factors, although it was difficult to compare our data with the data in this report since the definitions and metabolic disorders differed in our study and abdominal circumference was not recorded in our patients.

In conclusion, this study suggested that adults with childhood-onset GH deficiency after the cessation of GH have multiple metabolic co-morbidities. Lifelong GH replacement might be important for improving the overall metabolic profiles in these patients.

Acknowledgments

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