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Growth hormone replacement therapy in adults with growth hormone deficiency; thrice weekly low dose administration

Yoon-Sok Chung, M.D.,* Hyun-Chul Lee, M.D.,** Soo-Kwan Hwang, Ph.D.,***
In-Kyung Paik, M.S.,**** Jong-Ho Lee, Ph.D.**** and Kap-Bum Huh, M.D.**

Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, Korea*
*Department of Internal Medicine** and Physiology***, College of Medicine, Department of Food and Nutrition****, College of Human Ecology, Yonsei University, Seoul, Korea*

Recent reports on growth hormone (GH) therapy have shown that GH has various beneficial effects in GH deficient adults. In most of these studies, GH was administered daily. Because GH is still expensive and has to be delivered by subcutaneous injection, we studied the 6-month therapeutic effects of thrice weekly GH injection therapy and compared it with daily therapy. Twenty eight adult patients with GH deficiency were randomly assigned into group 1 (ten cases, thrice weekly injections of GH), group 2 (nine cases, daily injections), and group 3 (nine cases, placebo injections). Lean body mass, serum basal GH levels, and insulin-like growth factor 1 levels significantly increased after six months of GH therapy in both groups 1 and 2. According to computed tomography, the mean mid-thigh muscle mass significantly increased in group 1, while the visceral fat mass significantly decreased in group 2. GH levels significantly increased exercise rate-pressure product and hand grip strength only in group 1. These results suggest that thrice weekly injections of GH are as effective as daily injections in GH deficient adults.

Key Words : *Growth hormone therapy, Thrice weekly injections.*

INTRODUCTION

Recent reports(Jørgensen et al., 1989 ; Salomon et al., 1989 ; Rudman et al., 1990 ; Whitehead et al., 1992 ; Bengtsson et al., 1993) on GH therapy in GH deficient adults have shown that GH increased lean body mass, decreased fat mass, increased serum insulin-like growth factor 1 (IGF-1) levels, and had an insulinotropic effect without alteration of carbohydrate tolerance. GH has also been reported to improve exercise capacity and muscle strength (Jørgensen et al., 1989).

In most of the reported adult GH treatment trials, GH was delivered by daily injections (Jørgensen et al., 1989 ; Salomon et al., 1989 ; Whitehead et al., 1992 ; Bengtsson et al., 1993), which appeared to be more physiologic and effective than thrice weekly injections (Jørgensen et al., 1990). The primary purpose of this study was to compare daily high dose and thrice weekly low dose GH replacement therapy in adults with GH deficiency. We tried both

Address for correspondence : *Yoon-Sok Chung, M.D., Department of Endocrinology and Metabolism, Ajou University School of Medicine, 5 Wonchun-Dong, Paldal-Gu, Suwon 442-749, Korea, Tel : (0331) 219-2924, Fax : (0331) 213-5242.*

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daily and thrice weekly injection methods and compared the effects of GH on body composition, serum GH and IGF-1 levels, blood lipids, carbohydrate metabolism, exercise capacity, and bone mineral density.

MATERIALS AND METHODS

Subjects

We studied 28 Korean patients (13 male, 15 female) with adult GH deficiency. All of them were within the normal range of height for Korean adults, and all had acquired GH deficiency after the age of 20. The GH deficiency state was confirmed by insulininduced hypoglycemia (a peak serum GH response below 5 ug/l). Other entry criteria included a body weight of 90 to 120 percent of ideal body weight, normal hepatic and renal function, no evidence of malignancy, no psychiatric problems, and no other major diseases. The causes of GH deficiency were as follows : Pituitary tumor in 13 cases(seven cases of nonfunctioning tumor, five cases of prolactinoma, one case of gonadotroph tumor), 13 cases of Sheehan's syndrome, and two cases of post-traumatic hypopituitarism. We performed combined pituitary stimulation tests, and found that most of the patients had multiple hormone deficiencies ; namely, gonadotropin deficiency in 14 of 28 cases, glucocorticoid deficiency in 21 of 28 cases, thyroid hormone deficiency in 14 of 28 cases, and isolated GH deficiency in three of 28 cases. All of the patients had received appropriate adrenal, thyroid, and gonadal hormone replacement therapy during the study period. We randomly assigned the 28 patients into group 1 (ten cases, thrice weekly injections of GH), group 2 (nine cases, daily injections), and group 3 (nine cases, placebo injections). There were no differences in the causes of GH deficiency and clinical characteristics among the three groups(Table 1).

Methods

We used recombinant human methionyl GH (Eutropin® , Lucky Pharmaceutical Corporation, Seoul, Korea) in doses of 0.06 unit per kilogram of body weight per injection. The patients in group 1 received GH thrice weekly(0.18 U/kg/week) at bedtime(around 21 : 00 to 23 : 00) ; group 2 received GH once daily(0.42 U/kg/week) ; and group 3 received a placebo thrice weekly.

All investigations and blood samplings were done at 9 : 00 the following morning.

In observing physical findings, we recorded pulse, blood pressure, and evidence of edema. Among anthropometric parameters, we measured height and weight with indoor clothes and no shoes. Skin-fold thickness was measured with calipers (Lange, Cambridge, Maryland, USA) by the same dietitian at eight sites (subscapular, subcostal, abdomen, suprailiac, triceps, biceps, thigh, calf) three times to obtain the mean values. Central fat skin-fold thickness was calculated by adding subscapular, subcostal, abdomen, and suprailiac skinfold thickness ; and peripheral fat skin-fold thickness

Table 1. Clincal characteristics of 28 subjects

	Group 1 (n=10)	Group 2 (n=9)	Group 3 (n=9)
Age(yrs)	45±2	42±4	51±2
Sex(M : F)	5 : 5	4 : 5	4 : 5
Height(cm)	162±3	161±3	161±3
Weight(kg)	62.7±3.2	60.2±2.9	58.4±2.9
Lean body mass(kg)	45.1±2.8	42.9±3.0	43.4±3.1
Body fat(%)	28.2±1.5	27.2±2.0	26.1±2.0
Causes of GH deficiency(n)			
Sheehan's syndrome	4	4	5
Pituitary tumor	6	4	3
Head trauma	0	1	1
Duration(yrs)+	8.4±2.2	13.4±4.1	12.4±3.5

Data are expressed as the mean±SEM.
+Duration means duration of growth hormone deficiency.
No significant difference among three groups.

was calculated by adding triceps, biceps, thigh, and calf skin-fold thickness. Body fat content was measured by using a near infrared beam body fat analyzer (Futrex 5000, Futrex Inc., Maryland, USA) (Conway et al., 1984). Lean body mass was calculated by subtracting estimated fat mass from total body weight. We calculated total body muscle by using the equation that was proposed by Heymsfield et al.(1982).

Serum calcium, inorganic phosphorus, blood urea nitrogen, creatinine, total protein, albumin, and alkaline phosphatase were measured with an automatic analyzer. Serum iron and total iron binding capacity-(TIBC) were measured by potentiometry. Transferrin was calculated by using the formula 0.8×TIBC-43. Total cholesterol and triglyceride were measured with an automatic analyzer, while high density lipoprotein(HDL) cholesterol after precipitation was obtained by the enzyme method. Low density lipoprotein cholesterol was calculated using the equation ; total cholesterol-[HDL cholesterol+(triglyceride/5)].

Glucose tolerance was measured by using a 75 gram oral glucose load. Glucose, C-peptide, and insulin were sampled at 0, 1, and 2 hours. Serum glucose level was measured by glucose oxidase method. Serum C-peptide level was measured by radioimmunoassay method, using a kit manufactured by Incstar, USA. The intra-and interassay coefficients of variation were 5.7-6.7% and 14.3-15.3%, respectively. Serum insulin concentration was measured by immunoradiometric assay, using a kit manufactured by Dainabot, Japan. The intra- and interassay coefficients of variation were 1.2-1.9% and 1.4-3.3%, respectively. Serum glycated hemoglobin level was measured by affinity chromatography method.

The serum GH level was measured by radioimmunoassay, using a kit manufactured by Biodata, Switzerland. The intra-and interassay coefficients of variation were 2.5-3.9% and 5.8-8.5%, respectively. The plasma IGF-1 concentration was measured by immunoradiometric assay after acid-ethanol extraction, using a kit manufactured by Sangtec, Germany. The intra-and interassay coefficients of variation were 5.6-7.2% and 11.5-15.9%, respectively.

Exercise capacity was measured with a treadmill test, during which heart rate, blood pressure, and maximum oxygen uptake were measured. Exercise rate-pressure product(heart rate×systolic blood pressure) was calculated during maximum exercise. Hand grip strengh and back lift strength were measured by a hand gripper and a back lifter.

Bone mineral densities of lumbar vertebrae (L_2-L_4), femoral neck, trochanter, and Ward's triangle were measured by dual photon absorptiometry.

Subcutaneous and visceral fat mass at the umbilical level, and muscle mass at mid-thigh (the mid portion of the upper border of the patella to the greater trochanter) levels were measured by computed tomography (CT MAX-II, General Electric, Milwaukee, Wisconsin, USA). The fat tissue was indirectly estimated as Hounsfield number of −150∼ −50 and muscle tissue as −49∼ +100 (Ashwell et al., 1985 ; Sparrow et al., 1986).

Serum sodium and potassium levels were measured by ion selective electrode method. Serum osmolarity was measured by freezing point depression method.

Antibody to recombinant human methionyl GH was evaluated by ELISA method.

Before the start of the study period, the project dietitian instructed each subject to follow a diet that furnished about 30 kcal per kilogram per day consisting of protein, carbohydrate, and fat approximately 15 percent, 65 percent, and 20 percent, respectively. At each scheduled visit, the dietitian analyzed each subject's diet on the basis of a 24-hour dietary recall and instructed the subjects again about the standard diet. The subjects were told not to alter their lifestyles(including their use of tobacco or alcohol, and their level of physical activity) during the six-month study period.

Compliance was assessed by counting the returned empty vials and expressing that number as a percentage of the total number of vials needed for the treatment period.

This study protocol was carried out with the informed consent of each patient and according to the guidelines of the Helsinki Declaration of 1975, as revised in 1983.

The results were reported as the means±SEM of all the available data. SPSS PC+package was employed for statistical analysis. Analysis of Variance (ANOVA) was used for the comparisons of the initial values in all three groups. ANOVA for repeated measures (initial, three-month, and six-month values in all three groups) were performed. P values<0.05 were considered to be statistically signficant.

RESULTS

Anthropometric parameters

In all three groups, the mean overall body weight did not change(62.7±3.2 vs 62.4±3.0kg in group 1, 60.2±2.9 vs 61.6±2.9kg in group 2, 58.4±2.9 vs 59.4±2.7kg in group 3, respectively) ; The lean body mass increased significantly after six months of GH therapy(45.1±2.8 vs 46.3±2.9kg in group 1, 42.9±3.0 vs 44.6±3.4kg in group 2, respectively), but not in the control group(43.3±3.1 vs 42.5±2.8kg)(Fig. 1). In group 2, calculated total body muscle mass also increased significantly. Body fat content decreased slightly in groups 1 and 2(28.2±1.5 vs 26.1±1.5%, 27.2±2.0 vs 26.3±2.8%, respectively), but increased significantly in the control group(26.1±2.0 vs 28.8±2.2%) after six months. The central fat skin-fold thickness decreased significantly in the GH treated groups(101.7±7.2 vs 86.1 ±7.9mm in group 1, 89.4±5.4 vs 77.1±8.2mm in group 2) ; on the contrary, there was no change in the control group(84.9±7.8 to 86.9±6.7mm). There was no significant change in peripheral fat skin-fold thickness in any of the three groups(50.8±4.6 vs 48.4±5.2mm in group 1, 54.3±5.1 vs 51.2± 6.1mm in group 2, 44.8±4.4 vs 44.8±3.4mm in group 3, respectively).

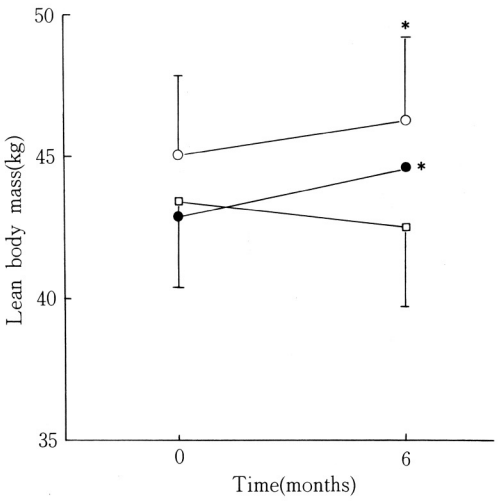

Fig. 1. Changes of lean body mass after 6 months trial of thrice weekly(○) and daily(●) GH or placebo(□). Points and bars means and SEM. *p<0.05 vs 0 months level.

Serum GH and IGF-1

The basal GH levels significantly increased in group 1(1.24±0.17 vs 2.63±0.42 μg/l) and showed a tendency to increase (with wide variation) in group 2(1.44±0.15 vs 5.05±2.11 μg/l) after six months of GH treatment ; but in the control group, there was no significant difference(1.17±0.15 vs 0.68±0.09 μg/l). The IGF-1 levels in group 1 significantly increased after three and six months of therapy(81±29 vs 182±40 vs 220±51ng/ml). Although there was a significant increase of IGF-1 in group 2 after three months, it showed a tendency to increase after six months because of the wide variation in data(63±15 vs 279±30 vs 238±76ng/ml). There was no significant change in the control group(51±5 vs 49±8 vs 56±10ng/ml) (Fig. 2).

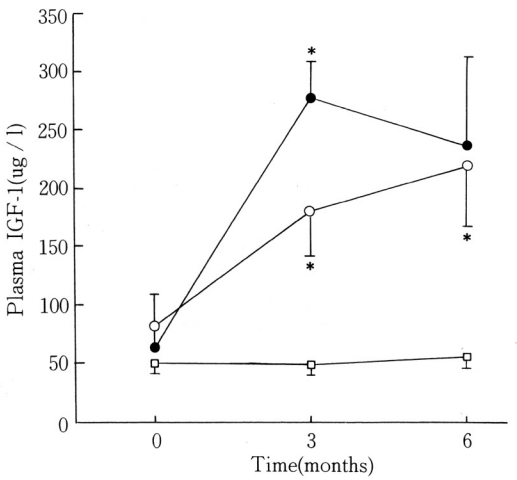

Fig. 2. Changes of plasma IGF-1 levels during 6months trial of thrice weekly(○) and daily(●) GH or placebo(□). Points and bars are means and SEM. *p<0.05 vs 0 month level.

Serum C-peptide and insulin

In group 1, the serum C-peptide levels did not change after six months ; but in group 2, the postprandial one-hour and two-hour C-peptides significantly increased(0.41±0,13 vs 1.05±0.15nmol/l, 0.31±0.10 vs 0.69±0.15nmol/l, respectively) after six months of GH therapy. However the C-peptide levels of the control group did not change. The postprandial one-hour insulin levels in group 1 significantly increased after six months, but there was no significant change in groups 2 and 3(Table 2).

Table 2. Change of serum C-peptide and insulin during oral GTT after 6 months therapy of growth hormone or placebo

	Group	0 Mo	3 Mo	6 Mo
C-peptide 0 hr (ng/ml)	1	1.53± 0.50	1.26± 0.18	0.88± 0.19
	2	0.83± 0.20	0.55± 0.18	1.24± 0.36
	3	1.03± 0.20	0.95± 0.18	0.95± 0.17
C-peptide 1 hr (ng/ml)	1	2.17± 0.71	2.20± 0.38	2.36± 0.84
	2	1.23± 0.38	2.09± 0.76	3.17± 0.44**
	3	2.75± 0.88	1.88± 0.51	2.76± 0.45
C-peptide 2 hr (ng/ml)	1	2.37± 0.73	1.54± 0.28	1.14± 0.36
	2	0.93± 0.30	1.18± 0.56	2.08± 0.44*
	3	1.47± 0.42	1.07± 0.32	2.06± 0.34
Insulin 0 hr (μU/ml)	1	14.27± 8.19	8.77± 2.56	10.09± 2.24
	2	7.89± 1.84	6.29± 1.97	8.08± 1.85
	3	9.26± 2.39	7.12± 1.86	5.03± 0.95
Insulin 1 hr (μU/ml)	1	34.65±10.98	38.99± 9.46	68.11±10.82*
	2	47.68±12.18	49.46±14.55	47.15±10.66
	3	52.59±13.79	36.57±11.21	37.45±11.65
Insulin 2 hr (μU/ml)	1	25.48± 6.77	16.83± 8.05	19.83± 6.60
	2	25.21± 6.84	17.61± 5.56	21.99± 8.77
	3	17.82± 6.92	12.14± 3.83	19.75± 6.42

Data are expressed as the mean±SEM.
GTT : glucose tolerance test.
* $p<0.05$ compared with 0 month value.
** $p<0.01$ compared with 0 month value.

Table 3. The changes of abdominal fat and thigh muscle areas measured by computed tomography scan after GH or placebo trial

	Group	Before Tx	After Tx
Total abdominal fat area(cm^2)	1	274±23	272±28
	2	243±30	217±26**
	3	284±25	300±21
Visceral fat area(cm^2)	1	92± 6	98± 9
	2	95±13	74±10*
	3	100± 9	103±10
Subcutaneous fat area(cm^2)	1	182±20	174±20
	2	158±13	143±18
	3	184±20	198±17
Thigh muscle area(cm^2)	1	218±14	236±18*
	2	236±18	240±17
	3	228±18	211±19

Data are expressed as the mean±SEM.
Tx : treatment.
* $p<0.05$ vs before treatment.
** $p<0.05$ vs group 3.

Body composition by computed tomography

The thigh muscle areas measured by computed tomography in group 1 significantly increased after six months of GH therapy ; but in groups 2 and 3, there was no significant change(Table 3). In group 2, the visceral fat areas at the umbilicus level significantly decreased ; and total abdominal fat areas were significantly smaller compared with group 3 after six months of GH therapy. In groups 1 and 3, there was no significant change in abdominal fat areas.

Carbohydrate and fat metabolism

There was no significant change of serum mean fasting and postprandial glucose levels, and mean glycated hemoglobin values in any of the three groups. Serum total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglyceride levels in all three groups did not change to any degree(Table 4).

Table 4. Measurements of blood lipids during 6 months therapy of growth hormone or placebo

	Group	0 Mo	3 Mo	6 Mo
T. cholesterol(mg/dl)	1	251±14	249±18	248±11
	2	272±27	266±20	258±21
	3	232±12	243±15	238±17
HDL-cholesterol(mg/dl)	1	48± 7	55± 7	53± 7
	2	51± 8	57±10	57± 7
	3	52± 6	60± 7	47± 8
LDL-cholesterol(mg/dl)	1	166±12	154±12	153± 6
	2	185±23	150±25	165±17
	3	142± 7	155±10	139±23
Triglyceride(mg/dl)	1	190±37	205±32	209±44
	2	182±39	143±35	182±43
	3	189±40	133±14	134±23

Data are expressed as the mean±SEM.
T. cholesterol : total cholesterol.
HDL-cholesterol : high density lipoprotein cholesterol.
LDL-cholesterol : low density lipoprotein cholesterol.
No significant difference between groups.

Exercise capacity

The exercise rate-pressure products, hand grip strengh, and back lift strength significantly increased in group 1, whereas only the back lift strength increased significantly in group 2 after six months of GH therapy. There was no change in the control group(Table 5).

Bone mineral density

There was no significant change in the bone mineral density of the lumber spine(L_2-L_4), femoral neck, trochanter, and Ward's triangle after six months in all three groups(Table 6).

Other biochemical measurements

The serum inorganic phosphorus and alkaline phosphatase levels significantly increased, from baseline values 1.03±0.03 to 1.23±0.03mmol/l and from 81±9 to 103±16IU/l, respectively, after six months of GH therapy in group 1. There was no significant change in groups 2 and 3. Blood hemoglobin, hematocrit, white blood cell count, total lymphocyte count, calcium, blood urea nitrogen, creatinine, total protein, albumin, serum iron, total iron binding capacity, and transferrin levels did not change in all three groups(data not shown). There was no significant change in serum sodium, potas-

Table 5. Changes of exercise capacity after 6 months trial of GH or placebo

	Group	Before Tx	After Tx
Maximum O_2 Uptake(ml/kg/min)	1	34.9±4.4	38.4±2.6
	2	34.2±3.0	35.5±2.1
	3	33.8±2.6	34.3±2.3
Systolic blood pressure(mmHg)	1	166±6	183±7*
	2	170±7	173±6
	3	183±8	188±7
Exercise rate-pressure product ($mmHg/min \times 10^{-2}$)	1	256± 9	287±11*
	2	260±11	260±12
	3	285±16	284±13
Hand grip strenght(kg)	1	31.0±2.7	37.6±3.2*
	2	33.6±1.8	35.3±3.1
	3	35.1±2.5	34.8±2.9
Back lift strengh(kg)	1	90.0±12.0	101.4±12.0**
	2	76.0± 9.4	85.7±10.2**
	3	86.3±10.4	90.0± 9.6

Data are expressed as the mean±SEM.
Tx : treatment.
* $p<0.05$ vs before treatment.
** $p<0.01$ vs before treatment.

Table 6. Change of bone mineral density after growth hormone therapy

BMD(g/cm^2)	Group	Before Tx	After Tx
Spine(L_2-L_4)	1	1.024±0.045	1.013±0.038
	2	1.037±0.044	1.034±0.049
	3	1.004±0.040	1.007±0.048
Femur neck	1	0.783±0.040	0.780±0.035
	2	0.813±0.036	0.826±0.052
	3	0.747±0.041	0.757±0.038
Ward's triangle	1	0.603±0.036	0.591±0.030
	2	0.661±0.050	0.683±0.062
	3	0.576±0.042	0.572±0.039
Greater trochanter	1	0.659±0.037	0.661±0.033
	2	0.709±0.048	0.721±0.051
	3	0.654±0.032	0.654±0.039

Data are expressed as the mean±SEM.
BMD : bone mineral density.
No significant differnece between groups.

sium, and osmolarity in all three groups(data not shown).

Compliance

No patient withdrew from the GH treated groups. The rates of compliance were 96±2% in group 1, 95±3% in group 2, and 90±5% in group 3, respectively.

Side effects

Side effects were noted in the GH treated groups only, and the overall occurrence was five out of 19(26%). Of the five side effects, two patients experienced side effects in group 1 and three patients in group 2. The side effects in group 1 included one case of pitting edema and one case of glucose intolerance. In group 2, the side effects included one case of pitting edema, one case of hypertension, and one case of impaired glucose tolerance. We found circulating GH antibodies after six months of GH therapy in only one out of 19 patients, but there was no evidence of reduced hormone effect in that patient.

DISCUSSION

In this study, we administered GH at a dose of 0.06 unit per kilogram of body weight, which other investigators(Bierich, 1987 ; Gunnarsson & Wilton, 1987 ; Thompson et al., 1972) had shown to be the ideal therapeutic dose in children and adolescents with growth hormone deficiency.

The significant increase of lean body mass in the GH injected groups could be explained by the anabolic effect. Cheek & Hill(1974) reported the anabolic effect of GH on skeletal muscle in hypophysectomized rats. Our results were also compatible with hypophysectomized rats and other human studies-(Jørgensen et al., 1989 ; Salomon et al., 1989 ; Rudman et al., 1990 ; Whitehead et al., 1992 ; Bengtsson et al., 1993).

There are many methods of measuring body fat content(Ashwell et al., 1985 ; Sparrow et al., 1986 ; Conway et al., 1984). Body fat measurements were similar in all three methods(skin-fold thickness, near infrared beam body fat analyzer, and computed tomography) in this study. As noted in our study, Salomon et al.(1989), Rudman et al.(1990), and Bengtsson et al.(1993) reported that body fat content significantly decreased after GH treatment ; and they postulated that these results may be due to the lipolytic effect of GH.

In this study, the serum GH and IGF-1 levels were measured 10 to 12 hours after the GH injection. The elevated GH and IGF-1 levels were probably due to exogenous GH, because endogenous GH secretion was depleted.

There was no significant change in serum cholesterol and triglyceride level after GH treatment, but Salomon et al.(1989) reported that serum total cholesterol decreased significantly. Hintz et al.(1982) also reported that serum total cholesterol decreased significantly in normal adults after GH treatment.

Salomon et al.(1989) reported that fasting C-peptide and insulin levels significantly increased after GH treatment, which was also observed in this study. These results suggest an insulinotropic effect of GH. Although the mean glucose and glycated hemoglobin levels were not changed in our study, two cases of glucose intolerance were noted after GH therapy. Cohn et al.(1992) reported that three cases of hyperglycemia occurred after 12 months of GH therapy in 20 elderly men. They suggested that these results may be due to the effect of GH on peripheral insulin resistance(Cohn et al., 1992 ; Daniels & Martin, 1991), and it may be dose dependent because glucose intolerance improved after a half dose reduction of GH, as in our study.

The better exercise capacity after the thrice weekly injection method(group 1) compared to daily injections(group 2) may be explained by the slightly higher increase in lean body mass in group 1.

Rudman et al.(1990) reported that the bone mineral density of L_1-L_4 vertebrae in men over 60 years old significantly increased after six months of GH treatment. However, Whitehead et al.(1992) and Marcus et al.(1992) reported that bone mineral density of the lumbar spine and the femur in elderly women did not change after 12 months of GH therapy. This study failed to demonstrate any significant increase in bone mineral density. This may be due to the short term of the follow-up period. Alkaline phosphatase was reported to increase in some studies (Whitehead et al., 1992 ; Bengtsson et al., 1993), as shown in this study. They proposed that the increased alkaline phosphatase may reflect increased osteoblastic activity.

During GH therapy, some patients had evidence of pitting edema and hypertension. Adverse reactions of fluid retention and edema had also been reported by other investigators (Jørgensen et al., 1989 ; Salomon et al., 1989). These side effects may be due to the salt retaining effect of GH on the kidney, and may be dose dependent because the side effects improved after a half dose reduction of GH.

In this study, therapeutic effects in growth hormone deficient adults with thrice weekly low dose injections were somewhat similar to the therapeutic

effects with daily injections. These results were contrasted with other reports of the effects on growth rate in children with GH deficiency (Hermanussen et al., 1985 ; Albertsson-Wikland et al., 1986 ; Kikuchi et al., 1988). They reported that the growth rates of children with daily injections of GH were significantly accelerated compared to thrice weekly injections. In one study, however, daily administration did not seem superior to thrice weekly schedules(Soyka et al., 1970), and others reported successful results with weekly injections(Rosenbloom et al., 1980) and intermittent therapy(Kirkland et al., 1973). In this study, we evaluated the GH effect on body composition, biochemical markers, and exercise capacity-not growth rate ; thus, effective GH dosage or frequency might be different. Of five recent studies of adult GH trials(Jørgensen et al., 1989 ; Salomon et al., 1989 ; Rudman et al., 1990 ; Whitehead et al., 1992 ; Bengtsson et al., 1993), only one study(Rudman et al., 1990) was performed with thrice weekly low dose injections, while the others usually used daily injections at a dose of approximately 0.5U/kg/week. Despite thrice weekly low dose injections(0.18U/kg/week), Rudman et al.(1990) reported similar beneficail effects of GH in adults. The mean age of the subjects in Rudman et al.'s trial was 67.5years old. However, the mean ages of the subjects of Jørgensen et al.(1989), Salomon et al.(1989), Whitehead et al.(1992), and Bengtsson et al.(1993) were 23.8, 38.5, 29.4, and 46.5years old, respectively. Thus, a relatively lower dosage of GH might be sufficient to change body composition in an older age group, compared with a younger age group. The mean age of our study subjects was 43.5years. Thus, a weekly dosage of 0.18U/kg might be sufficient to change body composition, biochemical markers, and exericse capacity.

Considering that GH is administered subcutaneously, daily injections were more uncomfortable than thrice weekly injections. The recombinant human growth hormones were produced in large quantities by genetic engineering, but it is still an expensive drug. Given the results, we therefore propose thrice weekly low dose injections of GH in adults with GH deficiency, especially in somewhat aged people.

In conclusion, thrice weekly low dose GH replacement therapy was as effective as daily replacement in adults with GH deficiency. Long term follow-up studies of GH effects at different dosage and frequency may be needed.

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REFERENCES

Albertsson-Wikland K, Westphal O, Westgren U : *Daily subcutaneous administration of human growth hormone in growth hormone deficient children. Acta Paediatr Scand 75 : 89-97, 1986.*

Ashwell M, Cole TJ, Dixon AK : Obesity : *New insight into the anthropometric classification of fat distribution shown by computed tomography. Br Med J 290 : 1692-4, 1985.*

Bengtsson B-Å, Edén S, Lönn L, Kvist H, Stokland A, Lindstedt G, Bosaeus I, Tölli J, Sjöström L, Isaksson OGP : *Treatment of adults with growth hormone(GH) deficiency with recombinant human GH. J Clin Endocrinol Metab 76 : 309-17, 1993.*

Bierich JR : *Multicentre clinical trial of authentic recombinant somatropin in growth hormone deficiency. Acta Paediatr Scand 337(suppl) : 135-40, 1987.*

Cheek DB and Hill DE : *Effect of growth hormone on cell and somatic growth. In : Knobil E, Sawyer CH eds. Handbook of physiology and endocrinology. Amerian Physiology Society. Washington, D.C. 159-185. 1974.*

Conway JM, Norris KH, Bodwell CE : *A new approach for the estimation of body composition : infrared interactance. Am J Clin Nutr 40 : 1123-30, 1984.*

Cohn L, Feller AG, Rudman I, Rudman D : *Serono Symposia, Tarpon Springs, Florida, Abstract 12, 1992.*

Daniels GH, Martin JB : *Neuroendocrine regulation and diseases of the anterior pituitary and hypothalamus. In : Wilson JD, Braunwald E, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, Root RK, eds. Harrison's principles of internal medicine. McGraw-Hill : New York. 1661. 1991.*

Gunnarsson R and Wilton P : *Clinical experience with Genotropin worldwide : An update March 1987. Acta Paediatr Scand 337(suppl) : 147-152, 1987.*

Hermanussen M, Geiger-Benoit K, Sippell WG : *Catch-up growth following transfer from three times weekly im to daily sc administration of hGH in GH deficient patients, monitored by knemometry. Acta Endocrinol 109 : 163-168, 1985.*

Heymsfield SB, McManus C, Stevens V, Smith J : *Muscle mass : reliable indicator of protein-energy malnutrition severity and outcome. Am J Clin Nutr 35 : 1192-1199, 1982.*

Hintz RL, Rosenfeld RG, Wilson DM, Bennett A, Finno J, McClellan B : *Biosynthetic methionyl human growth hormone is biologically active in adult man. Lancet 1 :1276-1279, 1982.*

Jørgensen JOL, Pedersen SA, Thuesen L, Jørgensen J, Ingemann-Hansen T, Skakkebaek NE, Christiansen JS : *Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet 1 : 1221-1225, 1989.*

Jørgensen JOL, Møller J, Møller N, Lauritzen T, Christiansen JS : *Phamacological aspects of growth hormone replacement therapy : Route, frequency and timing of administration. Horm Res 33(suppl 4) : 77-82, 1990.*

Kikuchi K, Sudo M, Miyamoto A, Ohie T, Mori C, Mikawa H : *Growth response to daily subcutaneous administration of growth hormone. Acta Paediatr Jpn 30 : 557-563, 1988.*

Kirkland RT, Kirkland JL, Librik L, Clayton GW : *Results of intermittent human growth hormone(hGH) therapy in hypopituitary dwarfism. J Clin Endocrinol Metab 37 : 204-211, 1973.*

Marcus R, Holloway L, Butterfield G : *Effects of growth hormone in elderly women. Serono Symposia, Tarpon Springs, Florida, Abstract 13, 1992.*

Penney DG, Dunbar JC, Baylerian MS : *Cardiomegaly and haemodynamics in rats with a transplantable growth hormone secreting tumor. Cardiovasc Res 19 : 270-277, 1985.*

Rosenbloom AL, Riley WJ, Silverstein JH, Garnica AD, Netzloff ML, Weber FT : *Low dose single weekly injections of growth hormone : Response during first year of therapy of hypopituitarism. Pediatrics 66 : 272-276, 1980.*

Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schilenker RA, Cohn L, Rudman IW, Mattson DE : *Effects of human growth hormone in men over 60 years old. N Engl J Med 323 : 1-6, 1990.*

Salomon F, Cuneo RC, Hesp R, Sönksen PH : *The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med 321 : 1797-1803, 1989.*

Soyka LF, Bode HH, Crawford JD, Flynn FJ : *Effectiveness of long-term human growth hormone therpy for short stature in children with growth hormone deficiency. J Clin Endocrinol Metab 30 : 1-14, 1970.*

Sparrow D, Borkan GA, Gerzof SG, Wisniewski C, Silbert CK : *Relationship of fat distribution to glucose tolerance. Diabetes 35 : 411-415, 1986.*

Thompson RG, Rodriguez A, Kowarski A, Blizzard RM : Growth hormone : *Metabolic clearance rates, integrated concentration and production rates in normal adults and the effects of prednisone. J Clin Invest 51 : 3193-3199, 1972.*

Whitehead HM, Boreham C, McIlrath EM, Sheridan B, Kennedy L, Atkinson AB, Hadden DR : *Growth hormone treatment of adults with growth hormone deficiency : Results of a 13-month placebo controlled cross-over study. Clin Endocrinol 36 : 45-52, 1992.*