Sustained-release Recombinant Human Growth Hormone improved body composition and QoL in adults over 50 years with somatopause

Jeong Kyung Park
Department of Medicine
The Graduate School, Yonsei University

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Directed by Professor Eun Jig Lee

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This certifies that the Master's Thesis of
Jeong Kyung Park is approved.

Thesis Supervisor : Eun Jig Lee

Thesis Committee Member#1 : Kyung Soo Park

Thesis Committee Member#2 : Yoon-Sok Chung

The Graduate School
Yonsei University

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ABSTRACT

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Jeong Kyung Park

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The Graduate School, Yonsei University

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Context: The elderly experiencing somatopause and the resultant metabolic impairment can obtain partial recovery from administration of recombinant human GH (rhGH). However, aged adults suffer inconvenience from daily injection of existing rhGH.

Objectives: To evaluate the effects, safety, and compliance of weekly administered low dose of sustained-release recombinant human GH (SR-rhGH) in aged adults with somatopause.

Design: This is a 26-week prospective, single-arm, multicenter phase IV trial in adults.

Intervention/Participants: A total of 38 subjects, aged ≥ 50 years with somatopause (serum IGF-1 < 150 ng/ml) were enrolled and each received 2 mg of SR-rhGH for 26 weeks.

Results: Mean baseline IGF-1 level of 123.4 ± 41.6 ng/ml increased to 174.8 ± 59.6 ng/ml after administration of SR-rhGH at 4 weeks and it was maintained for the remainder of the study period. At 26 weeks, average lean body mass increased by 0.45 kg, waist circumference reduced by 1.06 cm, and Quality of Life was improved significantly ($P<0.01$ in each index). There was a simultaneous increase in serum levels of biochemical markers of bone resorption and formation. Estrogen substitute in women attenuated the beneficial effects of SR-rhGH on body composition and metabolic indices.

There was no significant change in the body fat distribution or fat mass. Adverse events included pruritus (10.5%), arthralgias (5.3%), and edema (5.3%), but their symptoms were well tolerable.

Conclusions: Body composition and Quality of Life can be restored in part by the replacement of low dose SR-rhGH for 26 weeks in patients with somatopause without significant adverse effects.

Key words: growth hormone replacement, somatopause

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I. INTRODUCTION

Normal aging is paralleled by a progressive decline in growth hormone (GH) secretion.[1] Adolescents have the highest level of GH, followed by a progressive decline in GH secretion with advancing age; each decade of increasing age attenuating the GH production rate by 14%.[2,3] Therefore, most elderly adults are confronted with somatopause. A decreased GH secretion provides central fat accumulation, sarcopenia, dyslipidemia, increased cardiovascular mortality and diminished quality of life (QoL).[4,5] Especially, sarcopenia, a complex syndrome that is associated with decreased muscle mass and increased fat mass, is increasingly recognized by physicians to be associated with higher risks for multiple adverse outcomes in the elderly. Sarcopenia is considered a major contributor in the pathway leading to an elder patient's frailty.[6] For these elderly populations, a number of clinical trials of GH replacement therapy have been conducted,[7-9] and several studies demonstrated

beneficial effects on lipid profile, body fat distribution, bone metabolism, and well-being.[8,10,11] Nevertheless, several concerns remain regarding diabetes mellitus (DM), peripheral edema, and arthralgias.[12] The technical difficulty of GH administration is also an important problem for elderly patients.

A sustained release formulation of recombinant human GH (SR-rhGH, Declage® LG Life Sciences, Ltd., Seoul, Korea) using sodium hyaluronate microparticles, was developed aiming at once-a-week injection.[13] This new formulation was expected to lead to better patient compliance with comparable efficacy and adverse effects. In the current study, we administered low dose of SR-rhGH for 26 weeks to patients aged > 50 years with somatopause and investigated the safety and the effects of the formulation on body composition and quality of life. We also assessed the role of gender differences and the influence of sex hormones.

II. MATERIALS AND METHODS

1. Study Design

This study was a prospective, single-arm, multicenter phase IV trial. The protocol was reviewed and approved by an independent Institutional Review Board at each participating center, and all subjects provided written, informed consent prior to registration for this study.

2. Study Population

Men and women aged ≥ 50 years with documented somatopause (serum IGF-1 levels of 150 ng/ml or lower) were eligible for this study. If subjects required glucocorticoid, thyroxine, or sex hormone replacements, doses of all hormone replacement was adjusted to maintain a state of stabilization for at least 4 weeks before GH administration. No subjects had received GH treatment within the past 3 months. Subjects were excluded if they had impaired glucose tolerance or diabetes mellitus, acromegaly, intracranial hypertension, active malignancy, or concurrent antitumor therapy, critical illness, history of cardiac or abdominal surgery, cognitive impairment, or GH deficiency following an organic cause such as pituitary tumor, head trauma, or other pituitary disorders. Patients with renal impairment (defined as serum creatinine > 1.6 mg/dl) or liver disease (defined as alanine aminotransferase or aspartate aminotransferase levels greater than three times the upper limit of normal) were also excluded.

3. Study Protocol

This study included a screening visit (-week 4), baseline visit, and 3 visits over the 26 week study period. After a 4-week screening period, participants received 6 IU (2 mg) of SR-rhGH subcutaneously weekly for 26 weeks. The dosage of administered SR-rhGH was adjusted upon physician's judgment. At every visit, vital signs, height, weight, and waist circumference were investigated and symptoms and signs of adverse effects were carefully monitored. Serum IGF-1 was assessed to evaluate the effectiveness of the drug at baseline and at 4, 13, and 26 weeks. Body composition, quality of life, and laboratory assessment [lipid profile, bone alkaline phosphatase (B-ALP), C-telopeptide (CTX), free thyroxine (fT4), thyroid-stimulating hormone (TSH)] were determined at baseline and at 26 weeks. Laboratory tests including complete blood count, total protein, albumin, liver function tests, blood urea nitrogen (BUN), creatinine, total bilirubin, uric acid, calcium, phosphate, sodium, potassium, HbA1c, fasting plasma glucose (FBS), and insulin were measured at baseline, at 13 weeks, and at 26 weeks. The homeostasis model assessment (HOMA-IR) was used to determine insulin resistance[14] and calculated as: [fasting glucose (mg/dl) x fasting insulin (μU/ml)] / 405. Participants were instructed not to change their diet and exercise patterns during the treatment period. Caloric intake was assessed by daily self-recording of episodes by the subjects in a nutrition diary at baseline and at 4, 13, and 26

weeks. At every visit, researchers inquired about compliance and the empty vial was returned for counting. Compliance was calculated at 26 weeks as the percentage of the number of actual injection per the number of scheduled injection.

4. Hormone Assays

All blood samples were taken after an overnight fast of 10 hours. Serum IGF-1 concentrations were measured with a commercially available standard enzyme-linked immunosorbent assay kit, according to the manufacturer's protocols (Immunodiagnostic Systems, Fountain Hills, AZ, USA). The coefficient of inter-assay variation was 7.4-9.1% and intra-assay variation was 2.6-4.4% in the concentration range of 180-360 ng/ml. TSH and fT4 were determined by chemiluminescence immunoassay (Siemens Healthcare Diagnostics, Cergy Pontoise, France).

5. Assessment of Body Composition

Body weight (kg), height (cm), body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), and waist circumference (WC, measured as the minimum circumference around level of umbilicus) were determined.

Measurements of fat mass (FM) and lean body mass (LBM) were obtained using whole body dual X-ray absorptiometry (QDR 4500A, Hologic

Inc., Bedford, MA, USA). Head, trunk, both arms and legs were included for calculation of FM and LBM. Computed tomography (CT) scans (SOMATOM Sensation 64, SIEMENS, Germany) were used to estimate levels of visceral, subcutaneous, and total adipose tissue (VAT, SAT, and TAT, respectively). At least five-slice CT scans were performed at the level of second to fifth lumbar vertebra (L2-L5) and at the mid-thigh lesion. Abdominal VAT and SAT were estimated as area (cm^2) at level of L2-3. TAT measurements were interpreted as the sum of VAT and SAT measurements.

6. Assessment of Quality of life

Quality of life was assessed using the 'Quality of Life-Assessment of Growth Hormone Deficiency in Adults' questionnaire (QoL-AGHDA), which has been shown to have good reliability, and reproducibility while constructing validity across a range of languages.[15] The score of QoL-AGHDA, ranging from 0 to 25, was assessed at baseline and wk26. A high score on the measure indicates poor quality of life.

7. Statistical analyses

Statistical analyses were performed using the SPSS software package for Windows (Version 16.0; SPSS Inc., Chicago, IL, USA). The efficacy of SR-rhGH was analyzed using serum IGF-1, body composition, lipid profile, quality of life comparing between baseline values and those at week 26 and the

significance was determined by paired t-test, if the data were normally distributed, and by Wilcoxon's signed rank test if they were not. The safety of the SR-rhGH was estimated using vital signs, laboratory assessments comparing between baseline and week 26 by paired t-test or Wilcoxon's signed rank test as appropriate. The data were expressed as the mean ± standard deviation. A P-value of > 0.05 was regarded as significant.

III. RESULTS

1. Baseline Characteristics

Table 1 Demographic characteristics of the study subjects

Patients. n	33	
	50≤~<60	9
	60≤~<70	18
	70≤~	6
	Males (%)	9 (27.27)
	Females (%)	24 (72.73)
Age (years)	63.5 ± 7.6 (50~82)	
Weight (kg)	56.78 ± 8.6 (38.3~77.8)	
Height (cm)	158.67 ± 7.44 (144.8~177.0)	
BMI (kg/m^2)	22.52 ± 2.51 (17.8~26.0)	

BMI, body mass index

In total, 38 patients received at least one dose of SR-rhGH and were included in safety analyses. Five subjects dropped out early for the following reasons; lost to follow-up (one), withdrawal the consent (two), violation the protocol (two). Thirty three subjects were analyzed, the mean age was 64 ± 8 yr (50-82), and there were 24 (72.8%) females and 9 males (27.8%) (Table 1). Women were postmenopausal and six had been taking sex hormone replacement therapy (HRT). None of the male subjects had been taking testosterone replacement

therapy. The mean weight of all subjects was 56.8 ± 8.6 kg (38.3-77.8 kg), and the mean height was 158.7 ± 7.4 cm (144.8-177.0 cm). Calculated BMI was 22.5 ± 2.5 kg/m^2 (17.8~26.0). As shown in Table 2, at baseline, subjects overall exhibited high VAT/SAT ratio, indicating central obesity in spite of relatively low BMI. In comparison to women, men had a higher LBM (women, 45.6 ± 6.2 kg; men, 35.2 ± 3.2 kg; P<0.0001) and lower body fat mass (women, 32.7 ± 5.4 kg; men, 19.3 ± 8.7 kg; P=0.001). Women on estrogen substitution had higher LBM as those without sex hormone (37.9 ± 2.8 kg, 34.2 ± 2.9 kg respectively, P=0.014). There were no significant differences in baseline levels of IGF-1, BMI, and WC between men and women, and between women who received concurrent HRT and those did not.

Table 2 Effect of the treatment on vital sign, body composition, and QoL

	Baseline	**Week 26**	**Difference**
IGF-1 (ng/ml)	123.38 ± 41.59	169.52 ± 57.28	46.14 ± 37.17**
Vital sign			
Pulse rate (/min)	72.63 ± 9.30	69.69 ± 6.37	-1.97 ± 6.20
Systolic BP (mmHg)	125.18 ± 17.23	123.37 ± 16.71	-1.91 ± 11.36
Diastolic BP (mmHg)	74.37 ± 9.35	74.71 ± 12.29	0.20 ± 8.15
Calorie intake (kcal)	1453.78 ± 274.92	1485.58 ± 281.81	20.08 ± 166.96
Body size			
Waist circumference (cm)	82.25 ± 932	81.19 ± 8.88	-1.06 ± 2.04**
Weight (kg)	56.78 ± 8.60	56.94 ± 8.82	0.16 ± 1.21

BMI (kg/m^2)	22.52 ± 2.51	22.60 ± 2.64	0.08 ± 0.46
Body composition			
% Body fat (%)	29.06 ± 8.79	28.82 ± 9.04	-0.25 ± 1.59
FM (kg)	16.38 ± 5.64	16.40 ± 5.86	0.01 ± 0.91
LBM (kg)	37.99 ± 6.28	38.44 ± 6.38	0.45 ± 1.10*
Abdominal fat distribution			
Visceral fat (cm^2)	110.16 ± 69.85	107.15 ± 71.45	-3.01 ± 15.30
Subcutaneous fat (cm^2)	140.33 ± 67.61	135.66 ± 64.23	-4.67 ± 19.12
Total abdominal fat (cm^2)	250.49 ± 114.91	242.81 ± 115.36	-7.69 ± 27.96
VAT/SAT ratio	0.87 ± 0.53	0.96 ± 0.77	0.09 ± 0.68
Mid-thigh			
Subcutaneous fat (cm^2)	54.65 ± 29.14	54.08 ± 28.75	-0.58 ± 10.03
Muscle (cm^2)	83.26 ± 22.78	82.01 ± 22.55	-1.75 ± 8.60
AGHDA QoL	10.06 ± 5.41	7.33 ± 5.34	-2.73 ± 4.91**

** : P-value is less than 0.05*
*** : P-value is less than 0.01*
FM, Fat mass; LBM, lean body mass; VAT, visceral fat; SAT, subcutaneous fat

2. Serum IGF-1 concentration

After administration of SR-rhGH, IGF-1 levels increased from 123.4 ± 41.6 to 174.8 ± 59.6 ng/ml (P<0.0001) within 4 weeks and were maintained throughout the next 22 weeks (Figure 1). There was a greater response in females than in males. The differences in IGF-1 levels from baseline to week 26 were 37.2 ± 34.1 ng/ml in men and 49.5 ± 38.4 ng/ml in women respectively. In

women on HRT showed greater IGF-1 increments than in sex hormone naïve women at week 26 but this difference did not reached statistical significance (P=0.263).

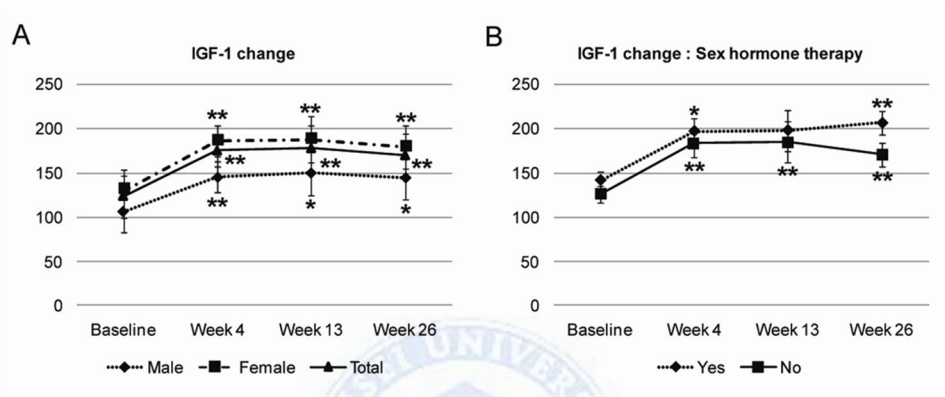

Figure 1. Serum level of IGF-1 (ng/ml) following administration of SR-rhGH. Data points are means, error bars are SEM. *, $P < 0.05$; **, $P < 0.01$. The significance was determined by a difference between baseline value and values of week 4, week 13, and week 26, respectively. **A**, IGF-1 levels increased within 4 weeks and were maintained near this value throughout the next 22 weeks. The response was more pronounced in female than in male subjects. **B**, The effect of SR-rhGH showed no difference between women on estrogen therapy and women without estrogen replacements.

3. Body Size

There was no significant change in intake calories from baseline to end of this study (Table 2). In body size analysis, the waist circumference reduced significantly after SR-rhGH administration (P=0.0021). However, in subgroup analysis, this difference was not observed in patient who received HRT. BMI and body weight were similar before and after treatment.

4. Body Composition

Fat mass showed no changes during treatment period and % body fat was slightly decreased without significance, whereas LBM increased significantly at 26 weeks (Table 2, P=0.0096). There were no significant differences between men and women in body composition. Concomitant use of sex hormone in women did not influence LBM, fat mass, and % body fat.

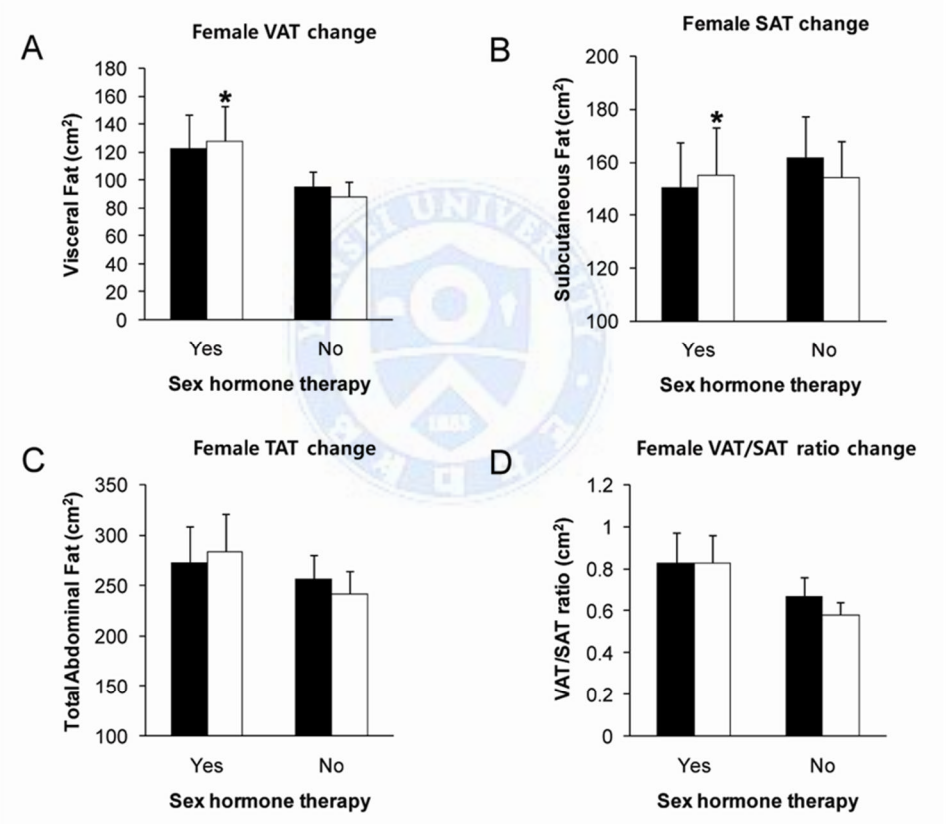

Figure 2. Estrogen substitute and SR-rhGH. The results represented changes of body composition in female with or without concurrent HRT are shown, where bars indicate mean value ± SEM. *, $P < 0.05$, baseline (black bars) vs. 26 weeks (open bars). Changes in VAT (**A**), SAT (**B**), TAT (**C**), and VAT/SAT ratio (**D**) are showing conflicting results between two groups.

5. Abdominal Fat Distribution

As described in Table 2, TAT, VAT, and SAT showed a trend of reduction, whereas VAT/SAT ratio tended to increase without significance. Abdominal fat distribution showed exciting results in subgroup analysis (Figure 2); women who received HRT demonstrated an increased VAT and SAT (P=0.0313, P=0.0449, respectively). TAT values within this subgroup also showed a tendency to increase. However, fat distribution of patients who did not received HRT, by contrast, showed a decrease, even in VAT/SAT ratio.

6. Mid-thigh Composition

Before and after treatment, the changes of subcutaneous fat and muscle of mid-thigh were not significant. In subgroup analysis, the total area of subcutaneous fat and muscle of mid-thigh did not change significantly over the course of the SR-rhGH administration.

7. Quality of Life

In general, AGHDA score (Table 2) improved significantly (P=0.0032) after SR-rhGH administration, but this difference was not significant in men (P=0.1076). Basal mean AGHDA score was higher in females than in males (female; 10.88 ± 5.79, male; 7.89 ± 3.69). It was also observed that women who were treated with sex hormones had higher AGHDA score (12.67 ± 6.77) at baseline, and did not show an improvement after SR-rhGH treatment.

Table 3 Effect of the growth hormone administration on serum profile

	Baseline	**Week 26**	**Difference**
Hematology			
WBC (10^3/μl)	5.52 ± 1.29	5.36 ± 1.46	-0.17 ± 1.30
Hematocrit (%)	39.69 ± 4.45	38.34 ± 4.52	-1.30 ± 2.39**
Hemoglobin (g/dl)	13.06 ± 1.42	12.87 ± 1.64	-0.21 ± 077
Platelet (10^3/μl)	245.95 ± 61.69	249.46 ± 74.58	-0.91 ± 43.42
Glucose metabolism			
Glucose (mg/dl)	95.61 ± 7.51	94.06 ± 8.40	-1.26 ± 7.44
HbA1c (%)	5.37 ± 0.42	5.66 ± 0.54	0.32 ± 0.63**
Insulin (μIU/ml)	4.40 ± 2.82	8.55 ± 7.81	3.91 ± 7.90**
HOMA-IR	1.09 ± 0.71	1.79 ± 1.29	0.67 ± 1.24**
Lipid profile			
T. cholesterol (mg/dl)	205.21 ± 37.57	199.56 ± 28.98	-6.25 ± 33.34
HDL (mg/dl)	54.09 ± 12.83	55.69 ± 12.51	1.28 ± 7.39
LDL (mg/dl)	119.91 ± 29.90	119.25 ± 27.47	0.00 ± 28.47
Triglyceride (mg/dl)	115.67 ± 75.41	119.34 ± 76.52	2.06 ± 53.70
Bone metabolic markers			
BAP (IU/liter)	26.56 ± 8.65	30.17 ± 12.31	3.61 ± 8.25*
CTX (ng/ml)	0.28 ± 0.17	0.39 ± 0.27	0.12 ± 0.17**
Thyroid function			
TSH (μIU/ml)	2.49 ± 2.17	2.57 ± 4.16	0.09 ± 2.33
Free T4 (ng/dl)	1.17 ± 0.17	1.08 ± 0.18	-0.10 ± 0.19**

** : P-value is less than 0.05*
*** : P-value is less than 0.01*
BAP, bone alkaline phosphatase; CTX, C-telopeptide

8. Assessment of Safety and Tolerability

One patient treated with SR-rhGH required a dose decrease to 1.5 mg at visit 3, due to high blood pressure. The mean systolic and diastolic blood pressures were unchanged throughout the study (Table 2). The 26-week SR-rhGH treatment reduced mean value of hematocrit compared with baseline (Table 3, p=0.0028). Though FBS showed no difference, HbA1c and serum insulin levels were increased significantly by 0.30 ± 0.65% (P=0.0001) and 2.91 ± 5.67 μIU/ml (P=0.0004), respectively (Table 3). Corresponding increase in calculated HOMA-IR was observed (by 0.92 ± 1.83, P=0.0009). Mean total cholesterol was decreased by 6.25 ± 33.34 mg/dl compared to its initial level, but this difference was not significant. The values of serum electrolytes, ALT, AST, ALP, BUN, and creatinine did not change significantly (data not shown). Whereas no significant difference in serum calcium concentration was observed between baseline and at week 26, serum phosphorous concentration increased by 0.24 ± 0.62 mg/dl after 13-week of SR-rhGH administration (P=0.0227), and there was no difference at 26 weeks compared with baseline. The bone metabolic markers, BAP, a bone formation marker, and CTX, a bone resorption marker, were increased significantly (P=0.0171, P=0.00004, respectively). In subgroup analysis for bone metabolic markers (Figure 3), there were no significant differences in males and females receiving sex hormones. Only women who were not treated with sex hormone showed a significant increase. In the thyroid function test, serum free T4 decreased by 0.08 ± 0.19 ng/dl

(P=0.0066) at 26 weeks, as compared to the level at baseline, without significant elevation of TSH.

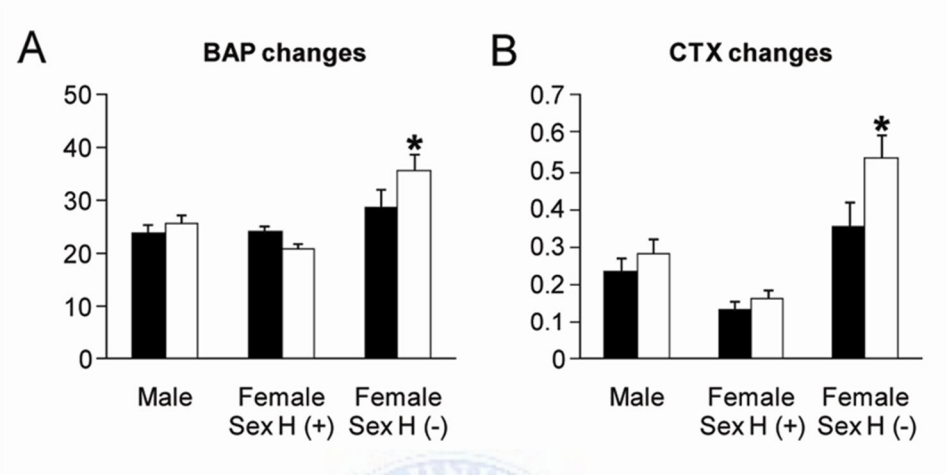

Figure 3. Changes over 26 weeks (mean ± SEM) in BAP (**A**, U/l) and CTX (**B**, ng/ml). Both values are showing a significant increase only in female without sex hormone substitute. *, $P < 0.05$ for within group changes.

The most common drug-related adverse events were pruritus on injection site in 4 patients. Two patients exhibited arthralgias and in one, symptoms persisted until the end of the study. Two experienced edema at injection site, and another two cases complained of body pruritus after injection of SR-rhGH but the symptoms disappeared within the testing period. Most events were mild to moderate in severity. SR-rhGH administration was not associated with significant adverse effects. Returned vial counts suggested that compliance was excellent, with 99.7% of vials injected into participants.

IV. DISCUSSION

There has been a controversy surrounding replacement of rhGH in the elderly experiencing somatopause and the resultant functional and metabolic impairment including sarcopenia. The first evidence for GH replacement in the elderly was reported by Rudman and colleagues in 1990.[8] They demonstrated improvement in LBM, adipose-tissue mass, and bone mineral density (BMD) after administration of rhGH in men over 60 years old. Subsequently, further studies in the elderly have been conducted, yielding controversial results.[16-21]

In the current study, we examined the efficacy and safety in administration of SR-rhGH for the first time. During 26 weeks of SR-rhGH administration, serum IGF-1 levels increased to the normal range within 4 weeks and they were maintained throughout the treatment period (Figure 1). This pattern was consistent with an earlier study.[8] We detected that the IGF-1 level was higher in females than in males at baseline, compatible with a previous report.[22] Serum IGF-1 increased further in females than in males during SR-rhGH administration, which conflicted with earlier reports[12,23] that the effect being more pronounced in males than in females. This result may be due partly to the small number of men studied. It seems be also associated with that baseline mean age was higher in men than in women (65.0 vs. 62.9 years respectively) although the difference was not significant.

A reduction in IGF-1 concentrations during oral estrogen replacement has been observed in postmenopausal women.[24] There has been some sequential

evidence that estrogen administration lowers IGF-1 concentrations in women.[22,25] However, baseline IGF-1 level was higher in women with HRT than those in women without HRT, although it was statistically insignificant. This opposite result possibly related to high LBM value at baseline in women received estrogen. Moreover, women on HRT were younger than those without HRT (61.5 vs. 63.4 years). Span *et al*.[23] confirmed that serum IGF-1 initially increased equally in both groups of estrogen-substituted and nonsubstituted women. The difference between two groups was statistically significant only after 18 months of rhGH supplements. This delayed blunting effect on IGF-1 might explain why IGF-1 increment was not lower in women received estrogen during our 26-week study.

According to the literature, participants who received GH increased their LBM and decreased their fat mass.[8,20,21] Our study consolidates previous reports in elevation of LBM, and decrease of WC after SR-rhGH administration. However, these effects of SR-rhGH were insignificant compared with previous studies that supplied GH therapy with concurrent lifestyle intervention.[26-28] Using CT scans for body fat analysis, we did not detect a significant change in VAT, SAT and TAT. Though participants of this study had lower baseline BMI than those of previous studies, the mean VAT/SAT ratio of cases was 0.87, suggesting central obesity. A concurrent exercise intervention study might have led to better responses to the SR-rhGH. Furthermore, previous report showed

dose-dependent changes in body composition.[29] In our study, relatively low dose of SR-rhGH supplied compared to existing trials[8,30] might also influence insignificant effects on body composition.

We reproduced similar results to previous reports[31,32] on biochemical markers of bone metabolism. The administration of SR-rhGH for 26 weeks significantly increased serum levels of biochemical markers of bone resorption and formation. Joseph and colleagues[32] confirmed a simultaneous increase in bone resorption and formation with the increase in bone formation markers becoming significantly higher than resorption only by 6 months. It suggests there may be delayed increase in BMD after prolonged GH administration.

There was an additional benefit related to QoL but the difference was not significant as found in previous studies, which administrated GH for more than 12 months.[33,34] However, there was an obvious improvement of QoL through the 26-weeks administration of SR-rhGH, especially in women without estrogen substitution. It is expected that long-term trial in postmenopausal females would provide better outcomes in assessment of QoL.

In subgroup analysis of VAT and SAT, females with HRT showed a significant increase in visceral and subcutaneous fat, whereas nonsubstituted women showed a decrease at 26-week (Figure 2). Waist circumference also decreased significantly after administration of SR-rhGH, but not in females with HRT. Munzer and colleagues suggested that HRT attenuated the rhGH-mediated effects through their placebo-controlled study.[30] Holloway *et al.*[21] also found a

blunted effect of rhGH on body composition and metabolic indices in postmenopausal women receiving estrogen as compared with women without estrogen replacement. Our results also confirmed that estrogen significantly attenuated the response to SR-rhGH despite IGF-1 increments. It is suggested that estrogens inhibit GH effect not only by reducing IGF-1, but also by other way such as increasing resistance.

Previous studies have shown that participants treated with GH experienced higher rates of soft tissue edema, arthralgias, and carpal tunnel syndrome than those not receiving GH.[12,30] In this study, two (5.3%) patients experienced edema and another two (5.3%) patients presented arthralgias. In general, the rates of adverse events were not significantly greater among subjects who administrated once-weekly injection of SR-rhGH compared with those receiving 3 times/week injection of rhGH.[17]

There was a slight but significant decrease in hematocrit concentration at 13 weeks (P=0.0152) and at 26 weeks (P=0.0028) compared with the level at baseline. It has been reported that GH deficiency is associated with reducing total body water (TBW), which is mainly due to a decrease in extracellular water.[35] The published literature has demonstrated that GH increases TBW and plasma volume using radionuclide dilution method.[36] This may have contributed to the slight decrease in hematocrit values shown in our results. However, increase in body weight was not observed.

Another distinguishing result is the decline of free T4 without

significant elevation of TSH. This result supports Jorgensen's theory that growth hormone increases the serum free T3 and decreases free T4, suggesting either suppression of D3 activity or increased T4 to T3 conversion.[37] Losa *et al.* confirmed this theory through a clinical study which free T4 level decreased at 6 months after GH treatment in adult growth hormone deficiency patients.[38] Showing in our study, although a decrement of free T4 was slight and remained within the normal range, it is recommendable to monitor thyroid function during administration of rhGH.

In recent meta-analysis of GH replacement in the GH-deficient adults, circulating glucose and insulin levels were found to be significantly increased after receiving GH,[39] whereas it is debatable whether insulin sensitivity is decreased or unchanged during prolonged GH replacement. We demonstrated that HbA1c, plasma insulin, and HOMA-IR were significantly increased at 26 weeks, namely, administration of SR-rhGH for 26 weeks decreased insulin sensitivity. Placebo-controlled studies are needed to compensate for the physiological decrease in insulin sensitivity with increasing age.

Apart from the single-arm study design, a limitation of this study was the small sample size. Although we found beneficial effects of SR-rhGH in LBM, WC, and QoL, the findings may not apply to the male population. Additional studies are required to verify these results in larger populations.

V. CONCLUSION

Our study suggests that body composition and Quality of Life can be restored in part by the replacement of SR-rhGH for 26 weeks in patients with somatopause. A once-weekly regimen of SR-rhGH was well tolerated without significant adverse effects. Further placebo-controlled studies examining long-term effects will be invaluable in characterizing the efficacy of SR-rhGH on elder's sarcopenia.

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ABSTRACT(IN KOREAN)

50세 이상 성인 성장호르몬결핍증에서 서방형 유전자재조합 인성장호르몬 투약 후 신체조성과 삶의 질 향상

<지도교수 이은직 >

연세대학교 대학원 의학과

박 정 경

노화와 함께 나타나는 성장호르몬의 상대적 결핍은 여러 가지 대사장애를 초래하지만 성장호르몬 투여로 일부 회복을 기대할 수 있다. 하지만 기존의 성장호르몬은 매일 주사하는 번거로움으로 순응도가 떨어지는 단점이 있었다. 이에 본 연구에서는 서방형 인성장호르몬을 성장호르몬 결핍이 있는 성인에게 투여 후 효과와 안정성, 순응도에 대해 살펴보고자 하였다.

본 연구는 전향적 다기관 연구로서 총 38명의 50세 이상 성인 중 혈중 IGF-1 농도가 150 ng/mL 이하인 환자를 대상으로 26주 동안 서방형 성장호르몬을 1주 간격으로 투약 하여 관찰하였다. 투약 4주 후 IGF-1는 평균 123.4 ± 41.6 ng/ml 에서 174.8 ± 59.6 ng/ml 로 상승하였고 이는 연구 기간 지속되었다. 26주 시점에서 건체중은 0.45 kg 증가하였으나 허리둘레는 1.06 cm 감소하였으며 삶의 질 평가 또한 유의하게 증가하였다. 골흡수, 골형성 표지자의 증가 또한 관찰되었고 이는 여성호르몬을 투약 중인 군에서 더 두드러지게 나타났다. 이상반응은 소양증, 관절통, 부종이 확인 되었으나 중증 이상은 관찰되지 않았다.

결론적으로 성장호르몬 결핍 성인에게 26주 간의 저용량 서방형 성장호르몬을 투약 후 유의한 이상 반응 없이 신체조성과 삶의 질이 향상되었다.

핵심되는 말 : 성장호르몬 보충, 성인 성장호르몬 결핍증

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