

## Effect of Growth Hormone (GH) Replacement on Plasma Carboxy-Terminal Propeptide of Type I Procollagen (PICP) and Pyridinoline Cross-Linked Carboxyterminal Telopeptide of Type I Collagen (ICTP) Levels in GH-Deficient Adult Patients

YOSHIO MURAKAMI, MIYOKO SUGITANI, KUNIO KOSHIMURA,  
MOTOI SOHMIYA, AND YUZURU KATO

First Division, Department of Medicine, Shimane Medical University, Izumo 693, Japan

GH exerts a positive effect on bone mineral metabolism. It was reported that bone mineral density was increased by recombinant human (rh) GH replacement therapy in adults with panhypopituitarism [1]. An increase in plasma bone Gla protein levels during GH administration was also demonstrated in adult patients with panhypopituitarism and isolated GH-deficiency [2].

Plasma levels of carboxy-terminal propeptide of type I procollagen (PICP) and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP) reflect the production and degradation of type I collagen, respectively, which were considered as biochemical bone markers for bone formation and resorption [3].

In this report, we determined the plasma levels of PICP and ICTP in GH-deficient adult patients during rhGH replacement therapy.

low in these patients. Associated hypothyroidism, hypocortisolism and hypogonadism had been treated, and the treatments were not changed throughout the study.

In protocol I, six patients received rhGH (0.125 IU/kg per week for 4 weeks and 0.25 IU/kg per week for 12 weeks, sc). A control group of five patients received vehicle. In protocol II, the initial dose of 0.01 IU/kg per day was increased to 0.01 (1 case), 0.03 (2 cases) or 0.05 IU/kg per day (2 cases). The sc injection of rhGH was continued for 36 weeks. Blood samples were obtained, and plasma was separated and stored at  $-20^{\circ}\text{C}$  until the assay for PICP and ICTP.

Plasma PICP and ICTP levels were assayed with commercial RIA kits (Orion Diagnostica, Espoo, Finland) according to the manufacturer's recommendations.

### Subjects and Methods

Sixteen GH-deficient adult patients participated in the study. The plasma IGF-I level and plasma GH response to insulin-induced hypoglycemia were

### Results

Basal plasma levels of PICP (mean  $\pm$  SD,  $109.0 \pm 40.1$  ng/ml) and ICTP ( $4.2 \pm 2.3$  ng/ml) in GH-deficient patients did not differ from those in normal female subjects (PICP:  $98.1 \pm 28.7$  ng/ml, ICTP:  $2.5 \pm 0.9$  ng/ml).

In protocol I, both plasma PICP and ICTP levels were increased by GH replacement (mean  $\pm$  SEM at 16 weeks, PICP:  $162.6 \pm 16.4$  ng/ml *vs.* control:  $90.3 \pm 17.4$  ng/ml,  $P < 0.05$ , ICTP:  $15.4 \pm 3.0$  ng/ml

Correspondence to: Dr. Yoshio MURAKAMI, First Division, Department of Medicine, Shimane Medical University, 89-1 Enya-cho, Izumo 693, Japan

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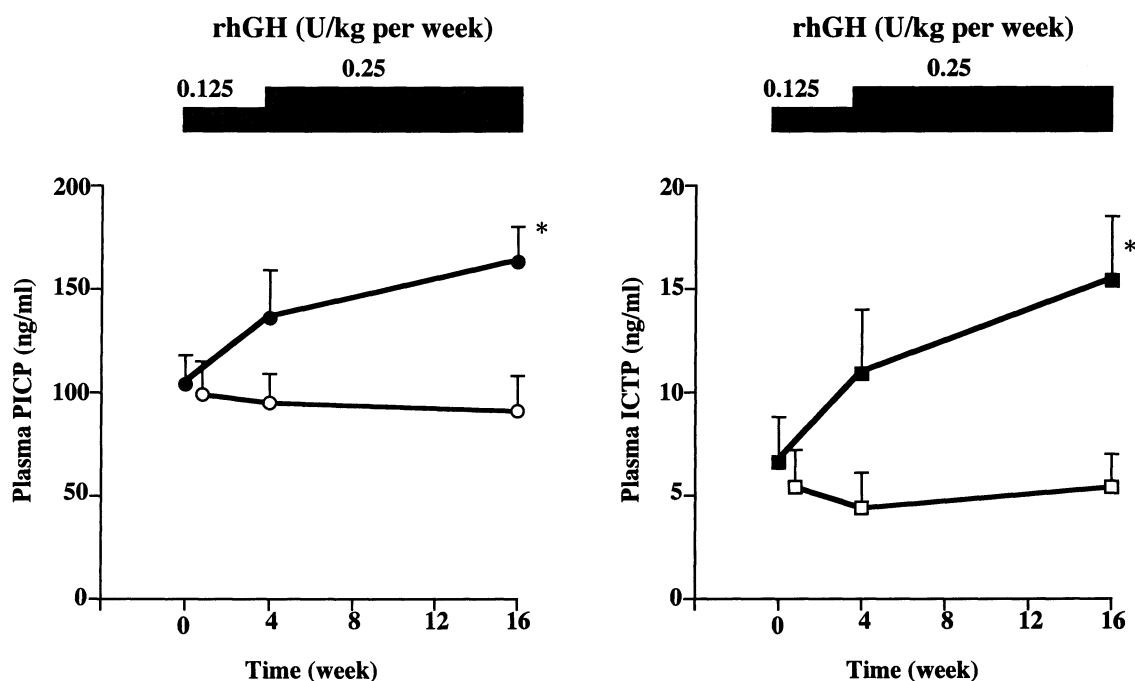


Fig. 1. Effect of daily subcutaneous injection of rhGH on plasma PICP (left) and ICTP (right) levels in 6 GH-deficient adult patients (protocol I). rhGH (0.125 to 0.25 U/kg per week, closed) or vehicle (open) was injected sc. \*:  $P < 0.05$  vs. control.

vs. control:  $5.4 \pm 1.6$  ng/ml,  $P < 0.05$ ) in GH-deficient adult patients (Fig. 1).

In protocol II, peak plasma PICP and ICTP levels were obtained at 8 to 20 weeks, and the levels remained high during the rhGH administration. Fig. 2 shows representative profiles of plasma PICP and ICTP levels in two patients. In both patients, plasma PICP and ICTP were increased in parallel. A patient who received the lowest dose of rhGH (0.01 IU/kg per day) exhibited an increase in plasma PICP and ICTP comparable to that following higher doses of rhGH (0.03 and 0.05 IU/kg per day) (Fig. 3). There was no difference in the peak/basal ratios of plasma PICP (0.01 IU/kg per day: 178%, 0.03 IU/kg per day: 125 to 188%, 0.05 IU/kg per day: 143 to 177%) or those of plasma ICTP levels (0.01 IU/kg per day: 269%, 0.03 IU/kg per day: 243 to 265%, 0.05 IU/kg per day: 194 to 233%) among groups of different rhGH doses.

## Discussion

Insulin-like growth factor (IGF-I) is an anabolic factor for osteoblasts. Bone mineral density

determined by dual-energy X-ray absorptiometry and the plasma IGF-I level positively correlates in adults with acquired GH-deficiency [4].

Basal levels of plasma PICP, a bone formation marker, in GH-deficient adults were similar to those in control subjects in the present study. This finding is similar to those in reports by other investigators stating that serum bone Gla protein (BGP) levels in GH-deficient adults were similar to those in normal subjects [2]. Sartorio *et al.* [5] found that the serum BGP level in adults with childhood-onset GH-deficiency was lower than that in the normal population. These discrepancies could be attributed to the duration of GH-deficiency. Plasma ICTP levels, a bone resorption marker, in GH-deficient adults were similar to those in control subjects. This finding is in agreement with another report [5], and suggests the presence of normal bone resorption activity in GH-deficient subjects.

In this report, we demonstrated a simultaneous increase both in plasma PICP and ICTP levels, a marker of type I collagen production and degradation during rhGH replacement therapy, suggesting that GH could activate the bone remodeling of adults with GH deficiency. In

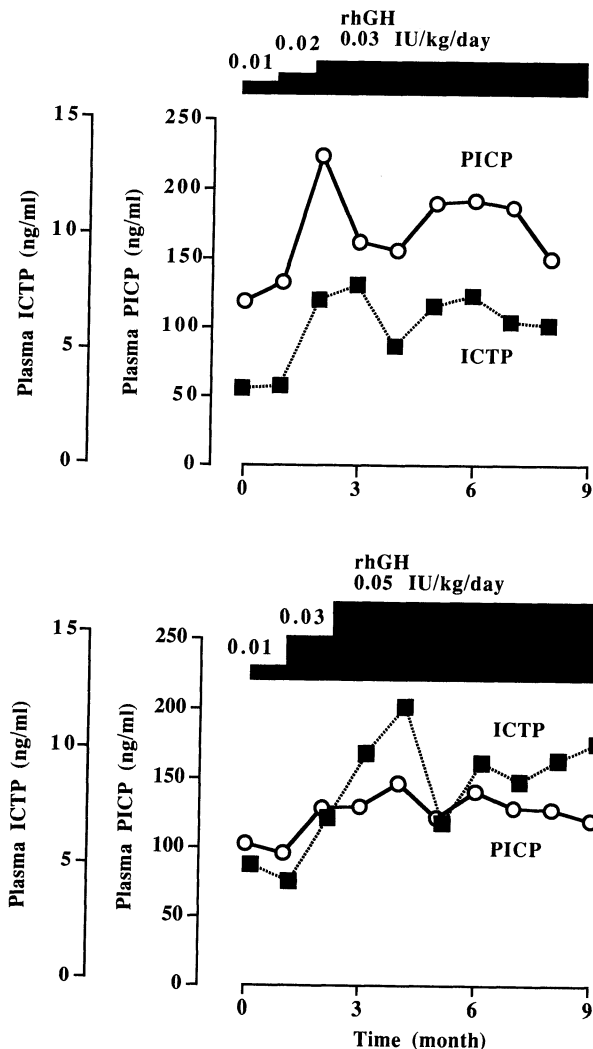


Fig. 2. Representative profiles of plasma PICP (open circle) and ICTP (closed square) levels during rhGH replacement therapy in two adult patients with GH-deficiency (protocol II). Upper panel: 0.03 IU/kg per day, Lower panel: 0.05 IU/kg per day.

contrast, it was reported that serum BGP levels were increased in acromegalic patients and that the BGP concentrations were acutely declined after surgery [2].

In protocol II, in which rhGH was administered for 36 weeks, peak plasma PICP and ICTP levels

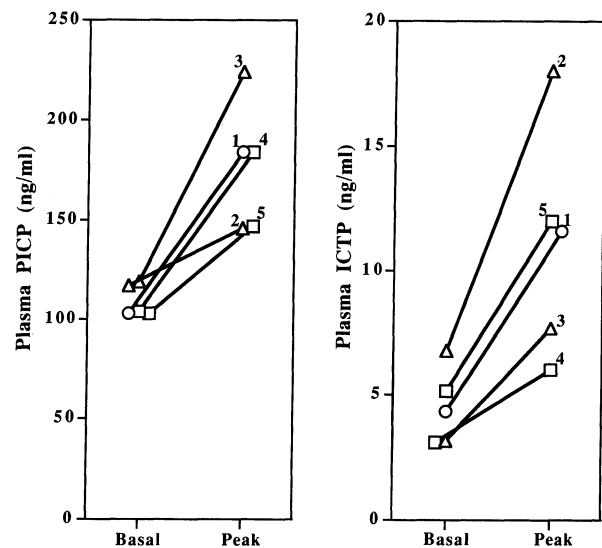


Fig. 3. Basal and peak levels of plasma PICP (left) and ICTP (right) during rhGH replacement therapy in 5 GH-deficient adult patients (protocol II).  $\circ^1$ : patient 1 treated with 0.01 IU/kg per week.  $\triangle^2$ ,  $\triangle^3$ : patient 2 and 3 treated with 0.03 IU/kg per week.  $\square^4$ ,  $\square^5$ : patient 4 and 5 treated with 0.05 IU/kg per week.

were obtained as early as at 8 to 20 weeks of the treatment. Other investigators [5] also reported that the maximal effect of rhGH on biochemical bone markers was evident after 3 months in the 6-month trial. Thus the effect of GH replacement therapy on the bone remodeling might be achieved in a relatively early phase of the treatment. In addition, we failed to demonstrate a positive correlation between the dose of rhGH and peak plasma values for PICP and ICTP. The peak/basal ratios of plasma PICP and ICTP were similar in the groups of different rhGH doses as well. The precise dose relationship between rhGH and the effect on bone remodeling in GH-deficient adult patients remains to be elucidated.

In conclusion, our present findings suggest that rhGH replacement accelerates both bone formation and resorption in GH-deficient adult patients and that a low dose of rhGH is effective for bone remodeling in these patients.

## References

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