Effects of mirthful laughter on growth hormone, IGF-1 and Substance P in patients with rheumatoid arthritis

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Abstract

Objective

Growth hormone (GH) plays an ancillary role in the regulation of immune function. GH has been shown to be associated with joint symptoms such as pain and swelling. On the other hand, mirthful laughter has favorable effects on the neuroendocrine-immune system. We evaluated the levels of serum GH, insulin-like growth factor-1 (IGF-1) in RA patients and evaluated the effect of mirthful laughter on GH and IGF-1.

Methods

We compared with the levels of serum GH, IGF-1 and substance P (SP) in patients with RA and healthy subjects (control group) before and after exposure to "Rakugo", a traditional Japanese comical story that induces mirthful laughter.

Results

The basal level of serum GH in the RA group was significantly higher than in the control group. After experiencing mirthful laughter, the level of serum GH in the RA group significantly decreased, approaching that in the control group. The serum IGF-1 level was lower in the RA group than in the control group. There was no significant difference in the level of serum SP between the RA group and the control group.

Conclusion

The basal level of serum GH in the RA group was significantly higher than in the control group, and the level of serum GH significantly decreased after experiencing mirthful laughter. These results suggest that the homeostasis of GH in patients with RA is disturbed, and the increased serum GH levels in RA patients may be associated with their stress condition.

Key words

Rheumatoid arthritis, growth hormone, insulin-like growth factor-1, substance P, stress, mirthful laughter.

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Introduction

Rheumatoid arthritis (RA) is a systemic disease characterized by chronic joint inflammation, leading to a progressive destruction of the articular cartilage and periarticular bone. Therefore, RA patients are under physical and psychological stress due to joint deformity, pain and anxiety regarding their illness. It has been shown that excessive mental stress affects the neuroendocrine-immune system, in turn affecting the activities of many diseases including RA (1-7). It has been shown that mirthful laughter has favorable effects on the musculo-skeletal, circulatory, respiratory, and neuroendocrine-immune system, and simultaneously relieves pain (8-11). We have recently reported the favorable effects of mirthful laughter on the neuroendocrine-immune system in patients with RA. In particular, the serum interleukin-6 (IL-6) level in RA patients is significantly higher than in healthy controls and falls rapidly after experiencing mirthful laughter (12-14).

Growth hormone (GH) is a peptide hormone secreted from the anterior pituitary gland under the control of hypothalamic hormones such as the growth hormone-releasing hormone and somatostatin. Multiple factors regulate the integrated secretion of GH. For example, physical and psychological stresses increase GH level. Neuropeptides, neurotransmitters, and opiates also affect the hypothalamus and influence GH secretion (15). Substance P(SP) is one of the neuropeptides which induces changes in the levels of neuroendocrine measures including GH (16). SP is released from both the central and peripheral endings of primary afferent neurons and functions as a neurotransmitter. SP has been supposed to be involved in the transmission of pain signals, due to high concentrations of this agent located in the dorsal root of the spinal cord (17). SP has multiple neurogenic inflammatory properties such as vasodilation (18), and immunomoduration (19). Moreover, SP may have a major role in the pathogenesis of several inflammatory disease such as RA(20).

Recently, a hypothesis has been proposed that GH plays an ancillary role in the regulation of immune function under conditions of stress (21). Interactions between the neuroendocrine and immune systems play important roles in maintaining homeostasis, since the cells of the neuroendocrine and immune systems share common signal molecules and receptors (22). Therefore, hormones and neuropeptides can modulate the activity of immune cells. It is well accepted that GH acts on the growth of skeleton and soft tissues, and the mitogenic effects of GH on various cells have also been described, for example, chondrocytes, fibroblasts (23), adipocytes (24), myoblasts (25), and immune cells such as mononuclear cells (26), macrophages (27), and lymphocytes (28). Furthermore, GH plays a role as an immune mediator, for example, promoting the synthesis of IL-1, IL-2 (29), and tumor necrosis factor-α (TNF-α) (30). These actions were thought to be mediated directly or indirectly by the production of insulin-like growth factor-1 (IGF-1). These results suggest that GH and IGF-1 may affect the pathophysiology of RA. However, the role of GH in the pathogenesis of RA remains to be elucidated. In this study, we determined the levels of GH, IGF-1, and SP in serum and evaluated the effect of mirthful laughter on the levels of GH, IGF-1, and SPin patients with RA.

Materials and methods

Subjects

Studies were conducted in 41 female RA patients recruited from the outpatient clinic of our Department of Joint Disease and Rheumatism. Inclusion criteria for this study were diagnosed according to the 1987 revised criteria of the American College of Rheumatology (31) and a duration of disease of more than 1 year. Healthy subjects (control group) consisted of 24 healthy females enrolled as volunteers. Exclusion criteria were that the subjects were taking drugs acting on the central nervous system and/or were suffering from minor or major psychiatric diseases, and were taking drugs because conditions potentially interfering on growth hormone secretion such as some adrenergic drugs. The mean age

Table I. Characteristics of patients with RAand controls. Values are median and range.

	RA	Controls
Number of patients	41	24
Age (yrs)	63.9 (31~ 78)	64.8 (25 ~ 82)
Duration of disease (yrs)	18.4 (2 ~ 47)	ND
C-reactive protein (mg/dl)	1.44 (0.02 ~ 6.39)	0.12 (0.02 ~ 1.06)
Corticosteroids (%0	87.8	0
NSAID (%)	78.0	0
DMARDS (%)	56.1	0
Methotrexate (%)	56.1	0

ND: not done; DMARD: disease modifying antirheumatic drug; NSAID: nonsteroidal anti-inflammatory drug.

of the RA subjects was 63.9 years (range 30-77 yrs) and that of the healthy subjects were 64.8 years (range 24-81 yrs). There was no significant difference in the mean age between the RA and control groups. The mean duration of RA in the patients was 18.4 years (range 2-47 yrs). In the RA group, 36 were taking prednisolone (87.8%) at a dose of < 5mg/day, 23 were taking disease-modifying antirheumatic drugs (DMARDs) (56.1%) except for methotrexate, 23 were taking methotrexate (56.1%) and 32 were taking nonsteroidal anti-inflammatory drugs (NSAIDs) (78.0%). Patient's characteristics are summarized in Table I. The patients were instructed to take their drugs in the morning. Prior to the study, written informed consent was obtained from all the patients and healthy subjects, and the study was approved by the ethics committee of the Nippon Medical School.

Methods

Mirthful laughter was induced by exposure to "Rakugo", a traditional Japanese comical story, told by a professional storyteller for one hour from 13:00 to 14:00. This session was held in our lecture hall in the Nippon Medical School, Tokyo, Japan on April 12, 2003. The following variables were determined immediately before and after exposure: (1) the mood using the face scale of Lorish *et al*. (32); (2) the degree of pain using a self-assessment 10-cm visual analog scale (VAS) (not applicable to healthy subjects); (3) the degree of laughter using VAS (only after exposure) (33); and (4) serum GH, IGF-1 and SP levels.

Both serum GH and serum IGF-1 levels were measured by solid-phase radioimmunoassay (Daiichi Radioisotope Laboratories, Tokyo, Japan). SP was quantified by an antigen competition enzyme immunoassay (Caymen Chemical Co., Ann Arbor, Mich.) (34).

Statistical analyses

Data are presented as the median and range. The Wilcoxon signed rank test was used to compare each parameter before and after experiencing mirthful laughter. The Mann-Whitney's U-test was employed to compare the results between the RA and control groups. Spearman's rank correlation test was used to analyze correlations among the measured items. A p value < 0.05 was considered statistically significant.

Results

Comparative study using face scale and VAS

Before exposure to "Rakugo", the face scale score in the RAgroup was significantly higher than in the control group. After exposure, the face scale score significantly decreased in both groups. However, the face scale score in the RA group was still significantly higher than in the control group. There was no significant difference in the VAS of laughter between these groups. The VAS of pain significantly decreased in the RA group. These results are summarized in Table II.

Table II. Face scale score, VAS of pain, VAS of laughter, and serum levels of GH, IGF-1, SPbefore and after exosure to "Rakugo" (median and range).

		Before	After	p value (a)
Face scale score	Ra	7.6 (1 ~ 16)*	4.9 (1 ~ 18)**	< 0.0001
	Control	5.0 (1 ~ 10)	2.4 (1 ~ 8)	< 0.001
VAS of pain	RA	3.4 (0 ~ 8.1)	2.7 (0 ~ 8.0)	< 0.05
	Control	ND	ND	
VAS of laughter	RA	ND	7.5 (1.6 ~ 10.0)	
	Control	ND	8.6 (5.5 ~ 10.0)	
GH (ng/ml)	RA	4.63 (0.19 ~ 18.2)**	1.29 (0.09 ~ 5.99)	< 0.0001
	Control	2.21 (0.26 ~ 14.7)	0.85 (0.06 ~ 4.29)	<0.01
IGF-1 (ng/ml)	RA	125.2 (49.0 ~ 330.0)**	127.8 (50.0 ~ 330.0)*	0.13
	Control	158.3 (57.0 ~ 330.0)	161.3 (54.0 ~ 320.0)	0.25
SP (ng/ml)	RA	18.6 (7.7 ~ 68.4)	15.4 (10.22 ~ 28.6)	<0.001
	Control	19.2 (12.3 ~ 35.7)	16.8 (12.2 ~ 27.3)	< 0.001

ND: not done; * p < 0.05; ** p < 0.01: RAvs Control (Mann-Whitney's U-test); p value (a): before vs after exposure to "Rakugo" (Wilcoxon signed rank test).

Comparative study of GH, IGF-1 and SP in serum

Before experiencing mirthful laughter, the serum GH level in the RA group was significantly higher than in the control group. After the experience, the serum GH level significantly decreased both in the RAgroup and in the control group (Fig. 1). In particular, a marked decrease in the serum GH level in the RA group was observed. After experiencing mirthful laughter the serum GH level in the RA group decreased, approaching that in the control group, and there was no significant difference between these groups.

The serum IGF-1 level was significantly depressed in the RA group when compared with those in the control group before and after the experience. Both groups showed no significant change in the levels of IGF-1 before and after the experience (Fig. 2).

No significant difference in the level of serum SP was observed between the RA and the control groups. However, the level of serum SP significantly decreased after experiencing mirthful laughter in both groups (Fig. 3). These results are also summarized in Table II.

Correlation between GH and parameters

In the RA group, the serum GH level positively correlated with face scale score (Fig. 4a) and the VAS of pain (Fig. 4b) after experiencing mirthful laughter. The serum IGF-1 and SPlevel did not correlate with the serum GH level before and after experiencing mirthful laughter. The serum SP level did not correlate with the VAS of pain before and after experiencing mirthful laughter. IGF-1 level tended to correlate negatively with the duration of disease in patients with RA(Fig. 4c).

In the control group, the serum GH level did not correlate with the face scale score and the serum SP level before and after experiencing mirthful laughter. The serum IGF-1 level tended to correlate with the serum GH level (ρ = 0.407, p = 0.051) only before experiencing mirthful laughter.

Discussion

In this study, we showed that before ex-

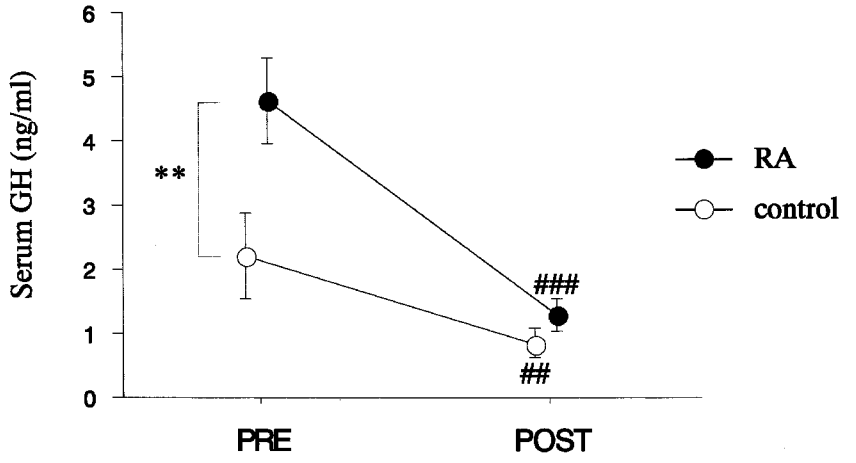

Fig. 1. Effect of mirthful laughter on the level of serum GH in RA.
Data are mean ± SEM. **: p < 0.01 as compared with RAgroup and control group.##: p < 0.01, ###: p < 0.001 as compered before and after experiencing mirthful laughter.

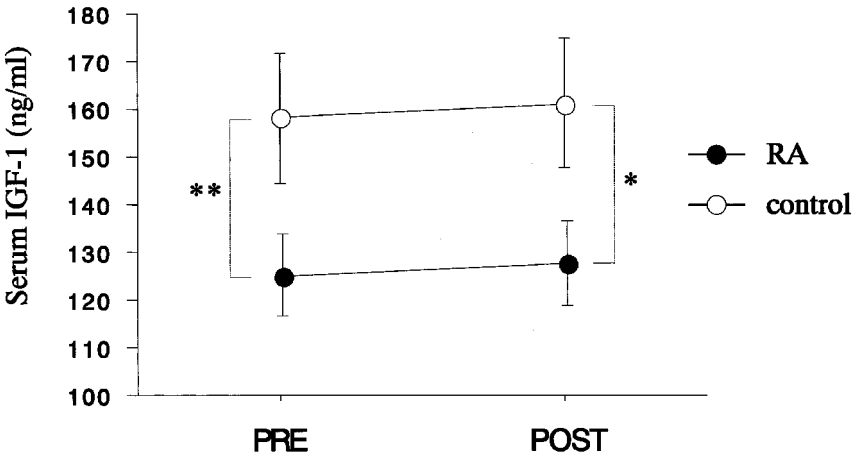

Fig. 2. Effect of mirthful laughter on the level of serum IGF-1 in RA.
Serum IGF-1 level was depressed in the RAgroup when compared with the control group before and after experiencing mirthful laughter. Data are mean ± SEM. *: p < 0.05 and **: p < 0.01 as compared with RAgroup and control group.

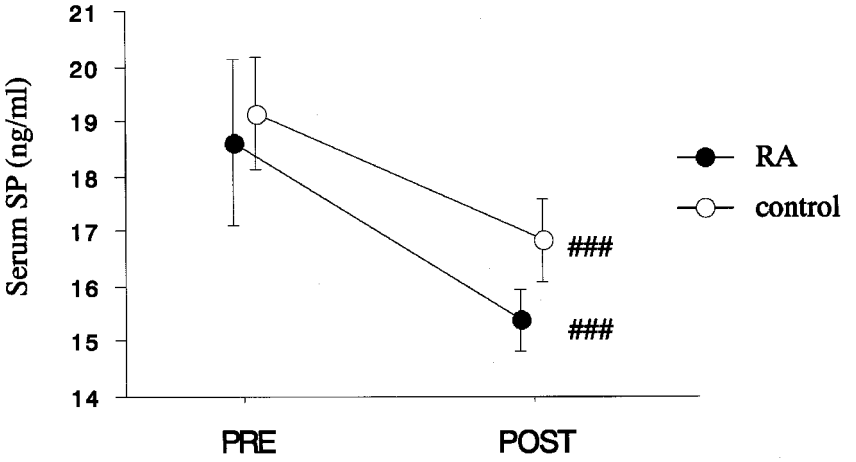

Fig. 3. Serum SP level in the RA group and control group before and after experiencing mirthful laughter.
No significant difference was observed between RAand control groups before and after experiencing mirthful laughter. Data are mean ± SEM. ###: p < 0.001 compared before and after experiencing mirthful laughter.

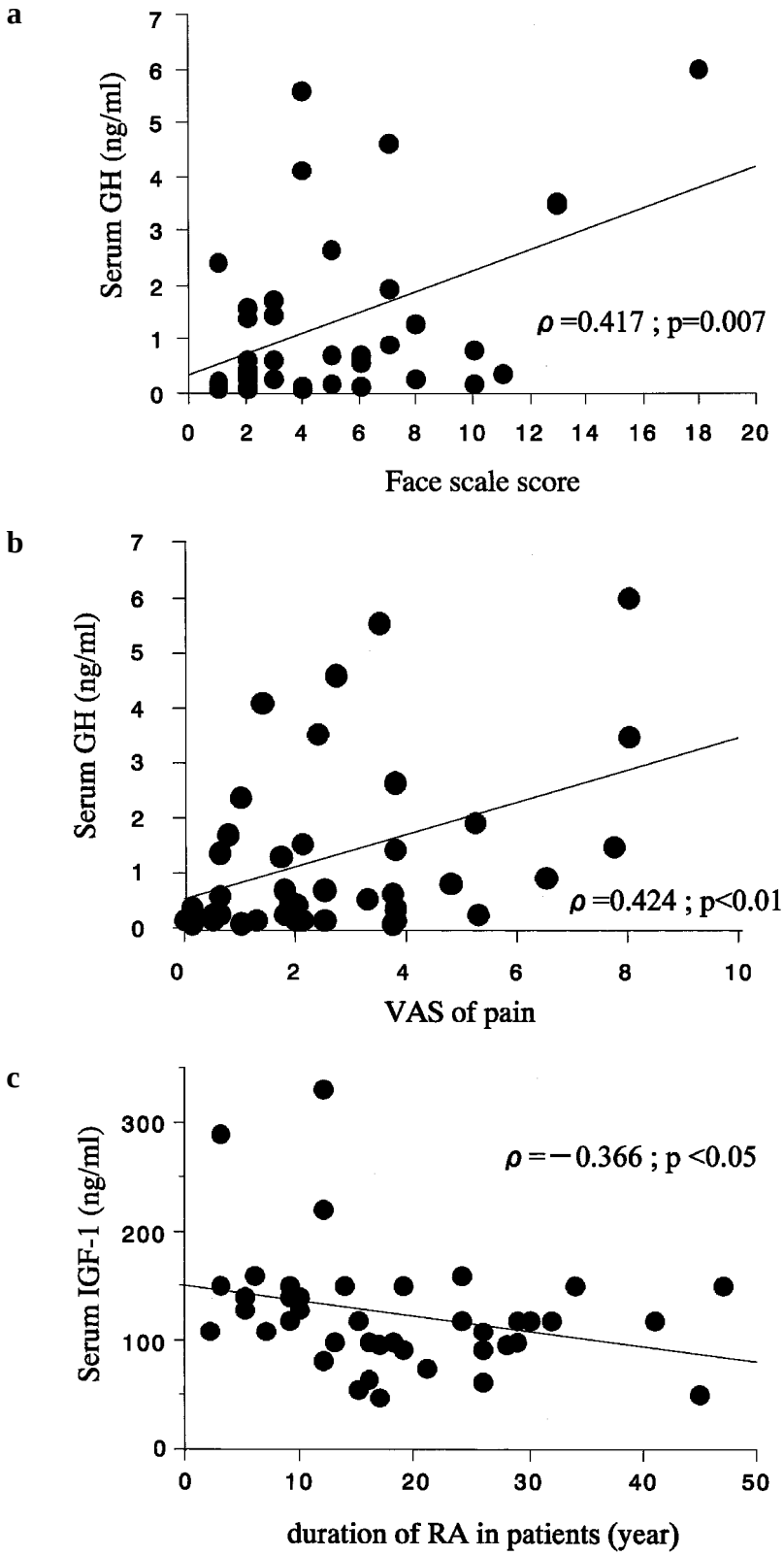

Fig. 4. Correlation between GH and parameters.
(**a**) Positive correlation between face scale score and the serum GH level after experiencing mirthful laughter was observed in RApatients.
(**b**) Positive correlation between the VAS of pain and the serum GH level after experiencing mirthful laughter was observed in RApatients.
(**c**) Negative correlation between the serum IGF-1 level and duration of RAin patients was observed.
Statistical analysis was performed by Spearman's rank correlation test.

periencing mirthful laughter, the serum GH level in the RA group was significantly higher than in the control group. There are only a few studies investigating the involvement of GH in the pathophysiology of RA (35-38). Although, several contradictions in the level of serum GH in RApatients were reported in those studies, all of those reports concluded that the GH axis in patients with RA is notably disturbed. GH has been shown to associate with joint symptoms such as pain and swelling; thus a high GH level in a joint would appear to be undesirable (39, 40).

In this study, before and after exposure to "Rakugo", the face scale score in the RAgroup was significantly higher than in the control group. These results might be caused by stressful conditions in RA patients. It is known that physical and psychological stresses increase GH level (15). After exposure to "Rakugo", the face scale score significantly decreased in both groups. These results suggest that exposure to "Rakugo" significantly induced a positive emotional state in both groups as determined by the face scale score. In the RA group, the serum GH level positively correlated with the face scale score after experiencing mirthful laughter.

In order to make a comparison between two groups: one that enjoyed "Rakugo" versus the other group that did not enjoy "Rakugo", the RAgroup is separated into two groups according to the VAS of laughter: one that is above average of the VAS of laughter and the other that is below average of VAS of laughter. The reduction rate of GH is substantially correlated to the cheerful feeling due to Rakugo in the RA group (data not shown). In this study, the VAS of pain significantly decreased in the RA group after experiencing mirthful laughter. These results are consistent with our previous observations that mirthful laughter reduced pain in patients with RA. Moreover, the serum GH level positively correlated with the VAS of pain. It seems that pain is one of the causes of stress in RA patients. Therefore, these observations suggest that stress may induce GH hypersecretion in RApatients, and mirthful laugh-

ter markedly decreases the serum GH level due to the reduction of stress.

GH mediates its growth promoting activity in the peripheral target tissues directly or indirectly by stimulating the production of IGF-1 mostly in the liver. However, in this study, a low IGF-1 level, despite increased GH secretion, was observed in RA patients. Moreover, the serum IGF-1 level was depressed in the RAgroup compared with the controls before and after experiencing mirthful laughter. Consistent with this, Lemmey *et al.* have shown that the serum IGF-1 level was significantly depressed in RA, and their results indicate that the reduction in circulating IGF proteins is more related to their sedentary lifestyle than to the inflammatory process (41). Interestingly, our results showed that the serum IGF-1 level tended to correlate negatively with the duration of RA in patients. Several studies showed that the serum IGF-1 level decreased in both arthritic animals and patients with RA (42, 43). Previous reports demonstrated that proinflammatory cytokines such as IL1-β and TNF-α could decrease the level of circulating IGF-1 (44, 45). De Benedetti *et al*. also reported that IL-6 caused growth impairment through a decrease in IGF-1 in IL-6 transgenic mice under the control of neurospecific enolase promoter (46). They hypothesized that over-production of IL-6 may act negatively on liver IGF-1 gene expression. These results suggest that high levels of pro-inflammatory cytokines in RA patients decrease the serum IGF-1 level. However, the mechanism by which pro-inflammatory cytokines cause reduced serum IGF-1 level is not fully clarified.

In this study, the level of SP significantly decreased after exposure to mirthful laughter in both groups. Recently, several studies have suggested that the serum SP level reflects the mood of subjects (47, 48). Thus, the significant decrease in the level of SP in both groups may reflect a positive emotional state induced by mirthful laughter. In this study, the serum SP level did not correlate with the VAS of pain before and after experiencing mirthful laughter in RA patients. It has been considered that SP mediates neurogenic inflammation. However, as yet, the role of SP in the pain and inflammation associated with joint disease remains controversial (49). Some studies have shown that SP influences the level of several neuroendocrine measures including GH. It has been demonstrated that the administration of SP leads to a decrease in sleep-associated GH secretion (16). In contrast, SPstimulates GH secretion by acting directly on the anterior pituitary and indirectly on the hypothalamus (50, 51). Since the findings regarding the effects of SP on GH secretion are controversial, further studies are necessary to determine whether SP influences the GH axis in RApatients.

Several researches have shown that psychosocial stressors may influence disease onset and/or exacerbations of disease (1, 4). In fact, stress is the cause most given by patients for flare-ups in their RA (5). It is reported that in RA patients, psychoimmune processes are also implicated in short-term changes in RA activity (6). Psychosocial stressors may influence disease activity by disturbing the homeostasis of the neuroendocrine-immune systems in RA(4, 6). It has been reported that positive thinking and laughter seem to have favorable effects on disease (8). Bennett *et al*. reported that mirthful laughter may reduce stress and improve natural killer cell activity (11). In RA patients, arthralgia is reduced effectively by coping with stress (52, 53). The reduction of stress may be preferable for the treatment of RA. Our results suggest that stress may induce GH hypersecretion in RApatients, and mirthful laughter markedly decreases the serum GH level due to reduced stress. Taken together, reducing the serum GH level by experiencing mirthful laughter may assist current therapy for RA. However, it is not clear how long the endocrine effect of mirthful laughter lasts. Further studies are necessary to determine the effects of mirthful laughter on GH secretion in RApatients.

In conclusion, we have demonstrated that the basal serum GH level in RA patients was significantly higher than in healthy subjects, and the level of GH significantly decreased after experiencing mirthful laughter. The serum IGF-1 level was significantly depressed in the RA group when compared with the control group. These results suggest that the GH and IGF-1 secretion in patients with RA is disturbed, and the increased serum GH level in RA patients is associated with stress. Understanding the interaction between GH and stress in RApatients may open new treatment strategies for RA.

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