

A Pilot Study in Normal Volunteers of the Effects of the Renuva™ System on Growth Hormone and Insulin-Dependent Growth Factor-1

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Abstract: *Background:* The Renuva™ System is a dietary supplement sold to prevent symptoms of age-related growth hormone decline.

Objective: Test the ability of the Renuva™ System to increase growth hormone (GH) and insulin-like growth factor-1 (IGF-1).

Methods: The Renuva™ System is a two-part dietary supplement to maintain a healthy endocrine system. The “Generator Drink” contains amino acids and nicotinic acid. The “Infuser Spray” contains growth hormone releasing peptides in a patented oral delivery system. The Renuva™ System was given to 13 healthy volunteers ≥ 40 years. Two of 13 subjects were given just the “Infuser Spray” to swallow, and four subjects were given just the “Generator Drink” on a second occasion. GH and IGF-1 were measured at -10, -5, 0, 30, 60, 90, 120, and 180 minutes.

Results: Thirteen subjects receiving the two-part Renuva™ System increased GH $98 \pm 50.2\%$ (SEM) ($p < 0.05$) from baseline, and IGF-1 rose 35.8 ± 45.0 ng/mL ($p < 0.02$) from baseline at 120 minutes. Average IGF-1 levels of 2 subjects receiving just the “Infuser Spray” was less 174.8 ± 20.8 ng/ml than average IGF-1 post-baseline values during the test using both the Infuser Spray and Generator drink (213 ± 37.2 ng/mL, $p < 0.002$). Average IGF-1 levels of 4 subjects receiving just the “Generator Drink” was less (202.6 ± 124.7 ng/mL) than average IGF-1 post-baseline values when using both the Infuser spray and the Generator drink (234.8 ± 32.2 ng/mL, $p = \text{NS}$).

Conclusion: The Renuva™ System increases GH and IGF-1. Both the Generator Drink and the Infuser Spray appear to contribute to the increase in IGF-1.

Key Words: Aging, Amino acids, Growth hormone, Growth hormone releasing peptides, IGF-1, Nicotinic acid.

INTRODUCTION

Growth hormone (GH) levels decrease with aging and low growth hormone levels result in decreased energy, decreased stamina, decreased lean body mass, compromised skin texture, an erosion of cognitive powers, a decrease in memory, and other related symptoms [1]. People who are GH deficient have an insulin-like growth factor-1 (IGF-1) level less than 350 U/L [1]. Less than 5% of the population in the 20-40 year age group has growth hormone deficiency, but 30% of those over 60 years of age are growth hormone deficient [1]. The implications of being partially deficient in IGF-1 (greater than 350 U/L but less than normal for a younger age) are not definitely known, but since growth hormone decreases with age, it is reasonable to assume that partial deficiency is common and that those with partial deficiency would be likely to benefit from increased levels of growth hormone and IGF-1.

Treating growth hormone or IGF-1 deficiency has been demonstrated to reverse many of the undesirable physiological effects that are attributed to aging [1]. The effects of growth hormone treatment on aging characteristics include increased energy, increased stamina, increased lean body mass, better sleep, improved skin texture, improved hair texture, improved memory, and improved cognition. Treatment with growth hormone injections for adult growth hormone deficiency is not entirely benign. Clinical trials of adult growth hormone deficiency with injections of growth hormone was associated with edema, arthralgias, extremity pain or stiffness, paresthesias, myalgias, fatigue and headache that were greater in prevalence than the placebo group. Concerns about predisposing to type 2 diabetes or stimulating tumor growth also exist.

Growth hormone releasing hormone (GHRH) is primarily responsible for the secretion of GH [2]. Other peptides, growth hormone releasing peptides (GHRP), are also capable of causing GH secretion [2]. Nicotinic acid suppresses free fatty acids that normally suppress GH secretion, thus, raising GH levels in the serum [3].

The Renuva™ System consists of a two-part dietary supplement system designed to stimulate secretion of endoge-

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nous GH and subsequent IGF-1 elevation. The “Generator Drink” contains amino acids (arginine, glutamine, glycine, lysine, ornithine and glutamic acid) known, in larger amounts, to stimulate endogenous GH secretion and nicotinic acid (38 mg), which releases GH secretion from suppression by free fatty acids. The “Infuser Spray” contains GHRP in a patented oral delivery system that facilitates absorption and transport across the blood brain barrier [4]. Growth hormone releasing peptides, when injected into humans, cause the rise and fall of GH over a 3-hour period with the maximal blood levels of GH occurring at 30 minutes (2).

This trial was intended to study the effects of the two-part Renuva™ System on the secretion of endogenous GH and IGF-1, a dietary supplement sold through public commercials and the internet to support and maintain a healthy endocrine system.

MATERIALS AND METHODOLOGY

The protocol was submitted and accepted by an independent Human Subjects Committee prior to the commencement of the study. Healthy men and women, 40 years of age or older, on no regular prescription medications other than hormone replacement therapy or birth control signed informed consent documents, and were subsequently screened for entry into the study. A medical history and physical examination were obtained on each subject, and a pregnancy test was performed on women of child bearing potential. Blood samples for a standard clinical chemistry panel and a complete blood count were obtained.

Thirteen subjects passed the screening and returned to the clinic the following morning, having fasted (except for water) from 9:00 pm the previous night. The subjects had an intravenous line placed for drawing blood. Samples were drawn for GH and IGF-1 analysis at times -10, -5, and 0 minutes to obtain a stable baseline value starting between 7:30 and 8:00 a.m. The Renuva™ System (Generator and Infuser) was administered immediately following the 0 time blood sample. The subjects drank the generator drink fol-

lowed by spraying the infuser into the buccal cavity where it could be absorbed.

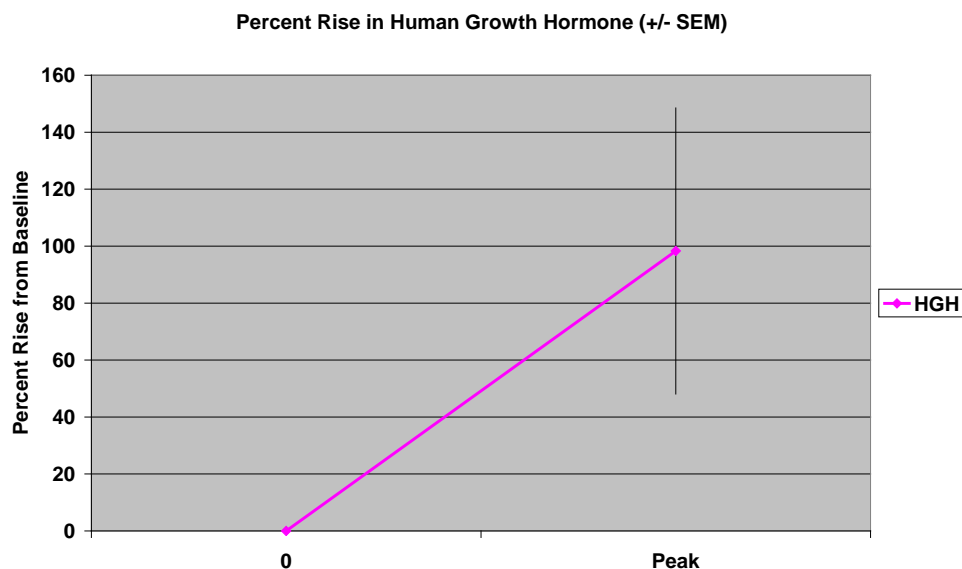
Blood samples were then taken at 30, 60, 90, 120, and 180 minutes post-administration. Serum from the three baseline samples was pooled to insure that a stable baseline was obtained, since GH is secreted in pulses. All blood samples were spun, the serum placed in cryovials, and the samples stored in a freezer. The blood samples were packed in dry ice and sent to Pennington Biomedical Research Institute (Baton Rouge, LA) where the GH and IGF-1 analyses were performed.

Two subsets of the original cohort of 13 had a second test in an identical manner except that subjects one and two were administered only the Infuser spray, and were told to “drink or quickly swallow” the spray, as opposed to allowing buccal absorption as was done in the original study. Subjects three, four, five and six had only the Generator drink administered. This was to develop pilot data for determining to what degree each of the two components of the Renuva™ system contributed to the rise in GH or IGF-1, and to determine if swallowing the spray gave different results than allowing for buccal absorption. Study results were analyzed by t-test compared to baseline values.

RESULTS

There were 9 men and 4 women that completed the study. One woman was post-menopausal but not on hormone replacement therapy. Three women were pre-menopausal and only one was on birth control pills.

GH has a pulsatile secretion. As such, it is difficult to measure, and the data are often difficult to interpret. Since the secretion of IGF-1 is dependent on GH levels and secretion, IGF-1 is used as a clinical surrogate of GH secretion. The growth hormone levels in the thirteen subjects tested varied considerably from undetectable to between 9 and 10 ng/mL. The mean peak growth hormone levels from baseline did not rise in this set of 13 subjects. The mean rise was -0.7



There was a significant percentage rise in GH from baseline in the 13 subjects given the Renuva™ System.

Fig. (1). The thirteen subjects receiving the 2-part Renuva™ increased growth hormone as a percent above baseline ($p < 0.05$).

± 1.7 (SD) which was not significantly different from baseline. The rise in GH as a percentage of the baseline value however did rise significantly 98 ± 50.2 (SEM) ($p < 0.05$) (Fig. 1).

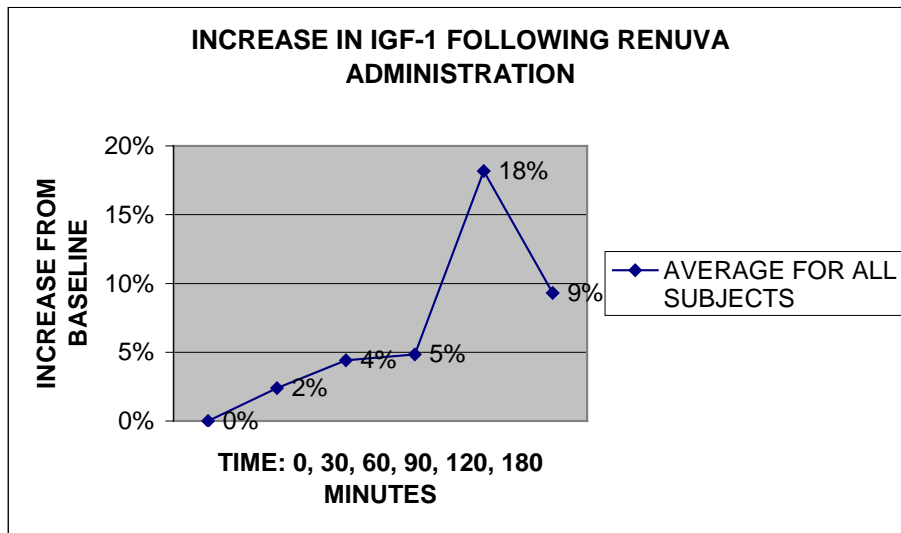
When the average levels of IGF-1 for the 13 subjects were plotted at each time point (Fig. 2), there was a lag time of about 90 minutes in which the IGF-1 slowly increased. At 120 minutes, shown in Fig. (3), there was a significant increase of IGF-1, compared to baseline (35.8 ± 45.0 ng/mL, $p < 0.02$). While the increase diminished at 180 minutes, it was still higher than baseline levels.

Since there was variability in the timing that subjects achieved peak levels of IGF-1, the data was also analyzed as the average peak IGF-1 values, regardless of time obtained, compared to baseline (Fig. 4). These peak values were also

found to be significantly higher than the baseline values (50.8 ± 34.2 , $p < 0.001$).

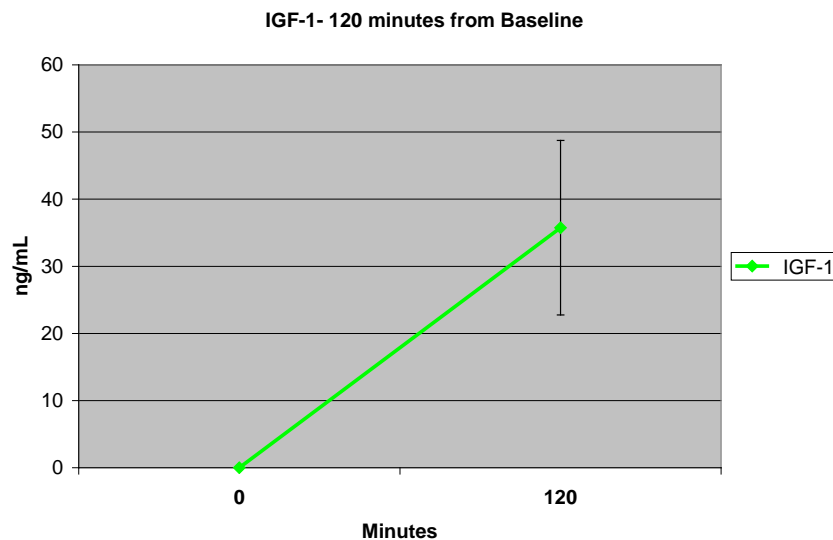
The peak post baseline IGF-1 values in the two subjects who repeated the test following the “Infuser Spray” alone were not different than the peak IGF-1 value during the test using both the “Infuser Spray” and the “Generator Drink” (314.5 ± 62.5 vs. 258.5 ± 58.2 , $p = \text{NS}$). The average post-baseline IGF-1 values in the two subjects who repeated the test following the “Infuser Spray” alone were significantly less (174.8 ± 20.8 ng/ml) than the average post-baseline IGF-1 values during the test using both the “Infuser Spray” and “Generator Drink” (213 ± 37.2 ng/mL, $p < 0.002$) (Fig. 5).

The average post-baseline IGF-1 values for the 4 subjects who repeated the test following the “Generator Drink” alone



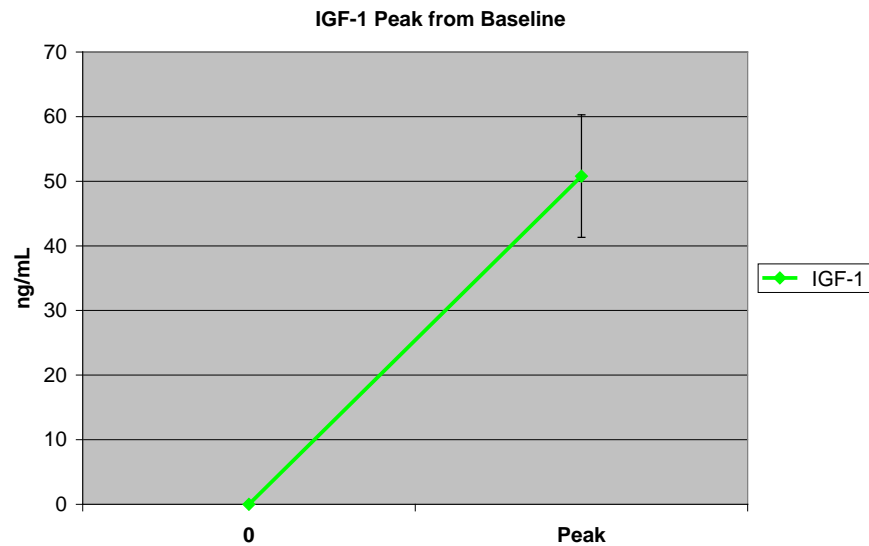
IGF-1 rises in response to the Renuva™ System with a lag time of about 90 minutes.

Fig. (2). There was an approximate 90 minute lag prior to the rise in the mean values of IGF-1 in the 19 subjects who received the 2-part Renuva™ System.



There was a significant rise of IGF-1 in response to the Renuva™ System 120 minutes (35.8 ± 45.0 ng/mL, $p < 0.02$).

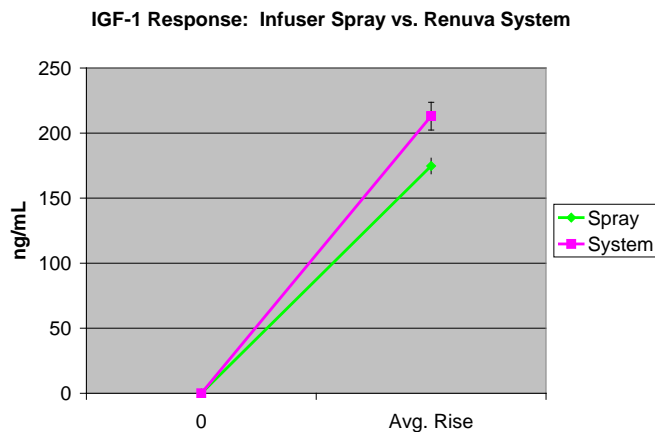
Fig. (3). The 19 subjects who were administered the 2-part Renuva™ System had a significant rise in IGF-1 at 120 min compared to the baseline value ($p < 0.02$).



The average peak IGF-1 in response to the Renuva™ System was significantly higher than the baseline values (50.8 ± 34.2 , $p < 0.001$).

Fig. (4). The 19 subjects who were administered the 2-part Renuva™ System had a significant rise in the peak IGF-1 value compared to the baseline value ($p < 0.001$).

were less (202.6 ± 124.7 ng/mL) than the average post-baseline IGF-1 values during the test using both the “Infuser Spray” and “Generator Drink” (234.8 ± 32.2 ng/mL, $p = NS$) (Fig. 6).



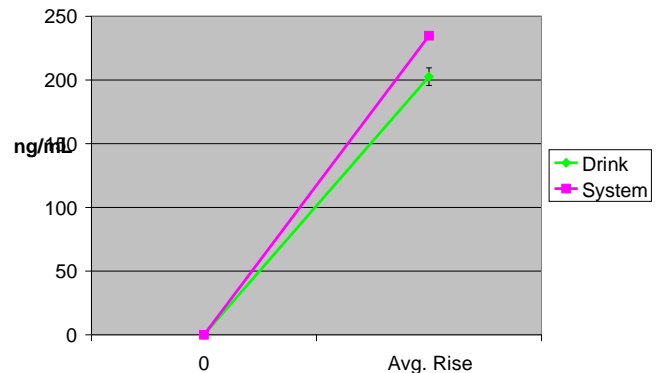
The average post-baseline IGF-1 values in the 2 subjects given the “Infuser Spray” alone was less (174.8 ± 20.8 ng/ml) than the average IGF-1 post-baseline values during the test using both the “Infuser Spray” and “Generator Drink” (213 ± 37.2 ng/mL, $p < 0.002$).

Fig. (5). The average post-baseline IGF-1 values in the two subjects who repeated the test following the “Infuser Spray” alone were significantly less than the average post-baseline IGF-1 values during the test using both the “Infuser Spray” and “Generator Drink” ($p < 0.002$).

DISCUSSION

The Infuser contains a dose of 1,500 nanograms of growth hormone releasing peptides 2 and 6 per daily dose (information from Anti-Aging Formulas) complexed in a proprietary delivery-system polymer (macro-molecular complex) that the University of Illinois has demonstrated to have the ability to transport large molecules across membranes

IGF-1 Response: Generator Drink vs. Renuva System



The average post-baseline IGF-1 values following the “Generator Drink alone was less (202.6 ± 124.7 ng/mL) that the average post-baseline IGF-1 values during the test using both the “Infuser Spray” and “Generator Drink” (234.8 ± 32.2 ng/mL, $p = NS$).

Fig. (6). The average post-baseline IGF-1 values for the 4 subjects who repeated the test following the “Generator Drink” alone were significantly less than the average post-baseline IGF-1 values during the test using both the “Infuser Spray” and “Generator Drink” ($p = NS$).

[4]. The macro-molecular complex delivers large proteins and polypeptides efficiently into the blood stream in a time-release manner to mimic intravenous infusion pharmacokinetics. The delivery of polypeptides across the mucosa when combined with the macro-molecular complex is 90% efficient (information from Anti-Aging Formulas). Thus, 1,350 nanograms of growth hormone releasing peptide should be released into the blood stream in a time-release manner from this 1,500-nanogram dose. The infusion of growth hormone releasing hormone at 2.5 ng/kg/min increases growth hormone significantly in man [5]. This dose is equivalent to 175 ng/min in a 70 kg man. Acute doses of growth hormone

releasing hormone and growth hormone releasing peptide 2, of 1 microgram/kg each, increase growth hormone significantly in man [6]. The acute doses of growth hormone releasing hormone and growth hormone releasing peptides required to increase growth hormone are, therefore, similar. Thus, one could reasonably presume that an infusion of growth hormone releasing peptide of 2.5 ng/kg/min would increase growth hormone, since this dose of growth hormone releasing hormone was sufficient to do so. The 1,350 nanograms of growth releasing peptide delivered by the Infuser would presumably be the equivalent of an 8-minute infusion of growth hormone releasing hormone or growth hormone releasing peptide at 175ng/min, or 2.5 ng/kg/min in a 70 kg man.

The proprietary delivery system developed by the University of Illinois is capable of not only transporting growth hormone releasing peptides into the blood in a manner mimicking intravenous infusion, but it is also capable of facilitating passage across the blood-brain barrier [4]. Since the University of Illinois has documented passage of intact human growth hormone, the smaller growth hormone releasing peptides should easily reach central sites where growth hormone is released [4].

Anti-Aging Formulas' Renuva™ Generator includes the following amino acids: Arginine, glutamine, glycine, lysine, ornithine, and glutamic acid. The scientific literature suggests that growth hormone can be stimulated by the oral intake of the following amino acids: Lysine 1200 mg with arginine 1200 mg [7], 2 grams of glutamine [8], or 5.6 grams of glycine [9]. Since arginine is converted to ornithine, the ornithine in the Generator can be considered like arginine. The mixture of amino acids in the Generator formula is 17% of the amino acids needed to stimulate growth hormone orally without considering the growth hormone releasing peptides in the Infuser.

The Renuva™ Generator also contains 38 mg of niacin per daily dose. A 56 mg dose of oral nicotinic acid, given over 2 hours during exercise, increased growth hormone 30 ng/ml in humans [10]. Furthermore, an oral mixture of amino acids and nicotinic acid with similarities to the Renuva™ Generator increased human growth hormone. Forty-two healthy subjects between 40 and 76 years of age were given 4.92 grams of a glycine and glutamine combination along with 20 mg of nicotinic acid twice a day for three weeks. At the end of the three-week period, human growth hormone increased 1.34 ng/ml ($p < 0.03$) [11]. Since the dose of nicotinic acid in the Renuva™ Generator (38 mg per day) is similar to the 40 mg per day used in the cited study and since the daily dose of amino acids in the cited study is larger than the daily dose of amino acids in the Renuva™ Generator, it is not surprising that the Renuva™ Generator increased IGF-1 (a more stable surrogate marker for growth hormone) and confirmed the findings of the cited study.

The pilot studies suggest that the "swallowed" Infuser spray alone increases peak IGF-1 levels in a manner similar to the entire Renuva™ System, but without the Generator, the peak IGF-1 is not sustained, and the IGF-1 secreted over the time course of the study is significantly decreased. The

Generator alone increases peak IGF-1 above baseline. Although statistical significance was not obtained, possibly due to the small numbers, the average IGF-1 levels over the time course of the study with the Generator drink alone was decreased compared to the entire two-part Renuva™ System. Thus, one can conclude that the Generator alone is capable of increasing levels of IGF-1, but the entire two-part Renuva™ System is more efficient in increasing IGF-1 levels. One could also conclude that the combination of amino acids and niacin in the lower dosages found in the Renuva™ Generator act together to increase both IGF-1 and GH. In previous studies, it was shown that these same amino acids, when taken individually, had to be given in higher dosages than found in the Renuva™ system, in order to increase IGF-1 and GH.

CONCLUSIONS

The administration of the two-part Renuva™ System significantly increased the percent increase of GH from baseline and increased IGF-1 levels in normal volunteers. The time of IGF-1 peak response was found to be slower than that reported when GH-releasing peptides were injected, but the overall response seemed to be similar. Both the components of the Renuva™ System appear to contribute to the IGF-1 response.

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