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Is Growth Hormone an Effective Adjunct to Standard Treatment Regimens for Promoting Fat Mass Loss and Retention of Lean Body Mass in the Treatment of Obesity?

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Abstract

Objective: The objective of this systematic review is to determine whether growth hormone is an effective adjunct in the treatment of obesity for promoting fat loss while retaining lean body mass.

Study Design: This is a systematic review of studies performed measuring the effects of growth hormone as adjunct treatment to standard regimens including bariatric surgery, severe calorie restriction, and lifestyle modifications.

Data Sources: The data sources included an open prospective RCT analyzing GH as adjunct to LASGB (Savastano,2009), a single blind placebo controlled study analyzing GH as adjunct to severe calorie restriction (Tagliaferri,1998), and randomized double blind placebo controlled trial analyzing GH as adjunct to lifestyle modifications (Albert,2004).

Outcomes Measured: These included percent fat mass (FM%), fat mass percent change, fat mass (kg), lean body mass percent (LBM%), lean body mass (kg), lean body mass percent change, and weight decrement (kg).

Results: The results of this review showed that in all cases, fat mass loss was greater in the groups treated with growth hormone, while lean body mass retention was also greater in the growth hormone treated groups. The degree to which the growth hormone treated groups showed statistically significant improvements over the placebo group varied depending on the standard treatment regimen, as well as the time period of observation.

Conclusion: Growth hormone is an effective adjunct to standard treatment regimens for promoting fat mass loss and retaining lean body mass in the management of obesity.

Keywords: obesity, growth hormone, bariatric surgery

Introduction

More common in western industrialized nations, obesity is one of the most common conditions encountered by medical professionals, effecting people of all ages, races, and genders. Clinically defined as a body mass index greater than 30 (BMI: kg/m^2), obesity effects nearly one in three people in the U.S, although rates amongst those in a lower socioeconomic class and lower education levels are even higher. In a 2008 study, the age-adjusted prevalence of obesity was 33.8% (95% CI, 31.6%-36.0%) overall, 32.2% (95% CI, 29.5%-35.0%) among men, and 35.5% (95% CI, 33.2%-37.7%) among women [1].

The importance of recognizing and treating obesity can be seen in its prevalence as a major risk factor or exacerbating factor for many of the most common medical conditions, including many types of cancer, depression, ischemic heart disease, diabetes mellitus type 2, asthma, hypertension, osteoarthritis, low back pain, and GERD. Another important measurement of the impact of obesity is seen in the financial impact that it has on overall medical costs. In 2008, obesity accounted for 9.1% of all medical spending in the U.S., up from 6.5% in 1998. Overall, an obese patient had $4,871 in medical bills per year, compared with $3,442 for a non obese patient[1]. Although these statistics are easily understood and observed by most medical professionals in practice, they are likely understated and the full impact of obesity on health and the healthcare system is underestimated and not fully understood.

Another difficulty in the management of obesity is the lack of knowledge about an optimal strategy to treat obesity. Some of the more common methods include lifestyle modifications such as diet and exercise, calorie restriction, surgery, and pharmaceuticals designed to aid in weight loss. Recent studies have shown that many obese subjects also suffer

from functional growth hormone deficiency. A substantial body of evidence supports the theory that neuroregulation of secretion of GH by the pituitary is closely related to the amount of adipose tissue in the body. This relationship between adipose tissue stores and GH is part of a regulation of feeding and fasting, with the purpose of maintaining proper body weight and body composition. Specifically, those with higher levels of adipose tissue tend to have lower levels of GH secretion, a condition that seems to be reversible upon normalization of body adipose tissue stores[3]. This paper evaluates three studies comparing standard treatment regimens alone versus growth hormone as an adjunct to those treatment regimens. The reason for the addition of growth hormone to a standard treatment regimen is based on the fact that maintenance of lean body mass (LBM) is of great importance in maintaining metabolism and function during the treatment of obesity. The goal of any treatment regimen should be to lose fat body mass (FBM) while maintaining LBM.

Objective

The goal of this review is to determine if growth hormone (GH) is a safe and effective adjunct treatment to standard regimens in the management of obesity. The hypothesis is that weight loss strategies are more successful at decreasing FBM and retaining LBM with growth hormone as an adjunct to the standard treatment regimen.

Methods

The studies located were RCT's that involved populations undergoing treatment for obesity, as well as a set of that population receiving GH as an adjunct to the standard treatment regimen. The standard treatment regimens included lifestyle modifications, Laparoscopic Adjustable Gastric Banding (LASGB), and calorie restriction. Comparison was done of the

outcomes of those receiving the standard treatment, versus those receiving GH in addition to the standard treatment. Outcomes measured included FBM loss, %FBM loss, LBM retained, %LBM retained, and weight loss. The types of studies used included randomized double blind study, single blind placebo controlled study, and an open label prospective randomized controlled study. PubMed and Cochrane databases were used to gather information. Criteria used for the selection of these studies included 1) literature published in English between 1996-present, 2) Studies chosen all dealt with POEMS, 3) Studies being used for statistical analysis were RCT's, 4) Studies being analyzed had not been previously used in a meta analysis or systematic review, 5) RCT studies used showed statistical significance for results ($p<0.05$). Any studies not adhering to these criteria were not used. Choosing the English language and studies on Humans only, and using the keywords: "growth hormone", "obesity", and "bariatric surgery", the search was narrowly focused as to avoid unnecessary or irrelevant studies that did not include POEMS that were not applicable. From these searches of the databases, 3 studies were procured that were used to derive scientific data with statistical analysis. These studies were: 1) Open prospective randomized controlled trial, comparing LASGB alone versus LASGB in addition to growth hormone (GH) in the treatment of obesity. 2) Single blind placebo controlled study, comparing calorie restriction regimen versus calorie restriction in addition to GH in the treatment of obesity. 3) Randomized double blind placebo controlled trial, comparing lifestyle modification alone versus GH in addition to lifestyle modification in the treatment of obesity.

Outcomes measured in the studies had to be POEMS, such as body weight lost, weight loss due to body fat loss, and lean body mass retained. To help measure these outcomes, in addition to conventional methods of measuring weight, dual energy x-ray absorptiometry scan (DEXA) was used to measure body composition.

Results

The major characteristics of the trials used in this study are displayed in Table 1. Although inclusion and exclusion criteria varied to some degree amongst the studies, patients from all three studies underwent similar assessments for obesity.

Table 2 shows the comparison of Growth Hormone (GH) as an adjunct to bariatric surgery, specifically Laparoscopic Adjustable Silicone Gastric Banding (LASGB), versus LASGB alone. The major outcomes analyzed in this study were fat mass percentage (FM%), fat mass percentage change, lean body mass percentage (LBM%), lean body mass percentage change, and weight decrement. These outcomes were measured at the initiation of the study, after three months, and again after six months, by conventional measures of body weight, as well as dual energy x-ray absorptiometry (DEXA) to analyze body composition and differentiate between fat tissue and lean body tissue. The results were as follows: Fat mass percentage (FM%) and Lean Body Mass percentage(LBM%) were measured for both the control group and growth hormone group and were roughly equal at baseline for both groups. At 3 and 6 months, the GH group showed a significant decline in FM% as well as a significant increase in LBM%. P values for the GH group showed statistical significance. The control group did not show similar results. In this group, FM% actually increased at the 3 month period, while LBM% decreased. At 6 months however, both FM% and LBM% returned to levels near baseline. The data for the control group did not have a p-value that demonstrated statistical significance. Fat mass percentage change was also reported in this study, and the GH group once again showed significant results, declining by 7.3 +/- 8.0% at 3 months and 20.7 +/- 9.3% at 6 months. The

control group saw a moderate increase in FM% change at 3 months of +8.6 +/- 9.2% and returned to levels near baseline at 6 months. Another important value reported in this study was weight decrement. For the GH group, weight declined by 10.7 +/- 4.2 kg at 3 months, and 15.2 +/- 5.7 kg at 6 months, while the control group saw a decline of 12.0 +/- 7.9 kg at 3 months and 21.3 +/- 8.0 kg at 6 months. P values for these data showed significance for both groups. At first glance it would appear that the control group showed a more significant effect on weight loss than the GH group, but after considering that lean body tissue weighs more than fat tissue, it is understood that subjects who retained more LBM maintained a higher weight.

Table 2. Comparison of Body Composition and Weight Changes in GH as Adjunct to LASGB vs LASGB alone

	Group A (GH treated) n=12				Group B (Not GH treated) n=11			
	Baseline	3 months	6 months	P value	Baseline	3 months	6 months	P value
FM%	47.2 +/- 4.9	43.7 +/- 4.6	37.6 +/- 4.2	0.005	47.5 +/- 4.5	51.2 +/- 3.7	47.6 +/- 5.2	0.103
FM% change		-7.3 +/- 8.0	-20.7 +/- 9.3	0.001[1]		8.6 +/- 9.2	0.8 +/- 13.7	0.014
LBM%	52.7 +/- 4.9	56.3 +/- 4.6	63.1 +/- 7.2	0.005	52.5 +/- 4.7	48.7 +/- 3.7	54.7 +/- 7.2	0.061
LBM change (kg)		-2.8 +/- 3.8	2.6 +/- 4.1	0.004		-12.0 +/- 5.9	0.4 +/- 6.5	<0.0001
LBM % change		7.2 +/- 8.0	18.2 +/- 7.9	0.002[2]		-6.8 +/- 8.6	4.1 +/- 8.3	0.024
Weight Decrement (kg)		-10.7 +/- 4.2	-15.2 +/- 5.7	0.005		-12.0 +/- 7.9	-21.3 +/- 8.0	0.006

FM= Fat Mass, LBM= Lean Body Mass

[1] Authors report the amount of fat mass lost in Group A at 3 and 6 months was more statistically significant compared to Group B

[2] Authors report that % LBM retained in Group A at 3 and 6 months was more statistically significant compared to Group B

Table 3 shows the comparison of GH as an adjunct to severe calorie restriction in obese women versus calorie restriction alone. The outcomes measured in this study were body weight, BMI (kg/m^2), fat mass, lean body mass, and percent lean body mass loss. These outcomes were measured at the beginning of the study, and after four weeks. Conventional measures were used to calculate weight, and DEXA scan was used to analyze body composition and determine fat mass and lean body mass. The results of this study showed Body Weight and BMI were roughly equal for both the GH group and placebo group at baseline and 4 weeks, as both showed a moderate decline over the 4 week period. Fat mass also showed similar declines in both groups, from 49.07 +/- 2.10 to 43.71 +/- 2.42 in the GH group, and 47.02 +/- 1.44 to 42.73 +/- 1.66 in the placebo group. The most notable difference between the two groups was seen in the maintenance of Lean Mass. The placebo group showed a decline from 43.83 +/- 1.15 to 40.04 +/- 1.14 kg, a decrease of 8.6 +/- 1.01%. The GH group showed a decline from 42.14 +/- 1.42 to 40.61 +/- 1.29 kg, a decrease of only 3.5 +/- 1.39%.

Table 3. Comparison of GH in Addition to Severe Energy Restriction vs Energy Restriction Alone

	Placebo Group			GH treated Group		
	Baseline	After 4 Weeks	P value	Baseline	After 4 weeks	P value
Body Weight (kg)	93.6 +/- 0.80	86.5 +/- 0.67	<0.05	93.0 +/- 2.64	87.0 +/- 2.35	<0.05
BMI (kg/m^2)	36.3 +/- 0.49	33.6 +/- 0.61	<0.05	35.3 +/- 0.98	33.0 +/- 0.93	<0.05
Fat mass (kg)	47.02 +/- 1.44	42.73 +/- 1.66	<0.05	49.07 +/- 2.10	43.71 +/- 2.42	<0.05
Lean mass (kg)	43.83 +/- 1.15	40.04 +/- 1.14	<0.05	42.14 +/- 1.42	40.61 +/- 1.29	<0.05
% Lean mass loss	-	8.6 +/- 1.01	>0.05		3.5 +/- 1.39	<0.05[1]

[1] P value <0.05 between groups

Table 4 illustrates the comparison of GH as adjunct therapy to lifestyle modifications versus lifestyle modifications alone. The outcomes measured in this study were body fat mass,

lean body mass, and change in body fat mass. These outcomes were measured at the initiation of the study, at six months, and at nine months, using DEXA scan as a means to differentiate between fat mass and lean body mass. Body fat mass showed a small decrease in both the control group and the GH group from baseline to the 6 and 9 month periods. Lean body mass remained relatively the same for both groups from baseline to the 6 and 9 month periods. The most notable and statistically significant difference between the two groups occurred in change in body fat mass, where the control group showed a smaller decline of 0.68 +/- 2.37 kg from baseline to 9 months, while the GH group showed a decline of 2.89 +/- 3.76 kg from baseline to 9 months. The p value between the two groups for this decline was 0.001.

Table 4. Comparison of Low Dose GH in Addition to Lifestyle Modifications vs Lifestyle Modifications alone

	Control Group				GH treated Group			
	Baseline	6 months	9 months	P value	Baseline	6 months	9 months	P value
Body Fat mass (kg)	42.0 +/- 9.6	40.5 +/- 10.0	40.7 +/- 10.1	Not reported	37.9 +/- 8.8	34.5 +/- 9	35.2 +/- 9.5	0.0001[1]
Lean Body Mass (kg)	60.5 +/- 10.0	61.1 +/- 11.0	61.4 +/- 10.5	Not reported	62.4 +/- 12.1	63.5 +/- 12.7	61.4 +/- 10.5	>0.05
Change in Body Fat mass (kg)	-	-	-0.68 +/- 2.37	-	-	-	-2.89 +/- 3.76	0.001[2]

[1] P value for 9 month was 0.004, while P value for baseline and 6 months was 0.0001

[2] P value between groups was 0.001

Discussion

The focus of this paper was to determine whether the addition of Growth Hormone to standard treatment regimens was an effective adjunct in the treatment of obesity. It was theorized

that GH had an effect on fat mass loss and lean body mass retention. In all three of the studies cited, fat mass loss was increased, while lean body mass was retained at a higher rate. The degrees of these effects varied, as well as the statistical significance of the data, depending on the methods, type of intervention, size of the study, and length of time that the results were observed. There were significant limitations in all of the studies, the greatest being time period. It is well understood that weight loss is a long term goal which takes months and often years to accomplish significant results. In the Savastano study, the outcomes were measured up to 6 months from the beginning of the study. In the Albert study, data were collected up to 9 months from the initiation of the study. The Tagliaferri study had the shortest duration of observation of only 4 weeks. Another limitation of this research is the size of the studies cited, the largest of the three containing only 59 participants. In that study, nearly one third of the initial participants dropped out before completion of the study. This is not uncommon in weight loss studies, due to the difficulty of maintaining the conditions set forth at the beginning of the study. In addition, the inclusion and exclusion criteria for studies, while important to minimize compounding variables, likely caused the studies to focus on a segment of the obese population that is uncommon to encounter in practice. Therefore, the true safety and efficacy of GH on patients with co-morbid conditions in addition to obesity cannot be fully understood based on these studies alone.

Although they were not the focus of this research, the studies discussed in this paper did report some data that were important to note. In both the Savastano and Albert studies, subjects treated with GH reported improved lipid profiles versus the placebo groups without negative effects on insulin sensitivity or glucose tolerance. In addition, the Tagliaferri study showed a decline in Resting Energy Expenditure (REE) in the placebo group (from 8807 +/- 498 to 7580 +/- 321 kJ/24hr, $P<0.05$) and adjusted for LBM(201.7 +/- 13.85 to 190 +/- 9.87 kJ/kg LBM/24h,

NS), while the rhGH treated group actually showed an increased REE (from 8367 +/- 580 to 8903 +/- 478 kJ/24 hr, NS) and adjusted for LBM(197.9 +/- 11.76 to 219.3 +/- 9.87 kJ/kg LBM/24h, $P<0.05$). This data supports the proposed theory that GH supports retention of LBM in addition to increasing energy metabolism by LBM, leading to increased metabolic energy consumption by the body. Although fat mass loss was not markedly increased in the rhGH group versus the placebo group (5.36 kg vs. 4.29 kg), the short duration of the study likely limited the observation of a more substantial difference in fat mass loss.

Conclusion

Growth Hormone is an effective adjunct to standard regimens in the treatment of obesity. The addition of GH promoted fat mass loss while also contributing to lean body mass retention compared to the standard treatment regimens addressed in this research.

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