The investigators evaluated the findings by analyzing and comparing the data from two groups of patients according to weight loss: those who lost at least 20% of excess body weight with those who had lost less than 20% of excess body weight.

Dr. Lerner said that predictors of weight loss were drawn from data that were collected at the patients' initial visits. Several factors were significant predictors of weight loss of at least 20% of excess body weight, including older age, taller height, lower body mass index (BMI) and BMI z-score, waist circumference/height, 30-minute glucose and 120-minute insulin levels on an oral glucose tolerance test, 1,25 dihydroxy vitamin D level, and no history of polycystic ovary syndrome; these factors were predictive at a significance of $0.01<p< 0.05$.

Thus, the ideal adolescent patient for gastric banding is characterized by achievement of 95% of final height, based on bone age assessment; a BMI >30 to 40 kg/m^2 with significant obesity-related comorbidity or BMI >40 kg/m^2 in the presence of milder obesity-related comorbidity; demonstration of ability to adhere to a lifestyle modification program prior to surgery and to both comprehend and be able to cope with nutritional and behavioral ramifications of bariatric procedures; no presence of eating disorders or other psychiatric illnesses, such as depression or exposure to abuse; and a supportive family environment [Keidar A et al. *Curr Opin Clin Nutr Metab Care* 2011].

Among the adolescents who lost at least 20% of excess body weight, decreased glucose and insulin levels on oral glucose tolerance test, lower systolic and diastolic blood pressures, alkaline phosphatase, uric acid, and sex hormone-binding globulin, and higher levels of high-density lipoprotein ($p<0.05$) were observed. These data indicate the potential for improved metabolic parameters for morbidly obese adolescents who lose at least 20% of excess body weight.

GH Replacement Improves CV Risk Factors in Viscerally Obese Premenopausal Women

Written by Rita Buckely

Effects of Growth Hormone (GH) on Body Composition and Cardiovascular (CV) Risk Markers in Women with Visceral Adiposity was a 6-month randomized, double-blind, placebo-controlled trial to determine whether low-dose GH administration would reduce abdominal adiposity and CV risk markers in premenopausal women with reduced GH secretion due to abdominal obesity. Miriam Bredella, MD, Massachusetts General Hospital, Boston, Massachusetts, USA, presented findings from the study.

Abdominal adiposity confers a 3-fold increased risk for heart disease in women compared with accumulation of body fat in the gluteal femoral region [Rexrode KM et al. *JAMA* 1998]. Data also suggest that visceral adiposity may be associated with reduced endogenous growth hormone and that decreased growth hormone secretion may be associated with increased CV risk markers [Utz A et al. *J Clin Endocrinol Metab* 2008].

The study included 79 obese premenopausal women. The primary outcome measure was abdominal fat depots, including: visceral adipose tissue and the muscle area of the mid-thigh, as determined by computed tomography scan; fat and lean body mass, determined by dual-emission X-ray absorptiometry; intramyocellular (IMCL) and intrahepatic lipids (IHL), determined by proton magnetic resonance spectroscopy; high-sensitivity C-reactive protein (hs-CRP); total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C); apolipoprotein B (apo B); fibrinogen; tissue plasminogen activator (tPA); carotid intima-media thickness (CIMT); and endothelial function.

At 6 months, the mean GH dose was 1.7±0.6 mg/day. This resulted in a mean increase in the IGF-1 standard deviation score (SDS*) from -1.7±0.5 to -0.1±1.4 in the GH group. Compared with placebo, administration of GH led to an increase in muscle area (2.0±5.4 vs -3.0±6.8 cm^2; p=0.03) and total lean mass (2.0±1.7 vs 0.1±2.1 kg; p=0.001), and a decrease in the trunk:extremity fat ratio (0.01±0.05 vs -0.03±0.06; p=0.006)

Change in IGF-1 level was associated with a 6-month decrease in visceral adipose tissue (VAT) (r=-0.56; p=0.002). This suggested that subjects with the greatest increases in IGF-1 levels had the greatest decreases in VAT. VAT decreased within the GH group, but the change was not significant when compared with placebo.

Compared with placebo, GH decreased hsCRP (-1.1±1.2 vs 0.07±1.2 mg/L; p=0.01), apo B (-9.1±17.9 vs 6.1± 17.5 mg/dL; p=0.005), apo B/LDL-C (a measure of LDL-C size and atherogenecity) (-0.009±0.1 vs 0.1±0.2; p=0.01), and tPA (-0.4±5.0 vs 4.5±10.3 ng/ml; p=0.03). Total cholesterol, LDL-C, HDL-C, fibrinogen, IMCL, and IHL did not change compared with placebo, but IMCL increased compared with baseline in the GH group. No effect on CIMT or endothelial function was observed.

GH increased fasting glucose (2.4±7.2 vs -0.9±3.6 mg/dL) and 2-hour glucose (18.6±32.8 vs -0.7±26.7 mg/dL)

compared with placebo (p<0.05), with no difference in 2-hour glucose levels between groups at 6 months. Baseline fasting glucose predicted a 6-month change in 120 minute glucose levels within the growth GH (r=0.48; p=0.01). Five subjects had a 120-minute glucose level greater than 200 mg/dL, one of whom was on placebo. No subjects had fasting glucose levels ≥126 mg/dL. Additional side effects were limited.

Based on these findings, the authors concluded that GH replacement in viscerally obese premenopausal women has beneficial effects on markers of CV risk and body composition but is associated with a decrease in glucose tolerance in a minority of women.

*Note: Another term for SDS is z-score. The IGF-1 standard deviations score, or z-score, is a measure of how normal/abnormal the IGF levels are compared with a normal-for-age level; eg, an IGF-1 SDS of 0 is normal for age, but a SDS of -2 means that the IGF-1 level is 2 SD below the mean.

Pasireotide May Provide Option for Medical Therapy Targeting the Underlying Cause of Cushing Disease

Written by Lori Alexander

A Phase 3 trial showed that pasireotide, a multireceptor-targeted somatostatin analog, led to rapid and sustained decreases in cortisol levels and provided clinical benefit in patients with Cushing disease. Surgery is the first-line treatment for this disease, and most current medical options block adrenal cortisol production but do not treat the underlying disease. Pasireotide may provide the first reliable pituitary-directed medical therapy that targets the underlying cause of Cushing disease.

Beverly M.K. Biller, MD, Neuroendocrine Clinical Center, Massachusetts General Hospital, Boston, Massachusetts, USA, explained that pasireotide has high affinity for sst_5, the most prevalent somatostatin receptor on adrenocorticotropic hormone-secreting pituitary adenomas. The drug was found to inhibit production of adrenocorticotropic hormone in corticotroph adenomas *in vitro* and was promising in a 15-day Phase 2 study.

The multicenter Phase 3 trial included 162 patients with persistent/recurrent Cushing disease (n=135) or patients with *de novo* disease who were poor surgical candidates, refused surgery, or had surgically unapproachable tumors (n=27). The patients were randomly assigned in a double-blind manner to receive pasireotide at a dose of 600 µg (n=82) or 900 µg (n=80) subcutaneously twice a day. At 3 months, a urinary free cortisol (UFC) level was determined. If the level was ≤2 times the upper limit of normal (ULN; defined as 145 nmol/24 hr) and was less than the baseline level, the randomly assigned dose was continued (double-blinded) until Month 6. The study was unblinded for all other patients, and the dose was increased by 300 µg twice daily, with treatment continuing until Month 6. These latter patients were considered to be nonresponders for the primary efficacy analysis. Months 6 to 12 were open-label, with the dose titrated as needed. The primary endpoint was a UFC level less than the ULN at 6 months without the need for an increase from the randomized dose.

At 6 months, the primary endpoint was met in 14.6% of the patients in the 600-µg group and in 26.3% in the 900-µg group; the results at 12 months were similar (13.4% and 25.0%, respectively), confirming the durability of the effect. The predetermined criterion for the primary endpoint (a lower bound of the 95% CI>15%) was met for the 900-µg group (Table 1). The median decrease in UFC from baseline to Month 6 was approximately 48% for both groups. Higher rates of UFC normalization were associated with lower baseline levels of UFC. Patients who had an inadequate biochemical response could be identified on the basis of UFC levels within 1 to 2 months with 90% accuracy.

Table 1. Results of Primary Endpoint at Six Months.*

Twice-daily dose	No. (%) of Responses	95% CI
600 µg (n=82)	12 (14.6)	7.0 to 22.3
900 µg (n=80)	21 (26.3)	16.6 to 35.9
Overall (n=162)	33 (20.4)	14.2 to 26.6

*The predetermined criterion for the primary endpoint was a lower bound of the 95% CI>15%.

Pasireotide was associated with significant improvement in signs and symptoms of hypercortisolism, regardless of whether a normal UFC level was achieved. At Month 12, there were substantial decreases in blood pressure, low-density lipoprotein-cholesterol level, and body weight, as well as an increase in the health-related quality of life. Dr. Biller noted that the safety profile of the drug was generally similar to that of other somatostatin analogs, with the important exception of an increased frequency of hyperglycemia. At least 1 hyperglycemia-related adverse event occurred in 73% of patients overall. There were no cases of diabetic ketoacidosis or hyperosmolar coma, and the fasting glucose levels returned to baseline once pasireotide was discontinued. Gastrointestinal events occurred frequently, with 58% of patients overall reporting diarrhea and 52% reporting vomiting. As expected with an effective treatment for Cushing disease, hypocortisolism occurred in some patients (8%); this complication responded to dose reduction and/or temporary corticosteroid substitution.