Growth Hormone Reduces Hepatic Steatosis, Inflammation and Fibrosis in Adults with Overweight/Obesity and Nonalcoholic Fatty Liver Disease

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Background: Overweight/obesity are associated with relative growth hormone (GH) deficiency, and GH deficiency has been implicated in the development of nonalcoholic fatty liver disease (NAFLD). NAFLD and its progressive form, nonalcoholic steatohepatitis (NASH), are associated with significant morbidity and mortality, and no approved therapies currently exist. We hypothesized that GH administration would reduce hepatic steatosis, inflammation and fibrosis in individuals with overweight/obesity and NAFLD.

Methods: A randomized, double-blind, placebo-controlled trial of GH administration in adults with overweight/obesity and NAFLD was conducted (NCT02217345). Fifty-three adults ages 18-70 years with BMI ≥25 kg/m^2 and NAFLD were randomly assigned to receive daily subcutaneous GH or placebo for 6 months. Target IGF-1 was upper quartile of normal. Primary endpoints included intrahepatic lipid content (IHL) by proton magnetic resonance spectroscopy (1H-MRS) and radiographic inflammation and fibrosis by LiverMultiScan corrected T1 score (cT1). Secondary endpoints included alanine transaminase (ALT), visceral adipose tissue (VAT) by dual-energy x-ray absorptiometry (DEXA), hsCRP and HOMA-IR. Data are reported as mean ± SD.

Results: Forty-one subjects completed the 6-month study. Mean age (45±12 years), BMI (33±5 kg/m^2), sex distribution (50% female) and baseline IHL (21.4±14.5%) did not differ between the GH and placebo groups. Over the 6-month study period, there was no difference in change in weight between the groups (GH -0.7±3.8% and placebo -0.6±4.0%, p=0.7). Change in absolute percent IHL was significantly greater in the GH vs placebo group (-5.1±10.5% vs 3.8±6.9%, p=0.003), resulting in a net treatment effect of an 8.9% reduction in IHL (95% CI 3.3-14.6%). Improvements in serum ALT (-10±13 IU/L vs -2±12 IU/L, p=0.009) and cT1 score (-11±63 ms vs 27±57 ms, p=0.037) were greater in the GH vs placebo group. There were also significant reductions in DEXA VAT area (-10±9 cm^2 vs 0±20 cm^2, p=0.050) and hsCRP (-0.8±0.9 mg/dL vs -0.3±1.7 mg/dL, p=0.017) in the GH vs placebo group. In multivariable models controlling for age, sex, change in weight and change in HOMA-IR, significant effects of GH vs placebo were observed on IHL (p=0.012) and ALT (p=0.015) with a trend towards improvement in cT1 score (p=0.088). In a secondary analysis excluding all subjects with >3% weight loss, which has been shown to independently impact NAFLD outcomes, there were significant improvements in IHL (p=0.001), ALT (p=0.040) and cT1 score (p=0.050) in the GH vs placebo group. No subjects were discontinued due to hyperglycemia (fasting glucose ≥126 mg/dL or HbA1c ≥6.5%). Mild edema was the only treatment-emergent side effect that had a significantly greater incidence in the GH vs placebo group (19% vs 0%, p=0.048).

Conclusion: GH administration reduces hepatic steatosis and markers of hepatic inflammation and fibrosis in adults with overweight/obesity and NAFLD. The GH/IGF-1 axis may offer targetable

therapeutic options for NAFLD/NASH.

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