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Effect of growth hormone on cognitive function in young women with abdominal obesity

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Dear Editors,

The hormonal milieu of obesity, including relative growth hormone (GH) deficiency and resultant relative insulin-like growth factor-1 (IGF-1) deficiency, may mediate the emerging association between midlife adiposity and longitudinal cognitive decline. Given published data demonstrating an association between relative deficits in GH and IGF-1 and cognitive decline in older individuals, targeting the somatotrophic GH/IGF-1 axis has been identified as one possible approach to mitigate cognitive decline. Some studies of GH treatment in hypopituitary adults with adult-onset GH deficiency have reported improvements in cognitive function in several domains relative to placebo, but in older adults without pituitary disorders, results from studies targeting the somatotrophic GH/IGF-1 axis have

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Disclosures:

None of the manuscript authors have any conflicts of interest relative to this manuscript to declare.

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Author contributions

RB, JS, MAB and KKM contributed to the design of the study, interpretation of data, and manuscript preparation. CCW contributed to the statistical analysis. AVG contributed to the acquisition of data. SMM contributed to the interpretation of cognitive data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

been mixed (1). Interestingly, one recent randomized double-blind placebo-controlled study of GH releasing hormone (GHRH) in healthy older adults (both cognitively intact and with mild cognitive impairment) reported beneficial effects of GHRH treatment on executive function (2).

However, the effects of these hormones on cognitive function have not been studied in young, otherwise healthy, individuals with abdominal obesity, which is characterized by relative GH deficiency. In the current pilot study, we sought to assess whether GH treatment exerts beneficial effects on cognition, in a cohort of young women with abdominal obesity, who are otherwise healthy and without pituitary disease.

Methods

We examined the effect of low-dose GH supplementation on cognitive function in a subset of 22 otherwise healthy women with abdominal obesity in a double-blind, randomized, placebo-controlled clinical trial of GH treatment for 6 months; the primary trial analyses revealed beneficial effects on body composition and cardiovascular risk markers. (3) Inclusion criteria included age 20–45 years, body mass index (BMI) ≥ 25 kg/m², waist circumference ≥ 88 cm, IGF-1 below the normal, age-appropriate median and eumenorrhea. Exclusion criteria included smoking, diabetes mellitus or other chronic illnesses, and estrogen or glucocorticoid use (3), English as a second language and color-blindness. Subjects were randomized to receive daily subcutaneous recombinant human GH (Genentech, Inc., South San Francisco, CA, USA) or placebo, for 6 months. Starting GH dose was 4 μ g/kg per day, with adjustments at all visits, for an IGF-1 level target in the upper normal age-appropriate range. The placebo group received sham dose adjustments (3). The Partners Healthcare Institutional Review Board approved this study, and written, informed consent was obtained prior to initiating any procedures.

Endocrine testing

IGF-I was measured using the Immulite 2000 Immunoassay System (Siemens Medical Systems, Erlangen, Germany), a solid-phase enzyme-labeled chemiluminescent immunometric assay with a coefficient of variation (CV) $< 5\%$.

Cognitive testing

Subjects underwent cognitive testing at baseline and at 6 months. All scoring was performed at the Massachusetts General Hospital Psychology Assessment Center by trained psychometricians under the supervision of a senior neuropsychologist (JS). When available, alternate test forms were administered at baseline and at 6 months to minimize practice effects. Raw scores for each cognitive test were scaled to each test's norming population (where mean = 100 and standard deviation = 15). Group mean standard scores for each of these tests were between 100 and 115, suggesting higher than average cognitive function.

Cognitive tests were then grouped by a senior neuropsychologist (JS) into cognitive domains to most closely approximate the domains (executive function, verbal memory) assessed in the GHRH trial in older individuals (2). Cognitive domain scores for each subject were calculated by summing individual test standard scores, and dividing by the number of tests:

Executive function: D-KEFS Color-Word Interference, Condition 3: Inhibition (response time); D-KEFS Verbal Fluency, Condition 3: Category Switching; Trail-Making Test, Part B (response time).

Verbal memory: California Verbal Learning Test, Second Edition (CVLT-II): Trials 1–5 learning, long delay free recall.

Statistical Methods

We compared absolute changes in cognitive function between subjects receiving GH or placebo using t-tests, as well as a linear regression adjusting for age and level of education, as is standard in cognitive function studies. Our primary endpoint was absolute change in executive function, given the positive effects of GHRH reported in an older cohort (8). To determine whether there was a dose response with final GH dose, or with IGF-1 level, which increases in response to GH treatment, we examined the relationship between change in each cognitive domain score and both final GH dose, as well as absolute change in IGF-1 Z-scores, using Pearson correlation.

Results

Subjects who received GH for 6 months (N=13) were similar to the placebo group (N=9) in age (35 ± 5.3 vs. 38 ± 6.4 years), education (15.9 ± 2.3 vs. 16.0 ± 3.4 years), ethnicity (69% vs. 89% White), BMI (35.0 ± 7.3 vs. 36.3 ± 6.5 kg/m²), waist circumference (110 ± 12 vs. 112 ± 15 cm), and baseline IGF-1 Z-scores (-1.9 ± 0.5 vs. -2.0 ± 0.5) ($p>0.05$ for each). At baseline, the two groups also had similar scores on the Wechsler Test of Adult Reading, a proxy for IQ (106 ± 12.4 vs. 114 ± 6.2 ; $p>0.05$). For the GH-treated group, final mean GH dose was 1.9 ± 0.6 mg daily, resulting in a mean IGF-1 increase of 105 ± 123 ng/ml, a final mean IGF-1 level of 238 ± 77 ng/ml, and final IGF-1 Z-score of -0.6 ± 1.1 . For the placebo group, final IGF-1 Z-score was -2.1 ± 0.4 .

In our primary analysis, GH treatment vs. placebo for 6 months resulted in an improvement in executive function standard score (GH group: 99.2 ± 13.2 to 108.4 ± 8.9 ; placebo group: 109.4 ± 11.1 to 111.9 ± 9.5 ; mean difference between the groups of 6.8). This was suggestive with the t-test ($p=0.088$) and significant in the regression after we adjusted for age and education (estimate=8.00, $p=0.040$) (Figure 1).

There was no relationship between the change in IGF-1 and absolute change in executive function standard scores (Pearson correlation, $r=0.28$, $p=0.21$) over the 6-month treatment period. There was also no correlation between the absolute change in executive function scores and final GH dose (Pearson correlation, $r=0.15$, $p=0.56$). GH treatment did not result in changes in verbal learning and memory compared with placebo (GH group: 99.7 ± 10.9 to 102.3 ± 10.9 ; placebo group: 105.2 ± 11.8 to 104.0 ± 10.1 , $p>0.05$).

Discussion

Here, we suggest that GH treatment for 6 months may exert beneficial effects on executive function in young otherwise healthy women with abdominal obesity. Executive function reflects an individual's ability to regulate cognitive processes including the ability to direct,

organize, plan and execute behaviors to achieve a goal; it is critical in decision making. We have previously reported an inverse relationship between executive function and insulin resistance in young women with obesity. (4) Our data from this exploratory study, along with reports of positive effects of GHRH on executive function in older adults, suggest that further studies targeting the somatotrophic GH/IGF1 axis may be warranted to establish a protective effect on cognition.

Limitations of this pilot study include the small sample size and exploratory nature of the nested cognitive sub-study. The current results would directly inform a larger trial designed to further our understanding of the clinical significance of our findings.

In summary, our exploratory analysis provides a preliminary signal that GH treatment in young individuals with abdominal obesity may improve executive function. Larger confirmatory studies powered to detect cognitive changes in overweight individuals are warranted.

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Figure 1.

Executive function improved in women with abdominal obesity treated with GH vs. placebo for 6 months (executive function domain units = average of the standard score across 3 cognitive tests, where mean for each test = 100 and standard deviation = 15).