Low and Normal IGF-1 Levels in Patients with Chronic Medical Disorders (CMD) is Independent of Anterior Pituitary Hormone Deficiencies: Implications for Treating IGF-1 Abnormal Deficiencies with CMD

Braverman E1, Oscar-Berman M2, Lohmann R2, Kennedy R2, Kerner M2, Dushaj K2 and Blum K1,2,4-8*

1Department of Psychiatry and McKnight Brain Institute, University of Florida College of Medicine, Gainesville, Florida, 32610, USA
2Department of Clinical Neurology, Path Foundation NY, 10010, USA
3Department of Psychiatry, Neurology, and Anatomy and Neurology, Boston University School of Medicine and Veterans Affairs Medical Center, Boston, Massachusetts, 02130 USA
4Global Integrated Services Unit University of Vermont Center for Clinical and Translational Science, College of Medicine, Burlington, Vermont, 05405, USA
5Dominion Diagnostics, LLC, North Kingstown, Rhode Island, 02852, USA
6Center for Genomics and Applied Gene Technology, Institute of Integrative Omics and Applied Biotechnology (IIOAB), Nonakuri, Purbe Medinpur, West Bengal, 721172, India
7Department of Clinical Medicine, G & G Healthcare Services, LLC, North Miami Beach, Florida, 33162, USA
8Department of Addiction Research & Therapy, Malibu Beach Recovery Center, Malibu, California, 90265, USA

Abstract

Over time, based on evidence–based medicine, a number of hormonal test levels including IGF-1 had been raised or lowered to meet new criteria standards. In particular, IGF-1 plasma levels have been shown in several studies to be an independent diagnostic tool in Adult Growth Hormone Deficiency (AGHD). Many endocrinology studies link low IGF-1 plasma levels with low levels of other anterior pituitary hormones (i.e., LH, FSH, and TSH). Low IGF-1 is considered by most to be between 84-100 µ/l and numerous studies recommend that raising IGF-1 to high normal range reverses Chronic Medical Diseases (CMD), improves bone mineral density (BMD), and fibromyalgia. Moreover, some studies suggest that low levels of IGF-1 by itself independent of anterior pituitary deficiencies is sufficient to determine AGHD in humans. In order to determine the relationship of low IGF-1 with that of LH, FSH, and TSH levels in subjects with CMD, we evaluated these levels ± SD in 944 patients. Patients with IGF-1 below 84 µ/l, 100 µ/l, and 150 µ/l were accessed. 9.22% had less than 84 µ/l (SD ± 12.52); 19.9% had less than 100 µ/l (SD ± 9.54); and 51.6 had less than 150 µ/l (SD ± 26.0). Specifically, the percentages found for low LH, FSH, and TSH were only 4.2%, 4.8%, and 6.5%. We conclude that IGF-1 deficiencies occur independent of comorbid deficiencies of LH, FSH, and TSH. Finally, we propose that based on the present investigation, IGF-1 low levels between the range of 84-100 µ/l may be too low to be considered as an independent diagnostic marker to treat AGHD with CMD.

Keywords: Adult Growth Hormone Deficiency (AGHD); IGF-1 plasma levels; Chronic Medical Diseases (CMD); Anterior pituitary hormones; Luteinizing Hormone (LH); Thyroid-Stimulating Hormone (TSH); Follicle-Stimulating Hormone (FSH)

Introduction

Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) most definitely play essential roles in growth in childhood, and continue to have important metabolic actions in adults [1]. It is well known that Adult Growth Hormone Deficiency (AGHD) is characterized by increased visceral adiposity, abnormal lipid profiles, premature atherosclerosis, decreased quality of life, and increased mortality [2]. GH is generally considered to exert anti-insulin actions, whereas IGF-1 has insulin-like properties [3]. Interestingly, GH deficient adults and those with acromegaly are both predisposed to insulin resistance [4]. High doses of GH treatment have major effects on lipolysis, which plays a crucial role in promoting its anti-insulin effects, whereas IGF-1 acts as an insulin sensitizer that does not exert any direct effect on lipolysis or lipogenesis [5]. Moreover, Growth Hormone Deficiency (GHD) is the most common pituitary hormone disorder, occurring in approximately 20% of patients when multiple tests of GH are used [6].

One of the most devastating reasons for death among teenagers and young adults is acute brain injury due to trauma. There are 1.5-2.0 million Traumatic Brain Injuries (TBI) in the United States annually, with an associated cost exceeding 10 billion dollars. TBI is the most common cause of death and disability in young adults less than 35 years of age. The consequences of TBI can be severe, including disability in motor function, speech, cognition, and psychosocial and emotional skills. Many studies have consistently demonstrated a 30-40% occurrence of pituitary dysfunction involving at least one anterior pituitary hormone following a moderate to severe TBI [7]. In terms of CMD, there are a number of studies that have shown the relationship between GH; specifically, bone density [8]. According to Amelio et al. [9], bone produces different hormones, like osteocalcin (OC), which influences energy expenditure in humans. The under-carboxylated form of OC has a reduced affinity for hydroxyapatite; hence, it enters the systemic circulation more easily and exerts its metabolic functions for the proliferation of pancreatic β-cells, insulin secretion, sensitivity, and glucose tolerance. Leptin, a hormone synthesized by adipocytes, also has an effect on both bone remodeling and energy expenditure; in fact, it inhibits appetite through hypothalamic influence and in bone,

*Corresponding author: Kenneth Blum, Department of Psychiatry, University of Florida College of Medicine, and McKnight Brain Institute, Gainesville, USA, E-mail: dnd2gene@aol.com

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it stimulates osteoblastic differentiation and inhibits apoptosis. Finally, amylin (AMY) acts as a hormone that alters physiological responses related to feeding and plays a role as a growth factor in bone. Interestingly, Elbornsson et al. [10] recently showed the benefit of GH replacement therapy over a 15 year period increasing BMD in adults with adult onset of GHD.

Fibromyalgia (FM) is another CMD characterized by widespread pain and fatigue and is considered a syndrome with different pathogenic mechanisms. Controversial data on GH axis disturbances have been published. Some preliminary trials have shown promising effects of GH therapy on tender points and quality of life in FM [11]. In fact, Cuatrecasas et al. [12] showed patients with FM had an IGF-1 of 150 µg/l or less. The mean peak of GH during an insulin tolerance test (ITT) was 13.3 ± 9.9 ng/ml in 127 patients in which the test was performed. In 22 of the 127 (17.3%), ITT peak GH was 5 ng/ml or less, and in 8 (6.3%), the peak GH was 3 ng/ml or less. Mean baseline GH (n=127) was 1.47 ± 2.58 ng/dl, and 8 of 120 (6.8%) showed an insufficient IGF-1 response (<50% over baseline) to the IGF-1 generation test.

The GH-IGF-1 axis plays a role in normal brain growth, but little is known of the effect of growth hormone deficiency on brain structure. However, Webb et al. [13] reported on 15 children (mean of 8.8 years of age) with isolated growth hormone deficiency [peak growth hormone <6.7 µg/l (mean 3.5 µg/l)] and 14 controls (mean of 8.4 years of age) with idioptic short stature [peak growth hormone >10 µg/l (mean 15 µg/l) and normal growth rate]. Compared with controls, they found children with isolated GH had lower Full-Scale IQ (P < 0.01), Verbal Comprehension Index (P < 0.01), Processing Speed Index (P < 0.05), and Movement-Assessment Battery for Children (P < 0.008) scores. Verbal Comprehension Index scores correlated significantly with IGF-1 (P < 0.03) and insulin-like growth factor binding protein-3 (P < 0.02) standard deviation scores in isolated GH. Moreover, they also found that in patients with isolated GH, white matter abnormalities in the corpus callosum and cortico-spinal tract and reduced thalamic and globus pallidum volumes relate to deficits in cognitive function and motor performance.

Finally, Polish scientists Tołwińska et al. [14] evaluated with high resolution echocardiography selected parameters of endothelial function and measured medial thickness in carotid communis arteries (IMT) in children with GH before replacement therapy. They found that IMT in patients with GH showed a more advanced degree of atherosclerotic changes in this group compared to healthy controls. In addition, Tołwińska et al. [14] suggest that ultrasonographic evaluation of premature atherosclerosis in children with GHD is a basis for future estimation of possible effects of replacement therapy.

In a broader sense, GHD in adults is associated with considerable morbidity and mortality. The diagnosis of GHD is generally straightforward in children as growth retardation is present; however, in adults, diagnosis of GHD is often challenging. Therefore, other markers are needed to identify adults who have GHD and could potentially benefit from GH replacement therapy. Consensus guidelines for the diagnosis and treatment of adult GHD recommend provocative testing of GH secretion for patients who have evidence of hypothalamic-pituitary disease, patients with childhood-onset GHD, and patients who have undergone cranial irradiation or have a history of head trauma [15].

Many report that suspicion of GHD is also heightened in the presence of other pituitary hormone deficits. Tests for GHD include measurement of the hormone in urine or serum or measurement of stimulated GH levels after administration of various provocative agents [16]. The results of several studies indicate that non-stimulated serum or urine measurements of GH levels cannot reliably predict deficiency in adults, especially related to Body Mass Index (BMI) [17]. In fact, Ghigo et al. [18] and Petersenn et al. [19] have suggested that based on consensus of the literature, the GH Research Society Consensus (RSC) from Port Stevens in 1997 [18] and its Consensus Statements should be appropriately amended. Accordingly, they further suggest one should evaluate patients with hypothalamic or pituitary disease as well as those with childhood-onset GHD to identify obvious risk as adults for severe GHD (Figures 1 and 2).

In terms of testing for AGHD, there has been much controversy as to the most appropriate measure. Specifically, Aimaretti et al. [20] reported that total IGF-1 levels are often normal even in patients with total anterior hypopituitarism. They suggested that this does not rule out severe GHD and therefore, ought to be verified by provocative testing of GH secretion. However, they further believe despite the low diagnostic sensitivity of this parameter, very low levels of total IGF-1 can be considered definitive evidence of severe GHD in a remarkable percentage of total anterior hypopituitarism and as such, these patients could therefore skip provocative testing of GH secretion.

Feletti et al. [21] performed a meta-analysis showing the unequivocal link between GHD and cognitive performance as well as improvements with GH replacement therapy. In addition, there have been numerous studies showing improvement with GH replacement therapy (raising IGF-1 levels) for a number of abnormalities including: BMD (from 138.1 to 279.4); fibromyalgia (from 98.6 to 173.3); brain processing speed and memory (from 150 to 250); head trauma (from 74 to 362.6); cognitive function (from 135 to 213); carotid intimal media thickness (from 51.8 to 234.4); insulin sensitivity (from 103.5-231.1); reduction of abdominal fat accumulation (from 146 to 267); and 100
point increases of IGF-1 levels are associated with a 7 point increase in IQ (Table 1).

Finally, many endocrinology studies link low IGF-1 levels with low levels of other anterior pituitary hormones (i.e., LH, FSH, TSH) [22], but in terms of CMD, the relationship between GH and these other anterior pituitary hormones, to our knowledge, have not received adequate attention. Thus, our laboratory decided to investigate the relationship of low IGF-1 levels with that of LH, FSH and TSH plasma levels in subjects with CMD.

Methods

Subjects and testing

This study was approved by the PATH Foundation NY Institutional Review Board (IRB) with an improved consent form that each patient filled out prior to any treatment or data retrieval. This was a post-hoc analysis of all presenting data. All subjects signed an approved IRB consent form based on an approval from the PATH Foundation NY IRB committee (registration #IRB00002334) and ethics board approval from PATH Foundation NY. The criterion for study inclusion was at least one P300 test for each patient. Trained EEG medical and psychometric technicians conducted the tests. All test interpreters were blinded to other patient results. All subjects were part of a catchment study involving brain electrical activity mapping and aging research.

The data set consisted of both genders (male and female) from the age range of 18-90 years with mixed race including: Caucasian, Hispanic, Asian and African–American. A total of 944 patients were recruited from the PATH Medical clinic over a two-year period ending on March 24, 2009. The diagnosis of CMD was carefully derived from a number of clinically relevant tests, such as a complete biochemical panel analysis (CBC, etc.) and neuropsychological tests including: Test of Variables of Attention (TOVA); Wechsler Memory Scale-III (WMS); The Central Nervous System Vital Signs Memory Test (CNSM); Mini-Mental State Examination (MMSE); Brain Event–Related Potentials (P300); and echocardiograms (ECHO), electrocardiogram (EKG or ECG), DEXA (Dual-energy X-ray absorptiometry measuring percent body fat) along with a number of diagnostic parameters (Table 2).

We evaluated plasma levels of IGF-1, LH, FSH and TSH (x±SD) on all 944 subjects. In order to analyze the relationship between anterior pituitary hormones and levels of IGF-1, we divided patients

<table>
<thead>
<tr>
<th>Disorder Improved with Raising IGF-1 Levels</th>
<th>Start Level of IGF-1 µl**</th>
<th>Post Treatment Level IGF-1 µl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Mineral Density</td>
<td>138.1</td>
<td>279.4</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>98.6</td>
<td>173.3</td>
</tr>
<tr>
<td>Brain Processing Speed/Brain Memory</td>
<td>150-</td>
<td></td>
</tr>
<tr>
<td>I.Q.</td>
<td>There is a 7 point increase in IQ for every 100 point increase in IGF-1 level</td>
<td>There is a 7 point increase in IQ for every 100 Point Increase in IGF-1 level</td>
</tr>
<tr>
<td>Head Trauma (improvements in anxiety, depression and short and long term memory</td>
<td>74</td>
<td>362.8</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>103.5</td>
<td>213</td>
</tr>
<tr>
<td>Carotid intimal media thickness (Reduction)</td>
<td>51.8</td>
<td>234.4</td>
</tr>
<tr>
<td>Abdominal fat reduction/HIV</td>
<td>146</td>
<td>267</td>
</tr>
<tr>
<td>Cognition</td>
<td>135</td>
<td>213</td>
</tr>
</tbody>
</table>

Table 1: GH replacement therapy showing improvement as a function of increased IGF-1 levels.
according to the following IGF-1 cut-offs: below 84 µ/l; 100-84 µ/l; and below 150 µ/l.

Analysis of hormones

IGF-1 and IGFBP-3 were used as the hormone measures. Venipuncture was done in non-fasting subjects between 8:30 AM and 7:30 PM at baseline examination of the PATH Medical Clinic Program. Blood samples were collected in 5 ml tubes containing a 0.5 ml sodium citrate solution. All tubes were stored on ice before and after blood sampling. Platelet-free plasma was obtained by 2-stage centrifugation (10 minutes at 1600 g at 4°C and 30 minutes at 7000 g at 4°C). Platelet-free samples were immediately frozen in liquid nitrogen and stored at −80°C. Assays were performed blinded to information on the subject. Plasma levels of estradiol and sex hormone-binding globulin were estimated with double anti-body radioimmunoassays (Bioreference Lab, New York, NY). As measures of the levels of bio-available and free estradiol, testosterone, and nonprotein-bound estradiol were respectively calculated in the basis of hormone and binding protein levels, for the analysis of GH and IGFBP-3, the laboratory performed standardized procedures [23,24]. For this particular study, we are only reporting the IGF-1 plasma levels.

Results

Table 3 represents the results of our systematic analysis showing the relationship of the IGF-1 (N=944) and percentage (%) (SD ± X) denoted as a function of our arbitrary cut-off points. We found the following in our patient population diagnosed with CMD: 84 µ/l=9.22 µ/l (SD ± 12.52); 100 µ/l= 19.9 (SD ± 9.54); and 150 µ/l= 56.1 (SD ± 26.0).

Most interestingly, when we calculated the plasma levels of LH, FSH and TSH using a low reference range as represented in Table 4 and as such, we surprisingly found only a small percentage of patients had comorbid anterior pituitary hormone deficiencies (between the range 84–100 µ/l of IGF-1 plasma levels: low LH=4.2%; FSH=4.8%; and TSH=6.5%). Specifically, only 0.3% had more than one hormone deficiency and none had three or more.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Baseline Range (Males)</th>
<th>Baseline Range (Females)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH</td>
<td>1-10 U/L</td>
<td>Follicular, 1-20 U/L</td>
</tr>
<tr>
<td></td>
<td>Midcycle, 25-100 U/L</td>
<td>Postmenopausal, 20-100 U/L</td>
</tr>
<tr>
<td>FSH</td>
<td>1-10 U/L</td>
<td>Follicular, 1-10 U/L</td>
</tr>
<tr>
<td></td>
<td>Midcycle, 6-30 U/L</td>
<td>Postmenopausal, 1-8 U/L</td>
</tr>
<tr>
<td>TSH</td>
<td>0.4-4.2 mIU/L</td>
<td>0.4-4.2 mIU/L</td>
</tr>
</tbody>
</table>

Table 3: IGF-1 levels and percentage breakdown.

Discussion

To reiterate, AGHD is marked by a number of neuropsychiatric, cardiac, metabolic, muscular, bone symptoms and clinical features. The most common of these are increased body fat (particularly abdominal fat), decreased lean body mass (including muscle), functional strength, thin skin and cool extremities, decreased psychological well-being and energy, reduced bone density, an increase in c-reactive protein, low-density lipoprotein (LDL), fibrinogen, plasminogen activator inhibitor-1 (PAI-1), a decrease in high-density lipoprotein (HDL), decreased insulin sensitivity, and decreased quality of life [25].

Most importantly, in some patients with AGHD, IGF-1 elevation is resistant to direct GH treatment. However, as we reported earlier [26], the interaction of IGF-1 and IGFBP-3 is quite complex, but seems to involve the integrity of the GH receptor. Previous work from Wilson’s laboratory has shown that the constant subcutaneous infusion of IGF-1 to monkeys with normal pituitary glands results in a sustained elevation in circulating concentrations of IGFBP-3; whereas, the acute administration of IGF-1 to monkeys pretreated with a GH receptor antagonist produces a brief, but significant, elevation in serum IGFBP-3. Experiments from Wilson’s group [27] indicate that IGF-1 administration during GH receptor antagonism restores circulating levels of IGFBP-3. It remains to be determined whether IGF-1 directly affects hepatic synthesis and secretion of IGFBP-3 [27].

Therefore, the use of IGF-1 alone may not be enough to raise IGFBP-3 levels, but in combination with GH receptor agonistic activity, it may induce the increases as we observed in earlier reports from our laboratory [26] and others [28]. These benefits, which are consistent with literature findings [28], and based on unpublished work in our laboratory (a subject of another paper to be published elsewhere), an increase of IGF-1 levels to the high normal range seems to reverse CMD and associated illnesses (Table 1).

Conclusion

Since we now found that only a small percentage of CMD patients have abnormal low levels of LH, FSH and/or TSH between IGF-1 levels of 84-100 µ/l, we cautiously propose that IGF-1 low levels may be too low to be considered as an independent diagnostic marker to treat AGHD with CMD patients. More research is required to determine any difference we observed in our clinical study and what has been observed in the current literature.

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Conflict of Interest
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