Pitfalls of Insulin-like Growth Factor-I and Growth Hormone Assays

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KEYWORDS

• Growth hormone • Insulin-like growth factor I • Immunoassay • Binding protein • Standard preparation • Antibody • Provocative testing

KEY POINTS

- Accurate assessment of growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels is essential for diagnosis of acromegaly and GH deficiency.
- The use of different assay methods results in considerable variation of GH and IGF-I levels measured in different laboratories.
- Adherence to consensus guidelines, including the use of appropriate reference preparations, should lead to more cohesive measurements in the future.

INTRODUCTION

Growth hormone (GH) is best known for its ability to promote growth; however, it is also responsible for a variety of metabolic effects, such as inhibition of glucose uptake and breakdown of fat. Many of the growth-promoting actions of GH are mediated by insulin-like growth factor-I (IGF-I), which is secreted systematically by the liver and locally by target tissues. Increased as well as decreased action of the GH–IGF-I axis results in a severe phenotype, even more so when present from childhood. Gene mutations in the *GH-1* gene that encodes pituitary GH or in an upstream or downstream molecule can cause GH deficiency or insensitivity, which results in short stature unless treated. GH deficiency can also be acquired later in life, most often

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caused by head trauma or irradiation. At the other extreme is acromegaly, which is an excess of GH secretion, usually caused by a pituitary adenoma. If acromegaly starts before puberty, it can result in a giant phenotype. Adult acromegaly has a less prominent phenotype because the excess growth focuses on extremities and internal organs. Nevertheless, the condition is associated with increased morbidity and mortality if left untreated.

Accurate measurement of GH and IGF-I is crucial for diagnosis and monitoring of the disorders of the GH–IGF-I axis. For each of these hormones, there are multiple steps where the reliability of the laboratory analyses can be affected. A classic paper from 2007 had the same GH sample measured in 104 centers and an IGF-I sample in 23 centers across the UK using variable assay methods. The results varied more than 3-fold for GH and up to 2.5-fold for IGF-I.[1] Clearly, choosing an established and reliable assay method is highly important, but not enough if there are problems with sampling conditions or determining appropriate cutoffs for making a correct diagnosis. The aim of this review is to introduce the potential pitfalls in GH and IGF-I measurements and to help avoid them. Regarding assay design, we focus on immunoassays even though biological assays that evaluate the biological activity of GH and IGF-I also exist.[2–4] However, because the biological assays depend on activation, proliferation, or differentiation of living cells, their reproducibility is not good enough for routine clinical purposes.

GROWTH HORMONE

GH is a rather stable protein and does not require more than standard care during sample processing. Total GH as well as the different GH isoforms exhibit a remarkable preanalytical stability.[5] Furthermore, a recent study demonstrated that 22 kD GH concentrations as measured by an immunoassay did not change over a period of more than 10 years when samples were stored at −80°C.[6] Traditionally, the preferred matrix to measure GH is serum, but most of the currently available assays can also be used with plasma samples. Even though GH sample handling is easy, there are plenty of other factors that make measuring GH and interpreting measured GH concentrations a challenge. First, the biology of GH secretion is complex: circulating GH concentrations depend highly on when, how, and of whom GH is measured. GH is secreted in a pulsatile manner and the magnitude of pulses follows a circadian pattern. Furthermore, nutritional status, exercise, sleep, stress, and body temperature all affect GH levels, additionally contributing to the high intraindividual variation in GH levels. Therefore, a stimulation or suppression test is used to obtain peak or nadir GH values, which then are used for diagnosis. Age has a major impact on GH levels; GH levels peak at late adolescence and decline from age 20 such that only very low levels can be detected at and after age 60.[7] Additionally, women have two to three times higher mean GH levels than men do.[8] In the current obesity epidemic, one has to also take into account the effects of body mass index (BMI) on GH levels; obese individuals have lower GH secretion as well as faster GH clearance rates.[9,10] Abdominal fat is also a negative regulator of GH and is correlated with decreased GH levels, even in individuals with normal BMI.[11]

In general, a stimulation test and a following peak GH value are used for diagnosis of GH deficiency and a suppression test with GH nadir is applied when diagnosing acromegaly. There are several validated GH stimulation tests, such as the traditional insulin tolerance test, but the use of GH-releasing hormone in combination with arginine, which inhibits somatostatin, is suggested to provide the most accurate results in children as well as adults.[12,13] For the GH-releasing hormone + arginine test,