

PROVIDER HANDOUT

Premature Aging and Growth Hormone Deficiency



IGF-1 Testing of Human Growth Hormone In Blood Spot

Background

Human Growth Hormone (GH) stimulates bone and muscle growth in children. In adults it helps to maintain a healthy body composition, but GH levels drop dramatically with age—about 14% per decade beginning at age 20 until around 60 years when levels plateau. This physiologic decrease in GH is thought to be the primary factor in the aging process, but the extent to which levels drop or become unbalanced can make a huge difference in quality of life during the aging process. Individuals who wish to optimize the aging process are increasingly working with physicians to identify and monitor GH deficiencies linked to premature aging and disease.

Purpose

Why test IGF-1 instead of Human Growth Hormone? GH levels fluctuate radically throughout the day making random serum measurements unreliable as diagnostic and therapeutic markers. Insulin-Like Growth Factor-1 (IGF-1) is a stable biologic mediator of GH as it is produced by the liver in response to the average GH level throughout the day. There is excellent correlation with GH release and extracted IGF-1 measurements from serum; therefore, IGF-1 measurement in blood is an indirect method of assessing GH levels (Ref: 1,5,6,7,8,9).

Physicians Note: As with any indirect measurement, it's important to keep in mind known factors that may stress the liver and interfere with IGF-1 production including: oral estrogen, protein deficiency, low insulin levels, liver failure, hypothyroidism, pregnancy, overuse of asthma inhalers, renal failure and acute catabolic stress (e.g., surgery, trauma, hip fractures and infectious disease). (Ref 2, 3,6,9,10)

Candidates for IGF-1 Testing

Patients who exhibit signs of Growth Hormone Deficiency including premature aging, chronic illness, heart disease, insulin resistance, reduced capacity for exercise and/or symptoms of thinning, sagging skin, poor sleep, memory impairment, slowing cognition, low stamina, low sex drive and overall poor quality of life.

"IGF-1 measurement is a useful GH deficiency screening test in adults between 20 and 60 years of age. Levels more than one standard deviation below the age-adjusted mean necessitate additional provocation testing. Serum concentrations less than 84ng/ml predict the presence of GH deficiency in >99% of cases. Concentrations above the age-adjusted mean strongly indicate the patient does not need further stimulation testing unless there is very strong clinical evidence of growth hormone deficiency (e.g., multiple hormone deficiencies and a history of pituitary surgery or radiation)."
David R. Clemmons, MD, Chief, Division of Endocrinology and Metabolism, University of North Carolina, Chapel Hill

Advantages

There are several good reasons to choose blood spot testing over serum:

- Minimally invasive specimen collection (finger stick)
- Small sample size
- Safer specimen procurement and handling
- Specimen stability at ambient temperatures for weeks to months
- Ease of monitoring facilitates safe, appropriate prescribing of hormone therapies.
- Simple shipping options

Filter paper blood spot testing has been shown to be as effective as serum for IGF-1 testing. IGF-1 levels in serum show excellent correlation with IGF-1 in blood spot (Ref 7) making blood spot testing techniques as employed by ZRT Lab an ideal means for monitoring Growth Hormone levels. Analytes in blood serum can be very unstable is not handled properly. ZRT uses a "state of the art" immunoradiometric (IRMA) sandwich assay proven to be exceptionally sensitive and specific for each analyte tested.

Benefits

An IGF-1 level outside the normal range can serve as a starting point for correcting the causes contributing to premature aging and adult growth hormone deficiency to restore balance and with it, healthy aging and quality of life. Growth Hormone levels are correlated with reported symptoms to provide physicians more diagnostic clues.



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IGF-1 References

1. Abs R, Bengtsson B, et al. GH Replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. *Clinical Endo* (1999) 50: 703-713
Study basically shows safety of GH in AGHD without increase in tumor recurrence or diabetes in patients treated for more the 800 patient years. Also, IGF-1 was used and shown to be the method of choice for titration of rhGH therapy.
2. Ghigo E, Arvat E, et al. Diagnostic and therapeutic uses of growth hormone-releasing substances in adult and elderly subjects. *Bailliere's Clin Endo and Met* (Jul 1998) 12(2): 341-358
This study validates the use of GHRH provocation testing (with arginine) for the diagnosis of AGHD instead of ITT, and that injectable rhGH is the most effective replacement strategy. The cutoff limit for diagnosis needs to be adjusted for the particular provocation test, e.g., arginine with GHRH is 16 ug/l with less than 9 ug/l as the criteria for severe deficiency.
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Study concludes that conjugated equine estrogen 0.625mg/day (HRT) PO increased GH and IGF-1 levels, while lowering insulin levels in post menopausal women. There was no evidence that this was correlated to reversal of GH metabolic effects.
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Free IGF-1 are decreased in GHD, but measurements of free IGF-1 in a single, fasting serum sample do not offer a better separation of patients with GHD from individuals with normal GH status than can be achieved by measurement of total IGF-1.
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The administration of oral, but not transdermal, E2 at the usual clinical doses used in postmenopausal women decreased IGF-1 levels and the response of GH to GHRH in older women. No substantial changes were detected in IGFBP-1, IGFBP-3, insulin, or C peptide levels.
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Study employs the immunoradiometric (IRMA) sandwich assay with antibodies specific to IGF-1. These assays are found to be quick and accurate, and produce a high degree of specificity. The addition of acid-ethanol extraction or saturation with IGF-II improves reliability. "Despite the problems, IGF-1 measurement is currently the best indirect method available for screening and monitoring patients with GHD
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Conclusion: "Exogenous oral estrogen exerts inhibitory effects on all three components of the IGF-1 ternary complex. These effects are route and dose dependent, but independent of endogenous GH status. These findings indicate that IGFBP-3 and ALS are directly or indirectly estrogen-sensitive hepatic proteins".
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Placebo controlled study of AGHD. Conclusion: "Elderly patients with GHD respond to replacement therapy in similar manner as younger subjects, with an improvement in body composition and an increase in markers for bone metabolism. Side effects are few, and elderly GHD patients can be offered treatment. As long-term risks are unknown, GH doses should be titrated to keep IGF-1 within the age-related physiological range.
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Review article with the conclusion: GH enhances lumbar bone density and appears to maintain femoral density. Author suggests that IGF-1 therapy may be more effective therapy than GH. Studies reported were too short to draw that conclusion (see reference 17).
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Retrospective study comparing two groups of AGHD women: those taking oral E2 and those not taking oral E2. Note: transdermal application of E2 patients was included in the latter group. Conclusion: Women taking oral estrogen need about twice the amount to normalize IGF-1 than women using transdermal estrogen. We believe that the difference is related to an effect of oral estrogen on hepatic IGF-1, the major source of circulating serum IGF-1. A potential cost savings of GH could be realized if women needing GH replacement therapy and exogenous estrogen chose transdermal rather than oral treatment.
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Review article. Conclusions: Abnormal circulating IGF-1 levels are a suitable parameter to aid in the diagnosis of GHD or acromegaly in adults, particularly if they are below 40 years of age. A determination of accurate normative values is, however, essential to this process. Normative values are assay specific and individuals with confounding disease must be excluded from these data. IGFBP-3 levels should also be monitored in adult patients receiving GH replacement therapy. In addition to IGF-1, ALS is a useful parameter for diagnosing and monitoring acromegaly.
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Study of 36 AGHD patients. Conclusion: "six months of GH replacement therapy in hypopituitary adults had favorable cardiovascular effects, including increased exercise tolerance and improved diastolic function."
15. Serri O, St-Jacques P, et al. Alterations of Monocyte Function in Patients with Growth Hormone (GH) Deficiency: Effect of Substitutive GH Therapy. *J Clin Endocrinol Metab* (1999) 84: 58-63
Twelve AGHD patients were followed for 3 months on GH therapy. Conclusion: "Our results demonstrate that markers of monocyte activation are increased in patients with GHD and GH replacement partly reduces these abnormalities. Reduction of cellular activation of monocytes by GH therapy could potentially contribute to reduce the risk of cardiovascular events in patients with GHD.