HOLTORF MEDICAL GROUP, INC.
CENTER FOR HORMONE IMBALANCE, HYPOTHYROIDISM AND FATIGUE
23456 Hawthorne Blvd. Suite160, Torrance, CA 90505 Tel: 310-375-2705 Fax: 310-375-2701

Large amounts of peer reviewed research, including long-term data, has demonstrated that growth hormone replacement has been shown to improve energy (1,2), strength (1), cardiac function (3,4,5), blood pressure (6), cholesterol levels (3,6,7,8), insulin sensitivity (6,7,9) cognitive function (10,11), immunity (12,13) and psychological well-being (1,2); decrease body fat (1,3,6,7,9,13,15); increase lean muscle (1,6,14,15); prevent and reverse heart disease (1,3,16,17); prevent and improve osteoporosis (3,7,18); and increase quality of life (2,3,8).

There is an exponential decline in growth hormone release after age 21 with a 50% decline every 7 years. Almost all individuals over 40 years old have a growth hormone deficit and at age 60 growth hormone production is indistinguishable from those of hypopitutitary patients with organic lesions in the pituitary gland. Life with low growth hormone is shown to be poor in quality and quantity (19).

While many endocrinologists feel the diagnosis of growth hormone deficiency requires the use of growth hormone stimulation testing (dynamic testing), growth hormone and other stimulation tests are shown to be inaccurate, highly variable, nonphysiologic, lack adequate sensitivity to detect relative growth hormone deficiencies, do not correlate with the presence of deficiency and do not predict who will respond to therapy (20-32). Requiring stimulation testing to confirm growth hormone deficiency is unnecessary, expensive and carries significant risk to the patient. Thus, they neither are appropriate to perform nor required for the diagnosis of growth hormone deficiency. A clinical diagnosis of growth hormone deficiency, often with support of low or low-normal IGF-1 levels, are the most appropriate means of making the diagnosis of relative growth hormone deficiency.

Hoeck et al evaluated the accuracy of the insulin tolerance test (ITT), which is considered to be the most reliable (and risky) of the dynamic tests. They found that there was no correlation between results of repeated ITT's, and the results were no better than flipping a coin. The authors conclude, *"The results of this study illustrate the complexity of the regulation of growth hormone secretion and indicate that the ITT is less useful for diagnosing growth hormone deficiency in adults than previously anticipated. The diagnosis of growth hormone deficiency in adults and especially in adult females should not be based on the results of a single ITT alone (24)."*

> *"stimulation testing is often limited and relies on testing procedures that are, generally, nonphysiolgical, arbitrary, invasive, risky, and subject to considerable interassay variability"*

Similarly, Hoeck and Jakobsen, et al evaluated the accuracy and reliability of commonly used stimulation tests. On each subject, 2 ITT, 2 GHRH, 2 clonidine + GHRH were done and then a pyridostigmine + GHRH stimulation tests were done on an extended group of subjects. It was found that there was no correlation in the results of the different tests and the results were not reproducible. The authors conclude, *"In the individual subject, there was no systematic correlation between the peak growth hormone responses in the different stimulation tests. In conclusion, we found that the stimulated growth hormone responses were highly variable in all tests, and that the peak GH responses differed (25)."* The authors expressed caution in the use and interpretation of stimulation tests in the diagnosis of growth hormone deficiency.

This use of growth hormone stimulation testing in the diagnosis of growth hormone deficiency was reviewed by Rosenfeld et al in the Journal of Endocrinology and Metabolism. The authors state, *"[stimulation testing] is often limited and relies on testing procedures that are, generally, nonphysiolgical, arbitrary, invasive, risky, and subject to considerable interassay variability (20)."*

Moorkens et al evaluated the growth hormone secretion in chronic fatigue syndrome patients as compared to normal controls. This study compared physiologic nocturnal secretion, IGF-1 levels and response to various commonly used stimulation tests. This study found that CFS patients have an abnormally low production of growth hormone, as demonstrated by reduced nocturnal secretion of growth hormone and a significantly decreased GH response to ITT (both peak and AUC). The commonly used stimulation tests were shown, however, to have no correlation with ITT testing results (which again has significant risk), and that these stimulation tests were shown to lack the sensitivity to detect significant growth hormone deficiency in these patients (32).

In a prospective randomized placebo controlled study, Rahim et al assessed the accuracy and reliability of commonly used stimulation tests by performing four different stimulation tests on each individual (ITT, glucagon, arginine and clonidine). As with other studies, this study also found that there was no correlation between the response to different agents in the same individual. Subjects who failed to achieve a growth hormone peak greater than 20mU/l in one test were not the same individuals who responded poorly to other tests. Again, the results of the stimulation tests were no better than flipping a coin. This study also demonstrated the risk and side-effects of performing such testing; all patients suffered from significant hypotension; over half of the patients could not carry out normal daily activities for the rest of the day after the tests; venous thrombosis occurred in over a third of patients and over 10% had significant nausea and vomiting (26). There have also been reported deaths and neurological damage associated with growth

(over)

hormone stimulation testing (33).

Cacciari et al investigated the sensitivity of utilizing growth hormone stimulation tests in 98 children with clear evidence of impaired growth hormone production compared to 274 healthy controls. They found that growth hormone deficiency correlated with IGF-1 levels, but that standard arbitrary cutoffs of what is considered to be a normal IGF-1 level and the use of growth hormone stimulation tests with standard cutoffs lacked sufficient sensitivity. The majority of patients with clear evidence for growth hormone deficiency would have been inappropriately labeled as normal and children who would likely have benefited from treatment would have been left untreated. The authors conclude, *"Our data adds weight to the opinion that present criteria for defining growth hormone deficit may be too restrictive. Consequent implications regarding therapy are evident (27)"*

"...growth hormone stimulation testing, particularly as currently conducted in the USA, is neither precise nor accurate in quantifying a patients growth hormone secretory status ."

Wilson et al reviewed the use of growth hormone stimulation tests in determining a person's growth hormone secretory status in a 2005 edition of Growth Hormone & IGF Research. They state, *"Historically, growth hormone stimulation testing has played a prominent role in diagnosing growth hormone deficiency. There are growing concerns, however, that growth hormone stimulation testing, particularly as currently conducted in the USA, is neither precise nor accurate in quantifying a patients growth hormone secretory status (28)."*

Tassoni et al tested the variability of growth hormone stimulation tests in the Journal of Endocrinology and Metabolism. They performed several commonly used stimulation tests in duplicate as well as 12-hour overnight physiologic growth hormone secretion testing. They found that there was little or no correlation between repeated testing in the same individuals (coefficient of variance being 89% in one group and 66% in another) as well as little correlation with physiologic night-time growth hormone secretion. When the same stimulation test was repeated on the same individual, over half had disparate results (showing deficient on one test and normal on the other). Again, the results were almost no better than flipping a coin. They state that growth hormone stimulation tests cannot be used with any confidence to diagnose or rule-out growth hormone deficiency and recommend that repeated 12-hour overnight physiologic growth hormone secretion testing be utilized. This requires, however, that multiple venous samples be obtained throughout the night via an indwelling catheter, which is not practical outside of a research setting. The authors state, *"In conclusion, the usual approach for evaluating growth hormone secretion does not take into account the variability of the response to the various tests. This may be misleading, especially for patients that have hormone secretion at the lower limit of normalcy (30)."*

Gandrud et al reviewed the use of growth hormone stimulation testing in the 2004 Growth Hormone & IGF Research. This extensive review clearly demonstrates that growth hormone stimulation tests lack precision and accuracy, are not concordant with the proper diagnosis of growth hormone deficiency and do not predict response to therapy. They recommend that the diagnosis of growth hormone deficiency should be based on clinical parameters as well as IGF-1 and state, "…the insulin tolerance test using the current cutoff for failure should not be considered the gold standard for the diagnosis of growth hormone deficiency…We examined the pitfalls associated with growth hormone stimulation tests, specifically, the lack of reliability and accuracy of these tests, and their inability to predict who will benefit from growth hormone therapy. We recommend that growth hormone stimulation tests no longer routinely be used for the diagnosis of growth hormone deficiency…(31)."

Conclusion: Aging adults are shown to have a relative deficiency of growth hormone and supplementation with growth hormone can be of significant benefit. A clinical diagnosis of growth hormone deficiency, often with support of low-normal IGF-1 levels, are the most appropriate means of making the diagnosis of growth hormone deficiency. Growth hormone stimulation tests are shown to be inaccurate, unreliable, highly variable, risky, nonphysiologic and lack adequate sensitivity to detect relative growth hormone deficiencies. Thus, the growth hormone stimulation tests generally do not add significant useful information in the clinical management of these patients and are not recommended.

References

1. Gibney J, Wallace JD, Spinks T, Schnorr L, Ranicar A, et al. The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients. J Clin Endocrinol Met 1999;84(8):2596-602.

2. Bennett RM, Clark SC, Walczyk J. A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. Am J Med 1998;104(3):227-31.

3. Johannsson G, Svensson J, Bengtsson BA. Growth hormone and ageing Growth Hormone and IGF Research 2000;10(2):25-30.

4. Maison P, Philippe C. Cardiac Effects of Growth Hormone in Adults With Growth Hormone Deficiency: A Meta-Analysis. Circulation. 2003;108:2648.

5. Cho GY, Jeong IK, Kim SH, Kim MK, Park WJ, Oh DJ, Yoo HJ. Effect of growth hormone on cardiac contractility in patients with adult onset growth hormone deficiency. Am J of cardiology 2007;100(6):1035-9

6. Johannsson G et al. GH treatment of abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism and reduces diastolic BP. J Clin Endocinol Metab 1997;82:727-734.

7. Gotherstrom G et al. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. J Clin Endocrinol Metab 2001;86(10):4657-65.

8. Feldt-Rasmussen B, Lange M, Sulowicz

W, Gafter U, et al. Growth hormone treatment during hemodialysis in a randomized trial improves nutrition, quality of life, and cardiovascular risk. J Am Soc Nephrology 2007;18(7):2161-71.

9. Yuen KC , et al. Impact of treatment with recombinant human GH and IGF-I on visceral adipose tissue and glucose homeostasis in adults. Growth Horm IGF Res 2006;16:S55-61.

10. 7A. Aleman A et al. Insulin-Like Growth Factor-I and Cognitive Func¬tion in Healthy Older Men J Clin Endocrinol Metab 84:471–475, 1999.

11. Arwert LI, Veltman DJ, Deijen JB, Sytze van Dam P, Drent ML. Effects of Growth Hormone Substitution Therapy on Cognitive Functioning in Growth Hormone Deficient Patients: A Functional MRI Study. Neuroendocrinology 2006;83:12–19.

12. Clark R. The somatogenic hormones and insulin-like growth factor-1: stimulators of lymphopoiesis and immune function. Endocr Rev 1997;18(2):157-7.

13. Burgess W et al. The immune-endocrine loop during aging: role of growth hormone and insulin-like growth factor-I. Neuroimmuno¬modulation 1999;6(1-2):56-68.

14. . Rudman D. Effects of growth hormone in men over 60 years old. New England Journal of Medicine 1990;323(1):1-6.

15. Munzer T, Harman SM, Hees P, Shapiro E, Christmas C, et al. Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. J Clin Endocrinol Metab 2001;86(8):3604-10.

16. Pfeifer M et al. growth hormone (GH) treatment reverses early atherosclerotic changes in GH-deficient adults J Clin Endocrinol Metab 1999;84: 453–457.

17. Borson-Chazot F, Serusclat A, Kalfallah Y, Ducottet X, Sassolas G, et al. Decrease in carotid intima-media thickness after one year growth hormone (GH) treatment in adults with GH deficiency. J Clin Endocrinol Metab 1999;84:1329–1333.

18. Valimaki MJ et al Effects of 42 months of GH treatment on bone mineral density and bone turnover in GH-deficient adults. Eur J Endocrinol 1999;140(6):545-54.

19. Savine R, Sonksen P. Growth Hormone-Hormone replacement for the somatopause. Horm Res 2000;53(3):37-41.

20. Rosenfeld et al. Diagnostic Controversy: The diagnosis of childhood growth Hormone deficiency revisited. Journal of Endocrinology and Metabolism 1995;80(5):1532-40.

21. Cacciari E, Cicognani A, Pirazzoli P, Tassoni P, Salardi S, Capelli M, Zucchini S, Natali G, Righetti F, Ballardini D.Differences in somatomedin-C between short-normal subjects and those of normal height. J Pediatr. 1985 Jun;106(6):891-4.

22. Bennett R. Growth Hormone in Musculoskeletal Pain States. Current Pain and Headache Reports 2005, 9:331-338

23. Maghnie M et al. Diagnosis of GH deficiency in the transition period: accuracy of insulin tolerance test and insulin-like growth factor-I measurement. European Journal of Endocrinology 2005;152(4):589-96.

24. Hoeck HC, Vestergaard P, Jakobsen PE, Laurberg P. Test of growth hormone secretion in adults: poor reproducibility of the insulin tolerance test. Eur J Endo 1995;133:305-12.

25. Hoeck HC, Jakobsen PR, Vestergaard P, Falhof JF, Laurberg P. Differences in reproducibility and peak growth hormne responses to repeated testing with various stimulators I health adults. Growth Hormone & IGF Research 1999;9:18-24.

26. Rahim A, Toogood AA, Shalet SM. The assessment of growth hormone status in normal young adult males using a variety of provocative agents. Clin Endo 1996;45:557-62.

27. Cacciari E, Cicognani A, Pirazzoli P, Tassoni P, Salardi S, et al. Differences in somatomedin-C between short-normal subjects and those of nomal height. J Pediatrics 1985;106:891-4.

28. Wilson DM, Frane J. A brief review of the use and utility of growth hormone stimulation testing in the NCGS: Do we need to do provocative GH testing? Growth Hormone & IGF-1 Research 2005;15:S21-5.

29. Bennett RM, Clark SR, Campbell SM, Burckhardt CS. Low levels of Smoatomedin C in patients with fibromyalgia syndrome. Arthritis & Rheumatism 1992; 35(10):1113-6.

30. Tassoni P, Cacciari E, Cau M, Colli C, et al. Variability of growth hormone response to pharmacological and sleep tests performed twice in short children. J Endo Met 1990;71(1):230-4.

31. Gandrud LM, Wilson DM. Is growth hormone stimulation testing in children still appropriate? Growth Hormone & IGF-1 Research 2004;14:185-94.

32. Moorkens G, Berwaerts J, Wynants H, Abs R. Characterization of pituitary function with emphasis on GH secretion in chronic fatigue syndrome. Clin Endo 2000;53:99-106.

33. Shah A, Stanhope R, Matthew D. Hazards of pharmacological tests of growth hormone secretion in childhood. BMJ 1992;304:173-4.