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IT HAS BEEN SHOWN THAT CHRONIC fatigue syndrome and fibromyalgia patients have abnormal sleep patterns with a deficiency in stage 4 sleep (1). Stage 4 sleep is closely related to the pulsatile secretion of growth hormone and 80% of the total daily secretion of growth hormone is during this stage. It has also been shown that chronic fatigue syndrome/fibromyalgia patients are unable to mount a normal growth hormone response to exercise as compared to healthy individuals (2). Thus, it is not a surprise that growth hormone secretion is shown to be deficient in chronic fatigue syndrome/fibromyalgia patients (2-5), with lower than average IGF-1 levels (a marker for growth hormone secretion) (4,6,7). Supplementation of this deficiency with growth hormone is shown to result in significant symptomatic improvement in these conditions (6). As is the case with thyroid and cortisol production in these patients, where there are significant deficiencies in these hormones despite seemingly normal standard testing (8,9), it has also been shown that these patients have a relative growth hormone deficiency despite typically "normal" or low-normal serum markers of IGF-1 (2-4,7).

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Bennett et al found that 92% of patients with fibromyalgia have pituitary dysfunction that results in low growth hormone secretion and that fibromyalgia patients have significantly lower IGF-1 levels that averaged 138 +/- 56 versus 215 +/- 86 ( $p = 0.00000000001$ ) in non-fibromyalgia

patients, demonstrating significant growth hormone deficiency despite IGF-1 levels in the "normal" range (4). This is consistent with another study that also found that fibromyalgia patients had deficient growth hormone as demonstrated by IGF-1 levels that averaged 124 +/- 47 ng/ml versus 175 +/- 60 ng/ml ( $p = 0.000001$ ) in normal healthy individuals. The authors conclude, "These findings indicate that there is a distinctive disruption of the growth hormone-somatomedin C (IGF-1) neuroendocrine axis in a majority of fibromyalgia patients (7)."

In a subsequent double-blind, placebo-controlled study, the effectiveness of growth hormone supplementation in fifty women with fibromyalgia and low normal IGF-1 levels ( $< 160$  ng/ml) was studied. Patients were treated with growth hormone to maintain an IGF-1 of 250 ng/ml for 9 months. It was found that fibromyalgia patients treated with growth hormone had significant improvement in symptoms as measured by the Fibromyalgia Impact Questionnaire and a significant reduction in muscle pain as measured by the tender point score compared to placebo. The treatment group also noted an increased sense of well-being and an increased ability to sustain increased levels of activity without the usual increase in muscle pain. The authors conclude, "Women with fibromyalgia and low IGF-1 levels experienced an improvement in their overall symptomatology and number of tender points after 9 months of daily growth hormone therapy. This suggests that a secondary growth hormone deficiency may be responsible for some of the symptoms of fibromyalgia (6)." There was a lag of about 6 months before patients noted improvements, but other studies, as well as our own experience, demonstrate that beneficial effects typically occur approximately 2-3 months after starting replacement.

### Diagnosis of growth hormone deficiency

The diagnosis of growth hormone deficiency is a clinical diagnosis based on symptoms and is often supported by laboratory

## Growth Hormone Treatment of FM and CFS

(IGF-1) testing. As shown in the study by Bennett et al, a relatively low IGF-1 level in the normal range demonstrates a relative growth hormone deficiency and it is reasonable to give a trial of growth hormone replacement in these patients if the IGF-1 level is below 200 ng/ml and there is a clinical diagnosis of growth hormone deficiency.

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 (3,5,9-20). 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.

Allaine et al found significantly attenuated IGF-1 levels in CFS patients (214 +/- 17 ug/l versus 263 +/- 13 ug/l) as well as reduced IGF-II, IGFBP-1 and peak growth hormone response to insulin tolerance testing (ITT), demonstrating abnormal production of growth hormone in this patient population. If, however, standard cutoffs were used with the ITT to define a normal response, the CFS patients would have been labeled as having normal growth hormone production, although this clearly was not the case (5).

Hoeck et al evaluated the accuracy of the 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 GH secretion and indicate that the ITT is less useful for diagnosing growth

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*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 (14)."*

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 (15)."* 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, nonphysiological, arbitrary, invasive, risky, and subject to considerable interassay variability (10)."*

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 (3).

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 20 mU/l

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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 (17). There have also been reported deaths and neurological damage associated with growth hormone stimulation testing (21).

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 (16)."*

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 (18)."*

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 evaluation 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 (19).”

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...(20).”

**Conclusion:** Chronic fatigue syndrome and fibromyalgia patients 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 or low-normal IGF-1 levels, are the most appropriate means of making the diagnosis of relative 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 in this patient population.

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