

Growth Hormone for Adults with Prader-Willi Syndrome: What's the Scoop?

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Even before all the studies have been completed, the benefits fully examined, and the impact of possible side effects evaluated, growth hormone replacement therapy has become standard of care for infants and children with Prader-Willi syndrome (PWS). The rapidity with which growth hormone treatment has become standard care is highlighted when it is recognized that growth hormone was first approved by the FDA for use in children with PWS in the year 2000. For treated children, the apparent benefits are obvious, dramatic, and non-trivial; in addition to increased height there is a normalization of cranial proportions and facial features, normalization of hand and foot proportions, and for most, a slim body. With early treatment, most affected children no longer stand out from other children as "different", nor are they readily identifiable as having PWS¹.

Growth hormone replacement for those whose short stature results from congenital, traumatic or surgical endocrine system failures is relatively recent. First utilized in the late 1950s, availability was exceedingly limited as manufacture required human pituitary glands available only at autopsy. Biosynthetic growth hormone replacements were rushed to market when an excess of those treated with cadaver derived hormone contracted Creutzfeld-Jacob disease, a fatal neurodegenerative disorder whose causal mechanisms have only recently been specified. Because the range and depth of studies that were usually required prior to FDA approval of a drug were incomplete when the use of biosynthetic agents became imperative, a compromise system of surveillance was set up to monitor safety and efficacy—the model currently utilized for many new drug releases.

Short stature has always been considered one of the cardinal features of Prader-Willi syndrome (PWS) and was included in the initial syndrome description in 1956². Studies indicate that despite normal length and weight at birth, the growth rate in children decelerates over time, so that the average final adult height is approximately two standard deviations below the mean for a non-affected population³. That growth hormone deficiencies were the probable basis for the short stature was documented as early as 1971, and subsequent case-based treatment evidence demonstrated the impact of growth hormone treatment on linear growth. It was not until the late 1990s that well designed, "controlled" scientific studies documented that growth hormone therapy resulted in a significantly improved rate of linear growth when compared to those not receiving treatment⁴.

More importantly, however, was the concomitant improvement in body composition (increased lean—i.e., muscle—mass, increased bone mineral density, and for many, a reduction in the amount of fat tissue), improved metabolism (higher resting energy expenditure, improved respiratory parameters, and increased energy and strength)⁵. And in addition to the previously noted normalization in physical appearance, self-esteem, behavior, and attention are improved⁶. As the children in those original studies are now reaching adulthood, unpublished data indicates that the final adult heights for individuals treated with growth hormone treatment as children are significantly taller than those not treated.

Unlike most long-term treatments for other chronic conditions, the side effects and safety concerns for growth hormone therapy, in the

absence of pre-existing morbid obesity and respiratory compromise, appear minimal to almost non-existent. Most clinicians and researchers view the improved body composition and metabolism as far more valuable even than that of increased height.

As a member of one of the first U.S. teams researching growth hormone intervention therapy for youngsters with PWS, I recall my reaction when I saw the dramatically positive body changes evident at even the first six months follow-up visit following initiation of growth hormone treatment. One young lady was particularly striking in her presentation as she now had a "waist", her lower "abs" were flatter than mine, and her mother said "We can now buy her clothes off the rack for the first time." That she had also grown about three inches, her feet had increased by two shoe sizes and, along with her hands were now almost normally proportioned, at first glance seemed secondary.

My colleague on the project, Dr. Susan Myers, tells me I turned to her at that point and said "We have got to do an adult study to see if we get the same positive body composition effects".

With the advent of puberty, the window of opportunity closes for increasing height through growth hormone intervention due to a "capping" of skeletal growth potential. Further, GH levels normally decline with age in all populations. Entering adulthood already GH deficient presents significant health risks including osteoporosis, increased body fat, decreased muscle mass, increased risks for heart and vascular disease, fatigue, social isolation and psychological depression^{7,8}. Thus, in 1995, the FDA approved GH replacement therapy for those with either childhood or adult-onset GH deficiency. One of the more active areas of research currently is the use of GH in a geriatric population, often with stunning results.

Recent studies indicate that adults with PWS continue to have the same GH deficiency that was present in childhood, with the same health risks attendant to non-PWS GH deficient adults⁹. In addition to GH deficiency, most adults with PWS also are deficient in sex-steroid/sex hormone production, a deficiency that further increases the health risks associated with GH deficiency. Thus, in addition to a possible improved body composition, the potential for improved long-term health strongly suggested that the need to study GH therapy for adults with PWS was far from trivial. Dr. Myers now teasingly claims that from the time of the first six month follow-up visit in the study of children, I "hounded her" until we ultimately joined with several other teams of researchers to conduct a study of growth hormone treatment for 40 adults with PWS, ranging from young adults 19 years old to adults in their mid to late 40s. That study, and another conducted in Sweden are now completed and results are being published. So what can we understand from these studies at this point?

Similar to the outcomes of treatment for children, significant improvement in body composition is observed in adults with PWS, both males and females, treated with GH replacement therapy¹⁰. These include increased muscle mass and for many a reduction in fat tissue. There also appears to be a small positive impact on bone mineral density; however, these effects are not as dramatic as those noted in children probably because bone metabolism does not change as rapidly in adults as it does in children. Loss of fat tissue is

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particularly apparent in the trunk area, with the result that many show a waist and hip body form for the first time. Improvement in energy and strength as demonstrated in such measures as broad jumps, running, and arm curls showed improvement after only one month of treatment. Both attention and cognition showed improvement as well¹¹.

Unlike children, however, GH treatment for adults is not without some risk. Increased fluid retention, particularly in the feet and ankles, can initially occur and for some is sufficiently problematic to require treatment discontinuance. In addition, for some there may be a negative impact on glucose tolerance, leading to Type II diabetes. Finally, for some, the impact on scoliosis must be considered. Thus, like any proposed treatment, the risk/benefit ratio must be considered.

So, if a caregiver is considering this treatment for their adult with PWS, what must they do? Since GH replacement therapy for adults with PWS does not yet have full FDA approval, formal demonstration of GH deficiency through provocative GH stimulation testing is required, a requirement even for those who have been on growth hormone for a number of years during childhood. This timed procedure requires injecting a GH stimulating agent while fasting and measuring the peak level of GH secreted into circulating blood at specific points over a specified period of time. However, these procedures are neither straightforward nor simple. There is disagreement on what constitutes "deficiency". Depending on the decision-making criteria employed, GH deficiency is defined as peak stimulated GH levels of less than 3 – 7 ng/ml. While a number of provocative agents are available, peak stimulated levels may differ depending on the agent used, resulting in a requirement for two or more tests. Further complicating the variability related to stimulating agents, there can also be variability between analyzing laboratories. Thus, even true growth hormone deficiency can be masked by both the provocative agent used or the analyzing lab employed, resulting in a denial of treatment. In addition, these tests are not without risk, so tolerating two such tests constitutes a major medical procedure. What happens when one test indicates decreased GH levels, while the other is borderline or above the cutoff?

Once GH deficiency is documented, your physician may want to obtain a number of medical tests both prior to initiating therapy and again at least annually as part of therapeutic monitoring. These include an x-ray for scoliosis, a DEXA scan for bone mineral density and body composition, a sleep test to rule out life-threatening (but treatable) apnea, and multiple blood tests including a fasting lipid panel, fasting glucose, IGF-1, hemoglobin A1c, a general chemistry profile with liver enzymes, and thyroid function tests.

So one may ask "Is it worth it?" One adult, in her mid-40s when her therapy was started had shown enormous improvement on a number of physical measures, not the least of which, according to

her parents, was that she could now travel for four hours without having to take a "potty break" – an increase from the once an hour stop previously needed. After two years of treatment, she was in danger of losing funding for her medication. She personally called her insurance company and said "You can't take away my hormone, my brain is not confused any more!" Her hormone was continued. However, even with appropriate testing and documentation of growth hormone deficiency in adults, both those with and without PWS, obtaining coverage for GH therapy can be difficult in the United States.

REFERENCES

- ¹Myers S, Carrel, A.L., Whitman B, Allen D. (2000) Sustained benefit after 2 years of growth hormone on body composition, fat use, physical strength and agility, and growth in Prader-Willi syndrome. *Journal of Pediatrics* 137 (1): 42-49.
- ²Prader, A; Labhart, A; Willi, H (1956). Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myatonieartigem Zustand im Neugeborenenalter. *Schweizerische Medizinische Wochenschrift*. 86:1260-1261.
- ³Butler MG, Meaney FJ. (1991). Standards for selected anthropometric measurements in Prader-Willi syndrome. *Pediatrics*. 88 (4):853-860
- ⁴Myers SE, Carrel AL, Whitman BY, Allen DB. (1999) Physical Effects of Growth Hormone Treatment in Children with Prader-Willi Syndrome. *Acta Paediatr Suppl* 433:112-114
- ⁵Carrel A, M. S., Whitman BY, Allen DB., (1999). Growth Hormone Improve Body Composition, Fat Utilization, Physical Strength and Agility, and Growth in Prader-Willi Syndrome: A Controlled Study. *J. Pediatr*, 134, 215-221.
- ⁶Whitman BY, M. S., Carrell A, Allen D. (2002). The Behavioral impact of growth hormone treatment for children and adolescents with Prader-Willi syndrome: A 2-year, controlled study. *Pediatrics*, 109q2(2), e35.
- ⁷Wiren I, Bengtsson B, and Johannsson G. Beneficial effect of long-term GH replacement therapy on quality of life in adults with GH deficiency. *Clin Endocrinol* 1998; 48: 613-620.
- ⁸Sandberg D, Brook A, Campos S. Short Stature: A psychosocial burden requiring growth hormone therapy *Pediatrics* 1994; 94 (6): 832-840.
- ⁹Hoybye C, H. A., Jacobsson H, Thoren M. (2002). Metabolic profile and body composition in adults with Prader-Willi syndrome and severe obesity. *J of Clinical Endocrinology and Metabolism*, 87, 3590-3697.