

Stimulation of Collagen Synthesis and Linear Growth by Growth Hormone in Glucocorticoid-Treated Children

In this study, the collagen synthesis and insulin-like growth factor 1 (IGF-1) status before and after growth hormone (GH) treatment in children on chronic glucocorticoid (GC) therapy was investigated. Seven children with the following diagnoses were studied: autoimmune colitis, eosinophilic fasciitis, asthma, nephrotic syndrome, and renal transplant recipients for obstructive uropathy, hypoplastic kidneys, or focal segmental glomerulosclerosis. The chronologic age of the patients was between 8 3/12 and 15 7/12 years, the bone age was <10 years for girls and <12 years for boys, and the Tanner staging was prepubertal for all except for one girl, who was Tanner stage III. All had subnormal growth velocity for at least 6 months prior to the study while on stable dosages of GC. Height, weight, IGF-1 activity, glycosylated hemoglobin level, and C-terminal type 1 procollagen levels were measured at baseline and every 3 months thereafter following the initiation of treatment with recombinant human GH (0.3 mg/kg/wk) for 6 to 21 months (mean, 13.1 ± 4.9 months). Skeletal maturation and 2-hour postprandial serum glucose and insulin levels were assessed every 6 months. All patients showed increased growth velocity during treatment with GH. Mean growth velocity increased from 3.43 ± 0.65 cm/yr to 6.72 ± 0.84 cm/yr with GH therapy ($P < 0.005$). SDSs corrected for bone age ($P < 0.005$), IGF-1 levels ($P < 0.005$) and C-terminal type 1 procollagen levels ($P < 0.005$) also increased with GH therapy. C-terminal type 1 procollagen levels correlated well with growth velocity ($r = 0.652$), while IGF-1 levels did not ($r = 0.17$). Glycosylated hemoglobin levels rose during GH treatment. It was felt that since no child experienced significant improvement in his or her underlying illness or puberty stage, and since glucocorticoid dosages changed little during the study period (never decreasing below the baseline dose in 6 of 7 children), the improvement in GV

and type 1 collagen synthesis noted were likely the result of GH treatment. It was concluded that both inhibition of IGF-1 effects and collagen synthesis were responsible for the growth-retarding effects of GC therapy.

Allen DB, Goldberg BD. *Pediatrics* 1992;89:416-421.

Editor's comment: *This study appears to show benefits of GH treatment. It promoted growth and procollagen synthesis in children on long-term GC therapy. This study also offers a biochemical explanation for stunted growth due to GC treatment and for increased growth velocity with GH therapy. This study appears to support the hypothesis that impaired linear growth and skeletal maturation associated with chronic GC therapy results from: (1) inhibited IGF-1 activity and (2) impaired type 1 procollagen synthesis. Additionally, GC may suppress GH secretory response to GH-releasing hormone, but this was not measured by the authors. Each mechanism could potentially be improved by exogenous GH treatment if sufficient dosages are given to overcome these 3 competitive effects of GC. However, the data differ from that reported many years ago by other investigators who showed that GH had no beneficial effects on GC-treated children (J Clin Invest 1968;47:436-491). We also have treated several patients with corticosteroid-dependent asthma on GC therapy, and they showed marked improvement in growth after GH therapy. However, the effects of GH therapy were related to the dose of GC given while GH treatment was ongoing (presented at the 73rd Annual Meeting of the Endocrine Society, June 19-22, 1991; abstract No. 1315). GH treatment at the dosage usually employed for treatment of hypopituitarism or for Turner syndrome patients could not overcome the effects of pharmacologic doses of GC.*

It is difficult to ascertain from the studies reported by Allen and Goldberg whether improvement in disease activity (not quantitated) and/or alternate-day GC treatment resulted in catch-up growth coincidentally with GH therapy in their patients. Five of 7 patients received 15 to 50 mg/m²/d hydrocortisone equivalent on an alternate-day regimen, and the remaining 2 patients received only a physiologic dose of 15 mg/m² hydrocortisone equivalent.

The exact amount of GC administered on alternate days necessary to inhibit and/or allow growth is not known. The effect of alternate-day GC treatment on growth was studied by Whittington et al in patients with Crohn's disease (Gastroenterology 1977;72:1338-1344). In that study, the dose of prednisone given was from 52.5 to 157.5 mg/m²/d of hydrocortisone equivalent. Despite these pharmacologic doses, the patients showed catch-up growth when GC was given every other day.

In this study, the normal or elevated pretreatment values of IGF-1 were attributed, in part, to the obesity and/or hyperinsulinemia found in many GC-treated patients. Dissociation of serum GH and IGF-1 levels in obese individuals might result from insulin-mediated IGF-1 production and consequent suppression of GH secretion (J Clin Endocrinol Metab 1976;42:370-378 and Endocrinology 1979;73:209-213). Further, it was previously shown that within

hours of oral GC administration, IGF-1 activity falls precipitously while IGF-1 levels remain unchanged (J Clin Endocrinol Metab 1985;61:618-626). This inhibitory effect was reflected by the GC-induced stimulation/potential of circulating IGF-1 inhibitors. Thus, while IGF-1 levels rose with GH therapy in these patients, the poor correlation with growth velocity was not surprising.

The potential beneficial effects of GH treatment in patients receiving GC need to be considered in relation to increasing the risk of side effects when patients are treated with these 2 antagonistic drugs. Particular attention needs to be given to the administration of large doses of GH, which may be needed to overcome the pharmacologic effects of GC. This would potentiate carbohydrate intolerance as well as increase other potential toxicities. Thus, undertaking a trial with GH in growth-inhibited patients receiving GC without an investigative protocol is strongly discouraged. There may be other treatments of potential value to enhance growth while controlling the primary disease that may be of help in corticosteroid-dependent patients, ie, corticotropin therapy. (Acta Paediatr Scand 1990;79:77-83).

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