

Insulin-Like Growth Factor 1 Improves Glucose and Lipid Metabolism in Type 2 Diabetes Mellitus

Type 2 (non-insulin dependent) diabetes mellitus (DM) is associated with hyperinsulinemia and a degree of insulin resistance. In order to determine the effect of insulin-like growth factor 1 (IGF-1) in patients with type 2 DM, the investigators administered recombinant human IGF-1 (120 µg/kg body weight per dose) by twice daily SC injection for 5 days to 8 adults (2 females) with type 2 DM. During IGF-1 administration: total and free IGF-1 concentrations increased as anticipated; IGF-2 and basal growth hormone (GH) concentrations fell; fasting glucose, fructosamine, triglyceride, insulin, C-peptide, and proinsulin levels declined; postprandial concentrations of glucose, insulin, C-peptide, and proinsulin, and the insulin:glucose and proinsulin:insulin ratios fell. Basal concentrations of glucagon were not changed by IGF-1 administration. The decline in fasting concentrations of glucose, triglyceride, insulin, and C-peptide during treatment with IGF-1 correlated directly with their respective fasting control levels.

The authors suggested that IGF-1 in type 2 DM:

1. decreased glucose concentrations by interaction of free IGF-1 and/or IGF-1 bound to IGF-binding protein 1 with type 1 IGF and insulin receptors in muscle. (Free IGF-1 levels are increased by lower insulin values and, when combined with IGFBP-1, cross the vascular barrier more easily than does IGF-1 bound to IGFBP-3.);
2. suppressed insulin secretion by a direct effect on the pancreatic beta cell; and
3. improved insulin sensitivity by lowering glucose, insulin, GH, and triglyceride concentrations.

They concluded that IGF-1 may have a therapeutic role in the management of patients with type 2 DM.

Zenobi PD, Jaeggi-Groisman SE, Riesen WF, et al. *J Clin Invest* 1992;90: 2234-2241.

Editor's comment: This article complements others that report the beneficial effects of IGF-1 in insulin resistant states, such as type 1 (insulin-dependent) DM.¹ In patients with type 2 DM, IGF-1 probably lowered glucose values by increasing glucose transport into muscle, acting through IGF-1 and/or insulin receptors stimulated by free IGF-1 and IGF-1 bound to IGFBP-1 that crossed vascular barriers and then dissociated from rapidly degraded IGFBP-1. It is likely that IGF-1 may have important therapeutic potential in insulin-resistant states as may an incompletely processed form of pro-IGF-2.²

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1. Schoenle EJ, Zenobi PD, Torresani T, et al. Recombinant human insulin-like growth factor-I (rhIGF-I) reduces hyperglycaemia in patients with extreme insulin resistance. *Diabetologia* 1991;34: 675-679.
2. Zapf J, Futo E, Peter M, Froesch ER. Can "big" insulin-like growth factor-II in serum of tumor patients account for the development of extrapancreatic tumor hypoglycemia? *J Clin Invest* 1992;90:2574-2584.

Growth Hormone Deficiency During Puberty Reduces Adult Bone Mineral Density

Hyer et al measured bone mineral density (BMD) by dual energy X-ray absorptiometry in 60 adults (aged 23 to 76 years) with growth hormone deficiency (GHD, defined as a peak GH response below 5 mU/L after insulin-induced hypoglycemia). Ten of the 60 patients had GHD documented before the completion of puberty and 5 patients had received human GH (0.25 IU/kg IM 3 times a week for a mean of 6 years) until epiphyseal fusion. All patients received physiologic replacement of thyroxine, corticotropin, or sex steroids as needed. A control group of 17 subjects age-matched to these 10 patients also was studied. The larger group of GHD adults was matched to a normal reference population studied with an identical scanner. BMD was measured at the lumbar spine (L2 - L4), the femoral neck, and at Ward's triangle (a region of the proximal femur consisting predominantly of trabecular bone). The coefficient of variation for BMD measurement is 1% at the lumbar spine and 2% at the femoral neck.

The 10 subjects with GHD identified during puberty had a longer duration of GHD than the other 50 subjects, and those who were treated with GH were taller than those who were not treated. The mean BMD in the 5 untreated subjects was significantly lower than that of the controls and that of the GH-treated subjects. The 50 subjects with adult-onset GHD had mean BMDs of 89.9 ± 2.2% (lumbar spine), 96.1 ± 1.1% (femoral neck), and 96.0 ± 2.7% (Ward's triangle) when compared with the reference population. A significant negative correlation was found between the duration of GHD in all subjects and BMD measured at the lumbar spine or Ward's triangle.

Editor's comment: These findings suggest that untreated GHD during puberty results in diminished BMD at adulthood and that there may be some reduction in BMD with GHD acquired during adulthood. However, it should be noted that the standard errors of the mean for BMD determinations in the large group of GHD adults are very close to the coefficients of variation for the BMD measurement at the 3 sites. Thus, although a significant negative correlation was shown between duration of GHD and BMD measured at 2 sites, the clinical significance of these findings is not clear.

We recently reviewed reports of diminished BMD in adult men with a history of constitutional delay of puberty and in adult men with treated GHD (GGH 1992;8(3):13). In the latter study, the adults with GHD were all diagnosed and treated prior to epiphyseal fusion. In the present study, Hyer et al reported findings in a large cohort of adults who acquired GHD as adults and show somewhat different findings. Their findings, however, lend further support to the hypotheses that the diminished BMD associated with pubertal delay is secondary to a relative GH insufficiency during early adolescence. In a recent report in the *Journal of Pediatrics* (1993;122:37-45), Saggese measured BMD in 26 children aged 6.5 to 10.7 years with isolated GHD and showed diminished BMD at the distal radius (corrected for chronologic stature and bone ages) that was significantly increased by 12 months of GH therapy. These findings suggest a need for a larger prospective study to describe the relationship between BMD and GH secretion.

Hyer SL, Rodin DA, Tobias JH, et al. *Arch Dis Child* 1992;67:1472-1474.

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