

Diabetes Control and Growth Hormone: New Insights

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Type I diabetes is characterized by a variety of metabolic and hormonal abnormalities in addition to hyperglycemia. Elevations in plasma growth hormone (GH) levels frequently have been observed in Type I diabetics, but the mechanisms by which these elevations occur have been difficult to establish. Arguments that GH hypersecretion plays a role in perpetuating the metabolic derangements of diabetes have waxed and waned in popularity. The introduction of intensive insulin treatment regimens and other new in vivo techniques has provided considerable information about the complex interrelationships between metabolic control of diabetes and GH secretion and action. Studies in these areas have produced results that have implications concerning GH regulation in nondiabetic subjects as well.

Influence of Metabolic Control on GH Secretion

Hansen was the first to show reversibility of GH hypersecretion in response to exercise by intensive treatment with multiple injections of insulin. Similarly, basal and post-exercise GH concentrations have been restored to normal following continuous subcutaneous insulin infusion (CSII) treatment, which also normalized the elevated mean 24-hour GH concentrations.

Several studies have tried to ascertain the level at which diabetes affects central regulation of GH secretion. Although there is little evidence to suggest that metabolic control of diabetes directly influences the pituitary, indirect effects have been demonstrated. For example, the pituitary response to

stimulation with GH-releasing factor is normal when diabetics are hyperglycemic, but not when they have normal plasma glucose concentrations. On the other hand, hypersecretion of GH has been observed in poorly controlled patients in response to several stimuli, such as arginine, L-dopa, and clonidine, that are thought to act through the hypothalamus. Furthermore, improved control with CSII reduces to normal the GH response to clonidine (an α_2 -adrenergic agonist), but does not affect the pituitary response to GH-releasing factor.

Deranged hypothalamic regulation of GH secretion in diabetes may be more selective than the above might indicate. For example, Simonson et al used a modification of the insulin clamp procedure to study the effects of improved metabolic control with CSII on the GH response to hypoglycemia, the classical hypothalamic stimulus. Surprisingly, the GH response to a lowering of plasma glucose from 90 to 50 mg/dL was normal when the patients were poorly controlled and suppressed to subnormal values after eight months on CSII.

Influence of Metabolic Control on Insulin-Like Growth Factors

Because GH levels tend to be increased rather than reduced in poorly controlled diabetes, investigators began to look for possible diabetes-induced defects in other circulating growth factors, particularly insulin-like growth factor I (IGF-I). Early studies in diabetics receiving conventional treatment yielded contradictory results, with normal, elevated, and reduced levels of IGF-I being reported. These discrepancies may have resulted from differences in methodologies (eg, bioassay v radioimmunoassay), variability in the level of diabetic control, and failure to account for the increase in IGF-I that accompanies normal pubertal development. Thus, it is noteworthy that Blethen et al recently found a negative correlation between glycosylated hemoglobin and age-adjusted IGF-I values in conventionally treated adolescents with diabetes.

Recent studies of CSII have clearly demonstrated that inadequate insulin replacement results in a defect in IGF-I synthesis. Not only were IGF-I levels reduced in poorly controlled diabetic patients, as compared with age- and sex-matched normal controls, but IGF-I levels increased by 25% after only one week of CSII despite a fall in GH values. A further increase in IGF-I concentrations is observed with more prolonged improvement in metabolic control. Lanes et al showed that IGF-I response to exogenous GH administration was blunted in poorly controlled diabetics when compared to the response in relatively well-controlled subjects.

In contrast, metabolic control of diabetes appears to have little effect on IGF-II values. IGF-II levels have been reported by Amiel et al to be normal in both adults and adolescents with diabetes, and no change in mean values was noted after CSII. However, in the latter study, four of 19 patients with very low IGF-I levels also had depressed IGF-II concentrations (which returned to normal with improved metabolic control). Thus, except in the most severely affected patients, compensatory increases in GH appear to be sufficient to maintain adequate IGF-II production.

Influence of GH on Metabolic Control

Hypersecretion of GH may also help perpetuate the metabolic derangements of diabetes to a much greater extent than is generally appreciated. In a recent study, Press et al administered exogenous GH as hourly intravenous pulses to a group of diabetics who were optimally controlled with CSII. Prior to GH administration, mean 24-hour plasma glucose and GH levels were within the normal range. However, when serum GH was raised to levels seen in poorly controlled patients, a progressive rise in plasma glucose was observed. Surprisingly, the hyperglycemia was primarily due to a marked stimulation of hepatic glucose production. GH is usually thought to increase glucose concentrations in diabetics, as in non-

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diabetics, by inhibiting glucose uptake in peripheral insulin-sensitive tissues.

The adverse metabolic effects of GH demonstrated in this study were not confined to plasma glucose levels. Levels of circulating fatty acids, ketones, and branched-chain amino acids were also increased. Therefore, GH elevations can themselves produce the entire spectrum of abnormalities associated with poor diabetic control, despite previously optimized insulin treatment. It follows that some of the metabolic benefits of more intensive insulin regimens may be derived from GH-lowering effects.

The "dawn" phenomenon is a significant cause of glycemic lability in insulin-dependent diabetics. Plasma glucose and basal insulin requirements vary considerably during the night. Both reach a nadir between 2 and 4 AM and then rise together as daylight approaches. It was originally thought that these changes reflected diurnal fluctuations in plasma cortisol. However, a delayed anti-insulin effect exerted by the early nocturnal surges of GH may be a more likely explanation; however, not all investigators agree with this concept.

Diabetes in adolescents is particularly difficult to control. Although control problems are usually attributed to psychosocial and dietary factors, the hormonal changes of puberty might also play a role. If such is the case, the puberty-associated rise in GH would be expected to be a contributing factor. In a recent study, insulin sensitivity was determined in preadolescents and adolescents, with and without diabetes, using the euglycemic, hy-

perinsulinemic insulin clamp technique. It should be noted that insulin-mediated glucose metabolism was reduced in diabetic patients and healthy children with the onset of puberty. Furthermore, the degree of insulin resistance was directly correlated with mean 24-hour GH concentrations.

Influence of Metabolic Control on Linear Growth

The observation that most conventionally treated diabetic children appear to be growing at a normal rate despite a host of metabolic and hormonal derangements is a testament to compensatory mechanisms that help sustain growth. However, Tattersall and Pyke found that patients who had developed diabetes before puberty were shorter as adults than their non-diabetic identical twins. The view that diabetic children may not be achieving their full growth potential is supported by studies that employ intensive treatment. Adolescents with diabetes—even those with normal stature and apparently normal growth rates on conventional therapy—show a sharp increase in growth velocity during treatment with either CSII or multiple injections.

Although it is attractive to speculate that the increased growth seen in well-controlled adolescents is the result of optimized therapy, such an interpretation is limited by difficulties in assessing growth velocity changes during puberty. To examine this further, we used a clonal stem cell assay for proliferation of erythroid progenitors (burst forming units-erythroid [BFU-E]) to determine the effect of CSII on cellular

growth in vitro. This assay system has been useful in assessing other causes of growth retardation. Blood was obtained from eight diabetic patients before and after one week of CSII. Numbers of BFU-E-derived colonies were not different from normal during conventional treatment, but increased sharply after one week of CSII. These changes in the in vitro cellular growth are strikingly similar to the long-term effects of intensive treatment on linear growth in adolescents. The ability to detect very rapid changes in cellular growth with the BFU-E assay illustrates the primary importance of improvements in fuel metabolism.

Summary

Viewed together, the observations presented in this article have important clinical implications. In the poorly controlled diabetic patient, a vicious cycle—whereby hypersecretion of GH acts as a compensatory response to a reduction in IGF-I—may become established. The associated rise in GH causes a worsening of metabolic control, further impairing the somatotrophic action of GH. The efficacy of intensive treatment may be due to an interruption of this cycle that lowers circulating GH concentrations. Normalization of hormonal milieu and improvement in growth rates are associated with good diabetic control. Consequently, physicians should make every reasonable effort to normalize glucose metabolism in juvenile diabetic patients. For those interested in reading further about the role of insulin in growth, an abstract entitled "Insulin as a Growth Factor" appears on this page.

References are available upon request to Dr. Blizzard.