

Growth and the Child with Diabetes Mellitus

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Prior to the discovery of insulin, linear growth failure was common among children with IDDM (1). And descriptive studies of growth velocity in the early insulin era identified significant subsets of children with marked growth failure (2). An extreme example of stunted growth, the Mauriac Syndrome—characterized by obesity, hepatomegaly and delayed puberty—was described and successfully treated with appropriate insulin administration and, more specifically, newer longer-acting insulin preparations (3). Today, children with this syndrome rarely are seen. Since the introduction of insulin therapy in IDDM more than 60 years ago, marked changes in the species, purity, duration of action, and mode of delivery have occurred, and improved methods for monitoring disease activity have been developed. Growth failure is not a common finding in pediatric diabetes clinics today; instead, it is seen only in the exceptional child with chronic underinsulinization and/or IDDM-associated acquired hypothyroidism.

Studies of intermediary metabolism and glucose counterregulation, however, have identified marked abnormalities in the hypothalamic-pituitary-growth axis in children with IDDM, even in those who are growing normally. Such findings suggest that even today's more modest levels of hyperglycemia and/or underinsulinization could be associated with potentially serious consequences for children in the future, including the development and progression of diabetic retinopathy. In this report, we review current knowledge concerning the pathophysiology of the growth axis in IDDM children and the mechanisms responsible for the abnormalities observed. In addition, we review studies of children with alterations in linear growth prior to the onset of clinical diabetes mellitus.

NORMAL GROWTH—Growth is a complex physiological process regulated by nutrition, genetic potential, and hor-

mones of the pituitary, thyroid, and gonadal axes. With adequate nutrition and physiological thyroid hormone status, growth is predominantly regulated by growth hormone (GH). Pituitary GH is secreted in a pulsatile fashion under the stimulatory control of hypothalamic GHRH and the inhibitory control of SRIF (somatostatin) (4,5). In the circulation, GH is bound to high-affinity GHBP, which reflect the status of the tissue GH receptor. GH acts primarily at the liver to generate a series of growth factors, the most important of which is IGF-I (6). IGF-I is bound to a series of IGFBP, of which at least six have been identified. The most important IGFBP for growth is IGFBP-3. IGF works at the tissues by increasing gene expression and protein synthesis (7). During puberty, mean 24-h GH increases as a result of a two- to threefold increase in GH pulse amplitude, with a relatively consistent number of pulses (8). IGF-I and IGFBP-3 also rise during childhood and peak during puberty (9). These changes are responsible for the mid-pubertal growth spurt (8,10).

The increases in GH during puberty are coincident with increases in fasting and stimulated serum insulin concentrations (11,12), suggesting a decrease in insulin sensitivity. Insulin sensitivity is inversely correlated with BMI, serum DHEA sulphate, and log IGF-I concentrations (13). The decreased insulin sensitivity during puberty is restricted to peripheral glucose metabolism, and the compensatory hyperinsulinemia may amplify insulin's effect on amino acid metabolism, thereby facilitating protein anabolism (14).

GROWTH IN THE CHILD WITH IDDM—Previous investigators have reported that children with IDDM in "poor" glucose control fail to grow at normal rates, although children with fair-to-good glucose control grow normally (15,16). More recent studies of the

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IDDM, insulin-dependent diabetes mellitus; IGF-I, insulinlike growth factor; GH, growth hormone; GHRH, growth hormone-releasing hormone; GHBP, growth hormone binding proteins; IGFBP, insulinlike growth factor binding proteins; BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; SRIF, somatotropin-release/inhibiting factor (somatostatin); DHEA, dehydroepiandrosterone; AChE, acetylcholinesterase

relationship between glucose control and growth, however, suggest little or no significant retardation with modest hyperglycemia (17–19). However, Rudolf et al. (17) demonstrated marked increases in growth velocity to supranormal rates in a group of 9 adolescents with IDDM when glucose control was markedly improved following 6 mo of intensive insulin treatment. Despite a wide variation in initial levels of glucose control (HbA_1 12.4 ± 3.0 SD) in these subjects, initial growth rates were appropriate for age and stage of sexual development. The increase in growth velocity was accompanied by a significant increase in insulin dose (1.0 ± 0.2 U/kg/d to 1.3 ± 0.2 U/kg/d), corroborating insulin's importance as a growth factor.

A recent study by Wise et al. (18) of the relationship between changes in height Z scores and level of glucose control does not report absolute heights. The changes in Z scores are all < 0.5 SD U. Although statistically significant, the results do not appear clinically relevant.

STUDIES OF GH SECRETION —

The most commonly reported abnormality in GH secretion in IDDM children (and adults) is a marked increase (3 to 4 times normal) in mean 24-h GH concentrations (20–23). Studies using frequent blood sampling and sophisticated deconvolution analysis have demonstrated that these elevations are not caused by an increase in frequency of GH neurosecretory events (bursts), but rather to an increase in the maximal rate of GH secretion per burst (19,24). Several investigators have demonstrated a reduction, but not normalization, in mean 24-h GH concentrations with short-term (up to 2 wk) reductions in mean 24-h glucose concentration (21,22,25,26). Others, however, have found no relationship between integrated (mean) GH levels and mean glucose levels (23). The failure to identify such a relationship may be the result of having selected an inappropriately large age range of subjects.

Nieves-Rivera et al. (19) have recently shown that even though an inverse relationship between HbA_1 concentration and the mass of GH per secretory burst exists for all age-groups, somatotrope responsiveness to a similar degree of glycemic control differs at different pubertal stages. Once puberty is well established (Tanner stages 4 and 5), GH secretion does not differ between diabetic and normal boys despite modest hyperglycemia (HbA_1 $10.8\% \pm 0.6$ to $12.2\% \pm 0.7$).

The mechanism for the augmented pituitary GH secretion is unclear, but there is evidence to suggest the probability of hypothalamic dysfunction characterized by dysregulation of GHRH and/or SRIF synthesis and/or release (27). The exaggerated pituitary GH response to exogenous GHRH in hyperglycemic IDDM subjects is inappropriate for the circulating level of glucose, i.e., hyperglycemia fails to suppress GH responses to GHRH as in nondiabetic subjects (28). This response is not the result of underinsulinization because similar responses have been observed in poorly controlled IDDM subjects during hyperglycemic hyperinsulinemic clamp studies (29). In addition, Guistina et al. (30), in studies of the effect of the AChE inhibitor, pyridostigmine, which is thought to decrease hypothalamic somatostatin tone, showed that IDDM subjects with longer disease duration, higher basal GH levels, and higher HbA_1 levels have exaggerated GH responses to GHRH but lesser GH release after pyridostigmine. Pyridostigmine and GHRH were synergistic in nondiabetic subjects. These findings suggest that a decrease in somatostatin tone may contribute to the abnormal pituitary GH response to GHRH. Studies of IDDM subjects in poor glucose control show that suppression of GHRH-induced GH secretion occurs only with a SRIF dose > 15 times that required in nondiabetic subjects (31). This suggests pituitary resistance to SRIF in IDDM. Studies in adolescents in poor glucose

control showed that 4 wk of improved glucose control is insufficient to suppress GH responses to GHRH, suggesting that the abnormality in hypothalamic somatostatin secretion may be chronic (32). GH responses to other secretagogues (e.g., clonidine and exercise) are exaggerated as well, but can be reduced after chronic intensive insulin therapy, which lowers mean 24-h glucose and HbA_1 concentrations (33,34). In summary, there is sufficient evidence to suggest abnormalities in the hypothalamic-pituitary-GH axis. Such abnormalities are more common in subjects with IDDM in poor glucose control and may not be ameliorated by short-term intensive insulin therapy. Whether these findings can be reversed by sustained improved glucose control remains to be determined.

TARGET EFFECTS OF GH IN

IDDM — GHBP, which reflect the status of the GH receptor, are reduced in children with IDDM when compared with control subjects (6). However, the level of GHBP apparently is not related to glucose control, which suggests there is also cellular GH resistance in IDDM children. Unfortunately, this study included few prepubertal children for whom the effects of glucose control on GH secretion and action may be more relevant.

Despite elevated serum GH levels in IDDM children, IGF-I levels are lower than in normal individuals. The relationship of IGF-I level to the degree of glucose control is variable; some investigators have observed an inverse relationship between IGF-I and HbA_1 concentrations (35), whereas others have not (36). Salardi et al. (37) compared IGF-I values in prepubertal and pubertal IDDM children to age- and sex-matched control subjects. Prepubertally, IGF-I levels were significantly lower in the IDDM subjects than in the control subjects, but no correlation was observed between IGF-I levels, duration of diabetes, and growth ve-

locity standard deviation score among 3 levels of glucose control. Studies from our laboratory confirm these findings. Among 25 IDDM boys with mean HbA_{1c} levels indicative of moderate hyperglycemia, IGF-I levels were decreased only in the prepubertal group, compared with control subjects (19). However, once puberty was established, IGF-I levels did not differ from those in normal adolescents. Although intensive insulin therapy increases low IGF-I levels (26), prolonged intensive therapy (up to 16 wk) may be necessary to increase these levels to near normal (38).

The pattern of elevated GH levels and paradoxical reductions in IGF-I levels is similar to that seen in nutritional deficiency (39–41). The response to intensive insulin therapy is similar to that seen in nondiabetic children with protein calorie malnutrition or anorexia after re-feeding (41–44) and chronic inflammatory bowel disease with therapy (45). Thus, the findings in diabetes are compatible with an intracellular energy deficit, which is not readily reversed by acute reductions in glucose levels. Likewise, administration of GH does not acutely generate IGF-I. (46).

IGFBP also are abnormal in IDDM children. IGFBP-3, which is regulated by GH, is abnormally low in IDDM children and does not increase with advancing age and puberty as in normal individuals (47,48). IGFBP-1, a low molecular weight protein not regulated by GH or IGF-I, is usually inversely related to IGF-I and IGFBP-3 concentrations, and is inversely correlated with insulin levels (48). IGFBP-1 levels in IDDM children were 4 times higher than those in normal individuals and correlated with poor metabolic control (49). Serum from adolescents with IDDM and increased IGFBP-1 concentrations have been shown to inhibit IGF-I bioactivity on cartilage *in vitro* (50). It would appear, therefore, that there are significant abnormalities in IGFBP, in addition to chronic abnormalities in somatostatin

tone, GH receptors, and in the generation of IGF-I in IDDM children.

GROWTH AT PUBERTY — Children with IDDM have impaired insulin action during puberty (51), suggesting that the insulin required (U/kg) to maintain euglycemia increases significantly (52). However, the importance of peripheral hyperinsulinemia and euglycemia for optimal growth in IDDM is not clear. Wise et al. (18) have demonstrated that growth deceleration is not observed during puberty unless glucose control is exceedingly poor. And Rudolf et al. (17) showed that high rates of insulin administration (1.3 U/kg/d) during adolescence can be associated with supranormal growth rates.

SEXUAL DEVELOPMENT — The relationship between sexual development and glucose control has not been studied in detail. Before the introduction of insulin therapy, menarche and subsequent menstruation occurred only rarely in girls who developed diabetes during childhood (1,53,54). Tattersall and Pyke (55) recorded the age at menarche in pairs of identical twins, one of whom had diabetes. Although normal intrapair differences in menarche average 2.8 mo, when diabetes developed in one twin before the onset of puberty, her menarche was delayed as much as 5 yr. More recent studies in larger childhood populations show that as many as 33% of boys and 20% of girls may have delayed skeletal maturation, presumably indicating delayed sexual development (56). However, the clinical experience of most pediatric diabetologists suggests that pubertal delay does not occur at an increased frequency in children with IDDM.

GROWTH BEFORE THE ONSET OF DIABETES — Stature at the time of diagnosis of IDDM has been reported var-

iously as short, tall, or as expected for age (57–62), but few studies have examined growth velocity before disease onset. Leslie et al. (63) recently reported growth velocities in 12 monozygotic twin pairs, in which one twin had IDDM. Of the pairs, 7 developed diabetes and 6 of these had a decrease in growth velocity before clinical onset. Of these 6, 4 had growth retardation before any abnormality in glucose tolerance. Recent population-based studies suggest that children with diabetes are taller than control subjects and/or siblings for a period of 3 to 7 yr before the onset of clinical disease (64–67), and that there may be a dose-response relationship between height and risk of diabetes. This is more likely for males than females (67) and particularly for children before the onset of puberty (65,66). In fact, children with IDDM onset after puberty usually are shorter than normal. Thus, age of diabetes onset (prepubertal vs. pubertal) may explain the discrepancy in height reported in earlier studies. The pathophysiological significance of growth before clinical diabetes onset is unclear because GH secretion and/or basal and stimulated insulin levels have not been determined. It has been speculated that rapid linear growth may increase insulin demand and deplete pancreatic β -cell mass, or that hyperinsulinemia, perhaps of genetic etiology, may accelerate growth and increase the vulnerability of β -cells (67). However, there is no firm evidence to support either hypothesis.

CONCLUSIONS — In summary, it would appear that there are significant abnormalities in GH secretion, GHBP reflecting GH receptor number, IGF-I production, and IGFBP concentrations in children with IDDM. Many previous studies have been confusing because they have not separated children based on their pubertal status. It is becoming clear that the prepubertal child may be more vulnerable to the effects of hyper-

glycemia on augmented GH pulse amplitude and reduced IGF-I. Once gonadal steroids are produced in sufficient quantities they become the dominant factor responsible for pituitary secretory activity (19). Thus, the age at which IDDM develops and the level of glucose control before puberty may have a significant bearing on adult height. We are unaware of reports of adult height with childhood-onset IDDM and the relationship to levels of chronic glucose control.

Clinically significant growth failure is unusual in contemporary pediatric diabetes clinic populations, but significant abnormalities in the hypothalamic-pituitary-GH axis exist even in normally growing children with IDDM. What happens postpubertally when GH secretion declines normally is unknown, but studies in adults with IDDM suggest that GH levels may remain elevated and IGF-I levels are reduced (27).

Adequate insulin therapy has obviated the problem of growth failure among children with diabetes, just as it has prevented deaths from recurrent ketoacidosis. However, just as it is unclear what level of glucose control can reduce the incidence of diabetic complications, it is unclear what level of glucose control can normalize the dysfunction observed in the hypothalamic-pituitary-GH axis. The relationship between elevated GH levels and diabetic retinopathy in adults with IDDM is well established. Whether this relationship has its origins in persistently elevated GH concentrations during childhood remains unclear. In addition, it is not known whether there are other potentially harmful growth factors that also may be dysregulated during moderate hyperglycemia and may predispose the child with IDDM to other significant and serious consequences in later life.

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