# Insulin-Like Growth Factors (IGFs) and IGF-I Treatment in the Adolescent With Insulin-Dependent Diabetes Mellitus

D.B. Dunger, T.D. Cheetham, and E.C. Crowne

**Insulin-dependent diabetes mellitus (IDDM) during adolescence is associated with complex derangements of the growth hormone (GH)/insulin-like growth factor (IGF) axis. Despite GH hypersecretion, IGF-I levels and IGF bioactivity are reduced. The diabetogenic effects of GH are well established, and GH hypersecretion has been implicated in the deterioration in glycemic control during adolescence and in the development of microangiopathy. Insulin deficiency or reduced portal delivery of insulin plays a central role in the development of these abnormalities, and although continuous subcutaneous insulin delivery may improve plasma IGF-I levels, it does not necessarily suppress GH levels. Recombinant IGF-I has been proposed as an adjunct to conventional insulin therapy, as restoring circulating IGF-I levels might lead to GH suppression. Placebo-controlled studies have shown a consistent reduction in GH secretion and related improvements in insulin sensitivity following a single subcutaneous IGF-I injection (40 μg/kg). Repeated daily subcutaneous IGF-I administration for 1 month resulted in a sustained increase in IGF-I levels, as well as a reduction in GH secretion and insulin requirements. There was no increase in hypoglycemia or other adverse effects. Recombinant IGF-I used in conjunction with insulin may therefore provide an additional approach to the management of IDDM during adolescence, allowing correction of abnormalities in the GH/IGF axis and leading to improved control and, hence, reduced risk of long-term complications. However, this hypothesis needs to be rigorously tested in long-term placebo-controlled studies.**



GLYCEMIC CONTROL as judged by serial glycosylated hemoglobin ($HbA_{1C}$) concentrations invariably deteriorates during adolescence in patients with insulin-dependent diabetes mellitus (IDDM), and this may be the explanation for the observed effects of puberty on the latency of diabetic complications. It is perhaps all too easy to attribute this deterioration in glycemic control to poor compliance and psychological problems. There is good evidence, however, that the hormonal changes of puberty and particularly changes in the growth hormone/insulin-like growth factor-I (GH/IGF-I) axis may also be relevant.[1] It has been argued that abnormalities of the GH/IGF-I axis may themselves result from poor control, but this is an oversimplification of the complex interactions between blood glucose, insulin, and the GH/IGF-I axis. In this article, we will put forward the evidence that supports a role for abnormalities of the GH/IGF-I axis in the pathogenesis of deteriorating glycemic control during adolescence, and discuss the possible use of recombinant human IGF-I (rhIGF-I) as an adjunct to standard insulin therapy in these patients.

## THE METABOLIC EFFECTS OF GH HYPERSECRETION

The increase in spontaneous GH secretion that characterizes normal puberty is accentuated in adolescents with IDDM, and both GH pulse amplitude and baseline concentrations are increased during overnight profiles.[2] GH clearance may be prolonged,[3] but even allowing for this, deconvolution analysis indicates that GH secretion is grossly elevated throughout puberty in males and females with IDDM as compared with controls.[4]

The diabetogenic effects of GH have been noted for many years, and it has been shown that changes in insulin sensitivity that occur during normal puberty correlate with the changes in overnight GH concentrations.[5] Thus, the greater increases in insulin resistance observed in subjects with IDDM during puberty have been attributed to GH hypersecretion. However, direct experimental evidence linking GH to changes in insulin sensitivity in IDDM has largely come from studies of the dawn phenomenon of increasing insulin requirements before breakfast.[6,7]

The dawn phenomenon can be demonstrated in adolescents with IDDM,[8,9] and it is quantitatively related to changes in GH hypersecretion during puberty.[10] Furthermore, it can be reversed by suppression of nocturnal GH release with agents such as pirenzipine.[10] Recent studies indicate that the changes in insulin sensitivity are directly related to GH pulse amplitude rather than to changes in baseline concentrations.[11] Changes in glucose uptake are maximal 120 minutes after the GH pulse, and the duration of insulin resistance relates to the peak GH levels.[12] Levels greater than 50 mU/L, which are often encountered during puberty, lead to sustained changes in insulin sensitivity lasting 6 to 7 hours. Although insulin sensitivity is closely related to GH levels overnight in IDDM, it is still unclear whether changes in insulin clearance may also be relevant.[13]

Less often documented are the effects of GH hypersecretion on overnight ketogenesis in adolescents with IDDM. In particular, the nocturnal surge in levels of β-hydroxybutyrate and acetoacetate appears to be directly related to GH secretion, and can be reversed with measures taken to suppress GH levels.[14] It has been argued that this observation may explain why many adolescents with IDDM decompensate with diabetic ketoacidosis rapidly overnight should they omit their evening insulin dose.

## ABNORMALITIES OF IGF-I AND IGF-BINDING PROTEINS

Whereas GH levels are invariably increased in adolescents with IDDM, circulating concentrations of IGF-I tend to be low or in the low-normal range.[15,16] This discrepancy

*From the Department of Paediatrics, The John Radcliffe Hospital, University of Oxford, Oxford, UK.*

*Address reprint requests to D.B. Dunger, MD, The John Radcliffe Hospital, Department of Paediatrics, Level 4, Headington, Oxford OX3 9DU, United Kingdom.*



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between GH and IGF-I levels appears to arise because of partial insensitivity to the effects of GH at the level of the hepatic GH receptor. Some confirmation of this has come from studies of the circulating GH-binding protein (GHBP), which appears to be identical to the extracellular domain of the GH receptor.[17] Low levels of GHBP have been observed in adolescents with IDDM.[18-21] Circulating concentrations of the major IGF-binding protein (IGFBP), IGFBP-3, are also reduced, since these are regulated by GH either directly or indirectly through the production of IGF-I.[22]

The hepatic GH receptor is, in part, insulin-dependent,[23] and Arslanian et al[24] have recently demonstrated that introduction of insulin therapy in newly diagnosed patients leads to a prompt increase in GHBP levels, but, interestingly, levels remain lower than those seen in normal subjects. The failure of standard insulin therapy to restore normal levels of GHBP and thus IGF-I appears to stem from the peripheral rather than the direct portal vein administration of insulin.[1]

Insulin also has a direct role in regulating IGF bioactivity through alterations in production of the small–molecular-weight IGFBP, IGFBP-1.[25] IGFBP-1 is largely produced by the hepatocyte, and its production is inversely regulated by insulin. In most bioassay systems, IGFBP-1 appears to act as an inhibitor, and the accentuated increase in IGFBP overnight in IDDM has been associated with a decrease in IGF bioactivity.[26]

## METABOLIC EFFECTS OF ABNORMALITIES OF IGF-I AND IGFBPs

The low levels of circulating IGF-I and the reduced IGF bioactivity during puberty have been linked to the blunted pubertal growth spurt in IDDM.[27,28] However, these abnormalities may also have indirect and direct effects on insulin sensitivity.

### *Indirect Effects*

The etiology of GH hypersecretion in IDDM is complex, but considerable attention has been given to the role of reduced circulating levels of IGF-I.[29] Animal studies indicate that IGF-I can affect somatostatin release by the hypothalamus,[30] and that it can modulate GH release by a direct action on the pituitary gland.[31,32] Furthermore, administration of rhIGF-I to normal subjects and individuals with Laron-type dwarfism has been shown to reduce GH levels.[33,34] Thus, it is reasonable to suppose that GH hypersecretion in IDDM results from increased feedback drive from reduced circulating levels of IGF-I.

In double-blind placebo-controlled studies of rhIGF-I administration in adolescents with IDDM, we were able to show consistent reductions in GH levels and GH secretion.[35] A single subcutaneous dose of rhIGF-I (40 μg/kg/body weight) led to sustained elevations in circulating IGF-I levels and improvements in IGF bioactivity. Mean 22-hour GH levels (15-minute sampling) were reduced from 33.6 ± 5.8 to 19.4 ± 4 mU/L. Deconvolution analysis revealed a significant overall reduction in the GH secretory rate, which was sustained throughout the 22-hour study period.[35]

Coincident with these changes in GH secretion, we were able to observe a significant reduction in the insulin infusion rate and insulin levels required to sustain euglycemia overnight.[36] Thus, we concluded that the improvements in insulin sensitivity overnight could, at least in part, be attributed to the reductions in GH secretion, and in subsequent studies we have been able to show a direct correlation between GH levels overnight and the insulin levels that needed to be sustained to achieve euglycemia. However, even with this low dose of rhIGF-I, we could not discount direct effects of "free IGF-I" on insulin sensitivity.

### *Direct Effects*

It is now many years since Zapf et al[37] first demonstrated that IGF-I exerted metabolic effects in vitro that closely resembled those of insulin, and it was shown subsequently that the structure of IGF-I shared remarkable sequence homology with human proinsulin and that the IGF-I and insulin receptors were structurally and functionally very similar. However, it has always been assumed that the insulin-like effects of IGF-I were not of physiological relevance, because IGFs circulate bound to a series of binding proteins[38] and the amounts of free IGF-I were so small as to be insignificant.

This view may have to be revised, since it is now known that IGFBPs have an important role in regulating bioavailability and thus bioactivity of IGF-I.[39] Lewitt et al[40] demonstrated that an infusion of IGFBP-1 leads to a prompt increase of blood glucose in experimental animals that is reversed by rhIGF-I administration. Thus, it could be argued that the reduced circulating levels of IGF-I and the high levels of IGFBP-1 in IDDM may contribute to overnight changes in insulin sensitivity by direct effects on glucose homeostasis.

We have recently investigated whether rhIGF-I may have direct effects on insulin sensitivity in subjects with IDDM. In these double-blind studies, either rhIGF-I (40 μg/kg subcutaneously) or placebo was given at 6 PM and the effects on insulin sensitivity were assessed overnight using a variable-rate insulin infusion. On both study nights, endogenous GH secretion was suppressed using somatostatin, and three GH pulses (peak, 30 to 40 mU/L) were produced by infusion of rhGH. Thus, on both nights, GH levels were identical and the differences observed could be attributed directly to the effects of rhIGF-I. Significant reductions in insulin infusion requirements and insulin levels necessary for euglycemia were observed after rhIGF-I, whereas levels of nonesterified fatty acids, β-hydroxybutyrate and acetoacetate were similar on the two nights.

The improvements in insulin sensitivity on the rhIGF-I night represented a reversal of the fluctuations in insulin sensitivity that followed the GH pulses observed on the placebo night, rather than any change in basal insulin sensitivity. Thus, it is possible that the pathogenesis of the dawn phenomenon is more complex than previously thought, and the effects of GH on insulin sensitivity in IDDM may

depend on the presence of coincident IGF-I deficiency. Further study will be required to separate the direct and indirect effects of rhIGF-I replacement on insulin sensitivity.

## FAILURE OF CURRENT INSULIN REGIMENS

The immediate response to any call for the use of rhIGF-I in IDDM is, "Why not use insulin?" However, there are major drawbacks to standard insulin therapy during puberty in IDDM. The long-acting insulins that we use as part of multiple injection therapy tend to lead to overinsulization during the early part of the night, and then levels of insulin wane toward the morning. This leads to an unacceptable risk of nocturnal hypoglycemia during the early part of the night and a failure to control the dawn increase in blood glucose concentrations.[41] Continuous subcutaneous insulin delivery (CSII) will improve the overnight free-insulin profiles and lead to increases in IGF-I levels,[16] but it will not necessarily lead to consistent reductions in GH secretion.[42-44] The explanation for this discrepancy may lie in the peripheral hyperinsulinism that invariably develops with CSII. Press et al[45] showed that hyperinsulinism may in fact lead to a paradoxical increase in the GH response to GH-releasing hormone in poorly controlled diabetic subjects.[45] Direct portal administration of insulin, on the other hand, leads to consistent reductions in GH secretion and increases in IGF-I levels and IGF bioactivity.[46,47]

## IGF-I THERAPY IN IDDM

CSII and intraportal delivery of insulin are not acceptable treatment options for most adolescents with IDDM, and the alternative strategy of restoring IGF-I concentrations using rhIGF-I is attractive. In short-term overnight studies, we have shown consistent reductions in GH levels and improvements in insulin sensitivity. In our studies of 17 subjects, basal overnight mean GH concentrations correlated with $HbA_{1c}$, and the greatest reductions in GH levels overnight following rhIGF-I were seen in subjects with the highest basal GH concentrations. Furthermore, the reductions in insulin sensitivity were directly related to the decrease in GH secretion following IGF-I administration.

We have recently examined the safety and efficacy of repeated daily subcutaneous administration of rhIGF-I over a period of 1 month. There was no increase in the incidence of hypoglycemia, and the increases in IGF-I levels, reductions in GH secretion, and basal insulin requirements were sustained throughout the study. Furthermore, a modest decrease in $HbA_{1c}$ levels was also observed.

No adverse effects were noted during this study, and in contrast to reports that increases in glomerular filtration rate may occur in normal subjects following rhIGF-I,[33] we observed a reduction in this parameter in five of six subjects that we studied. There was no evidence that rhIGF-I therapy led to any changes on retinal examination, and urinary albumin excretion was not affected. Nevertheless, these were short-term studies and do not exclude the possibility that rhIGF-I therapy might have adverse effects on diabetic microangiopathic complications.

The role of the GH/IGF-I axis in the pathogenesis of diabetic complications is discussed in greater detail in other sections of this supplement. Paracrine production of IGF-I has been linked to development of the glomerular changes in the diabetic kidney[48,49] and to vascular proliferation in the retina.[50] The link between circulating IGF-I levels and microvascular changes is more tenuous. Some early studies showed that proliferative diabetic retinopathy was associated with increased circulating levels of IGF-I,[51] but several recent studies have not been able to confirm this[52-54] or else suggest that the link is only evident in late-onset diabetes.[55] Generally poor glycemic control, an established risk factor for complications, is associated with reduced rather than elevated IGF-I levels.

The association between circulating GH levels and development of diabetic retinopathy has been more consistently observed.[56] This discrepancy between the relative roles of circulating GH and IGF-I levels in the etiology of microangiopathic complications may be explained by tissue differences in GH resistance. Whereas there is evidence of partial GH resistance at the level of the hepatic GH receptor, there is as yet no evidence to suggest that other tissue GH receptors are similarly resistant. Thus, whereas circulating IGF-I levels are reduced in IDDM, paracrine production of IGF-I may be enhanced. Under conditions of vascular proliferation and increased vascular permeability, increases in paracrine IGF-I production could actually lead to increases in circulating IGF-I levels. Hyperinsulinemia could also contribute to increased paracrine production of IGF-I.

## CONCLUSIONS

Thus, it can be argued that restoration of circulating levels of IGF-I with rhIGF-I and the consequent reductions in GH secretion and circulating levels of insulin could in fact reduce the risk of microvascular disease, but this hypothesis needs to be rigorously tested. If the short-term reductions in $HbA_{1c}$ that we observed during the 1-month study are sustained during long-term, double-blind, placebo-controlled studies, rhIGF-I may prove to have an important role as an adjunct to standard insulin therapy in IDDM.

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