Insulin-Like Growth Factor I Therapy for Diabetes Mellitus?

JERZY W. KOLACZYNSKI, MD
JOSE F. CARO, MD

Insulin-like growth factor I (IGF-I) is now produced by recombinant DNA technology, and the number of studies of its possible clinical applications is growing rapidly. Among these studies are trials using IGF-I in cases where insulin action is severely compromised, and the results presented so far are promising. For example, previously published case reports provide descriptions of diabetic patients with extreme insulin resistance in whom significant improvement in metabolic control was achieved during administration of IGF-I (1,2). More importantly, IGF-I has been shown to improve metabolic control in type II diabetic patients (3). These intriguing results raise the question of which differences between insulin and IGF-I action make the use of exogenous IGF-I the better choice for diabetes therapy, and which do not. These important issues are the major focus of this commentary.

First, we discuss data on the metabolic effects of IGF-I in normal and diabetic animals in vivo. Finally, we present known metabolic effects of IGF-I administration in humans and share our concerns that IGF-I therapy may be hazardous.

METABOLIC EFFECTS OF IGF-I IN NORMAL AND DIABETIC ANIMALS

— In both awake (4) and anesthetized normal rats (5), IGF-I exerts a hypoglycemic effect with a potency ~50 times smaller than that of insulin. The same difference in potency between insulin and IGF-I on glucose disposal was observed in experiments using the euglycemic clamp technique (5). Equivalent hypoglycemic doses of insulin and IGF-I, however, produced a similar disposition of glucose in muscle glycogen and lipids in adipose tissue (5). These data suggested that IGF-I effects were mediated via insulin receptors (5). On the other hand, in normal rats (4) and depancreatomized dogs (6) given doses of insulin and IGF-I that were equivalent in their glucose disposal effects, IGF-I was shown to produce smaller effects on adipose tissue lipolysis and hepatic glucose production than insulin. In addition, in the rat, IGF-I was more selective than insulin in stimulating glycogen synthesis in the liver and in skeletal and heart muscle (4), suggesting that IGF-I had no stimulatory effect on oxidative glucose disposal. Because only a single dose of IGF-I and insulin was used by both groups of investigators (4,6), no conclusions regarding the effect of dose specificity on the observed phenomena could be drawn.

In another study, the effects of IGF-I administration in 90% partially pancreatomized rats was compared with sham-operated control rats (7). In the control rats, infusions of IGF-I in doses ~30 times higher than insulin produced an equal effect in total body glucose disposal during euglycemic clamping. When the same protocol was used in partially pancreatomized rats, insulin-mediated glucose disposal was reduced, whereas IGF-I–mediated glucose disposal was similar to that in the control rats (7). In control rats, no additive effect of the two hormones was observed, whereas in the pancreatomized rats, IGF-I coinfused with insulin restored glucose utilization to normal (7). Similarly, in the diabetic BB rat (model of type I diabetes), the metabolic actions of insulin, but not IGF-I, were reduced (8). In another model of insulin resistance, obese Zucker rats, IGF-I could not overcome this defect (9). Resistance to the hypoglycemic action of IGF-I was also observed in obese mice (10,11).

Both obese Zucker rats and mice are hyperinsulinemic, but in the partially pancreatomized and diabetic BB rats, endogenous insulin levels are reduced. Insulin produces significant changes in the insulin-like growth factor binding proteins (IGFBPs). The expression of IGFBP-1 and IGFBP-2 has been shown to be markedly increased in liver and kidney in rats with diabetes induced by the selective destruction of pancreatic β-cells by streptozotocin (12,13). Furthermore, in diabetic animals, the expression of a protein corresponding in mass to IGFBP-3 is reduced in the liver (12). This change in binding proteins (increased BP-1 and BP-2, reduced BP-3) might well augment the hypoglycemic action of IGF-I. At present, it is safer, however, to speculate that a postreceptor defect in insulin action is located in a signal path-

From the Department of Medicine, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania.

Address correspondence and reprint requests to Jose F. Caro, MD, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, 1025 Walnut Street, Room 821, Philadelphia, PA 19107–5083.

IGF-I, insulin-like growth factor I; type II diabetes, non-insulin-dependent diabetes mellitus; type I, insulin-dependent diabetes mellitus; IGFBP, insulin-like growth factor binding protein.

Downloaded from http://diabetesjournals.org/care/article-pdf/17/1/92/442405/17-1-92.pdf by guest on 29 November 2022

way common to insulin and IGF-I in hyperinsulinemic rats and mice, but not in insulinopenic diabetic rats and dogs.

METABOLIC EFFECTS OF IGF-I IN HUMANS — Bolus intravenous injections of 13.3 nmol (100 μg)/kg IGF-I or 1 nmol (0.15 IU)/kg insulin produce nearly identical hypoglycemic responses in humans (14). Both hormones produce depression of fatty acids to the same low levels, but this depression lasted significantly longer after insulin than after IGF-I injection. A profound and prolonged hypoglycemic effect of 75 μg/kg IGF-I by intravenous bolus was also observed in patients with Laron-type dwarfism (15). Fasting hypoglycemia was produced during an 11-day long, constant, subcutaneous infusion of 16–24 μg/kg IGF-I in a 9-year-old Laron dwarf (16). In contrast, a subcutaneous infusion of either 7 or 14 μg/kg IGF-I, begun 24 h before and continued during oral glucose and meal tolerance tests in normal adult volunteer subjects, did not change fasting plasma glucose or glucose tolerance. Similar glycemic profiles, however, were achieved at significantly lower insulin and C-peptide levels during IGF-I infusions. IGF-I significantly depressed levels of growth hormone. The authors conclude that IGF-I administration may improve insulin sensitivity (17) by suppression of insulin and growth hormone secretion. It has to be stressed, however, that their conclusion of enhanced insulin sensitivity after IGF-I administration is only speculative, because no data were presented indicating improvement in insulin action that could be clearly distinguished from the summation of hypoglycemic effects of IGF-I and insulin. In this context, note that in Laron dwarfs, the reduction in insulin levels during administration of IGF-I was associated with postprandial hyperglycemia, probably because of reduced insulin secretory response (16).

IGF-I infusions (range 5–30 $\mu g \cdot kg^{-1} \cdot h^{-1}$) in the setting where glucose concentrations were clamped within the normal fasting range caused, in a dose-response manner, a reduction in the levels of insulin, fatty acids, triglycerides, β-hydroxybutyrate, leucine, and increased exogenous glucose consumption (18). IGF-I also had a sparing effect on protein catabolism as determined by the rates of leucine turnover and oxidation (18). These investigators concluded that IGF-I had metabolic effects qualitatively similar to insulin (18). These findings are in agreement with the results of another report documenting that, in the setting of primed (20 μg/kg bolus) constant (24 $\mu g \cdot kg^{-1} \cdot h^{-1}$) infusion of IGF-I and euglycemic clamping, IGF-I behaves as exogenous insulin (i.e., decreases C-peptide levels, inhibits hepatic glucose production, stimulates peripheral glucose uptake, inhibits lipolysis and protein catabolism [19]). Like insulin, it also stimulates oxidation of glucose and fatty acids. The authors conclude that the close similarity in IGF-I and insulin actions indicate that IGF-I acts via the insulin receptor, or else that the metabolic effects mediated by activation of the IGF receptor occur through a similar cascade of intercellular events (19). Moreover, it has been noted that exogenous IGF-I not only reduces plasma levels of insulin and C-peptide, but also depresses, although less potently, the levels of glucagon, probably because of the direct inhibitory effect of IGF-I on pancreatic A-cells and B-cells (18,19).

Although less potent than insulin, IGF-I can produce hypoglycemia, an effect that limits the application of IGF-I to reverse catabolic state or stimulate linear growth (20). The hypoglycemia induced by a bolus intravenous injection of IGF-I produces similar counterregulatory responses of glucagon, growth hormone, cortisol, and catecholamines during insulin-induced hypoglycemia (14). During hypoglycemia induced by primed constant infusions of IGF-I, the responses of glucagon and growth hormone were suppressed, the response of cortisol was normal, and catecholamines were elevated when compared with hormonal counterregulation during hypoglycemia of an identical rate of fall and nadir as that induced by primed constant insulin infusion (21). After IGF-I administration, glucose recovery was more sluggish than after insulin because of failure of endogenous glucose production to rise (21). When infusions of IGF-I and insulin were stopped, the insulin levels returned promptly to baseline values and IGF-I levels remained elevated. In the setting of hypoglycemic clamp studies performed with primed constant IGF-I infusion, a suppression of glucagon response only was observed, whereas other counterregulatory hormones responded in a manner similar to that observed during hypoglycemic hyperinsulinemic clamps (21).

The results of studies in nondiabetic humans demonstrate that some of the metabolic effects of IGF-I are different than expected from studies in vitro and in vivo in experimental animals. In this respect, IGF-I in humans seems to have a more profound effect on both endogenous glucose production and fatty acid levels, indicating significant action on the liver and adipose tissue. In humans, IGF-I may also stimulate glucose oxidation. That these effects are mediated via insulin receptors is a plausible explanation, but this may not be entirely correct. Clearly, more studies are needed to substantiate the role of IGF-I receptors in the liver, and the consequences of depressed insulin, glucagon, and growth hormone levels on the rate of hepatic glucose production and on lipolysis in adipose tissue. In spite of these unresolved questions, the results of studies in nondiabetic individuals may justify trials of IGF-I in clinical situations where profound insulin resistance cannot be overcome by insulin. In this respect, IGF-I has been shown to have a glucose-lowering effect in patients with the type A syndrome of insulin resistance (1). The syndrome, encountered in women, is characterized by acanthosis nigricans,

Downloaded from http://diabetesjournals.org/care/article-pdf/17/1/92/442405/17-1-92.pdf by guest on 29 November 2022

virilization, and extreme insulin resistance attributable to a structurally defective insulin receptor (22), whereas the IGF type I receptor appears intact. IGF-I, in two 100 μg/kg boluses, produced a slow (>6 h) hypoglycemic response with nadirs of 3.2–5.5 mM and a decrease in the markedly elevated insulin and C-peptide levels. In these patients, IGF-I, probably acting via its own receptors, was able to overcome the insulin receptor–associated defect in insulin action (1). One case report (2) documents an individual with a severe form of insulin resistance and frequent episodes of total unresponsiveness to intravenously administered insulin in doses as large as 3,000 U/h. In this patient, substitution of large doses (100–500 μg boluses) of IGF-I for insulin produced a prompt normalization of serum glucose that lasted as long as the total IGF-I concentration in the serum was >1,100 μg (0.14 μM). The authors conclude that the described effects of IGF-I were probably mediated via an IGF receptor signaling pathway that bypasses the insulin receptor defect (2).

In one report, Zenobi et al. (3) examined the metabolic effects of IGF-I in type II diabetic patients. IGF-I was administered subcutaneously in two daily 120 μg/kg injections for 5 consecutive days. The treatment significantly reduced the hyperglycemic response to mixed meals and decreased fasting and postprandial insulin and C-peptide levels. A decrease in growth hormone and total triglycerides also was noted. Interestingly, these effects persisted for 3 days after IGF-I administration was stopped. Based on these findings, the authors conclude that IGF-I administration improves insulin sensitivity and lipid metabolism in type II diabetes (3). Once again, however, the supposition that improvement in insulin sensitivity follows IGF-I administration (this would imply a potentialization of insulin action by IGF-I not just a summation of separate hypoglycemic effects of insulin and IGF-I) has not been sufficiently documented. Hypertriglyceridemia is associated with insulin resistance and is commonly present in poorly controlled, type II diabetic patients (23–25). A number of studies have shown that sensible insulin therapy in type II diabetes not only significantly improves glycemic control and insulin action but also reduces hypertriglyceridemia (23–25). Because this latter goal can be achieved by IGF-I as well, without raising but actually lowering insulin levels, the question arises whether IGF-I represents a better option in this regard.

CONCLUSIONS— Published data support the notion that IGF-I may, in selected cases, be an important adjunct to diabetes therapy. In the majority of diabetic patients, however, the standard therapeutic approaches (i.e., diet, exercise, insulin, and oral hypoglycemic agents) will normally suffice. IGF-I may be the therapy of choice in those rare situations where lack of effectiveness of exogenous insulin is attributable to nonfunctional or deficient insulin receptors. Based on published data, we may predict that here short-term IGF-I administration will result in significant metabolic improvement and even be life-saving. However, the safety and efficacy of the long-term substitution of IGF-I for insulin in such cases is unknown and difficult to predict. Such therapeutic decisions should always be weighed against the potential risks. IGF-I stimulates cell growth, but unfortunately, this stimulation does not discriminate between normal and tumor cells (26). In fact, growth of certain neoplasms is apparently IGF-I dependent (27). In this context, the notion that "IGF-I may prove to be a safe growth factor, since it is a 'differentiation' factor as well" (28) may not be entirely correct. IGF-I also stimulates the growth of arterial smooth muscle cells, one of the fundamental components of atherogenesis (29). In addition, IGF-I administration was associated with increase in kidney size as well as with rise in renal blood flow and glomerular filtration rate in normal human volunteers (30). In spite of the rise in glomerular filtration rate and renal hypertrophy after IGF-I administration, microalbuminuria does not develop in normal subjects (30). The same functional and morphological changes, however, if present in diabetes, are associated with microalbuminuria and progressing diabetic renal disease (31). IGF-I has been shown to bind to and increase glomerular mesangial cell proliferation (32,33); this expansion of mesangium is one of the most consistently observed structural changes in the diabetic kidney (34). Thus the question of whether or not IGF-I accelerates the progression of diabetic nephropathy is still open.

Moreover, published data suggest that serum IGF-I levels are increased in certain diabetic patients with proliferative retinopathy (35–37). IGF-I also has been shown to stimulate the proliferation of vascular endothelial cells in vitro (29,38). This process may stimulate both the healing of intimal lesions (i.e., beneficial effect) and the proliferation of microvessels (i.e., adverse effect) (38). Thus, the possibility remains that IGF-I administration may aggravate the progression of proliferative retinopathy.

In summary, a multitude of published reports suggests that IGF-I may be an interesting adjunct to diabetes therapy and, in some metabolic emergencies, may even be the drug of choice. More data are, however, needed to draw specific practical recommendations for long-term IGF-I use, so that its benefits clearly outweigh its risks. A satisfactory answer to the question of whether IGF-I is a friend when insulin fails remains a blank spot in our knowledge.

Acknowledgments— This work was supported in part by National Institutes of Health Grant RO1-DK-45592.

We are indebted to Drs. Barry Goldstein, Marshall Goldberg, and Robert Considine for careful review of the manuscript and to Drs. Gary G. Carpenter and Ewa Surmacz for valu-

Downloaded from http://diabetesjournals.org/care/article-pdf/17/1/92/442405/17-1-92.pdf by guest on 29 November 2022

able discussions. We also thank Diane Miller for typing the manuscript.

References

1. Schoenle EJ, Zenobi PD, Torresani T, Werder EA, Zachmann M, Froesch ER: Recombinant human insulin-like growth factor I (rhIGF-I) reduces hyperglycemia in patients with extreme insulin resistance. *Diabetologia* 34:675–79, 1991
2. Usala AL, Madigan T, Burguera B, Sinha MK, Caro JF, Cunningham P, Powell JG, Butler PC: Brief report: treatment of insulin-resistant diabetic ketoacidosis with insulin-like growth factor I in an adolescent with insulin-dependent diabetes mellitus. *N Engl J Med* 327:853–57, 1992
3. Zenobi PD, Jaeggi-Groisman SE, Riesen WF, Roder ME, Froesch R: Insulin-like growth factor I improves glucose and lipid metabolism in type II diabetes mellitus. *J Clin Invest* 90:2234–41, 1992
4. Jacob R, Barrett E, Plewe G, Fagin KD, Sherwin RS: Acute effects of insulin-like growth factor I on glucose and amino acid metabolism in the awake fasted rat: comparison with insulin. *J Clin Invest* 83: 1717–23, 1989
5. Schmitz F, Hartmann H, Stumpel F, Creutzfeldt W: In vivo metabolic action of insulin-like growth factor I in adult rat. *Diabetologia* 34:144–49, 1991
6. Giacca A, Gupta R, Effendic S, Hall K, Skottner A, Lickley L, Vranic M: Differential effects of IGF-I and insulin on glucoregulation and fat metabolism in depancreatomized dogs. *Diabetes* 39:340–47, 1990
7. Rossetti L, Frontoni S, DiMarchi R, DeFronzo RA, Giaccari A: Metabolic effects of IGF-I in diabetic rats. *Diabetes* 40: 444–48, 1991
8. Jacob RJ, Sherwin RS, Bowen L, Fryburg D, Fagin KD, Tamborlane WV, Shulman GI: Metabolic effects of IGF-I and insulin in the spontaneously diabetic BB/w rat. *Am J Physiol* 260:E262–68, 1991
9. Jacob RJ, Sherwin RS, Greenawalt K, Shulman GI: Simultaneous insulin-like growth factor I and insulin resistance in obese Zucker rats. *Diabetes* 41:691–97, 1992
10. Poggi C, Le Marchand-Brustel Y, Zapf J, Froesch ER, Freychet P: Effects and binding of insulin-like growth factor I (IGF-I) in the isolated soleus muscle of lean and obese mice: comparison with insulin. *Endocrinology* 105:723–30, 1979
11. Cascieri MA, Slater EE, Vicario PP, Green BG, Bayne ML, Saperstein R: Impaired insulin-like growth factor I–mediated stimulation of glucose incorporation into glycogen in vivo in the *ob/ob* mouse. *Diabetologia* 32:342–47, 1989
12. Gelato MC, Alexander D, Marsh K: Differential tissue regulation of insulin-like growth factor binding proteins in experimental diabetes mellitus in the rat. *Diabetes* 41:1511–19, 1992
13. Ooi GT, Orlowski CC, Brown AL, Becher RE, Unterman TG, Rechler MM: Different tissue distribution and hormonal regulation of messenger RNAs encoding rat insulin-like growth factor binding proteins 1 and 2. *Mol Endocrinol* 4:321–28, 1990
14. Guler HP, Zapf J, Froesch ER: Short-term metabolic effects of recombinant human insulin-like growth factor I in healthy adults. *N Engl J Med* 317:137–40, 1987
15. Laron Z, Erster B, Klinger B, Anin S: Effect of acute administration of insulin-like growth factor in patients with Laron-type dwarfism. *Lancet* 2:1170–72, 1988
16. Walker JL, Ginalska-Malinowska M, Romer TE, Pucilowska JB, Underwood LE: Effects of the infusion of insulin-like growth factor I in a child with growth hormone insensitivity syndrome (Laron dwarfism). *N Engl J Med* 324:1483–88, 1991
17. Zenobi PD, Graf S, Ursprung H, Froesch RE: Effects of insulin-like growth factor I on glucose tolerance, insulin levels, and insulin secretion. *J Clin Invest* 89:1908–13, 1992
18. Turkajl I, Keller U, Ninnis R, Vosmeer S, Stauffacher W: Effect of increasing doses of recombinant human insulin-like growth factor I on glucose, lipid, and leucine metabolism in man. *J Clin Endocrinol Metab* 75:1186–91, 1992
19. Boulware SD, Tamborlane WV, Matthews LS, Sherwin RS: Diverse effects on insulin-like growth factor I on glucose, lipid, and amino acid metabolism. *Am J Physiol* 262 E130–33, 1992
20. Clemmons DR: Editorial: Role of insulin-like growth factor I in reversing of catabolism. *J Clin Endocrinol Metab* 75:1183–85, 1992
21. Kerr D, Tamborlane WV, Rife F, Sherwin RS: Effect of insulin-like growth factor I on the responses to and recognition of hypoglycemia in humans: a comparison with insulin. *J Clin Invest* 91:141–47, 1993
22. Kadowaki T, Kadowaki H, Rechler MM, Serrano-Rios M, Roth J, Gorden P, Taylor S: Five mutant alleles of the insulin receptor gene in patients with genetic forms of insulin resistance. *J Clin Invest* 86:254–64, 1990
23. Yki-Jarvinen H, Kauppila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L, Rajala S, Ryysy L, Salo S, Seppala P, Tulokas T, Vikari J, Karjalainen J, Taskinen MR: Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 327:1426–33, 1992
24. Taskinen R-R, Kuusi T, Helve E, Nikkila EA, Yki-Jarvinen H: Insulin therapy induces anti-atherogenic changes of serum lipoproteins in non-insulin-dependent diabetes. *Arteriosclerosis* 8:168–77, 1988
25. Lindstrom T, Arngvist HJ, Olsson AG: Effect of different insulin regimens on plasma lipoprotein and apolipoprotein concentrations in patients with non-insulin-dependent diabetes mellitus. *Atherosclerosis* 81:137–44, 1990
26. Baserga R, Jameson BA, Surmacz E: The central role of the IGF-I receptor in the control of cellular proliferation. In *Molecular Oncology and Clinical Applications*. Cittadini A, Korda D, Baserga R, Pinedo H, Galeotti T, Eds. Basel, Birkhauser. 1993, p. 37–48
27. Malcaulay VM: Insulin-like growth factors and cancer. *Brit J Cancer* 65:311–20, 1992
28. Froesch ER, Guler H-P, Schmid C, Binz K, Zapf J: Therapeutic potential of insulin-like growth factor I. *Trends Endocrinol Metab* 1:254–60, 1990
29. King GL, Goodman DA, Buzney S, Moses A, Kahn CR: Receptors and growth-promoting effects of insulin and insulin-like growth factors on cells from bovine

Downloaded from http://diabetesjournals.org/care/article-pdf/17/1/92/442405/17-1-92.pdf by guest on 29 November 2022

retinal capillaries and aorta. *J Clin Invest* 75:1028–36, 1985
30. Guler HP, Eckardt KU, Zapf J, Bauer C, Froesch R: Insulin-like growth factor I increases glomerular filtration rate and renal plasma flow in man. *Acta Endocrinol* 121:101–106, 1989
31. Mogensen CE: Perspectives in diabetes: prediction of clinical diabetic nephropathy in IDDM patients: alternatives to microalbuminuria? *Diabetes* 39:761–67, 1990
32. Conti FG, Striker LJ, Lesniak MA, MacKay K, Roth J, Striker GE: Studies on binding and mitogenic effect of insulin and insulin-like growth factor I in glomerular mesangial cells. *Endocrinology* 122:2788–95, 1988
33. Doi T, Striker LJ, Elliot SJ, Conti FG, Striker GE: Insulin-like growth factor I is a progression factor for human mesangial cells. *Am J Pathol* 134:395–404, 1989
34. Mauer SM, Steffes MW, Ellis EN, Sutherland DER, Brown DM, Goetz FC: Structural-functional relationships in diabetic nephropathy. *J Clin Invest* 74:1143–55, 1984
35. Hyer SL, Sharp PS, Brooks RA, Burrin JM, Kohner EM: Serum IGF-I concentration in diabetic retinopathy. *Diabetic Med* 5:356–60, 1988
36. Isaksson GOP, Lindhal A, Nilsson A: In *Growth Hormone: Basic and Clinical Aspects*. Isaksson O, Binder C, Hall K, Eds. Amsterdam, Excerpta Medica, 1987, p. 307
37. Merimee JJ, Zapf J, Froesch FR: Insulin-like growth factors: studies on diabetes with and without retinopathy. *N Engl J Med* 309:527–30, 1983
38. Nakao-Hayashi J, Ito H, Kanayasu T, Morita J, Murota S: Stimulatory effect of insulin and insulin-like growth factor I on migration and tube formation by vascular endothelial cells. *Atherosclerosis* 92: 141–49, 1992

Downloaded from http://diabetesjournals.org/care/article-pdf/17/1/92/442405/17-1-92.pdf by guest on 29 November 2022