0021-972X/97/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 82, No. 9
Printed in U.S.A.

Editorial: The Interface Between Diabetic Retinopathy, Diabetes Management, and Insulin-Like Growth Factors

The cause of complications in the diabetic state has been a subject of intense research for over half of a century. Only recently, however, has a major clinical trial established the relationship of poor glycemic control to diabetic retinopathy (1). The precise relationship of other factors to diabetic complications is still not clear. In particular, the biochemical pathways involved in the development of these complications, the relative importance of these pathways in specific tissues, and the role of endocrine agents remain topics requiring further research.

The suspicion that some agent or agents in addition to hyperglycemia and insulin deficiency might be involved in the development of diabetic complications was first suggested by a report that regression of diabetic retinopathy followed infarction of the pituitary gland (2). An hypothesis which followed, linking growth hormone to diabetic retinopathy, was later modified and extended to insulin-like growth factor (IGF)-1, when it became apparent that most anabolic effects of GH were mediated by IGF (3–6), particularly type I.

Studies of circulating concentrations of IGF-1 in diabetic subjects, however, have given conflicting results, due in part to selection of patients, to the glycemic control in these patients, and to methodology in determining components of the IGF-1 system. In this issue of *JCEM*, Janssen *et al*. (7) (see page 0000) report on circulating concentrations of free IGF-1 and total IGF-1 and two of the six binding proteins of IGF-1, IGFBP-1, and IGFBP-3, in diabetic patients and controls. With the exception of free IGF-1 levels being only modestly greater in diabetic patients with retinopathy than in those without retinopathy, no definitive pattern of circulating IGF-1 and IGFBP distinguished diabetic patients with complications. This report serves to further clarify information on circulating IGF-1 and its major binding proteins; it does not shed light, as the authors recognized, on how IGF-1 might influence diabetic complications.

There is now ample evidence that supports an interfacing of IGFs to processes involved with diabetic complications, particularly retinopathy, and a better understanding of how this interfacing occurs is possible (8–15). It is appreciated, for example that paracrine and autocrine IGF-1 in all tissues thus far studied are dependent primarily on local tissue conditions, not only on growth hormone or circulating levels of IGF-1. Tissue IGF-1 may be normal or increased when there is a total deficiency of growth hormone (GH), and whereas IGF-1 infusions may increase tissue IGF-1 by 20–50%, a variety of local conditions can increase IGF-1 in these same tissues 5- to 20-fold while also enhancing IGF-1 action at other points in the IGF-1 system (8, 10, 14).

The IGF-1 system consists of IGF-1, IGF-11, the type 1 and type 2 IGF receptors, and six different IGF-binding proteins (BPs). IGF-BP proteases present in serum and produced by a variety of tissues add to the complexity of interpreting changes of IGF-1 (8–9). What appears certain is that IGF-1, if not directly then by changes in receptors or by changes of BPs, interfaces with key processes in the diabetic state. For example, the formation of microthrombi, which contribute to a variety of complications in diabetes, is tied in part to an effect of IGF-1 on the plasminogen-plasmin system (11, 12). In the diabetic human an antifibrinolytic state often exists as a result of increased levels of inhibitors of plasminogen activators (11, 12, 15). Plasminogin activators, enzymes produced by vascular endothelium, activate the conversion of the proenzyme plasminogen (PA) to plasmin. Plasmin in turn degrades fibrin within the vessel lumen, degrades basement membranes, and affects other processes related to vessel integrity. PA is tightly regulated by its natural inhibitor, plasminogin activator inhibitor (PAI-1), which is secreted bidirectionally by endothelial cells.

PAI-1 is over-expressed in capillaries of diabetics with nonproliferative disease compared with nondiabetics (11), and in an animal model developed by Grant *et al*. (12), in which retinopathy is induced solely with IGF-1, PAI-1 increases and correlates strongly with pathological findings.

It is now accepted that wound repair of many types requires an increase of IGF-1 in the damaged area (8–13). In diabetic subjects "tissue wounding" is a more common phenomenon than in normal subjects because of alterations in tissues induced by glycosylation; cross-linking of proteins, shear stress, and a variety of other tissue changes (15). Under these circumstances one may find in a localized tissue bed or organ both increased IGF-1 and increased glucose. This interfacing of elevated IGF-1 with hyperglycemia may in turn exaggerate the response caused by injury. It is worth taking note of this process: in wound repair, platelet derived growth factor (PDGF), fibroblast growth factor (FGF), and other factors function as competence factors required to transfer cells from a stationary state (G-0) into (G-1) (14). These factors induce the expression of early response genes such as c-*myc*, c-*fos*, and G-1 genes such as cyclins (14). IGF-1, on the other hand, acts as a progression factor, which enhances cell progression into S(syntheses) phase, which leads to division of the cell (14). IGF-1 is important to the cell cycle in virtually all cell types thus far studied (10, 16).

An extremely important consideration in viewing this action of wound repair in diabetes is that the action of IGF-1 on intracellular glucose transport in local tissue beds may be augmented when glucose levels (17) are elevated.

Received June 30, 1997. Accepted July 7, 1997.
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There is growing evidence that increased intracellular glucose causes biochemical reactions that culminate in neovascularization (10, 15, 17, 18). Increased intracellular transport of glucose initiated by levels of IGF-1 in local tissue beds can result in cellular hypertrophy and hyperplasia. Using cultured bovine retinal capillary endothelial cells, a cell type prominent in diabetic retinopathy, it has been shown that increasing intracellular glucose increases the membranous pool of protein kinase C (PKC) over 100% (17). PKC is a potent stimulus for neovascularization (17). IGF-1 enhancement of glucose transport and/or abnormally high intracellular glucose can cause cellular hypertrophy and also mitosis by other means. Natarajan et al. (18) have shown that glucose can increase cell volume, DNA synthesis, and cell number, in part by stimulating lipooxygenase pathways that produce 12 and 15 hydroxyeicosatetracnoic acids (12 & 15 HETE), both of which have potent neogenic effects. Studies in organisms as simple as yeast support these mechanisms (19).

IGF-1 also acts on other processes essential to repairing wounds. Normal wound healing requires directed migration of neutrophils, monocytes, and fibroblasts into the wound before cellular activation can result in production of growth factors, cytokines, and proliferation of fibroblasts. This is seen in virtually all human tissues (10).

In the eye, IGF-1 acts at a concentration found in the vitreous of diabetics, but not in normal subjects, to promote chemotaxis of retinal endothelial cells, an essential step in vascular neogenesis (8, 12). Figure 1 illustrates action of IGF-1 on the chemotaxis of endothelial cells.

In this process endothelial cells migrate from the deep layer of the retina through the internal limiting membrane to the vitreous cavity, where they are able to form new vessels. In the eye, IGF-1 also enhances formation of collagenase, one of several enzymes responsible for dissolving capillary basement membranes and the collagen matrix of the retina. Both structures must be dissolved to permit the migration of endothelial cells. In the absence of these two steps, new vessels can not form (12). Most recently this field has been given a big impetus by the studies of Smith, who has shown in transgenic mice expressing a GH antagonist that inhibition of GH, IGF-1, or both inhibits development of ischemia-induced retinopathy (19a).

In summary, one can indicate multiple points for the interfacing of IGF-1 to abnormalities arising in the diabetic state. This may be particularly relevant for tissues in which IGF-1 enhances the intracellular transport of glucose, but IGF can relate to actions as diverse as cellular migration (as with retinal endothelial cells) and abnormally increased formation of matrix.

At the current time I can only endorse recommendations for establishing normoglycemia or as close to normoglycemia as possible (1). Similarly, abnormally high cholesterol and lipoproteins should be decreased. These actions would predictably decrease wounding and hence tissue changes of IGF-1 associated with wounding. The potential use of IGF-1 analogues to inhibit IGF-1 action in selected tissue has been demonstrated, but is not feasible at this time for use in humans (20, 21).

Pietrzkowski and colleagues (20) have reported the inhibition of cellular growth by peptide analogues of IGF-1 with multiple prostatic cell lines, and in a review of the molecular

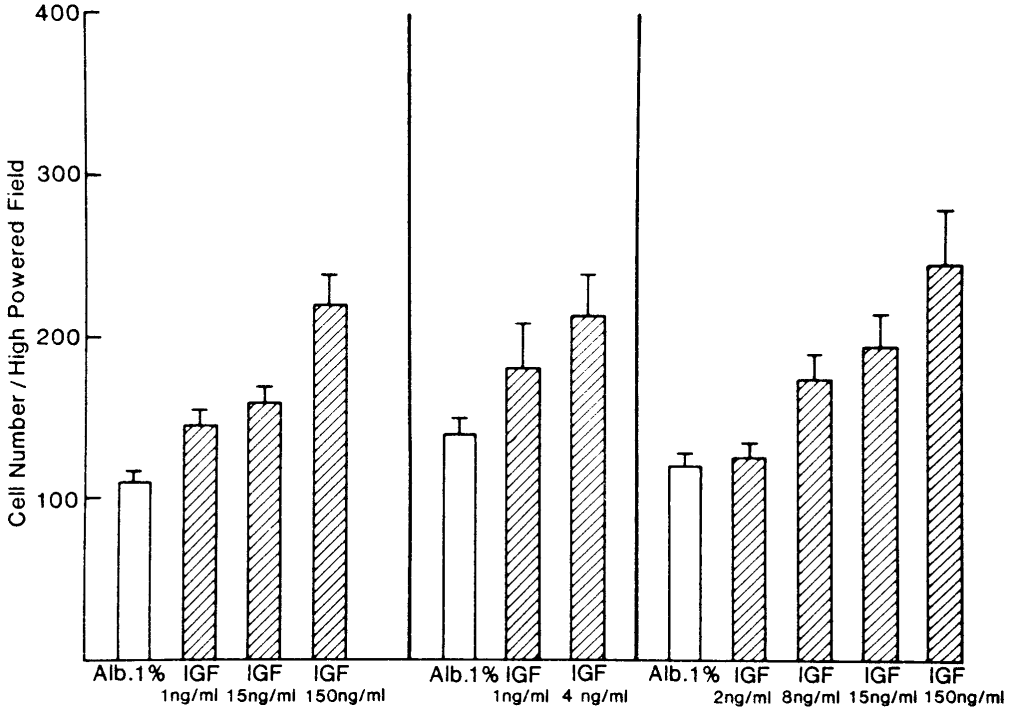

FIG. 1. Three separate studies are illustrated showing the effect of IGF-1 on chemotaxis with bovine fetal aortic endothelial cells. Cell number per high powered field, a measure of chemotaxis, is given on the vertical axis. Each bar represents the mean ± SEM of four separate experiments. Multiple studies confirm a similar chemotactic effect of IGF-1 on retinal endothelial cells and pigment epithelial cells. The chemotactic effect is noted with vitreous concentrations of IGF-1 as low as 4 ng/mL. (See ref. 12)

biology of IGF-1 receptors, Blakesly and LeRoith record inhibition of IGF-1 action by antibody to type 1 IGF-1 receptors (8).

Despite new insulin preparations and a yearly parade of new hypoglycemic agents, success in the control of hyperglycemia is anything but assured in a given patient. Similarly, one can expect no easy formulas for the control of IGFs.

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