Insulin-Like Growth Factor-I and the Gastrointestinal System: Therapeutic Indications and Safety Implications

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ABSTRACT Following the identification of insulin-like growth factor-I (IGF-I) as a potent trophic factor for the intestine over a decade ago, therapeutic indications have been identified for a range of candidate bowel disorders and diseases in which accelerated intestinal repair is desirable. Subsequent experimental studies in experimentally-induced animal models and genetically-modified mice have supported a therapeutic role for IGF-I in facilitating repair processes in gastrointestinal disorders including radiation enteritis, chemotherapy-induced mucositis and inflammatory bowel disease, conditions associated with either the pre-existence of malignancy or a predisposition to develop neoplasia. Moreover, recent evidence from in vitro, in vivo and human population studies is suggestive of an active role for IGF-I in the development and progression of certain cancers, and although causality remains unproven, antagonism of IGF-I action is being pursued as a potential chemo-preventive strategy. Novel milk and colostrum-derived bioactive formulations containing IGF-I are being developed as adjunctive treatment modalities for certain bowel disorders. Understanding the precise role of the IGF axis in cancer will either identify antagonism of the IGF-I/receptor interaction as an important approach in cancer prevention and risk reduction, or alternatively, support further development of IGF-I as a promising treatment modality for acute gastrointestinal disease.


KEY WORDS: • insulin-like growth factor-I • intestine • disease • treatment • cancer • risk

Insulin-Like Growth Factors. Insulin-like growth factors (IGF) I and -II are single chain 7.5 kDa polypeptides comprising 70 and 67 amino acids, respectively, with 70% amino acid sequence homology and IGF-II being more abundant prenatally in humans (1). IGFs are potent mitogens, capable of modulating epithelial cell kinetics by stimulatory effects on proliferation and inhibitory effects on apoptosis. The signaling pathways that culminate in IGF-I bioactivity are initiated by an interaction between the IGF-I ligand and its cell-surface–located type I IGF-I receptor (IGF-IR). The IGF-IR is a disulphide-linked dimer belonging to the tyrosine kinase family of receptors. Subsequent phosphorylation by receptor tyrosine kinase is the first step in a complex intracellular signaling process. IGF-II is additionally able to bind to a mannose-6-phosphate receptor known as the type II or mannose-6-phosphate IGF-II (Fig. 1).

IGF-I and the Gastrointestinal Tract. IGF-I has undergone clinical, or preclinical, development for the potential treatment of a number of acute and chronic disease conditions including Laron dwarfism insulin-resistant diabetes mellitus, osteoporosis, peripheral neuropathy, the motoneuron disease, amyotrophic lateral sclerosis and certain disorders of the gastrointestinal tract.

Epithelial cells, endothelial cells and fibroblasts are the principal target cells for IGF-I action in the intestine (3). Expression of IGF-I, IGF-II, insulin-like growth factor binding protein (IGFBP) species and IGF receptors has been described throughout the gastrointestinal tract, with receptors localized to both the mucosal and muscularis layers, and greatest concentration in the baso-lateral region of crypt enterocytes (4). Prior to the availability of genetically-modified mouse strains, initial reports of IGF-I as a trophic factor with gastrointestinal selectivity were generated from in vitro and in vivo studies in which IGF-I overexpression was simulated by administration of recombinant IGF-I peptides. Continuous administration of IGF-I to adult rats for 14 d resulted in preferential growth of the gastrointestinal organs (5), increasing gut weight as a fraction of body weight by up to 32% accompanied by increases in crypt cell population (+33%) and villus cell density (+20%). IGF-I is a potent stimulator of proliferation in the intestinal crypts, spurring progression through G1- to the S-phase of the cell cycle. Few investigations have described the impact of IGF-I administration on bowel function under normal conditions. However, a recent experimental study investigating the intestinal absorption of 3-methyl glucose suggested that the functional consequences of IGF-I-induced intestinotropism are primarily the result of an increase in mucosal mass in preference to an upregulation of specific epithelial glucose transporters (6).

Studies of IGF-I administration in vivo have revealed both linear and cross-sectional growth of the gastrointestinal organs affecting the mucosal and muscularis layers proportionally, suggesting clinical application in bowel conditions characterized by impaired growth and repair processes. Bowel resection, chemotherapy-induced intestinal mucositis, radiation enteritis and the inflammatory bowel diseases (IBD), Crohn’s disease and ulcerative colitis, would therefore appear to be likely candidate target conditions that may benefit from IGF-I administration in the first instance.

IGF-I and the Short Bowel Syndrome. Bowel resection may be necessitated by a broad range of intestinal disorders ranging from idiopathic inflammatory disorders such as IBD or necrotizing enterocolitis (NEC) to surgical removal of necrotic tissue or even accidental trauma. The resultant short
bowel syndrome (SBS) is characterized by impaired bowel function, often requiring partial or total parenteral nutrition (TPN), and commonly the use of ileostomy or colostomy collection devices. Lemmey et al. (7) first described improved intestinal function following IGF-I administration in 70% small bowel-resected rats. Recently, these studies have been extended to include massive small bowel resection involving the ileocecal valve (8), with continuous administration of IGF-I indicated as a supplemented therapy for SBS with ileocecal valve deficiency. Indications for IGF-I as a treatment modality for SBS have been further supported by its capacity to facilitate weaning from TPN to enteral feeding in association with maintenance of a greater body weight and serum IGF-I concentration in a rat model of SBS achieved by 60% jejuno-ileal resection (9).

Further applicability of IGF-I in the clinical setting of SBS has been demonstrated in an experimental study in which IGF-I markedly accelerated the healing of colonic anastomoses, an important determinant of successful surgical bowel resection (10). Perhaps the most promising indication for IGF-I utilization in SBS still awaits full investigation. Treatment of neonatal rats with the long-R1-IGF-I variant of IGF-I stimulates gut weight and length by up to 60 and 32%, respectively, with the variant peptide more potent for all growth parameters (11). Since long-R2-IGF-I binds poorly to inhibitory IGFBP, the increased responsiveness of the neonatal gut was attributed to increased IGFBP expression in neonatal intestinal tissues. The profound effect of this variant on bowel lengthening in the setting of neonatal resection warrants further investigation, with the devastating consequences of NEC as a likely target condition.

IGF-I and Gastric Ulceration. Recently, decreased IGF-I mRNA expression in chronically ulcerated gastric tissue has been described and accelerated healing of thermally-induced gastric injury reported in arthritic rats treated with IGF-I (12). The potential applicability of IGF-I treatment to gastric injury is further supported by an experimental study describing a previously unreported inhibitory effect of IGF-I on gastric acid secretion (13). Further studies of acute IGF-I administration and gastric repair are required in model systems of ulcerations manifested by nonsteroidal anti-inflammatory drugs or Helicobacter Pylori, for example, in order to further define the applicability of IGF-I to gastric injury.

IGF-I and Intestinal Mucositis. Intestinal mucositis can result from radiotherapy or chemotherapy, indicated for the treatment of a broad range of cancers. High dose abdominal irradiation is a common form of therapy for abdominal neoplasms as found in gynecological and pelvic malignancy, and symptoms such as diarrhea, cramps and vomiting are common during and after radiotherapy. Administration of IGF-I immediately following abdominal irradiation has been reported to improve small bowel integrity in rats (14). More recently, growth hormone and IGF-I have been demonstrated to protect intestinal cells from radiation-induced apoptosis in vitro (15) and in vivo utilizing IGF-I transgenic mice (16). Studies in which mucositis has been induced by chemotherapy drugs, such as methotrexate, have revealed similar beneficial effects of IGF-I administration following chemotherapy, typified by accelerated epithelial repair (17). However, concurrent administration of IGF-I has been contraindicated during periods of chemotherapy because there are indications that IGF-I had actually exacerbated intestinal cytotoxicity induced by methotrexate; the authors speculated that IGF-I had promoted recruitment of proliferating intestinal epithelial cells to the cytotoxic effects of methotrexate with this therapeutic regimen.

IGF-I and Inflammatory Bowel Disease. The idiopathic condition known as inflammatory bowel disease comprises two variants: ulcerative colitis affecting primarily the distal bowel and Crohn’s disease, which may affect any region of the alimentary system. There is evidence that IGF-I expression is associated with areas of fibrosis in experimental IBD and IGF-I has been implicated in the pathogenesis of fibrosis (18). This has been supported by a recent demonstration of up-regulated IGFBP and collagen expression and down-regulated collagenase expression in experimental rat colitis suggesting an important role for IGF-I in collagen synthesis in colitis, mediated by IGFBPs (19). Furthermore, a mechanism has been proposed whereby IGF-I could act on smooth muscle and fibroblasts/myofibroblasts to increase collagen synthesis and cellular proliferation, its effects modulated by locally expressed IGFBP-5 (20). It remains unclear whether increased IGF-I expression is primarily associated with the etiology of IBD, or alternatively an epiphenomenon of the fibrotic process. Nevertheless, short-term beneficial effects of IGF-I have been described in an acute model of IBD induced by oral ingestion of dextran sulfate sodium (21), this study describing a potential new mechanism of IGF-I action in acute colitis by reducing edema in the mucosa and submucosa.

Failure to thrive is a common feature of IBD in infants and adolescents, and although the etiology of IBD remains obscure, there has been on-going development of dietary and parenterally-administered supplements to improve nutrition and growth in IBD sufferers. Indeed, a recent experimental colitis study concluded that growth failure occurs as a result of a decrease in serum IGF-I levels, independent of under-nutrition (22), supporting a likely benefit for therapeutic intervention with IGF-I in growth failure associated with IBD. Not surpris...
ingly, the predisposition for IBD to precociously manifest colonic carcinoma has raised concerns for proposed therapeutic intervention by a mitogen such as IGF-I. Moreover, since many of the previously described indications for IGF-I therapy exist coincident with the existence of neoplasia, an understanding of IGF-I and its effects on cancer risk is essential.

**IGF-I and Cancer Risk.** Adverse side effects of IGF-I therapy have included reports of generalized edema, hypoglycemia, hypophosphatemia, carpal-tunnel syndrome arthralgias and myalgias. However, controversy currently surrounds the potential use of IGF-I in premalignant conditions. This is an active area of research and a number of excellent reviews are available on the subject (23,24). A discussion on the basis of in vitro and in vivo experimental evidence, and human population studies, is warranted.

**Experimental Studies.** Recently, Weber et al. (25) studied changes in levels of IGF-IR in colorectal carcinoma in 40 paired samples of normal and carcinomatous colonic tissue utilizing quantitative reverse-transcription-polymerase chain reaction, immunohistochemistry and ligand binding techniques, concluding that in addition to IGF-II, strong overexpression of IGF-IR occurs in the majority of colorectal carcinomas. Moreover, IGF-I has been demonstrated to protect HT-29 colon cancer cells from death factor-induced apoptosis by potentiating tumor necrosis factor-α-induced, mitogen-activated protein kinase and nuclear factor kappaB signaling pathways (26). It has been further postulated that IGF-IR activation may contribute to resistance to chemotherapy in mesenchymal neoplasia (27) and antagonism of the IGF-I ligand/receptor interaction is being actively pursued as a chemo-preventative strategy to block transformation, induce apoptosis (28) and augment response to chemoradiation (29).

IGFBP-3 itself is capable of inducing apoptosis in an IGF-independent manner. Perhaps the single most important human tumor suppressor, p53 is commonly mutated in human cancers and one of the genes induced by p53 has been identified as that encoding IGFBP-3 (30). Thus, IGFBP-3 induction by p53 may constitute a new means of cross-talk between the p53 and IGF axes, suggesting the ultimate function of IGFBP-3 may be to exert a protective role against the potential effects of IGF-I on transformation.

Growth hormone, either directly or via its downstream effector IGF-I, has been implicated as an important factor in the growth of malignant tumors. Recently, an antagonist of the GH/receptor interaction has been demonstrated to decrease tumor growth in a colon carcinoma animal model, although studies in cancer patients have not yet commenced (31). The data generated from animal models in relation to IGF-I and cancer risk, however, are inconclusive. For example, GH transgenic mice, with high IGF-I levels, do not develop breast, prostate, or colonic malignancies. Moreover, a study in which IGF-I was continuously administered to rats with chronic ulcerative colitis for up to 20 wk did not affect the progression or appearance of neoplasia in this premalignant setting (32). Nevertheless, it would appear that IGF-I could have more than merely a passive role in neoplasia and its progression on the basis of in vitro and in vivo studies, when combined with human population data. Indeed, information on the association between the IGF axis and cancer risk, and the important contribution of nutrition has been sourced primarily from human population studies.

**Human Population Studies.** Population studies are continuing to provide strong circumstantial evidence that IGF physiology influences cancer risk. It has been shown previously that slight elevations in serum levels of IGF-I are correlated with an increased risk for developing prostate, breast and lung cancer. More recently, case-controlled studies have found increases in the serum levels of IGF-I in subjects with ovarian and colorectal cancers. Nevertheless, epidemiological studies have not yet established causality. Cohen et al. (23) have offered several plausible explanations for elevated serum IGF-I levels in cancer patients. Firstly, an effect of IGF-I causing symptomatic benign tissue hyperplasia may have resulted in an ascertainment bias leading to an initiation of procedures resulting in the diagnosis of asymptomatic cancers. Secondly, elevated serum IGF-I may have originated within the tumor as suggested by some animal studies, and thirdly, serum IGF-I may actually be a surrogate marker of tissue IGF-I levels or nutritional factors. A recent study investigating circulating IGF-I levels in 292 female meat eaters, vegetarians and vegans found low IGF-I levels in plant eaters, contributing to the debate on high IGF-I levels and cancer risk in individuals consuming a Western diet (33). Moreover, a prospective study of IGF-I, IGF-binding proteins, and breast cancer risk in northern and southern Sweden concluded that levels of IGF-I and IGFBP-3 are not related to risk in younger women recruited before age 50 y, contrary to observations from previous studies (34). Accordingly, a definitive role for IGF-I in cancer development and progression awaits confirmation.

Serum IGFBP-3 levels have been shown to be negatively correlated with the risk of cancer suggesting increased cancer risk for individuals with both high IGF-I and low IGFBP-3 levels (24). Long-term studies are therefore required to assess the potential risks, including the long-term cancer risk associated with IGF-I administration. Finally, isolated reports of increased IGF-II levels in colorectal cancer in women suggest further studies of IGF-II are required to complete the understanding of the IGF axis and its role in cancer risk (35).

**IGF-I and Angiogenesis.** Recent evidence supports an active role for IGF-I in the process of angiogenesis and a significant association has been determined between local IGF-I mRNA levels and micro-vessel density in paired normal colon and carcinoma samples (36). Furthermore, administration of colon carcinoma cells transfected with a truncated dominant-negative form of the IGF-IR to nude mice resulted in decreased tumor growth and metastasis associated with decreased tumor cell proliferation, vascular endothelial growth factor (VEGF) expression, and vessel count (37). The IGF ligand-receptor system thus appears to play an important role in colon cancer growth including regulation of VEGF expression and angiogenesis.

**Enteral IGF-I Formulations.** Intestinal immaturity and mucosal ulceration provide an opportunity for enterally-administered IGF-I to interact with exposed receptors localized primarily at baso-lateral enterocyte sites. An enteral mode of IGF-I delivery is attractive because it combines a diminished likelihood of cancer-promotion at nongastrointestinal sites with fewer regulatory issues. The development of IGF-I–enriched formulations from natural sources such as milk and colostrum (38) is therefore being exploited as a treatment modality for a growing number of bowel disorders. Specialized separation and enrichment methodologies have been developed to strategically extract and enrich bioactive factors from these sources. Bovine whey, for example, has been utilized to produce an extract of growth factors containing high levels of IGF-I. This extract has been demonstrated to reduce symptoms of chemotherapy-induced intestinal mucositis (39) and to suppress colonic inflammation (40), although the contribu-
tion of IGF-I to the observed efficacy is unclear. Nevertheless, clinical trials have commenced in oral mucositis.

Conclusions. IGF-I has been investigated as a potential treatment modality for a broad range of disease states, and recently, therapeutic potential has been identified for a range of acute and chronic conditions. Efforts in the development of IGF-I with novel epitopes and novel delivery methods are desirable, with short bowel syndrome the most likely candidate condition. Although causality remains unproven, there are an increasing number of reports of an association between circulating IGF-I levels and the existence of cancer. The development of enterally-administered formulations enriched in IGF-I may alleviate some of these concerns for its potential to increase cancer risk. However, long-term safety data are lacking. Understanding the precise role of the IGF axis in cancer initiation and progression will either identify antagonism of the IGF-I/receptor interaction as an important approach to cancer chemoprevention, or alternatively, facilitate further development of IGF-I as a promising new treatment modality for gastrointestinal disease. Until such information is available, therapeutic indications for IGF-I should be restricted to acute periods with caution exercised in conditions associated with the existence of neoplasia or neoplastic predisposition.

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LITERATURE CITED