Insulin-like growth factor system and inflammatory bowel disease

K.H. Katsanos, E.V. Tsianos

SUMMARY
Few reports concerning the levels and the importance of insulin-like growth factors (IGFs) and IGF binding proteins (IGFBPs) in the serum of patients with inflammatory bowel disease (IBD) have been published.

Insulin-like growth factor (IGF) system has properties that are potentially relevant to IBD. The IGF system is a system complex composed of IGF-I and IGF-II as well as at least six different IGF binding proteins (IGFBP). IGF-I expression has been shown in lymphocytes, macrophages and fibroblasts. IGF-I is a potent mitogen for fibroblasts and smooth muscle cells and induces collagen synthesis in vitro, appearing to be important in tissue remodeling and repair. Proinflammatory cytokines such as interleukin-1 (IL-1) may play a role in IGF-I production linking the IGF system with the inflammatory process in IBD patients. It has been suggested that IBD patients may have low IGF-I and IGFBP levels. In recent years the effect of regulatory peptides such as growth hormone (GH) and IGF-I in intestinal growth and repair has been emphasized. Trials of growth hormone in combination with a high-protein diet in short bowel syndrome patients as well as Crohn’s disease (CD) patients have been encouraging. It has been suggested that the IGF and IGFBP system may be abnormal in IBD patients during this chronic inflammatory process, yet there is no data on the exact impact of inflammation on this down-regulation and the interaction between the interleukins and the IGF and IGFBP system, in IBD patients.

Key words: IGF system, IGF-I, IGF-II, IGFBP3, IGFBP, inflammatory bowel disease (IBD), Crohn’s disease (CD), ulcerative colitis (UC).

INTRODUCTION
Crohn’s disease (CD) and ulcerative colitis (UC) are inflammatory diseases of the gastrointestinal tract characterized by a chronic inflammatory process with remission and relapse periods. Ulcerative colitis is limited to the colon with lamina propria inflammation and usually bowel epithelium destruction while Crohn’s disease may affect any region of the gastrointestinal tract and is characterized by transmural inflammation and fibrosis. To reduce the inflammation and induce remission, inflammatory bowel disease (IBD) patients are treated with immunosuppressive, anti-inflammatory and recently immunomodulatory drugs. Nevertheless patients frequently have long-term complications of ongoing inflammation.

Abbreviations used in the text:
IGF = Insulin-like Growth Factor
IGFBP = Insulin-like Growth Factor Binding Protein
IL = Interleukin
IBD = Inflammatory bowel disease
UC = Ulcerative colitis
CD = Crohn’s Disease
GH = Growth Hormone
GHRH = Growth Hormone releasing hormone
RhGH = Recombinant human Growth Hormone
AGHR = Acquired Growth Hormone Resistance
m RNA = messenger Ribonucleic Acid
GHBP = Growth Hormone Binding Protein
ILr(a) = Interleukin receptor antagonist
PG-PS = peptidoglycan-polysaccharide-induced colitis
DSS = Dextran Sulphate Sodium PG-PS-induced colitis
and fibrosis such as abscesses, bowel obstruction, and fistulae formation. Extensive research efforts have focused on the role of cytokines in the induction and regulation of this chronic inflammatory process. Clinical studies of growth factors in intestinal fluid facilitate research on intestinal fibrogenesis and the diagnosis of fibrous stricture in CD.

Little is known about the role of growth factors in inflammatory bowel disease and its complications. Insulin-like growth factor (IGF) system is a complex system (Table 1) which has properties that are potentially relevant to IBD. The IGF system is a system complex being composed of IGF-I and IGF-II as well as at least six different IGF binding proteins (IGFBP). Two forms of IGF-I complex have so far been described in the circulation (Table 2). The IGFBP carry IGF-I in the blood and modulate its bioavailability, thereby inhibiting or potentiating the interaction of IGF-I with its receptor.

IGF-I is a potent mitogen for fibroblasts and smooth muscle cells and induces collagen synthesis in vitro, appearing to be important in tissue remodelling and repair. IGF-I expression has been shown in lymphocytes, macrophages and fibroblasts. In addition to this, it has been reported that increased IGF-I expression in multiple mesenchymal cell subtypes and increased numbers of cells with fibroblast/myofibroblast phenotype are involved in fibrosis associated with Crohn’s disease. Grosh et al showed that the majority of CD patients with strictures had detectable levels of IGF-I in their gut lavage fluid.

Proinflammatory cytokines such as interleukin-1 (IL-1) may play a role in IGF-I production linking the IGF system with the inflammatory process in IBD patients. Moreover it was suggested that IBD patients may have low IGF-I levels and the effect of regulatory peptides such as growth hormone (GH) and IGF-I in intestinal growth and repair has been emphasized in recent years. Trials of growth hormone combined with a high-protein diet in short bowel syndrome patients as well as in CD patients have been encouraging.

The IGF and IGFBP system derangement in IBD patients has not yet been sufficiently investigated (Table 3). The exact impact of inflammation on this apparent down-regulation and the interaction of interleukins with the IGF and IGFBPs have to be determined. It would be quite useful to know the exact impact of this derangement, in order to decide the type of intervention a patient needs, during this inflammatory process.

**The IGF/GH axis during catabolic conditions**

A number of catabolic conditions including trauma,

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**Table 1. The IGF system.**

<table>
<thead>
<tr>
<th>Insulin-like Growth factors</th>
<th>IGF receptors</th>
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<tbody>
<tr>
<td>IGF-I</td>
<td>-IGF-I receptor (tyrosine kinase) for both IGF-I &amp; IGF-II</td>
</tr>
<tr>
<td>IGF-II (fetal)</td>
<td>-IGF-II receptor (mannose-6-phosphatase) for only IGF-II</td>
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<tr>
<td></td>
<td>IGF Binding Proteins 1 - 6 (IGFBP 1-6)</td>
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</tbody>
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**Table 2. The two forms of IGF-I complex in the circulation.**

**Table 3. Reported low serum IGF-I and IGFBP-3 in Crohn’s disease (CD) and ulcerative colitis (UC) patients.**

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Diagnosis</th>
<th>Serum IGF-I</th>
<th>Serum IGFBP-3</th>
<th>Remarks on the paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Slonim</td>
<td>CD</td>
<td>↓</td>
<td>Not done</td>
<td>IGF-I statistical increase after GH administration</td>
</tr>
<tr>
<td>2</td>
<td>Dinca</td>
<td>CD/UC</td>
<td>↓</td>
<td>Not done</td>
<td>Assessment of osteopenia in IBD patients</td>
</tr>
<tr>
<td>3</td>
<td>Savage</td>
<td>CD</td>
<td>↓</td>
<td>Not done</td>
<td>IGF-I increases during therapy</td>
</tr>
<tr>
<td>4</td>
<td>Beattie</td>
<td>CD</td>
<td>↓</td>
<td>Not done</td>
<td>Studies in vivo and in vitro in human and animal tissues</td>
</tr>
<tr>
<td>5</td>
<td>Lund</td>
<td>CD/UC</td>
<td>↓</td>
<td>↓</td>
<td>Also IGF-I in RNA studied</td>
</tr>
<tr>
<td>6</td>
<td>Thomas</td>
<td>CD</td>
<td>↓</td>
<td>Same as controls</td>
<td>Study in growth retarded IBD children</td>
</tr>
<tr>
<td>7</td>
<td>Kirschner</td>
<td>CD/UC</td>
<td>↓</td>
<td>Not done</td>
<td></td>
</tr>
</tbody>
</table>
burn, endotoxemia or inflammation are associated with alterations in multiple components of the IGF system. The most consistent changes under these conditions are a decrease in IGF-I and an elevation in IGFBP-1 in the plasma23. Fasting can also lead to increased levels of GH, decreased IGF-I, decreased Growth Hormone Binding Protein (GHBP) and high IGFBP-1 as in Aquired Growth Hormone Resistance (AGHR)24. However, because the IGF-1 concentration decreases during the time when GH concentration is elevated the presence of GH resistance is suggested and such a condition has been reported in humans with sepsis and after therm injury in rats25. Different conditions manifest AGHR to different extents. In many, there is induction of a protease, which reduces IGF-I half-life while GH concentrations probably rise due to the removal of IGF-I negative feedback26. Because the liver is believed to secrete the majority of the IGF-I present in the blood a decreased hepatic synthesis would be a likely explanation for the decline of IGF-I in the circulation27. Theoretically, the decrease in plasma IGF-I could also be the result of an increased rate of IGF-I clearance from the circulation (Table 4). Although decreased IGF-I have been reported in malnutrition and pregnancy, no such change was observed after endotoxin injection27.

The following results strongly suggest that the ability of IL-1 to regulate muscle protein synthesis in sepsis is mediated secondary to changes in IGF-I and that the endogenous IL-1 production during infection is a key regulator of the GH/IGF axis28. Complex and, at times, contradictory evidence implicates IL-1, IL-6 and TNF-α as modulating levels of GHRH(growth hormone releasing hormone)29. It has also been shown that IL-1 can directly stimulate pituitary GH secretion and in vivo administration of nonlethal doses of either TNF-α or IL-1β in rats also alters the IGF system30.

**The IGF system receptors**

IGF-I receptor types I and II are distributed widely in the alimentary tract and the bowel is an established target-organ for IGF-I14. Decreased expression of growth factors and growth factor receptor-encoded mRNA in active chronic IBD may be related to the disease process, or it may be an effect of steroid therapy undergone by these patients36.

**Bowel IGF mRNA regulation in IBD**

The administration of recombinant IL-1 or TNF-α in animals mimics the changes in the IGF system produced by burn, endotoxemia and trauma; it has recently been reported that IL-1α and TNF-α regulate IGFBP-1 levels and mRNA abundance in vivo and in vitro37.

IGF-I mRNA was measured using RNAase protection in bowel and liver of rats with peptidoglycan-polysaccharide-induced (PG-PS) chronic granulomatous enterocolitis and hepatitis38. The localization of IGF-I and IL-1β mRNAs to distinct but adjacent sites may be suggestive of a paracrine interaction between cells expressing IGF-I and IL-1β39. Emerging evidence suggests that proinflammatory cytokines such as IL-1 may induce IGF-I in vitro, linking IGF-I to key mediators of the inflammatory response in IBD40,41. IL-1β mRNA is up-regulated in the serum during acute and chronic phases of PG-PS and Dextran Sulphate Sodium (DSS) induced colitis42. In this PG-PS model it was shown that IGF-I mRNA

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**Table 4. Probable causes of decreased serum IGF-I concentrations in IBD**

<table>
<thead>
<tr>
<th>Probable Cause</th>
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<tr>
<td>1. Inadequate IGF-I secretion</td>
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<tr>
<td>2. Decreased IGF-I half life</td>
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<tr>
<td>3. Low IGFBP levels</td>
</tr>
<tr>
<td>4. IGF receptor antagonism</td>
</tr>
<tr>
<td>5. Increased IGF-I clearance</td>
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is increased in an area of intense fibrosis surrounding granulomas in inflamed intestinal tissue implicating IGF-I in the pathogenesis of fibrosis.

**The IGF system and Interleukin-6**

Recombinant IL-6 stimulates acute secretion of GH and enhances IGFBP-1 production in humans, although the main effects of cytokines in AGHR are likely to be via effects on IGF-I production. Transgenic mice which overexpress IL-6 have growth impairment and reduced plasma concentrations of IGF-I, while animals with experimental colitis have increased plasma concentrations of IL-6 and abnormalities of the growth plate compared with controls.

**IGF system and growth in IBD**

Growth failure of IBD patients is not the result of GH deficiency and is not an irreversible phenomenon. On the contrary, it had been suggested for many years that judicious use of steroids usually produces compensatory growth acceleration and beneficial effects of GH combined with parenteral nutrition in the management of IBD growth retardation have also been reported (study in rats).

Growth failure in children with IBD is not a so uncommon a phenomenon. In a study of 23 children with CD, the median serum IGF-I concentration was lower in patients with active disease than in matched controls and lower in stunted than well grown patients, but insulin and IGFBP-1 concentrations were not significantly different between any groups. In a relevant study of GH secretion and action in growth-retarded children with juvenile chronic arthritis it was shown that, although stimulated and spontaneous GH secretion is normal in those children, the response to endogenous and exogenous GH with regard to IGF-I and IGFBP-3 production is impaired. This phenomenon indicates a degree of peripheral tissue insensitivity to GH action in such children. Plasma concentrations of IGF-I but not GH were significantly lower in a colitic group of rats and IGF-I administration to this group increased plasma IGF-I concentrations and linear growth by approximately 44-60%. It has been shown that approximately 30-40% of linear growth impairment in experimental colitis occurs as a direct result of inflammation that was independent of undernutrition. However it has been emphasized that the linear growth retardation induced by inflammation is due in part to a reduction in plasma concentrations of IGF-I.

**Perioperative use of GH or IGF**

It has been suggested that normal growth hormone secretion and a slightly subnormal serum level of IGF-I, which is related to nutritional status, characterize the endocrine status in CD.

Perioperative human GH (hGH) treatment of younger patients undergoing major abdominal surgery preserved limb lean tissue mass, increased postoperative muscular strength and reduced long-term postoperative fatigue. Moreover eight weeks of low-dose human recombinant GH treatment has been reported to increase body weight, lean body mass and fat-free mass in patients with short bowel syndrome, correlated to increase in IGF-I levels. After GH treatment in CD patients a significant increase in IGF-I was noticed. No significant changes in IGFBP-3 were noticed and no significant association between IGF-I levels and Crohn’s disease activity index scores were shown. The way in which GH may benefit CD patients is unclear. The increase in IGF-I after GH administration was consistent with that seen in adults with other diseases that are treated with GH. However these findings do not support the possibility that the beneficial GH effect is due to the action of IGF-I on the bowel since the degree of clinical improvement in individual patients was not correlated with their levels of IGF-I.

Major surgery is accompanied by extensive proteolysis of IGFBP-3, which is generally believed to increase IGF bioavailability due to diminished affinity of the IGFBP-3 fragments for IGFs. IGF-I and IGFBP-3 were assessed during enteral nutrition, drug therapy or intestinal resection as therapeutic interventions in CD and it was shown that IGF-I and IGFBP-3 were statistically significantly increased during conservative treatment but not with surgery.

**IGF in IBD: Future perspectives**

It is suggested that IBD follows several clinical patterns during its course and has several differences in its complications and extra-intestinal manifestations. Those differences have been observed in different countries and also within the same country (i.e. Greece) implying a multifactorial aetiopathogenetic model but also probable ethnic differences in terms of bowel response to inflammation.

The reported differences of IGF-I levels in serum, tissue and gut lavage fluid in IBD patients may imply that the IGF system is regulated by several different local and systemic mechanisms, probably influenced by endocrine/paracrine mechanisms and inflammation. In the future an analytic invesigation of these regulatory mechanisms may be of great help in IBD therapeutics.
The paradigms of patients with insulin-dependent diabetes mellitus (IDDM) in whom dual hormonal replacement therapy with insulin plus human recombinant IGF-I (HrIGF-I) improved glycemic control better than insulin alone (mono-therapy) and the systemic IGF-I administration which reduced the severity of DSS-induced colitis in rats promoting tissue repair of are of great importance. The real effects of IGF-I treatment on the colonic epithelium may be mediated directly whereas the reduced mucosal and submucosal inflammation may be mediated by a mechanism other than up-regulation of TGF-b1. It seems that a more systemic pathophysiological overview of the IGF system deterioration in IBD may offer new treatment options in inflammatory bowel disease patients.

REFERENCES

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