Review

Insulin-like growth factor system and inflammatory bowel disease

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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 is 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.

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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[1]. Extensive research efforts have focused on the role of cytokines in the induction and regulation of this chronic inflammatory process[2]. Clinical studies of growth factors in intestinal fluid facilitate research on intestinal fibrogenesis and the diagnosis of fibrous stricturing in CD.

Little is known about the role of growth factors in inflammatory bowel disease and its complications[3]. 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)[4]. Two forms of IGF-I complex have so far been described in the circulation[2] (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[5]. IGF-I expression has been shown in lymphocytes, macrophages and fibroblasts[6]. 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[7-9]. Grosh et al showed that the majority of CD patients with strictures had detectable levels of IGF-I in their gut lavage fluid[10,11].

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[4,12-16] 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[17]. Trials of growth hormone combined with a high-protein diet in short bowel syndrome patients as well as in CD patients have been encouraging[18-22].

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,

Table 1. The IGF system.

Insulin-like Growth factors	**IGF receptors**
IGF-I	-IGF-I receptor (tyrosine kinase) *for both IGF-I & IGF-II*
IGF-II (fetal)	-IGF-II receptor (mannose-6-phosphatase) *for only IGF-II*
	IGF Binding Proteins 1 - 6 (IGFBP 1-6)

Table 2. The two forms of IGF-I complex in the circulation.

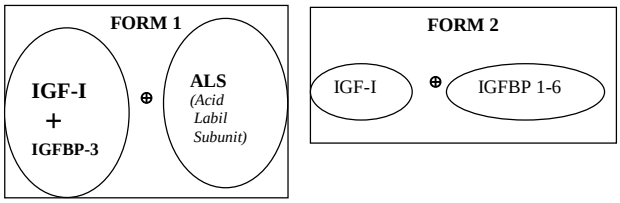

Table 3. Reported low serum IGF-I and IGFBP-3 in Crohn's disease (CD) and ulcerative colitis (UC) patients.

No	Author	Diagnosis	Serum IGF-I	Serum IGFBP-3	Remarks on the paper
1	Slonim	CD	↓	Not done	IGF-I statistical increase after GH administration
2	Dinca	CD/UC	↓	Not done	Assessment of osteopenia in IBD patients
3	Savage	CD	↓	Not done	
4	Beattie	CD	↓	Not done	IGF-I increases during therapy
5	Lund	CD/UC	↓	↓	Studies in vivo and in vitro in human and animal tissues Also IGF-I m RNA studied
6	Thomas	CD	↓	Same as controls	Study in growth retarded IBD children
7	Kirschner	CD/UC	↓	Not done	

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 plasma[23]. 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-I 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 rats[25]. 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 feedback[26]. 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 circulation[27]. 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 injection[27].

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 axis[28]. 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 system[30].

The IGF system and Interleukin-1

Proinflammatory cytokines, including IL-1 play an important role in acute and chronic inflammation. Endogenously produced IL-1 mediated the changes in IGF-I and IGFBP induced by chronic abdominal sepsis in rats[31]. IL-1β is overexpressed in inflamed intestinal tissue in Crohn's disease and ulcerative colitis[32]. It is tempting to speculate that the progression of liver and bowel inflammation, granuloma formation and fibrosis may involve an ordered interplay and paracrine interactions among cells expressing IL-1β, TGF-β and IGF-I[33].

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

1. Inadequate IGF-I secretion
2. Decreased IGF-I half life
3. Low IGFBP levels
4. IGF receptor antagonism
5. Increased IGF-I clearance

Both endotoxin and IL-1β have also been implicated in decrease liver and musle IGF-I content by decreasing its gene expression. The in vivo IL-1β administration in rats decreases IGF-I, increases IGFBP-1 and IGFBP-2 levels in plasma, liver and skeletal muscle and suppresses GH induced acid-labile subunit (ALS) mRNA levels and secretion in primary hepatocytes[34]. The IL-1 receptor antagonist attenuates acute and chronic enterocolitis whereas exposure to neutralizing antibodies against an IL-1 receptor antagonist prolongs intestinal inflammatory responses[35]. The infusion of a specific IL-1 receptor antagonist (IL-1ra) prevents the sepsis-induced changes in the IGF system which correlates with changes in protein synthesis[30].

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-I[14]. 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 patients[36].

Bowel IGF m RNA 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 vitro[37].

IGF-I mRNA was measured using RNAase protection in bowel and liver of rats with peptidoglycan-polysaccharide-induced (PG-PS) chronic granulomatous enterocolitis and hepatitis[38]. 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-1β[39]. 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 IBD[40,41]. IL-1β mRNA is up-regulated in the serum during acute and chronic phases of PG-PS and Dextran Sulphate Sodium (DSS) induced colitis[42]. In this PG-PS model it was shown that IGF-I mRNA

is increased in an area of intense fibrosis surrounding granulomas in inflamed intestinal tissue implicating IGF-I in the pathogenesis of fibrosis[43].

The IGF system and Interleukin-6

Recombinant IL-6 stimulates acute secretion of GH and enhances IGFBP-1 production[44] in humans, although the main effects of cytokines in AGHR are likely to be via effects on IGF-I production[24]. 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[23].

IGF system and growth in IBD

Growth failure of IBD patients is not the result of GH deficiency and is not an irreversible phenomenon[45]. On the contrary, it had been suggested for many years that judicious use of steroids usually produces compensatory growth acceleration[46-47] and beneficial effects of GH combined with parenteral nutrition in the management of IBD growth retardation have also been reported (study in rats)[48-49].

Growth failure in children with IBD is not a so uncommon a phenomenon[50]. 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 IGFPB-1 concentrations were not significantly different between any groups[51]. 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[52]. 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[53].

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[45].

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[54]. 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[55]. 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[56].

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[57]. IGF-I and IGFBP-3 were assessed during enteral nutrition, drug therapy or instestinal 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[51].

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 (monotherapy)[58] and the systemic IGF-I administration which reduced the severity of DSS-induced colitis in rats promoting tissue repair[59] are of great importance. The real effects of IGF-I treatment[60] 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[51]. It seems that a more systemic pathophysiologic overview of the IGF system deterioration in IBD may offer new treatment options in inflammatory bowel disease patients.

REFERENCES

1. Sartor RB. Pathogenesis and immune mechanisms of chronic inflammatory bowel diseases. Am J Gastroenterol 1997;92:5S-11S.
2. Lund PK. Molecular bias of intestinal adaptation: the role of the insulin like growth factor system. N Y Acad Sci 1998;859:18-36.
3. Dinca M, Fries W, Luisetto G, et al. Evolution of osteopenia in inflammatory bower disease. Am J Gastroenterol 1999;94:1292-1297.
4. Lund PK, Zimmermann EM. Insulin -like growth factors and inflammatory bowel disease. Baillieres Clin Gastroenterol 1996;10:83-96.
5. Lund PK. The alpha -smooth muscle actin promoter: a useful tool to analyse autocrine and paracrine roles of mesenchymal cells in normal and diseased bowel. Gut 1998; 42:320-322.
6. Graham MF, Drucker EM, Dieggelman RF, Elson CO. Collagen synthesis by human intestinal smooth muscle cells in cultures. Gastroenterology 1987;92:400-405.
7. Pucilowska JB, Mc Naughton KK, Mohapatra N, et al. IGF-I and procollagen alpha (I) are coexpressed in a subset of mesenchymal cells in active Crohn's disease. Am J Physiol Gastrointest Liver Physiol 2000;279:GI307-322.
8. Lawrance IL, Maxwell L, Doe W. Inflammation, location but not type, determines the increase in TGF-beta 1 and IGF-I expression and collagen deposition in IBD intestine. Inflamm Bowel Dis 2001;7:16-26.
9. Zimmermann EM, Li L, Hou YT, Mohapatra NK, Pucilowska JB. Insulin like growth factor I and insulin like growth factor binding protein 5 in Crohn's disease. Am J Physiol Gastrointest Liver Physiol 2001;280:1022-1029.
10. Grosh S, Humphreys K, Papachrysostomou M, Ferguson A. Detection of insulin-like growth factor -I and transforming growth factor -beta in whole gut lavage fluid: a novel method of studying intestinal fibrosis. Eur J Gastroenterol Hepatol 1997;9:505-508.
11. Han VKM, Ercole AJ, Lund PK. Identification and cellular sites of synthesis of somatomedin/insulin-like growth factors in the human fetus by in situ hybridization histochemistry. Science 1987;236:193-197.
12. Thomas AG, Holly JM, Taylor F, Miller V. Insulin like growth factor-I, insulin like growth factor binding protein-1 and insulin in childhood Crohn's disease. Gut 1993; 34:944-947.
13. Katsanos KH, Christodoulou D, Kitsanou M, Cholevas V, Gartzonica K, Eleftheriou A, et al. IGF and IGFBP in inflammatory bowel disease. 5th National Greek Congress of Internal Medicine, 1999:167.
14. Efstathiadou Z, Katsanos KH, Mpitsis S, Challa A, Tsianos EV, Tsatsoulis A. IGF-I and IGFBP3 in inflammatory bowel disease.27th National Greek Congress of Endocrinology and Metabolism, 2000:174.
15. Tsianos EV, Katsanos KH, Christodoulou D, et al. IGF-I and IGFBP in inflammatory bowel disease. Gastroenterology 2000;118:A1373.
16. Katsanos KH, Tsatsoulis A, Christodoulou D, Challa A, Katsaraki A, Tsianos EV. Reduced serum insulin-like growth factor -1 (IGF-1) and IGF-binding protein-3 levels in adults with inflammatory bowel disease. Growth Hormone & IGF Research 2001;11:364-367.
17. Tenore A, Berman WF, Parks JS, Bongiovanni AM. Basal and stimulated serum growth hormone concentrations in inflammatory bowel disease. J Clin Endocrinol Metab 1997;44:622-628.
18. Roith D. Seminars in medicine of the Beth Israel Deaconess Medical Center. Insulin-like growth factors. N Engl J Med 1997;336:633-640.
19. Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. Endocr Rev 1994;15:80-101.
20. Zhang W, Bain A, Rombeau JL. Insulin-like growth factor-I (IGF-I) and glutamine improve structure and function in the small bowel allogrft. J Surg Res 1995;59:6-12.
21. Person PG, Ahlbom A, Hellers G. Diet and inflammatory bowel disease: a case control study. Epidemiology 1992;3:47-42.
22. Anonymous authors. Dietary and other risk factors of ulcerative colitis: a case control study in Japan. J Clin Gastroenterol 1994;19:166-171.
23. De Benedetti F, Alonzi T, Moretta A, et al. Interleukin-6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor I. J Clin Invest 1997; 99:643-650.
24. Jenkins RC, Ross RJM. Acquired growth hormone resistance in adults. Baillier's Clinical Endocrinol Metabol 1998;12:315-330.
25. Zeeh JM, Hoffman P, Sottili M, Eysselein VE, McRoberts JA. Upregulation of insulin like growth factor I binding sites in experimental colitis in rats. Gastroenterology 1995;108:644-652.
26. Blum WF, Albertson-Wikland K, Rosberg S, Ranke MB. Serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 reflect spontaneous growth hormone secretion. J Clin Endocrinol Metabol 1993;70:1610-1616.
27. Ross RJM, Miell J, Freeman E, et al. Critically ill patients have high basal growth hormone levels with attenuated

oscillatory activity associated with low levels of insulin-like growth factor-I. Clin Endocrinol 1991;35:47-53.
28. Fan J, Wojnar MM, Theodorakis M, Lang CH. Repulation of insulin - like growth factor (IGF)-I mRNA and peptide and IGF- binding proteins by interleukin-1 AM 1 Physiol. 1996;270:R621-R629.
29. Ghigo E, Arvat G, Aimaretti G, Broglio F, Giordano R, Camanni F. Diagnostic and therapeutic uses of growth hormone – releasing substances in adult and elderly subjects. Bailliere's Clinical Endocrinology and Metabolism, 1998;12:341-358.
30. Lang CH, Fan J, Cooney R, Vary TC. IL-1 receptor antagonist attenuates sespis-induced alteration in the IGF system and protein synthesis. Am J Physiol (Endocrinol Metab. 33)1996:E430-437.
31. Ballmer PE, McNurlan MA, Southorn BG, Grant I, Garlic PJ. Effects of human recombinant interleukin-1b on protein synthesis in rat tissues compared with a classical acute phase reaction induced by turpentine. Biochem J 1991;279:683-688.
32. Fiocchi C, Podolsky DK. Cytokines and growth factors in inflammatory bowel disease IN: Kirsner JB, Shorter RG (eds) Inflammatory bowel disease. Williams and Wilkins, Baltimore, MD, 1995:252-280.
33. Thissen JP, Verniers J. Inhibition by interleukin-1b and tumor necrosis factor-a of the insulin-like growth factor I messenger ribonucleic acid response to growth hormone in rat hepatocyte culture. Endocrinology 1997;138:1078-1084.
34. Delhanty PJ. Interleukin-1 beta suppresses growth hormone-induced acid-labile subunit m RNA levels and secretion in primary hepatocytes. Biochem Biophys Res Commun 1998;243:269-272.
35. Sävendahl L, Underwood LE, Haldeman KM, Ulshen MH, Lund PK. Fasting prevents experimental murine colitis produced by dextan sulfate sodium and decreases interleukin 1β and insulin-like growth factor I messenger ribonucleic acid. Endocrinology 1997;138:734-740.
36. Alexander RJ, Ranja A, Kaplan-Liss E, Mayer L, Raicht RF. Expression of growth factor receptor-encoded m RNA by colonic epithelial cells is altered in inflammatory bowel disease. Dig Dis Sci 1995;40:485-494.
37. Benbassat CA, Lazarus DD,Cichy SB, et al. Interleukin-1 alpha (IL-1 alpha) and tumor necrosis factor alpha (TNF alpha) regulate insulin-like growth factor binding protein-1 (IGFBP-1) levels and m RNA abundance in vivo and in vitro. Horm Metab Res 1999;31:209-215.
38. Zimmermann EM, Sartor RB, McCall RD, Parolo M, Bender D, Lund RK. Insulin like growth factor I and inteleukin 1β messenger RNA in a rat model of granulomatous enterocolitis and hepatitis. Gastroenterology 1993;105:399-409.
39. Zeeh JM, Mohapatra N, Lund PK, Eysselein VE, McRoberts JA. Differential expression and localisation of IGF-I and IGF binding protein m RNA in inflamed rat colon. Gastroenterology 1995;108:A 948.
40. Winesett DE, Ulshen MH, Hoyt EC, Mohapatra NK, Fuller CR, Lund PK. Regulation and localisation of the insulin like growth factor system in small bowel during altered nutrient status. Am J Physiol 1995;268:G631-G640.
41. Chowdhury A, Fukuda R, Fukumoto S. Growth factor m RNA expression in normal colorectal mucosa and in uninvolved mucosa from ulcerative colitis patients. J Gastroenterol 1996;31:353-360.
42. Haldeman KM, Mohapatra NK, Fuller CR, Sartor RB, Lund PK. Effect of growth hormone on expression of interleukin-1b and IGF-I in DSS-induced colitis(Abstract). 10TH International Congress of Endocrinology, San Frasisco CA, 1996:P452.
43. Cohen JA, Zimmermann EM, Sartor RB, Lund PK. IGF-I and IGF-II are overexpressed in inflamed and strictured intestine in Crohn's disease. Gastroenterology 1993; 104:A683.
44. Neidel J, Blum WF, Schaeffer HJ, et al. Elevated levels of insulin like growth factor (IGF) binding protein-3 in rheumatoid arthritis synovial fluid inhibit stimulation by IGF-1 of articular chondrocyte proteoglycan synthesis. Rheumatol Int 1997;17:29-37.
45. Savage MO, Beattie RM, Camacho-Hubner C, Walker-Smith JA, Sanderson IR. Growth in Crohn's disease. Acta Paediatr Suppl 1999; 88:89-92.
46. Conover CA, Divertie GD, Lee PDK. Cortisol increases plasma insulin like growth factor binding protein in humans. Acta Endocrinol 1993;128:140-143.
47. Kirschner BS, Sutton MM. Somatomedin-C levels in growth-impaired children and adolescents with chronic inflammatory bowel disease. Gastroenterology 1986; 91:830-836
48. Chen K, Nezu R, Inoue M, et al. Beneficial effects of growth hormone combined with parenteral nutrition in the management of inflammatory bowel disease: an experimental study. Surgery 1997; 121:212-218
49. Ghigo E, Arvat E, Aimaretti G, Broglio F, Giordano R, Camanni F. Diagnostic and therapeutic uses of growth hormone-releasing substances in adult and elderly. Baillier's Clinical Endocrinol Metabol 1998;12:341-358
50. Motil KJ, Grand RJ, Davis-Kraft L, Ferlic LL, Smith EO. Growth failure in children with inflammatory bowel disease: a prospective study. Gastroenterology 1993;105:681-691.
51. Beattie RM, Camacho-Hubner C, Wacharasindle S, Cotterill AM, Walker-Smith JA, Savage MO. Responsiveness of IGF-I and IGFBP-3 to the therapeutic intervention in children and adolescents with Crohn's disease. Clin Endocrinol (Oxf) 1998;49:483-489.
52. Tsatsoulis A, Siamopoulou A, Petsoukis Ch, Challa A, Bairaktari E, Seferiadis K. Study of growth hormone secretion and action in growth -retarded children with juvenile chronic arthritis (JCA). Growth hormone of IGF Research 1999;9:143-149.
53. Ballinger AB, Azooz O, El-Haj T, Poole S, Farthing MJG. Growth failure occurs through a decrease in insulin-like growth factor 1 which is independent of udernutrition in a rat model of colitis Gut 2000;46:695-700.
54. Kissmeyer-Nielsen P, Jensen MB, Laurberg S. Perioperative growth hormone treatment and functional outcome

after major abdominal surgery: a randomized, double-blind controlled study. Ann Surg 1999;229:298-302.
55. Ellegand L, Bosaeus I, Nordgren S, Bengtsson BA. Low-dose recombinant human growth hormone increases body weight and lean body mass in patients with short bowel syndrome. Ann Surg 1997;225:88-96.
56. Slonim AE, Bulone L, Damore MB, Goldberg T, Wingertahn MA, McKinley MJ. A preliminary study of growth hormone therapy for Cronh's disease. N Engl J Med 2000;342:1633-1637.
57. Skjaerbaek C, Frystyk J, Orskov H, et al. Differential changes in free and total insulin-like growth factor-I after major abdominal surgery:the possible role of insulin like growth factor binding protein-3 proteolysis. J Clin Endocrinol Metab 1998;83:2445-2449.
58. Thraikill K, Quattrin T, Baker L, et al. Dual hormonal replacement therapy with insulin and recombinant human insuline-like growth factor (IGF)-1 in insulin - dependent diabetes mellitus: effects on the growth hormone/IGF/IGF-binding protein system. J Clin Endocrinol Metabol 1997;82:1181-1187.
59. Howarth GS, Xian CJ, Read LC. Insulin-like growth factor-I partially attenuates colonic damage in rats with experimental colitis induced by oral dextran sulfate sodium. Scand J Gastroenterol 1998;33:180-190.
60. Fan J, Wojnar MM, Theodorakis M, Lang GH. Regulation of insulin like growth factor (IGF)-I m RNA and peptide, and IGF-binding proteins by interleukin-1. Am J Physiol 1995 (Regulatory Interactive Comp. Physiol 39):R621-629.