Acta Alimentaria, Vol. 28 (2), pp. 171–181 (1999)

HIGH RESOLUTION COMPUTED TOMOGRAPHY DETECTION OF ALIMENTARY FACTORS RELATED TO ARTHROPATHIES IN INFLAMMATORY BOWEL DISEASES

Á. MESTER[a], E. MAKÓ[a], S. NAGYLUCSKAY[b], K. KARLINGER[a], E. MÁRTON[a] and T. GYÖRKE

Semmelweis University of Medicine,
[a] Department of Radiology and Oncotherapy, H–1082 Budapest, Üllői út 78/A. Hungary
[b] Institute of Public Health, H–1089, Budapest, Nagyvárad tér 4. Hungary

(Received: 27 July 1998; accepted: 15 December 1998)

Alimentary factors of enterogen arthropathies were studied, in particular the early morphological detection, to prevent the disease progression by nutritional prescriptions. Authors compared the method of high resolution computed tomography (HRCT) with conventional X-ray and nuclear medicine investigations. The results showed the superiority of HRCT to detect cartilage erosions and ligamental calcifications in the sacroiliac joint and lumbar facet joint. The importance of nutritional factors is briefly discussed. The need for high quality and high quantity food of patients suffering from inflammatory bowel diseases (IBD) is well known. Elemental diet is effective for remission of IBD. Folic acid intake is extremely important. Total parenteral nutrition in acute active disease (Crohn's fistulas) has not been proved to effect IBD. Elimination of whole protein as a possible luminal factor for long term application can help, if elementary amino acids are in the diet. Eicosapentaenoic acid and docosahexaenoic acid (major components of fish oils) have beneficial effects. Polyunsaturated fatty acids in the diet can decrease the inflammation. Antioxidants, glutamine are essential in the diet. Removal of fat is effective to get remission. Alimentary complication in IBD patients can be the osteoporosis, so there is a need for regular bone densitometry. Conclusion of the study suggests that HRCT offers the most sensitive detection of enterogen arthropathy related changes. The predictive value of this diagnostic method is accurate enough to advise restrictive and/or supplemental diets for IBD patients. Dietary therapy allows circumvention of the adverse side-effects of repeated courses of steroids.

Keywords: arthritis, Crohn, inflammatory bowel diseases, sacroileitis

Alimentary factors associated with inflammatory bowel diseases (IBD) associated in arthropathies have got a rising importance in the recent period of scientific and clinical research.

Alimentary factors can explain, why the different localisation (small bowel/large bowel) of the inflammation, – for example Crohn's disease (CD) versus ulcerative colitis (UC) – involves more or less frequently the joints. Small bowel Crohn's manifestation versus colonic CD and/or ulcerative colitis causes a higher prevalence of the arthritis.

Vegetarian diet can have a beneficial influence on arthritis, such as rheumatoid arthritis (RA) (KJELDSEN–KRAGH et al., 1991). This can be connected to the immune globulin production (MIELANTS et al., 1995). FELTELIUS and co-workers (1994) found increased jejunal IgM in untreated ankylotic spondylitis (AS) patients.

Bowel inflammation and joint inflammation can occur by a common pathologic origin, on one hand, and on the other hand the arthropathy can be a secondary consequence of changes in the intestinal absorption. The third possibility is a combined manifestation of both action mechanisms (BRANDTZAEG et al., 1997).

Arthritis types, on one hand, are transient monarthritis episodes, which are characteristic. Destructive (erosive) arthritis and granulomatous synovitis are less common on the other hand (GRAVALLESE et al., 1988; NORTON et al., 1993; HERMANS, 1984). Sacroileitis is the most important axial articular involvement with a possible progression up to ankylosis (see ankylosing spondylitis). Sacroileitis is a more common central arthritis in IBD than in ankylosing spondylarthritis (AS).

Enterogen artropathies are multifactorial diseases. Genetic factors, such as human leukocyte antigen (HLA)–B27 are associated with ankylosing spondylitis (AS) with later occurrence of enteritis, and sometimes with Crohn's disease or ulcerative colitis which develop many years after the initial arthritis (PURRMANN et al., 1988; DE VOS et al., 1989).

Bacterial enteral infections can possibly be the first disease (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*) and consecutive reactive arthritis (ReA) can be a later manifestation (these bacteria express lipopolysaccharides on their outer membrane, and can exist intracellularly). In case of the Reiter's syndrome urethritis and conjunctivitis combine with arthritis.

The influence of the intestinal mucosal permeability – increased by inflammation – has an important, but not single pathogenic role. In case of CD patients, their healthy first degree relatives had increased intestinal permeability, too (KATZ et al., 1989; MIELANTS et al., 1991).

The antigen presentation (of bacteria) by HLA class I molecules to (memory)T–lymphocytes can explain why the strong correlation in–between bacterial exposure and genetic factors exists. In this context class II alleles, like DR103 may have importance, too. These molecules can bind and present fragments of class I molecules to the lymphocytes (molecular mimicry), which stimulate/prolongate inflammation and/or autoimmune mechanisms (ORCHARD et al., 1997).

The inflammation causes changes in the adhesion properties of the mucosal microvascular endothelium. By this process the "gatekeeper" function of the B and T cells (excreted by the Peyer's patches in the normal mucosa) decreases. Gut derived lymphoblasts have dual endothelial ("homing") affinity: both intestinal mucosa and synovial membrane of the joints (JALKANEN et al., 1986). In ReA mucosal macrophages transport bacterial antigens to the synovial endothelial cells (SALMI et al., 1997).

Nutritional factors of inflammatory bowel diseases

Nutrition and intestinal functions are strongly interrelated. The 1/2–2/3 of patients with Crohn's disease were weight-depleted and 3/4 of adolescents growth-retarded. Chronic malnutrition impairs digestive and absorptive function because food and nutrients are not only the major trophic factors to the gut but also provide the building blocks for digestive enzymes and absorptive cells. Weight loss greater than 30%, accompanying a variety of diseases is associated with a reduction in pancreatic enzyme secretion of over 80%, villus atrophy and impaired carbohydrate and fat absorption (O'KEEFE et al., 1996). Specific nutrients can induce disease, for example, gluten-sensitive enteropathy, whilst dietary factors such as fibres, among them resistant starch, short-chain fatty acids, glutamine and fish-oils are joined in prevention of gastrointestinal diseases such as diverticulitis, diversion colitis, ulcerative colitis, colonic adenomatosis and colonic carcinoma. The role of dietary antigens in the aetiology of Crohn's disease is controversial, but controlled studies have suggested that elemental diets may be as effective as corticosteroids in inducing a remission in patients with acute Crohn's disease.

A general need for high quality and high quantity food of IBD patients predominantly in the adolescent and young adult age groups, is evident. The IBD diseases often cause weight loss, by decreasing the appetite, and/or by diarrhoea. Chronic blood loss is common in the UC patients, with a consecutive need of iron intake. Lactose intolerance requires lactose free milk, or yoghurt to supply calcium. Unexpected osteoporosis can occur even in young adults, if calcium absorption decreases because of chronic IBD. In coeliac disease the prescription of wheat protein gluten is essential to prevent enteral inflammation (THOMPSON et al., 1993).

Elemental diet is effective for both inducing and maintaining remission of IBD. MUNAKATA and co-workers (1997) reported equal effectiveness between elemental diet, oligopeptide diet and intact nutrients treating active Crohn's disease. Although corticosteroid is also useful for treating active Crohn's disease, low dose of it is not effective for maintaining remission. Steroids have important role in combined therapy with elemental diet.

The importance of folic acid intake is extremely important, if 6–mercaptopurine (6MP) or sulfasalazine therapy is being used. It is also required to measure the B_{12} vitamin absorption ("Schilling test"). In malabsorption or bile salt deficiencies A, D and K vitamin support is recommended. Restrictive (so called "natural") diets are dangerous in severe cases (sepsis, obstructing lesions or extensive fistulas).

In case of IBD there has been no major alimentary factor like gluten in coeliac disease. Total parenteral nutrition in actual active disease (fistulas) has not proved to effect in IBD. Elimination of whole protein as a possible luminal factor for long term application can help, if elementary amino acids are in the diet. (O'MORAIN and co–workers /1984/ found this to be similarly effective to prevent exacerbation of Crohn's disease like prednisolone.) In ulcerative colitis fish–oil seems to have beneficial effects, because of its effect on the mucosal production of prostaglandins and leukotriens.

Dietary intake can be the initiator of intestinal inflammation (PRIKAZSKA et al., 1997). In this connection they reported observations about a group of patients suffering from Crohn's disease and ulcerative colitis. In patients with Crohn's disease, a preferred consumption of flour products, decreased intake of vegetables and fruit, lowered tolerance to milk and milk products, increased sugar consumption, increased proportion of smokers, no differences in diet regimen between sick and healthy subjects were noticed.

Antigens in food can

- induce/influence immune response: aggravation of inflammation,
- pass through an abnormally permeable mucosa.

Malnutrition is a common consequence of advanced IBD, predominantly in adolescence, and if small bowel shortening exist (fistulas and/or surgical resections).

Polyunsaturated fatty acids in the diet can decrease the inflammation by altering the metabolic pathway with formation of less active leukotriene B5 rather than leukotriene B4. FRENCH and co–workers (1997) compared Crohn's patients, normal subjects and subjects with inactive Crohn's disease consuming a high polyunsaturated to saturated fat ratio diet. He concluded that

- absorption of labelled [1–13C] 10:0 and [1–13C] 16:0 ingested with a test meal is reduced in Crohn's patients, and
- consumption of a high polyunsaturated to saturated fatty acid ratio diet improves the utilization of dietary C16:0 by Crohn's patients.

Eicosapentaenoic acid and docosahexaenoic acid are major components of fish oils, and strong competitive inhibitors of the synthesis from arachidonic acid of (inflammatory) prostaglandins.

Antioxidants (ascorbic acid, alpha tocopherol, beta-carotene, selenium, methionine) can decrease the inflammation caused by damaging oxygen species of leukocytes and other inflammatory cell activities.

Glutamine is an essential metabolic substrate for enterocytes. It can diminish the intestinal permeability (LENNARD-JONES et al., 1996).

Removal of large molecules from the food has a beneficial effect on gut inflammation:

- complete bowel rest (intravenous parenteral nutrition) doesn't influence significantly the IBD activity, because the essential substrates for epithelial cell metabolism are removed,
- elemental diet (amino acids, glucose, little fat with minerals and vitamins) and
- partially hydrolysed (polymeric) "peptide" diet (peptides, oligosaccharides, medium-chain length triglycerides) equally can influence bowel metabolism, reducing inflammation similarly to steroid therapy (OKADA et al., 1990; SEIDMAN et al., 1986; GORARD et al., 1993; GONZALEZ-HUIX, 1993; PARK, 1991).

Liquidized normal food has an advantage in case of intestinal strictures, by which stasis and its consequence: altered, pathogenic bacterial flora and their products, like formyl-methionyl-leucyl-phenylalanine (FMLP) can increase the inflammation.

Removal of fat can increase the beneficial effect of liquid diets. Monounsaturated fatty acids have less disadvantages. Linoleic acid (precursor of arachidonic acid) and long chain triglycerides can aggravate the inflammation (MIDDLETON, 1994). Short chain fatty acids (derived from bacterial fermentation of unabsorbed carbohydrate) are essential for colonocytes (HEATON et al., 1979; RITCHIE et al, 1987).

In cases of less severe patients, the alimentary advises are more simple: they can take a bland diet, poultry, white fish, lamb, white bread, cooked fruit and potato.

Alimentary complication in IBD patients can be the osteoporosis, even in young people late diagnosed with a high grade (GENANNT et al., 1976). The high grade osteoporosis (with compression of the vertebral body) causes asymmetric partial overload of the apophyseal facet joints, resulting in spinal pain syndrome (RYAN et al., 1992).

Enteral feeding has been shown to be as effective as primary therapy for Crohn's disease. However, in adolescents with growth failure and when corticosteroid therapy is contra-indicated or has failed, it may become the treatment of choice. Furthermore, diet therapy allows circumvention of the adverse side-effects of repeated courses of steroids. Comparison of feeds with differing composition suggests that a low fat content increases efficacy and various explanations have been offered. The reduction of colonic bacterial load may also be important. Because symptoms of Crohn's disease may be provoked by eating, there is a risk of falsely attributing symptoms to specific foodstuffs. However, in many individuals foods can be identified which affect disease activity, and their exclusion leads to prolongation of disease remission. Dietetic supervision during food testing is important to avoid detrimental effects on nutrient and micronutrient intake (KING et al., 1997).

The aim of our study was to find a highly sensitive and precise diagnostic tool, which can help the selection of patients, who need an additional alimentary therapy to stop the articular disease progression, increase the sensitivity of the detection of sacroiliac joint erosions, and to help by this the precise diagnosis of extraintestinal IBD manifestations.

The early morphological detection of erosions in sacroileitis is insufficient with conventional radiological techniques: X-ray detects erosions in 15% only, but bone scan is positive in 70%, suggesting transient sacroileitis (GRAVALLESE et al., 1988). In case of the apophyseal facet joint's erosions the conventional radiography is not useful at all. Bone scan can not differentiate in between degenerative and inflammatory apophyseal facet joint's involvement.

1. Materials and methods

Patients suffering of inflammatory bowel diseases (IBD), as Crohn's disease (CD), ulcerative colitis (UC) and malabsorbtion syndrome/coeliacia were investigated.

The diagnoses of IBD was established with abdominal CT (1500 ml of per oral iodine-benzol-alkyl contrast material, 10 g% iodine and/or 1500 ml diluted barium sulphuric suspension, 10 g%). The CT investigation was followed by fluoroscopic enteroclysis: naso-jejunal catheter (with 50 g% diluted barium sulphuric suspension). The inflammatory activity of the bowel was measured by 99m-Tc labelled monoclonal anti-granulocyte antibody radioisotope scan. The actual inflammatory activity of the joints was measured by 99m–Tc labelled pyrophosphate scans.

The sacroiliac joint high resolution computed tomography (HRCT) and lumbar facet joint HRCT were done in 25 cases with proved IBD. The HRCT was carried out with Siemens (DRG2 and SomatomPlus4) equipment, using thin section (1 or 2 mm) scanning with 10 mm interslice gap, and high resolution image reconstruction algorithm. The X-ray tube-detector system ("gantry") angulation was 20° in the caudo-cranial direction.

To evaluate the HRCT results, 99m-Tc radiolabelled pyrophosphate bone scintigraphy (whole body planar scanner) and X-ray plain films were compared.

2. Results and discussion

Sacroiliac joint erosions were detected in 8 of 25 cases, with plain films, but the HRCT visualised 17 of 25, i.e. only 8 of 17 was seen on the plain films. Unilateral was the sacroileitis in 4 of 8 plain film positive cases, but only in 5 of 17 had unilateral involvement with HRCT. (The HRCT changed unilateral category into bilateral.)

Calcifications in the ligamental parts of the sacroiliac joint/lumbar facet joint's capsular region were with erosions in 3, without erosions in 7 of 25 cases.

The nuclear medicine investigation was positive in 7 cases, but in the majority others, than the HRCT. There was no strong correlation in–between the HRCT and nuclear medicine matching.

Lumbar facet joint's erosions were not seen on any plain films. The HRCT detected erosive lesions in 5 of 14 enterogen arthropathy cases. Nuclear medicine bone scan positivity was found in 2 of 5 erosive cases, but in 2 non erosive lesions, too (suggesting degenerative changes).

The enterogen apophyseal facet joint erosions – detected first by our research – using HRCT, can occure as primary inflammatory manifestations. Enterogen arthropathy has two components in this case. First the destructive monarticular apophyseal lesions of the CD patients could be connected to their specific granulomatous inflammatory changes (LINDSTROM et al., 1972; NUGENT et al., 1976; HERMANS et al., 1984; AL–HADITI et al., 1984; TOUBERT et al., 1985). The other component is a secondary antibacterial immune–reaction, i.e. "post infect" arthritis (related to the pathologically increased bowel absorbtion). The third component of the morphology can be a degenerative joint space narrowing (with or without osteoporosis related overloading).

The lymphoma patient's erosive joint inflammation was most probably an enterogen arthropathy, too (by a prae-lymphomatic sprue/malabsorbtipon). The enterogen and other SNSA sacroileitis/apophyseal facet joint inflammation can not be visualised much more accurately with HRCT, versus plain film or radionuclide scan. Even the SPECT can not increase highly the detection (RYAN et al., 1992), because it is only positive for a short period of actual (florid) sacroileitis. The HRCT visualises all residual morphological changes of the cartilage. Rarely hyperuricaemia/gout can cause apophyseal facet joint erosions.

The HRCT sensitivity gives the possibility to detect sacroiliac/lumbar facet joint involvement in IBD patients earlier. The articular involvement detection can influence the drug therapy and alimentary prescriptions as well.

The correction from pseudo-unilateral into bilateral involvement can help the differentiation of enterogen and other seronegative/infect arthritis. By the accurate diagnosis the indication of correct causal therapy – included food restrictions – can be supported.

Erosions and ligamental calcifications are both connected with arthritis. The mechanism is most probably different, because they appear only partially together,

and often separated. Our hypothetical suggestion about the differences of the two versions could be:

- erosive lesions primary intraarticular manifestation of granulomatous inflammation, parallel with IBD versus
- secondary metabolic changes (by the increased bowel permeability) resulting inflammation/calcification in the ligamental parts of the joints.

The theory is based on the higher prevalence of erosive lesions in case of Crohn's disease versus malabsorbtion and ulcerative colitis.

The articular erosions in IBD patients are similar to the erosions of other (seronegative spondylarthritis) SNSA, but some pathological differences are present: granulomatous inflammation, similar with the intestinal granulomatous manifestation was present (NUGENT et al., 1976; HERMANS et al., 1984; AL-HADITI et al., 1984; TOUBERT et al., 1985). The possible mechanism seems to be the repeated infectious agents provoke joint inflammation. The reasons could be:

- changes of the bowel anatomy, for example following bypass surgery,
- autoimmune mechanisms by the molecular mimicry, for example after diarrhea, or similar to ankylosing spondylitis (AS, Bechterew) pathogenesis,
- the changed intestinal permeability after milk allergy or coeliacia,
- toxin mediated synovitis, for example pseudomembranosus enterocolitis.

The changes of the intestinal permeability can cause direct in situ antigen deposition (PHILLIPS et al., 1989). In cases of reactive arthritis colonoscopy proved relationship in-between the length of the inflamed intestinal mucosa and the arthritis (MIELANTS et al., 1987).

Other mechanism of intestinal seronegative sterile arthritis is the post-infect (*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*) reactive arthritis. Involvement of lymph nodes and bacteriemia (except *Shigella*) was detected (MIELANTS et al., 1987). The typical manifestation is, that after a period of 1–3 month acute "self-limiting" inflammation and specific (bacterial) immune–complexes can be detected in the synovial fluid of larger joints. Rarely true septic arthritis can occur (predominantly as post *Salmonella* complication in children) with direct cartilage destruction.

The HRCT offers the differentiation:

- in-between degenerative and inflammatory changes (joint space/subchondral lesions),
- intraarticular cartilaginous erosions / intraarticular ligamental calcifications / periartikular capsular / periarticular ligamental calcifications.

3. Conclusion

Elemental, hydrolysed and polymeric liquid diets appear to give equivalent results in reducing inflammation, and can be used as a first line of treatment instead of (or prior to) a corticosteroid drug therapy and/or in combination with steroids.

HRCT of axial joint involvement can be a predictor for the need of restrictive and/or supplemental diets.

References

AL-HADITI, S., KHATIB, G., CHHATWA, P. & KHATIB, R. (1984): Granulomatous diseases in Crohn's disease. *Arthritis Rheum.*, *27*, 1061–1065.

BRANDTZAEG, P. (1997): Review article: Homing of mucosal immune cells – a possible connection between intestinal and articular inflammation. *Aliment. Pharmacol. Ther.*, *11*/S3, 24–39.

DE VOS, M., CUVELIER, C., MIELANTS, H., VEYS, E., BARBIE, R. F. & ELEWAUT, A. (1989): Ileo-colonoscopy in seronegative spondylarthropathy. *Gastroenterology*., *96*, 339–344.

FELTELIUS, N., HVATUM, M., BRANDTZAEG, P., KNUTSON, L. & HALLGREN, R. (1994): Increased jejunal secretory IgA and IgM in ancylosing spondylitis: normalization after treatment with sulfasalazine. *J. Rheumatol.*, *21*, 2076–2081.

FRENCH, M. A., PARROTT, A. M., KIELO, E. S., RAJOTTE, R. V., WANG, L. C., THOMSON, A. B. & CLANDININ, M. T. (1997): Polyunsaturated fat in the diet may improve intestinal function in patients with Crohn's disease. *Biochim. Biophys. Acta*, *24*, 262–270.

GENANT, H. K., MALL, J. C., WADONFELD, J. B., HORST, J. V. & LANZI, L. H. (1976): Skeletal demineralisation and groth retardation in inflammatory bowel disease. *Invest. Radiol.*, *11*, 541–545.

GONZALEZ-HUIX, F., DE LEON, R., FERNANDEZ-BANARES, F., ESTEVE, M., CABRE, E., ACERO, D., ABAD-LACRUZ, A., FIGA, M., GUILERA, M. & PLANAS, R. (1993): Polimeric enteral diets as primary treatment of active Crohn's disease: a prospective steroid controlled trial. *Gut.*, *34*, 778–782.

GORARD, D. A., HUNT, J. B., PAYNE-JAMES, J. J., PALMER, K. R., REES, R. G., CLARK, M. L., FARTHING, M. J., MISIEWICZ, J. J. & SILK, D. B. (1993): Initial response and subsequent corse of Crohn's disease treated with elemental diet or prednisolone. *Gut.*, *34*, 1198–1202.

GRAVALLESE, E. M. & KANTROWITZ, F. G. (1988): Arthritic manifestation of inflammatory bowel disease. *Am. J. Gastroeneterol.*, *83*, 703–709.

HEATON, K. W., THORNTON, J. R. & EMMETT, P. M. (1979): Treatment of Crohn's disease with an unrefined-carbohydrate, fibre rich diet. *B.M.J.*, *2*, 764–766.

HERMANS, P. J., FIEVEZ, M. L., DESCAMPS, L. & AUPAIX, M. A. (1984): Granulomatous synovitis and Crohn's disease *J. Rheumatol.*, *11*, 710–712.

JALKANEN, S., STEERE, A. C., FOX, R. I. & BUTCHER E. C. (1986): A distinct endothelial cell recognition system that controls lymphocyte traffic into inflamed synovium. *Science*, *233*, 556–558.

KATZ, K. D., HOLLANDER, D., VADHEIM, C. M., MCELREE, C., DELAHUNTY, T., DADUFALZA, V. D., KRUGLIAK, P. & ROTTER J. I. (1989): Intestinal permeability in patients with Crohn's disease and their healthy relatives. *Gastroenerology*, *97*, 927–931.

KING, T. S., WOOLNER, J. T. & HUNTER, J. O. (1997): Review article: the dietary management of Crohn's disease. *Aliment. Pharmacol. Ther.*, *11*, 17–31.

KJELDSEN-KRAGH, J., HAUGEN, M., BORCHGREVINK, C. F., LAERUM, E., EEK, M., MOWINKEL, P., HOVI, K. & FORRE, O. (1991): Controlled trial of fasting and one year vegetarian diet in rheumatoid arthritis. *Lancet*, *338*, 899–902.

LENNARD-JONES, J. E. (1994): Practical management of the short bowel. *Aliment. Pharmacol. Ther.*, *8*, 563–577.

LENNARD-JONES, J. E. (1996): Nutrition -in: PRANTERA C., KORELITZ B. I. (Eds) *Crohn's disease.* Marcel Dekker, New York, Basel, Hong Kong. pp. 311–339.

LINDSTROM, C., WRAMSBY, H. & OSTBERG, G. (1972): Granulomatous arthritis in Crohn's disease. *Gut*, *13*(4), 257–259.

MIDDLETON, S. J., RUCKER, J. T., KIRBY, G. A. & HUNTER, J. O. (1994): Long chain triglicerides adversely affect dietary treatment of active Crohn's disease. *Gastreoenterology*, *106*, A734.

MIELANTS, H., VEYS, E., JOOS, NOENS, L., CUVELIER, C. & DE VOS, M. (1987): HLA-antigens in seronegative spondylarthropathies, reactive arthritis and arthritis in ankylosing spondylitis: relation to gut inflammation. *J. Rheumatol.*, *14*, 466–471.

MIELANTS, H., DEVOS, M., GOEMAERE, S., SCHELSTRAETE, K., CUVELIER, C., GOETHALS, K., MAERTENS, M., ACKERMAN, C. & VEYS, E. M. (1991): Intestinal mucosal permeability in inflammatory rheumatic diseases. Part II.: Role of the disease. *J. Rheumatol.*, *18*, 1542–1551.

MIELANTS, H., VEYS E. M., CUVELIER, C., DE VOS, M, GOEMAERE,. S, DE CLERCQ, L., SCHATTEMAN, L., GYSELBRECHT, L. & ELEWAUT, D. (1995) The evolution of spondylarthropathies in relation to the gut history. III. Relation between gut and joint. *J. Rheumatol.*, *22*, 2279–2284.

MUNAKATA, A. & HAGA, Y. (1997): Current medical therapies for Crohn's disease in Japan. ref., *Nippon Geka Gakkai Zasshi*, *98*, 406–411.

NORTON, K. I., EICHENFIELD, A. H., ROSH, J. R., STERN, M. T. & HERMANN, G. (1993): Atypical arthropathy associated with Crohn's disease. *Am. J. Gastroenterol.*, *88*, 948–952.

NUGENT, F. W., GLASER, D. & FERNANDEZ-HERLIHY, L. (1976): Crohn's colitis associated with granulomatous bone disease. *N. Engl. J. Med.*, *294*, 262–265.

O'KEEFE, S. J. (1996): Nutrition and gastrointestinal disease. *Scand. J. Gastroenterol. Suppl.*, *220*, 52–59.

O'MORAIN, C., SEGAL, A. W. & LEVI, A. J. (1984): Elemental diets as primary treatment of acute Crohn's disease; a controlled trial. *British Med. J.*, *288*, 1859–1862.

OKADA, M., YAO, T., YAMAMOTO, T., TAKENAKA, K., IMAMURA, K., MAEDA, K. & FUJITA, K. (1990): Controlled trial accompaning an elemental diet with prednisolone in the treatment of active Crohn's disease. *Hepatogastroenterology*, *37*, 72–80.

ORCHARD, T. & JEWELL, D. P. (1997): Review article: Pathophysiology of the intestinal mucosa in inflammatory bowel disease and arthritis: similarities and dissimilarities in clinical findings. *Aliment. Pharmacol. Ther.*, *11*/S3,10–16.

PARK, R. H. R., GALLOWAY, A. & DANESH, B. J. Z. (1991): Double blind controlled trial of elemental and polymeric diets as primary therapy in active Crohn's disease. *Eu. J. Gastroeneterol. Hepatol.*, *3*, 483–490.

PHILLIPS, P. E. (1989): How do bacteria cause chronic arthritis. *J. Rheumatol.*, *16*,_1017–1019.

PRIKAZSKA, M. & SIMONCIC, R. (1997): Nutrition and Crohn's disease. *Bratisl. Lek. Listy*., *98*, 107–110.

PURRMANN, J., ZEIDLER, BERTRAMS, J. JULI, E., CLEVELAND, S., BERGES, W., GEMSA, R., SPECKER, C. & REIS, H. E. (1988): HLA antigens in ankylosing spondylitis associated with Crohn's disease. Increased frequency of the HLA phenotype B27, B44. *J. Rheumatol.*, *15*, 1658–1661.

RITCHIE, J. K., WADSWORTH, J., LENNARD-JONES, J. E. & ROGERS, E. (1987): Controlled multicentre therapeutic trial of an unrefined carbohydrate, fibre rich diet in Crohn's disease. [Clinical Trial. Randomized Controlled Trial] *B.M.J. 295*, (6597): 517–520.

RYAN, P. J., EVANS, P., GIBSON, T. & FOGELMAN, I. (1992): Osteoporosis and chronic back pain: a study with single–photon emission computed tomography bone scintigraphy. *J. Bone Miner. Res.*, *7*, 1455–1459.

SALMI, M., RAJALA, P. & JALKANEN, S. (1997): Homing of mucosal leukocytes to joints. Distinct endothelial ligands in synovium mediate leukocyte – subtype specific adhesion. *J. Clin. Invest.*, *99*, 2165–2172.

SEIDMAN, E. G., BOUTHILLER, L. & WEBER, A. M. (1986): Elemental diet versus prednisolone as primary treatment of Crohn's disease. *Gastroenterology*, *90*, A1625.

THOMPSON, W. G. (1993): Nutrition and IBD –in: *The angry gut.* Plenum Press New York, London, pp. 269–285.

TOUBERT, A., DOUGADOS, M. & AMOR, B. (1985): Erosive granulomatous arthritis in Crohn's disease. *Arthritis Rheum*, *28*, 958–992.