Multivariate Identification of Metabolic Features in Inflammatory Bowel Disease

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Weight loss and malnutrition are commonly reported in inflammatory bowel disease (IBD), but differences between Crohn's disease (CD) and ulcerative colitis (UC) patients have rarely been pointed out. In this regard, a sample of 102 consecutive patients with a diagnosis of either CD (n = 63, 33 males) or UC (n = 39, 25 males) based on previously reported clinical, morphologic, and histopathologic criteria were studied. Twenty-six anthropometric and metabolic variables were measured upon admission. Body composition was assessed by both anthropometry and bioimpedance measurements, and energy expenditure and substrate oxidation were assessed by indirect calorimetry. The data were subjected to principal-component analysis and to factor rotation to derive a set of a few basic independent descriptors of the metabolic features of each subject. Six descriptors were found to be responsible for greater than 86% of the total sample variability and to associate very well with mutually disjoint subsets of the original variables. The six summarizing factors are listed in order of decreasing percentage of explained variation (size 41.8%, fatness 17.9%, fuel 12.2%, shape 5.4%, energy 5.2%, and steroid 3.9%). CD and UC patients differed significantly with respect to fatness (CD lower, $P = .004$) and carbohydrate (CHO) fuel preference (CD lower, $P = .030$). Hence, CD patients showed a reduced fat mass (FM) compared with UC patients, and from a metabolic point of view, too, CD and UC are not superimposable. In fact, the lower CHO oxidation (CHOox) rate and consequent preferential lipid utilization found in CD patients may be taken into account as a contributing cause of lipid tissue wasting and in planning therapeutic enteral regimens.

INFLAMMATORY BOWEL DISEASE (IBD) is a chronic disorder of unknown etiology substantially affecting the quality of life of the patient. Whether the two main forms of IBD, Crohn's disease (CD) and ulcerative colitis (UC), are different manifestations of the same disease or different diseases sharing some pathogenetic and clinical aspects of manifestation is still controversial.[1] Since IBD is frequently characterized by a marked impairment of the nutritional status, malnutrition often occurs in these patients, with a frequency of 18% to 62% in UC and 65% to 75% in CD.[2] Many studies have been performed to establish the most effective and safe therapeutic regimens for patients affected by CD or UC, but at present, treatment is only symptomatic.

Increasing attention has been recently devoted to the use of parenteral and enteral nutrition regimens[3-6] as a new therapeutic approach with the goal of reducing or entirely replacing the conventional steroid therapy, which has well-known long-term side effects. It therefore seems important to be able to assess whether differences in body composition and energy requirements are characteristic of CD versus UC, with a view to optimize individual treatment and correct nutritional deficiencies.

Royall et al[6] previously showed that CD patients have a significant reduction in fat mass (FM) with respect to control subjects; on the other hand, our group previously reported that CD patients preferentially use lipids as a fuel substrate in near-basal conditions.[7]

Currently, there is only one reported study that evaluated the metabolic characteristics of patients affected by either inactive CD or UC,[8] but no data are available regarding a comparison of the nutritional and metabolic assessment of IBD patients in different phases of disease activity.

The aim of the present study was to identify important anthropometric and metabolic descriptors of the IBD patient population, and to investigate possible differences in this respect between CD and UC subpopulations.

SUBJECTS AND METHODS

Subjects

A total of 104 consecutive patients with biopsy-proven IBD admitted to the Metabolism Unit of the Catholic University in Rome from January 1995 to April 1996 were enrolled in the study. The diagnosis and extent of disease were determined by previously reported clinical, morphologic, and histopathologic criteria.[9] In 64 patients (34 males and 30 females), CD was diagnosed; in the other 40 patients (26 males and 14 females), UC was diagnosed. The degree of illness was assessed according to the Crohn's Disease Activity Index (CDAI) described by Best et al[10] for CD patients and to both the CDAI and the Powell-Tuck index[11] for UC patients. Localization of the disease was as follows: for CD patients, 34 of 64 (53.1%) had colonic involvement, 15 of 64 (23.4%) ileal involvement alone, and 13 of 64 (20.3%) ileocolonic disease; for UC patients, 21 of 40 (52.5%) had pancolitis, 13 of 40 (32.5%) prevalent proctitis, and six of 40 (15.0%) distal colitis. Among the CD patients examined, six (9.4%) had ileal resection (>20 cm) in the 2 years preceding study enrollment, and two UC patients (5.1%) in a remission phase of disease activity underwent surgery (ileoanal anastomosis) 22 and 16 months, respectively, prior to the study.

The therapy for the patients was carefully recorded; in particular, systemic steroid therapy was considered in the analysis of factors that could influence the anthropometric and metabolic assessment of the patients. Among all patients examined, 75 (49 CD and 26 UC) have received systemic steroid therapy during their lifetime and 31 (18 CD and 13 UC) have received only local steroid treatment or other medication (mesalazine [nine UC] or cyclosporine [four UC]).

Patients on steroid treatment received the same daily dose for at least 4 to 6 months before the study, and none had fever or sepsis or received

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parenteral nutrition at the time of the experiment. Heavy smokers were excluded from the study protocol.

None of the patients were affected by hepatic and renal disease or endocrinologic disorders, and none of the examined women were pregnant and all were studied in the follicular phase of the menstrual cycle.

Experimental Protocol

The subjects were admitted to the metabolic ward on the morning before the examination session, and anthropometric and bioimpedance determinations were performed.

Body weight was measured to the nearest 0.1 kg by a beam scale. Skinfold thickness was measured to the nearest 0.2 mm at different sites (biceps, triceps, and subscapular) on the nondominant side of the body in a standardized position by the same investigator, as previously described,[12] using a Holtain skinfold caliper (Dietosystem, Italy). Measurements were obtained in triplicate and the mean was used as the final value to minimize intraoperator variability. Chest, waist, hip, and nondominant arm circumferences were also measured to the nearest 0.1 mm by the same observer using a flexible steel tape.[13]

Body composition was assessed by bioelectrical impedance analysis using a frequency of 1 to 100 kHz between a set of four electrodes attached to the dorsum of the hand and the foot (Human-IM Scan; Dietosystem) to measure total body water (TBW) and extracellular water. Fat-free mass (FFM) was calculated assuming that 73.2% of FFM is TBW, and FM was computed as the difference between body weight and FFM. Body composition was also assessed using the Hume-Weyers formulas.[14]

All indirect calorimetric assessments were performed after an overnight fast at 8 AM. Continuous indirect calorimetry was thus performed over a 60- to 90-minute period to measure respiratory gas exchange using an open-circuit ventilated-hood system (Deltatrac Metabolic Monitor; Datex Instrumentarium, Helsinki, Finland). The basal energy expenditure (basal metabolic rate [BMR]), nonprotein respiratory quotient (np-RQ), and substrate oxidation rates were calculated from the oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and urinary nitrogen excretion rates according to Ferrannini formulas.[15] Twenty-four-hour urine samples were collected to determine nitrogen excretion by a BUN Analyzer II (Beckman Instruments, Fullerton, CA). Harris-Benedict equations were used to calculate the theoretic value of energy expenditure for each subject on the basis of anthropometric characteristics.[16]

The study protocol followed the guidelines of the Catholic University Ethics Committee, and all subjects provided informed written consent.

Statistical Analysis

A chi-square test was used to check for differences in sex distribution between the two diseases.

Twenty-six anthropometric and metabolic variables were measured on each of the subjects upon admission. These ranged from anthropometric descriptors such as the age, body weight, height, body mass index (BMI), nondominant midarm, chest, waist, and hip circumferences and waist to hip ratio (WHR) as a measure of body fat distribution, and skinfold thickness measured at different sites (biceps and triceps of the nondominant arm and subscapular); to body composition variables such as FFM, FM, and TBW both predicted by the Hume-Weyers formulas (HWFFM, HWFM, and HWTBW) and assessed by bioimpedance measurements (FFM, FM, and TBW); to metabolic variables such as energy expenditure predicted by Harris-Benedict equations (HBEE) and determined by measurements of $\dot{V}CO_2$ and $\dot{V}O_2$ (milliliters per minute) by indirect calorimetry that allows assessment of the BMR and substrate oxidation (carbohydrate oxidation [CHOox] and lipid oxidation [LIPox]). The last considered descriptor in the analysis was the steroid therapy (steroid, expressed as milligrams of prednisone) used daily by the patient.

Table 1. Descriptive Anthropometric and Metabolic Variables for All Subjects by Sex and Disease (mean ± SD)

	CD (n = 63)		UC (n = 39)	
Variable	Females (n = 30)	Males (n = 33)	Females (n = 14)	Males (n = 25)
Age (yr)	31.9 ± 12.9	34.8 ± 15.1	42.7 ± 15 6	43.0 ± 17.5
BMI (kg/m²)	20.9 ± 3.09	21 6 ± 2.96	23.6 ± 4.11	23.3 ± 2.62
Weight (kg)	54.5 ± 8.92	64.5 ± 9.69	59.6 ± 11.9	70.7 ± 9.62
WHR	0.80 ± 0.07	0.87 ± 0.06	0 80 ± 0.06	0.89 ± 0.05
FFM (kg)	38.6 ± 6.18	52.4 ± 6.61	39.9 ± 6.99	54.54 ± 7.51
FM (kg)	15.9 ± 4.75	12.6 ± 6.96	17.8 ± 5.22	15.4 ± 5.24
BMR (kcal/24 h)	1,370 ± 130	1,620 ± 213	1,410 ± 168	1,670 ± 147
np-RQ	0.81 ± 0.04	0.81 ± 0.05	0.85 ± 0.10	0.83 ± 0.05

The data thus obtained were subjected to principal-components analysis with varimax orthogonal factor rotation to derive from the original set of 26 variables a considerably smaller set of basic independent descriptors.[17]

Table 1 summarizes the most important anthropometric and metabolic variables in the study sample. On each of these variables, a multivariate two-way ANOVA was performed using disease (CD *v* UC) and sex (male *v* female) as factors.

All results are presented as the mean ± SD unless otherwise stated. A type I error level of .05 was retained throughout.

RESULTS

Two patients with severe disease activity were excluded from the study, one (UC) because of a variability in intravenous steroid administration in the last 3 weeks and the other (CD) because of a need for total parenteral nutrition the day before admission.

Table 2 reports the disease characteristics of the two groups. The mean steroid therapy and the number of patients with active disease (CDAI > 150 and Powell-Tuck index > 4) at the time of the experiment are also shown in Table 2.

There was no significant difference in the sex distribution over the two disease groups (CD, 33 males and 30 females; UC, 25 males and 14 females; $P = .245$).

Figure 1 shows the scree plot obtained by diagraming for each of the possible successive principal components the amount of independent information it contributes, expressed as a percent of the total variation. It is evident that the first few components summarize most of the sample's information. Since the relative increase in the explained variation from the seventh component (2.6%) to the sixth component (3.9%) is large (over 50% of the seventh-component contribution) with respect to the neighboring increases, this elevation was chosen as the cutoff point and the first six components have been retained.

These six descriptors summarizing 26 variables measured in

Table 2. Steroid Dose and Disease Characteristics of the Subjects

Parameter	CD (n = 63)	UC (n = 39)
Disease duration from diagnosis (mo)*	42.8 ± 22.9	34.8 ± 16.9
Steroid dose (mg prednisone/d)*	12.7 ± 10.4	8.2 ± 6.96
CDAI > 150†	18 (28.6)	—
Powell-Tuck index >4†	—	10 (25.6)

*Mean ± SD.

†Number of patients (%).

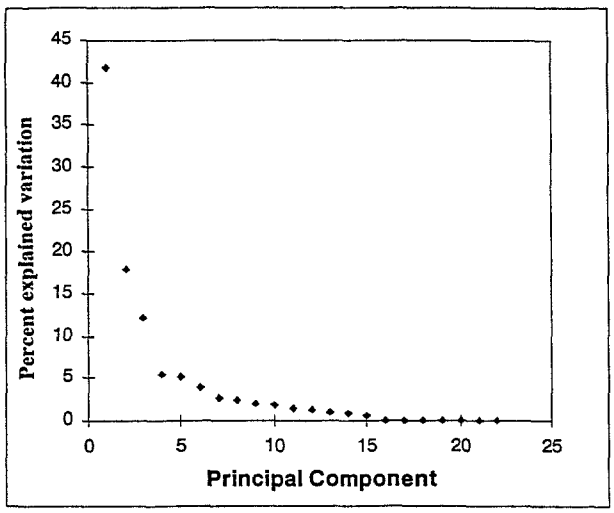

Fig 1. Scree plot depicting the decreasing amount of explained variation contributed by successive principal components. The first 6 are jointly responsible for >86% of the total variation.

102 subjects were found to be responsible for over 86% of the total sample variability; furthermore, they associate very well with mutually disjoint subsets of the original variables, which is important in attributing to the factors their distinct physiological meanings. Table 3 shows the correlation matrix between original variables and computed factors.

The first factor, size (41.8% explained variation), correlated highly with variables related to the overall size of the subject, in particular weight, FFM, height, and chest circumference, and measures of body composition or metabolism as predicted by the Hume-Weyers and Harris-Benedict formulas, ie, reflecting body size. The second factor, fatness (17.9% explained variation), correlated highly with all measures of the prevalence of fat tissue such as skinfold thickness, BMI, FM, and hip circumference. The third factor, fuel (12.2% explained variation), was highly positively correlated with the RQ and minute CHOox, and highly negatively correlated with minute LIPox. In other words, it was associated with the preference of the subject for carbohydrate over fat as a metabolic fuel. The fourth factor, shape (5.4% explained variation), was strongly associated with the waist circumference, WHR, and also age, which probably reflects the tendency of the subjects to acquire abdominal fat as they age. The fifth factor, energy (5.2% explained variation), simply an expression of energy expenditure, was highly correlated with HBEE, $\dot{V}O_2$, and $\dot{V}CO_2$. The sixth factor, steroid (3.9% explained variation), expresses the amount of (prednisone-normalized) steroid therapy. Table 4 shows the group mean ± SD for the six factors.

The interaction between sex and disease did not appear to significantly influence any of the descriptors. Males differed from females with respect to size (males larger, $P < .001$), fatness (females fatter, $P = .001$), and shape (males higher, $P = .002$). CD patients differed significantly from UC patients

Table 3. Six Identified Factors (orthogonally rotated) From Principal-Components Analysis

Variable	Factor 1. Size (41 8%)	Factor 2· Fatness (17 9%)	Factor 3: Fuel (12.2%)	Factor 4: Shape (5.4%)	Factor 5: Energy (5 2%)	Factor 6: Steroid (3.9%)
Height	.899					
Weight	.789	.559				
Chest circumference	.529					
HWTBW	.955					
HWFFM	.955					
TBW	.861					
FFM	.918					
HBEE	.926					
BMI		.848				
Arm circumference		.589				
Hip circumference		.747				
Skinfold thickness						
Biceps		.679				
Triceps		.786				
Subscapular		.812				
HWFM		.903				
FM		.756				
RQ			.985			
CHOox			.968			
LIPox			−.936			
Age				.781		
Waist circumference		.580		.743		
WHR				.586		
BMR	.620				.751	
$\dot{V}O_2$	.615				.733	
$\dot{V}CO_2$	.617				.723	
Prednisone therapy						.885

NOTE. For each factor, named for its obvious meaning, the relative percent explained variation is shown in parentheses. Corresponding to each factor and to each 1 of the original variables is the univariate correlation coefficient between the 2. All correlation coefficients <.35 have been omitted.

Table 4. Group Mean ± SD for the Six Identified Factors

Factor	CD (n = 63)	UC (n = 39)	Females (n = 44)	Males (n = 58)
Size	−0.105 ± 0.917	−0.169 ± 1.113	−0.840 ± 0.612	0.637 ± 0.729
Fatness	−0.183 ± 0.944	0.296 ± 1.028	−0.335 ± 1.142	−0.254 ± 0.797
Fuel	−0.160 ± 0.807	−0 259 ± 1.218	−0.060 ± 1.031	−0 046 ± 0.982
Shape	−0.151 ± 0.913	0.244 ± 1.095	−0.360 ± 0.858	−0.273 ± 1.020
Energy	−0.071 ± 1.052	0.116 ± 0.911	−0.211 ± 0.853	0 160 ± 1.078
Prednisone	0.025 ± 0.872	−0.040 ± 1.190	−0.038 ± 1.062	0.029 ± 0.959

NOTE. Each factor is standardized and has a whole-sampe value of 0.000 ± 1.000.

with respect to fatness (UC fatter, $P = .004$) and carbohydrate fuel preference (UC higher, $P = .030$).

DISCUSSION

Despite the evidence for pathophysiologic similarity between CD and UC, the hypothesis of different initial pathogenetic events in the determination of these IBDs has recently gained strength.[1]

It is commonly stated that CD is a systemic disease with frequent extraintestinal manifestations that can potentially affect the whole gut, while UC is a disease affecting only the intestinal mucosa. These typical characteristics may account for the differences between CD and UC not only from the morphologic,[18] clinical, and etiologic view but also from the epidemiologic, immunologic, and clinical view. It has been shown that the incidence of CD, contrary to the incidence of UC, is steadily increasing. In fact, CD incidence in Scottish children increased from 6.6 per million in 1968 to 22.9 per million in 1983[19] and 29 per million in 1988.[20] While autoimmune phenomena do occur, particularly in UC, there is no evidence that they are directly responsible for the tissue damage. On the contrary, it seems likely, especially in CD, that tissue injury may occur as an indirect effect of mucosal T-cell hyperactivation, perhaps in response to a normal enteric microbial antigen.[21] Increasing attention has recently focused on bone metabolism in IBD.[22,23] It was found that in newly diagnosed IBD patients, a low level of bone mineralization represents a feature of CD but not UC.[24]

Despite the above-mentioned differences between CD and UC, the diagnosis of CD and UC and the differentiation between them are presently based on nonspecific clinical and histologic patterns that are often obscured by intercurrent infectious or iatrogenic events[24] or altered by medication[25] or surgery.[26]

Notwithstanding the new and promising research on IBD clinical, pathogenetic, and therapeutic aspects,[26-29] the treatment is still only symptomatic, and a medical therapeutic approach is highly preferred, especially in patients with CD.[1] Furthermore, there is currently much interest and discussion on the use of nutritional therapy in IBD, and conflicting reports on the efficacy of enteral nutrition to induce remissions or prevent relapses in CD. While some investigators report that polymeric enteral diets could be considered as safe and effective as steroid treatment to induce short-term remission in patients with active disease,[4] a recent study[30] based on a MEDLINE review covering a 10-year period shows that steroids are better than enteral nutrition for inducing remission in the active phase of CD. Furthermore, it has been reported that total enteral, instead of parenteral, nutrition represents a safe and effective alternative choice as adjunct therapy to steroids in the treatment of patients with severe attacks of UC.[31] Apart from the decrease in food intake essentially due to the disease symptoms,[32] in the evaluation of factors that cause weight loss in IBD patients, an important role is played by the energy requirement of the subjects.

In this regard, no systematic study of the anthropometric and metabolic differences between CD and UC, particularly with patient samples of substantial size, is known to us from the literature. The high heterogeneity in the clinical and therapeutic features of IBD patients represents a complicating element for such a comparison. In the present investigation, besides studying a relatively large number of patients, we eliminated some of the most important confounding variables (such as the presence of fever or sepsis, administration of parenteral nutrition, a heavy smoking habit, or recent change in steroid treatment) that could affect the measurements.

In the present study, we observed that principal-components analysis well separates the entire group of measured variables into six meaningful and independent measures, and therefore, the multifaceted metabolic, anthropometric, and therapeutic composition of our patient sample can be interpreted using a small number of fundamental concepts. Two of these basic concepts, ie, those relative to body composition and fuel preference, are significantly different in the two studied diseases.

In previous studies, we reported an increased basal LIPox coupled with a decreased body FM in CD patients compared with a group of healthy subjects.[7,33] The lower body weight of CD patients compared with control subjects was essentially due to a FM reduction instead of a FFM depletion, confirming the finding by Royall et al[6] by direct assessment of body mass constituents. In this connection in the present study, no evidence of severe malnutrition or muscle atrophy was found and none of the patients complained of muscle soreness or performed high-level or prolonged physical activity, so muscle glycogen depletion is unlikely to have occurred in our series of CD patients.

In the present investigation, it was found that CD versus UC patients had a reduced body FM together with a lower CHOox rate and a preferential utilization of lipids as a fuel substrate. This finding may have practical implications. In fact, it could be relevant to consider these metabolic differences when choosing the type of energy substrate to be used in enteral or parenteral regimens with the goal of maintaining remission and improving the nutritional status of IBD patients: more lipids, in an easily absorbable form, should be offered to CD patients.

We may conclude that from a metabolic point of view, CD and UC are not superimposable, particularly regarding the

utilization of lipids. CD subjects appear to have a poor conservation of body fat coupled with an enhanced utilization of lipids as the fuel substrate, and these findings could be related to the more severe and extensive intestinal damage in UC, confirming our previous reports in inactive patients.[8] The hypothesis of preferential lipid metabolism must therefore be contemplated, in addition to the well-known lipid malabsorption, as a contributing cause of lipid tissue wasting in CD and in programing new therapeutic regimens based on enteral nutritional support.

REFERENCES

1. Podolsky DK: Inflammatory bowel disease. N Engl J Med 325:928-937 and 1008-1016. 1991
2. Fleming: Nutrition in patients with Crohn's disease: Another piece in the puzzle. JPEN J Parenter Enteral Nutr 19:93-94, 1995
3. Giaffer MH, North G, Holdsworth CD: Controlled trial of polymeric versus elemental diet in the treatment of active Crohn's disease. Lancet 335:816-819, 1990
4. Gonzàlez-Huix F, de Leon R, Fernàndez-Bañares A, et al: Polymeric enteral diets as primary treatment of active Crohn's disease: A prospective steroid controlled trial. Gut 34:778-782, 1993
5. Royall D, Jeejeebhoy KN, Baker JP, et al: Comparison of amino acid *v* peptide based enteral diets in active Crohn's disease: Clinical and nutritional outcome. Gut 35:783-787, 1994
6. Royall D, Greenberg GR, Allard JP, et al: Total enteral nutrition support improves body composition of patients with active Crohn's disease. JPEN J Parenter Enteral Nutr 19:95-99, 1995
7. Mingrone G, Greco AV, Benedetti G, et al: Increased resting lipid oxidation in Crohn's disease. Dig Dis Sci 41:72-76, 1996
8. Capristo E, Addolorato G, Mingrone G, et al: Metabolic features of inflammatory bowel disease in a remission phase of the disease activity. J Intern Med 243:339-343, 1998
9. Donaldson RM Jr: Crohn's disease, in Sleisenger MH, Fordtran JS, (eds): Gastrointestinal Disease. Philadelphia, PA, Saunders, 1989, pp 1327-1358
10. Best WR, Becktel JM, Singleton JW, et al: Development of a Crohn's disease study. Gastroenterology 70:439-444, 1976
11. Powell-Tuck J, Brown RL, Lennard-Jones JE: A comparison of oral prednisolone given as a single or multiple daily doses for active proctocolitis. Scand J Gastroenterol 13:833-837, 1978
12. Frisancho AR: New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr 34:2540-2545, 1981
13. Frisancho AR: New standards of weight and body composition by frame size and height for assessment of nutritional status of adults and the elderly. Am J Clin Nutr 40:808-819, 1984
14. Hume R, Weyers E: Relationship between total body water and surface area in normal and obese subjects. J Clin Pathol 24:234-238, 1971
15. Ferrannini E: The theoretical basis of indirect calorimetry: A review. Metabolism 37:287-301, 1988
16. Harris JA, Benedict FG: Biometric Studies of Basal Metabolism in Man. Washington, DC, Carnegie Institute, 1919 (Publication No. 279)
17. Mardia KV, Kent JT, Bibby JN: Multivariate Analysis. London, UK, Academic, 1979
18. Ottenjam R: Inflammatory bowel disease. Endoscopy 26:64-69, 1994
19. Barton JR, Gillon S, Ferguson A: Incidence of inflammatory bowel disease in Scottish children between 1968 and 1983; marginal fall in ulcerative colitis, threefold rise in Crohn's disease. Gut 30:618-622, 1989
20. Ferguson A, Ghosh S, Harny LM, et al: Analysis of disease distribution, activity and complications in the patient with inflammatory bowel disease. Scand J Gastroenterol 203:15-19,
21. Shanahan F: Current concepts of the pathogenesis of inflammatory bowel disease. Ir J Med Sci 163:544-549, 1994
22. Abitbol V, Roux C, Chaussade S, et al: Metabolic bone assessment in patients with inflammatory bowel disease. Gastroenterology 108:417-422, 1995
23. Ghosh S, Cowen S, Hannan WJ, et al: Low bone mineral density in Crohn's disease, but not in ulcerative colitis at diagnosis. Gastroenterology 107:1031-1039, 1994
24. Schumacher G, Sandstedt B, Kollberg B: A prospective study of first attacks of inflammatory bowel disease and infectious colitis: Clinical findings and early diagnosis. Scand J Gastroenterol 29:265-274, 1994
25. Dwarakanath AD, Nash J, Rhodes JM: "Conversion" from ulcerative colitis to Crohn's disease associated with corticosteroid treatment. Gut 35:1141-1144, 1994
26. Hanauer SB: Inflammatory bowel disease. N Engl J Med 334:841-848, 1996
27. Shanahan F: Pathogenesis of ulcerative colitis. Lancet 342:407-411, 1993
28. Belluzzi A, Brignola C, Campieri M, et al: Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. N Engl J Med 334:1557-1560, 1996
29. Van Dullemen HM, Van Deventer SJH, Hommes DW, et al: Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). Gastroenterology 109:129-135, 1995
30. Fernàndez-Bañares A, Cabré E, Esteve-Comas M, et al: How effective is enteral nutrition in inducing clinical remission in active Crohn's disease? A meta-analysis of the randomized clinical trials. JPEN J Parenter Enteral Nutr 19:356-364, 1995
31. Gonzàlez-Huix F, Fernàndez-Bañares A, Esteve-Comas M, et al: Enteral *vs* parenteral nutrition as adjunct therapy in acute ulcerative colitis. Am J Gastroenterol 88:227-232, 1993
32. Rigaud D, Angel LA, Cerf M, et al: Mechanisms of decreased food intake during weight loss in adult Crohn's disease patients without obvious malabsorption. Am J Clin Nutr 60:775-781, 1994
33. Capristo E, Addolorato G, Mingrone G, et al: Effect of disease localization on the anthropometric and metabolic features of Crohn's disease. Am J Gastroenterol 93:2411-2419, 1998