

Searching for biomarkers in clinical practice: the prevalence and clinical significance of hypergammaglobulinemia in inflammatory bowel disease patients

To the Editor,

The search of biochemical markers useful for the management of inflammatory bowel disease (IBD) patients in clinical practice is an important issue [1]. Hypergammaglobulinemia (HGG) is commonly described in patients with autoimmune, infective or inflammatory disorders, where an increment of antibodies production is observed. No data are available for the prevalence and clinical significance of HGG in IBD patients.

We conducted a retrospective cross-sectional study including IBD patients referred to the S. Andrea Hospital in Rome, Italy, in an outpatient visit, between January 2013 and December 2014. Inclusion criteria were: firm diagnosis of IBD [ulcerative colitis (UC) or Crohn's disease (CD)], and complete records of clinical [age, sex, localization, comorbidities, extraintestinal manifestations (articular, dermatologic or ocular IBD-related diseases diagnosed by specialist), disease activity] and biochemical [hemoglobin, C reactive protein, presence of HGG (defined as polyclonal increment of the gammaglobulins level above the normal lab-reported value)] parameters.

From a total of 388 IBD patients, 81 patients were excluded (uncertain diagnosis 12, lack of data 64, monoclonal HGG 3, multiple myeloma 1, autoimmune thrombocytopenia 1) and 307 patients were finally considered (UC 212, CD 95). First, the prevalence of HGG was calculated, and clinical and biochemical features in patients with and without HGG were compared by *t*-test and chi-squared test for parametric and non parametric data, respectively. Hypergammaglobulinemia was found in 46/307 (15%) of IBD patients [CD: 11/95 (12%), UC: 35/212 (17%)]. IBD patients with HGG had higher prevalence of extraintestinal manifestations [13/46 (28%) vs. 33/261 (12%), $p < 0.05$]. Therefore, we focused on all IBD patients with extraintestinal manifestations, representing a total of 27/95 (28%) with CD, and 19/212 (9%) with UC. In details,

articular manifestations were present in 41 (83%) patients (peripheral 29, axial 12), dermatological in 6 (13%) patients (psoriasis 5, erythema nodosum 1), and ocular in 2 (4%) patients (uveitis). Three patients had a simultaneous presence of two extraintestinal manifestations. Uni- and multivariate analysis of clinical and biochemical parameters (sex, elevated CRP, presence of symptoms of intestinal disease activity, CD, and HGG presence) was performed with the presence of extraintestinal manifestations as an independent variable. Only CD and HGG significantly correlated with the presence of extraintestinal manifestation at both uni- and multivariate analysis (univariate: $p < 0.001$ and $p < 0.01$; multivariate: $p < 0.0001$ and $p < 0.005$, for CD and HGG, respectively). IBD patients with HGG had a significantly higher association with extraintestinal manifestations as compared with IBD patients without HGG (OR 2.72, 95% CI 1.3 - 5.7, $p = 0.0079$). Considering separately, UC patients with HGG had a significantly higher rate of extraintestinal manifestations than UC patients without HGG (OR 4.5, 95% CI 1.6 - 12.1, $p = 0.0032$), while CD patients with HGG displayed only a trend for increment (OR 2.3, 95% CI 0.7 - 8.5, $p = 0.19$) (Fig. 1).

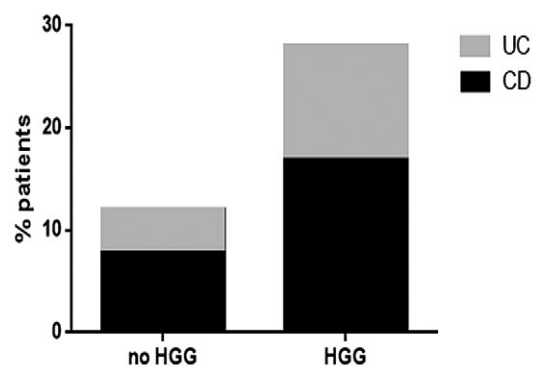


Fig. 1. Extraintestinal manifestations in patients with and without hypergammaglobulinemia (HGG).

In conclusion, in the present retrospective study, HGG was not uncommon in IBD patients, and it was associated with a higher prevalence of extraintestinal manifestation, particularly

in UC patients. In fact, as reported in the literature [2], the prevalence of extraintestinal diseases is generally lower in UC than in CD patients (9% vs. 28%), but the subset of UC patients with HGG displayed a prevalence similar to that of CD patients (23%). Further large prospective studies are required to confirm the presence of HGG in IBD patients with potential clinical relevance. Considering the preliminary results of our study, HGG may represent a simple, economic and readily available biochemical marker to identify IBD patients with a more complex disease (i.e. presence of extra-intestinal manifestations) who may need a more intensive management.

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Impaired pressure management in the Irritable Bowel Syndrome

To the Editor,

Irritable Bowel Syndrome (IBS) is the most prevalent functional gastrointestinal disorder. Epidemiological studies have demonstrated that psychological stress is a trigger of the first onset or exacerbation of IBS symptoms. Various animal models have been developed to expose the underlying mechanisms of visceral hypersensitivity and the influence of stress on visceral pain pathways [1, 2]. Until recently, the research of the link between functional gastrointestinal disorders and psychological stress had concentrated more on childhood abuse, prenatal traumatic events, anxiety disorders, depression, major life events (divorce or death of a close relative), and major social events (war, revolution, social changes) and also daily hassles [3]. Nevertheless, evidence that supports the role of occupational stress in the occurrence of IBS is lacking. This could be the result of the fact that investigations into IBS comprise somatic disorders and a psychological status whereby somatic symptoms aggravate the patients' psychological load, leading to an increase in anxiety and depression.

The Pressure Management Indicator (PMI) questionnaire, developed from the Occupational Stress Indicator, is a multidimensional diagnostic tool that permits the extraction of an occupational stress profile for individuals, groups, socio-professional categories, institutions and corporations [4]. The questionnaire measures the following dimensions of occupational stress: the stress scales (pressure from workload, relationships, career development, managerial responsibility, personal responsibility, home demands and daily hassles);

Table I. The effects of socio-professional pressure, and the four scales of the Pressure Management Indicator

Group	IBS patients (n=39) median (IQR)	Controls (n=37) median (IQR)	p value
<i>Socio-professional pressure effects variables</i>			
Job satisfaction	17 (17 - 30)	33 (31 - 34)	< 0.001
Organization satisfaction	23 (23 - 27)	29 (29 - 31)	< 0.001
Organization security	11 (10 - 15)	26 (24 - 27)	< 0.001
Organizational commitment	10 (9 - 19)	14 (11 - 19)	0.009
State of mind	12 (12 - 20)	26 (25 - 27)	< 0.001
Resilience	11 (10 - 13)	20 (19 - 20)	< 0.001
Confidence level	6 (5 - 12)	16 (15 - 17)	< 0.001
Physical symptoms	6 (6 - 15)	16 (15 - 17)	< 0.001
Energy level	8 (8 - 16.5)	20 (19 - 21)	< 0.001
<i>The four socio-professional pressure effects scales</i>			
Satisfaction	40 (40 - 57)	63 (61 - 64)	< 0.001
The organization	22 (18.5 - 33.5)	38 (36 - 46)	< 0.001
Mental wellbeing	29 (27 - 45)	62 (61 - 63)	< 0.001
Physical wellbeing	14 (14 - 31.5)	37 (36 - 38)	< 0.001
<i>Principal component of the four socio-professional pressure effects scales</i>			
Principal component	2.44 (-0.43 - 2.5)	-1.74 (-1.95 - -1.54)	< 0.001

IQR: interquartile range; SD: standard deviation.

the moderator variables (drive, impatience, control, personal influence and the coping strategies of problem focus, life-work balance, social support) and the outcome scales (covering job satisfaction, organizational satisfaction, organizational security, organizational commitment, anxiety-depression/state of mind, resilience, worry, physical symptoms and exhaustion) [4, 5]. The purpose of our study was to analyze the association between pressure management (PM) and IBS.

The PMI questionnaire was applied to 39 patients with IBS and 37 control cases. The four socio-professional pressure effects scales, including mental wellbeing, physical wellbeing, occupational satisfaction and also the socio-professional pressure effects variables were significantly associated with the presence of IBS (Table I). The scores were lower (negative effect) for the IBS group compared to the control group, for all the socio-professional pressure effects variables, and for all the four socio-professional pressure effects scales. Lower socio-professional pressure effects were significantly associated with lower age in the univariate analysis, and close to statistical significance level in the multivariate analysis with manual occupations compared with the expert ones. A major pitfall in the endeavor to understand IBS determinants is represented by the significant number of parameters including genotype, phenotype, asymptomatic disease and socio-cultural background, which affect the results. Our results on these small groups of patients suggest that PM is positively and directly associated with IBS ($p < 0.001$). The occurrence of IBS symptoms was significantly related to the presence of occupational stress resulting from the psychosocial work environment. Impaired pressure management might be an indicator of occupational stress in IBS patients.

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Serum levels of vitamin D are associated with the severity of the endoscopic appearance of diverticular disease of the colon according to DICA classification

To the Editor,

Diverticulosis of the colon is the most frequent structural alteration of the colon diagnosed at colonoscopy [1]. Recently, an endoscopic classification of diverticulosis and diverticular disease (DD), called “DICA” (Diverticular Inflammation and Complication Assessment), has been developed [2] being also predictive of the course of the disease [3].

Seasonal variation in hospitalizations for diverticulitis has been evidenced [4]. Seasonal variation also reflects variation in ultraviolet (UV) light exposure, the greatest contributor to vitamin D status. Vitamin D is a fat-soluble vitamin dependent largely on the exposure of the skin to UV light for its production, with dietary sources playing an important secondary role. Its active metabolite, 1,25-dihydroxyvitamin D [1,25(OH)₂D], is synthesized both in the kidneys and in extrarenal tissues including the colonic epithelium [5]. Previous studies have shown associations between vitamin D and other colonic diseases, including hospitalized diverticulitis [6]. Based on these data, we hypothesized that a similar link might exist between levels of vitamin D and DD severity according to DICA classification.

Patients enrolled in the recent retrospective study on DD at the first endoscopic diagnosis of DD were selected if vitamin D was also assessed. Mean vitamin D levels were assessed in those patients at the time of the diagnosis. A level < 10 ng/mL was defined as severe deficiency, between 10 and 30 ng/mL as moderate deficiency, and > 30 ng/mL as normal levels.

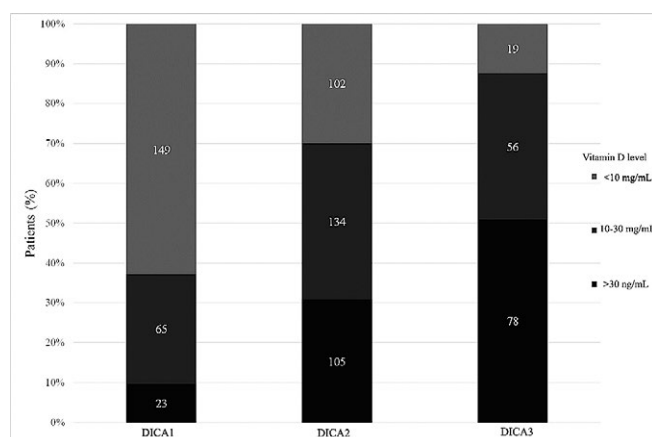


Fig. 1. Vitamin D levels according to DICA score.

Table I. Characteristics of the study group.

	DICA 1	DICA 2	DICA 3	P
Number of patients	237	341	153	
Mean age, years (95% CI)	66.7 (66.0 - 67.4)	66.3 (65.4 - 67.3)	66.6 (65.2 - 68.3)	0.798*
Sex, male (%)	112 (47.2)	173 (50.7)	59 (38.5)	0.043^
Comorbidity, no. of patients (%)				
coronary artery disease	49 (20.6)	63 (19)	30 (19.6)	
chronic renal failure	22 (9.2)	38 (11.1)	17 (11.1)	0.487^
diabetes	37 (15.6)	61 (17.8)	29 (18.9)	
obesity	14 (5.9)	27 (7.9)	13 (8.4)	

* One-way analysis of variance; ^ Chi-squared test; CI: confidence interval; DICA: Diverticular Inflammation and Complication Assessment.

Table I shows the baseline characteristics of our study population. Compared with DICA 1 and 2, DICA 3 patients were more likely to be male. Figure 1 shows the comparison of the serum vitamin D levels between DD patients according to the DICA score. A significant reduction of vitamin D level was present through the three DICA scores ($p < 0.000$, chi-squared test). In other words, endoscopic severity of DD seems to be linked with vitamin D concentration.

Our results are biologically plausible based on prior data showing the importance of vitamin D in colonic physiology. At the cellular level, vitamin D has been shown to have a pro-apoptotic and antiproliferative effect [7]. Vitamin D also appears to play a role in inflammatory bowel disease [8] and in the severity of acute diverticulitis [6]. Taken together, these data support a critical role for vitamin D in maintaining colonic homeostasis by modulating inflammation, maintaining epithelial integrity, and regulating intestinal proliferation.

Our study has two main strengths. Firstly, we used a large database of patients with measured vitamin D levels and follow-up evaluation for diverticular outcomes according to the DICA classification. Secondly, we examined the association between vitamin D levels collected before any treatment for DD, minimizing the likelihood of reverse causation. However, it is limited by the retrospective design, limiting also the impact of other potential diverticulitis risk factors, such as diet and physical activity, on these results. Additional studies in prospective cohorts with more detailed information on potential confounders of this association are warranted.

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