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TOPIC HIGHLIGHT

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Comorbidity in inflammatory bowel disease

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Abstract

Patients with inflammatory bowel disease (IBD) can be affected by other unrelated diseases. These are called comorbid conditions, and can include any secondary health problem that affects a person suffering from a primary or main disease, and which is neither linked physiopathologically to the primary condition, nor is it due to the treatments used for the primary condition or to its long-term anatomical or physiological consequences. Different comorbid conditions, as well as their influence on IBD, are discussed.

Key words: Comorbidity; Comorbid conditions; Crohn's disease; Inflammatory bowel disease; Ulcerative colitis

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COMORBODITY, THE CONTEXT, DEFINITION

It has always been difficult for physicians to attain a balance between specialization and the possession of general medical knowledge that makes it possible to optimize and expand the quality of care delivered to patients. The amount of information that a physician is supposed to manage is huge, and always growing. This is why, even when information tools are better than ever, we have perhaps reached a point in which Medicine achieves such a deep level of knowledge in specific areas, that sometimes the global perspective is lost. Or at least, is lost by physicians.

Health care professionals entrusted to assist patients with inflammatory bowel disease (IBD) must remember that our patients are also unfortunately exposed to other health problems (Table 1). We are not dealing here with the extraintestinal manifestations of IBD, whose importance we recognize and that we have probably learned to manage in a satisfactory way. Neither are we concerned with the adverse effects caused by the diverse therapies applied to our patients, such as osteoporosis or infections in the immunocompromised patients, or with the long-term consequences of the anatomical and physiological alterations induced by the disease. The problem that now demands our attention relates to a series of health problems that do not have a direct relationship to IBD as such, but that could alter the diagnosis, presentation and management of the intestinal disease. These conditions are generically known as "comorbidities". A working definition of comorbid conditions could include in this concept any secondary health problem that affects a person suffering from a primary or main disease, and which is neither linked physiopathologically to the primary condition, nor is it due to the treatments used for the primary condition or to its long-term anatomical or physiological consequences. The delimitation of what is and is not a comorbid condition is not easy, and we are

sure that many readers will think that this review should have perhaps addressed a different scope of diseases. In fact, agreement between the authors has required some debate. Our selection may be incomplete, but we are sure that all the conditions that we have included deserve important consideration when caring for a patient with IBD.

It is of paramount importance to differentiate comorbidity from multimorbidity. The first concept deals with the association of a group of diseases with a given condition, whereas multimorbidity refers to the association of multiple diseases in a single person[1]. Another term bordering the concept of comorbidity, is that of patient complexity. In this concept, other extramedical factors are taken into account, such as personal, cultural or social situations that might significantly influence the way in which the health system has to take care of a given person.

Why is comorbidity important?

Firstly, it is obvious that comorbid conditions cannot be overlooked in a patient with IBD. The existence of comorbidity can significantly change several scenarios of medical practice[2]. (1) Clinical manifestations of IBD and its activity can be altered or confused by associated diseases; (2) Prognosis of IBD will also be influenced; (3) Whenever a patient with significant comorbidity is seen by us, we step outside the realms of medical evidence. As a rule, randomized controlled trials exclude patients with comorbidity, and so their conclusions are not necessarily applicable to such situations; (4) The use of drugs for the treatment of IBD is limited by the increased importance their pharmacologic or collateral effects can have on a person with comorbid conditions; and (5) Frequently, it is more important than ever to set up multidisciplinary teams to empower patient care, or, at least, to assure that channels of collaboration and mutual consultation are as fluid and reliable as possible.

Is it possible to quantify comorbidity? What are its generic consequences?

Different sets of clinical indices have been developed and proposed for the specific study of comorbidity. Not all of them have been developed in the same way, nor have they been applied to similar populations. This is why they are not always comparable, and to pick one or another must be done very carefully. Charlson's index is widely used[3], probably due to its unique combination of simplicity and performance. However, it has been validated in multiple populations, but not in IBD patients.

In the general population, multimorbidity is associated with a significantly worse quality of life[4-6]. The specific case of IBD has not been addressed yet, but it is known that in other chronic conditions there is an increased cost of care and a higher complexity of medical activities[7], which are accompanied by poorer outcomes and unfavorably influence indices such as emotional impact, ability to cope, mortality, days of admission or postoperative complications[8-11].

What is the quantitative importance of comorbidity in IBD?

Data on the importance of comorbidity in IBD patients are scarce. Its prevalence has been poorly studied, and refers to other related diseases[12] such as pulmonary thromboembolism[13], arthritis[14] or immune-based conditions[15]. These immune-mediated inflammatory disorders, which include IBD itself, associate with each other and determine a higher risk for other chronic diseases, with a corresponding increase in resource costs.

Although the main determinant of quality of life in patients with IBD is activity of the disease[16], other comorbidities not directly related also have an impact on the physical scores, especially cardiovascular diseases[17-20].

It is not known whether the presence of several chronic diseases can determine poorer results following the medical treatment of this disease; however, it has been well described that they strongly influence surgical outcomes, because preoperative comorbidities are, alongside with age, the main predictors of the occurrence of postoperative complications[18-20].

Finally, among the identified causes of mortality in IBD are several processes that reflect the patient's comorbidity, such as postsurgical cardiovascular complications, age and infections[19]. It is true that many factors favor infections in IBD patients, such as immunosuppressants and malnutrition, but both age and comorbidity probably have their corresponding effects[20].

HEPATIC COMORBIDITY

The potential association between primary sclerosing cholangitis (PSC) and IBD is well known. However, we shall not deal with this condition here, and instead will focus on other liver diseases which can be observed in our patients, and may well alter the course of their disease.

During the long-term follow-up of a patient with IBD, a transient elevation in liver function tests is frequently observed. The cross-sectional prevalence of high aminotransferase levels varies between 5% and 50%, but more adjusted figures show, that around 20%-40% of patients have elevated aminotransferases at some time during the course of their disease, whereas a chronic alteration in such values can be detected in approximately 10% of these patients[21-23]. These elevations in liver function tests are usually discrete, in a range below twice the upper normal level[21,24]. There is no clear correlation between the degree of alteration of liver function tests and the presence of active IBD. An investigation of the underlying cause is frequently frustrating and unyielding, with a small percentage of definitive diagnoses[22].

The causes of altered hepatic biochemistry are manyfold, but the most frequent causes are steatosis and drug toxicity[21]. The evaluation of such patients has to be sensible and reassuring. The first step is to categorize the type and degree of altered hepatic biochemistry. Four different situations could perhaps be defined: (1) Slight (< 2

Table 1 Putting comorbidity into context: secondary health problems in patients with inflammatory bowel disease

Extraintestinal manifestations	Adverse effects of treatments	Comorbid conditions	Direct consequences of the disease
Peripheral and axial arthritis	Steroids: cataracts, glaucoma, mood changes, osteoporosis…	Cardiovascular	Abdominal and retroperitoneal scarring: hydronephrosis, intestinal obstruction, female infecundity…
Erythema nodosum, pyoderma gangrenosum, oral aphtae	Immunosuppressors: infections, neoplasia, liver toxicity, myelosuppression…	Hepatic, biliary, pancreatic, digestive	Consequences of intestinal resection: malabsorption, short bowel syndrome, oxalate nephrolithiasis
Uveitis, episcleritis, blepharitis	Biologics: infections, neoplasia, demyelinizing disease, infusion	Metabolic: obesity	Persistent inflammation: osteoporosis, amyloidosis
Primary sclerosing cholangitis	Reactions, drug-induced lupus	Neuropsychiatric	

× upper normal level) and transient elevation of aminotransferases (aspartate aminotransferase/alanine aminotransferase), γ-glutamyl transferase, alkaline phosphatase or bilirubin: it is probably appropriate not to alarm the patient and check the altered values after a short period, proceeding to investigate the cause if the alteration persists; (2) Sustained elevation has to be approached as it would in the general population, with special attention to the usual data in the anamnesis (epidemiological sources of exposure, potential liver toxics…) and ordering a battery of tests that could pinpoint the cause of such elevation. No precise indications have been published to determine which tests should be explored, and in what order. A possible selection could include the following: hepatitis B and C serology, and anti-neutrophil-cytoplasma, antitransglutaminase, antinuclear, anti-smooth-muscle and antimitochondrial antibodies; exploring copper and iron metabolism and investigating other less frequent or characteristic causes of altered liver function tests, could be left for a second step. A liver ultrasound should be obtained at an early stage, to explore the presence of a bright pattern, indicative of steatosis[25], detect cholelithiasis and its complications, explore the bile ducts and rule out signs of chronic liver disease or portal hypertension; (3) Some alterations in the liver function tests tend to be more specific, and deserve a different approach, such as predominant cholestasis, suggesting PSC, or elevation of aminotransferases more than 10 times the upper normal level, indicative of acute hepatocellular damage, which should bring to mind the possibilities of acute viral or toxic hepatitis; and (4) The alteration of liver tests in a patient with previously normal values, after starting a new therapy (notably thiopurine immunusuppressors) has to be approached and managed as possible liver toxicity[26].

Some causes of altered liver tests deserve a special comment, due to their prevalence or their importance.

The range of lesions collectively known as steatosis (including both uncomplicated fatty liver and steatohepatitis) are more and more frequent in the general population, but also in IBD patients, in which it accounts for the majority of diagnoses when investigating altered liver tests[21]. The usual causes of liver steatosis in the general population will also be present in IBD patients, such as metabolic syndrome, overweight/obesity and alcohol abuse. However, other possible reasons should be considered in our patients, notably glucocorticosteroid exposure, malnutrition and parenteral nutrition[27]. It is an exclusion diagnosis, and only the presence of a bright liver pattern in the ultrasound examination has been signaled as relatively specific[25]. More specific causes of liver disease have to be ruled out, notoriously those that can be appropriately managed, such as the viral hepatitides, autoimmune liver disease and drug-induced liver injury. A liver biopsy is rarely needed to confirm steatosis, but ultrasound follow-up will detect the potential development of portal hypertension or hepatocarcinoma.

Viral hepatitides B and C are, in older series, somehow more frequent in IBD patients than in the general population[28-31]. However, the current situation is different. In a Spanish national prospective study[32], the presence of markers of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection was prospectively studied in a series of more than 2000 patients. Evidence of current or past infection was present in 9.7% of cases, which is similar to figures observed in the general population: in ulcerative colitis (UC), hepatitis B surface antigen (HBsAg) was present in 0.8%, anti-HBc in 8% and anti-HCV in 1.3%, and in Crohn's disease (CD) HBsAg was present in 0.6%, anti-HBc in 7.1% and anti-HCV in 2.3%. 12% of patients had serological evidence of effective anti-hepatitis B vaccination (anti-HBs without anti-HBc). Multivariate analysis determined that age, family history of hepatitis and moderate to severe IBD were associated with HBV infection or contact, whereas HCV was mainly associated with previous transfusion of blood or blood products, but only if this was performed before 1991, when anti-HCV screening became widespread in local blood banks. Similar data have been communicated by other authors[33]. It is important to remember, that any prevalence of HCV and, especially, HBV markers has to be kept in mind, because the infection can reactivate under immunosuppressive therapy, necessitating prophylactic measures in some cases (antiviral therapy in HbsAg+ patients), and close follow-up in the remaining patients[34].

GASTROINTESTINAL COMORBIDITY

Helicobacter pylori disease

The prevalence of infection by *Helicobacter pylori* (*H. pylori*), as determined by serology, ranges between 15% and 50%. It is always lower than the corresponding prevalence in the general population, and is inversely correlated with sulfasalazine exposure[35-38]. The diminishing use of this drug makes it possible that this situation has

changed lately. The positivity of the urea breath test is also lower then in the general population[39]. However, the prevalence of peptic ulcer in transversal studies can reach 5%[38]. It is important to remember, that about 15% of CD patients will show histologic or even endoscopic lesions in the upper gastrointestinal endoscopy, and that the absence of *H. pylori* in these lesions is an important criterion when identifying them as truly related to IBD.

The indication for gastroprotection in patients exposed to glucocorticoids deserves a mention. The decision to co-prescribing proton pump inhibitors with glucocorticoids is quite usual, at least in our environment, but it is not sustained by medical evidence[40]. Gastroprotection should only be indicated on rare occasions when NSAIDs and glucocorticoids are prescribed jointly. To automatically prescribe proton pump inhibitors in the general patient, will lead to unnecessary higher costs, exposure to yet another set of adverse events and, most importantly, an increased number of tablets taken daily, which generally adversely influences adherence to therapy[41].

Celiac disease /gluten-sensitive enteropathy

Celiac disease and CD share some physiopathological, epidemiological and clinical features[42]. They frequently form part of the differential diagnosis. In older times, it was difficult to rule out celiac disease in a population with IBD, mainly due to the clinical superposition, but also to the possibility of finding very similar histologic changes (duodenal mucosal infiltrate, villous atrophy in Crohn's) and some parallel serologic alterations (positivity of antigliadin antibodies). The higher specificity of both antiendomysium and antitransglutaminase antibodies in the diagnosis of celiac disease, has finally allowed the performance of studies on the prevalence of this condition in patients with an unequivocal diagnosis of IBD.

Following the communication of isolated cases of associated Crohn's and celiac disease[43], an intriguing study was published[44], in which a very high prevalence (15%-20%) of antigliadin or anti endomysium antibodies was detected in a short series of CD patients. The high specificity of these determinations could make it reasonable to deduce that this association is extraordinarily frequent. However, later investigations of better quality have been unable to confirm these results[45-47]. The systematic search for celiac disease in CD patients cannot be recommended, according to the available evidence.

On the other hand, and although data are scarce, it seems that both UC and CD are more frequent in persons with celiac disease than in the general population. This has been described in two clinical series, with an IBD prevalence about 10 times higher than expected[45,48].

Biliary and pancreatic diseases

Cholelithiasis is a very prevalent condition in the general population[49]. Some circumstances explain its increased incidence in IBD patients, mainly the distortion of bile metabolism induced by the functional or anatomical alterations of the gut. Thus, it cannot strictly be considered a comorbid condition. The interest in cholelithiasis as a comorbid condition is mainly due to the possible overlap between its manifestations and those of the IBD or of extraintestinal manifestations, such as PSC. Management does not differ from the approach in the general population.

Pancreatic disease can ensue following the use of medications, the extraintestinal activation of inflammatory phenomena or can appear as an associated autoimmune disease[50]. In any case, it cannot be listed as a comorbid condition.

OBESITY

Presently, obesity is considered an emerging epidemic in Western societies, where it is more prevalent in disadvantaged social classes[51]. It also affects affluent classes in countries with emerging economies. The prevalence of this condition is growing, and some of its causes are sedentary behaviour, changing socioeconomic status and variations in traditional diets[52].

An increasing prevalence of obesity in patients with IBD has been described recently. In the past, this was considered an exception, but today, figures range from 15% to 20% in some series, with a further 40% of patients being overweight[53]. Although there is no evidence that obesity alters the course of the disease, at least in CD[54], obesity is related to unfavorable outcomes such as colonic adenomas, surgical morbimortality, cardiovascular risk and thrombotic disease.

CARDIOVASCULAR COMORBIDITY

Cardiovascular disease (CVD) is the main cause of death in developed countries[55] and its prevalence increases with age. Therefore, IBD patients are very likely to experience these entities throughout their life or, at least, be affected by some of the associated risk factors. The impact of CVD on IBD is the same as for the general population, increasing complications and remaining a common cause of mortality[56], especially when the disease is more severe or surgery is needed[18]. Anecdotally, in the 1950s when Truelove *et al*[57] published the first clinical trial with corticosteroids in UC, which demonstrated a decrease in mortality, the cause of death in 2 of the 5 patients who died was CVD, namely pulmonary thromboembolism. We will discuss IBD as a predisposing factor for CVD in more detail and the possible effects of IBD treatments on cardiovascular morbidity together with the undesired consequences of drugs used in the management of CVD for EII.

Venous thrombosis

Venous thromboembolism (VTE) has been considered a manifestation which is directly related to intestinal inflammatory activity, but in other chronic inflammatory diseases such as rheumatoid arthritis the incidence of VTE is not greater than in the general population[58].

Table 2 Acquired thrombotic risk factors in inflammatory bowel disease

Inflammation
Immobility (surgery or hospitalization)
Surgery
Fluid depletion
Central venous catheters
Drug therapy: Corticosteroids, anti-TNF drugs?
Smoking
Hyperhomocysteinemia (vitamin deficiencies)
Oral contraceptives
Increased levels of lipoprotein A

TNF: Tumor necrosis factor.

Furthermore, IBD patients in remission also have an increased risk of VTE[59], therefore additional factors other than inflammation are involved. This is why we have considered it a manifestation not directly linked with IBD.

In a recent population study[59], the incidence of VTE in IBD was 26 cases/10 000 person-years (PY) with a Hazard ratio of 3.4 (95% CI: 2.7-4.3). These data are similar to those observed in a previous Canadian population study, where the incidence of deep vein thrombosis (DVT) was 31.4/10 000 PY and 10.3/10 000 PY for pulmonary embolism (PE) for CD patients and 30/10 000 PY and 19.8/10 000 PY in patients with UC, respectively[60]. Again, the risk was 3 times higher in IBD compared with controls. There was also a time trend which increased with an annual average of 17% in odds of VTE[61]. There are no major differences between CD and UC, although the incidence in hospitalized patients may be somewhat higher in UC (OR = 1.32), probably because its frequency increases when the colon is involved[61]. IBD activity increases the likelihood of VTE with rates up to 8 times higher than controls[60]. Although VTE episodes are less frequent in outpatients, in this subgroup the differences with controls were even more marked (HR = 15.4) than during hospitalization periods (HR = 3.2)[59]. Similarly, although the majority of thromboembolic events occur in patients over 60 years, differences with controls are greatest in young patients (< 40)[60]. Other aspects that may increase the risk are involvement of the colon in the case of UC (pancolitis in 76% of episodes of VTE *vs* 2% of proctitis) and fistulizing pattern in CD[61].

Causes of thrombosis in IBD are many-fold; in most patients, recognized acquired prothrombotic factors can be identified, such as inflammation, immobilization, surgery, central catheters, corticosteroids, and smoking (Table 2)[62,63]. Nevertheless, in a significant percentage of patients (20%-50%) no obvious cause can be identified[64-66]. This supports the notion, that IBD itself acts as a predisposing factor for thrombosis. Inherited thrombophilias have no role in VTE associated with IBD because VTE is significantly less frequent than in thrombotic non-IBD subjects[67].

The appearance of VTE in a patient with IBD carries a poor prognosis reaching a mortality of 22%-25%[65,66], significantly higher than the control group (OR = 2.1). Hospital stay also increased by 48% and associated health costs doubled[61].

The most common location of VTE is lower extremity DVT with or without PE[58], which would include three-quarters of all episodes, but many locations have been described such as cerebral sinus[68-71], retinal vein[72-75], portal venous system[76-81] and hepatic or cava veins[82-87]. Portal system thrombosis is particularly important both for its potential complications and for its non-negligible frequency, being reported in up to 6% of patients after restorative proctocolectomy and ileal pouch-anal anastomosis[78,88]. A probable long-term complication is portal hypertension, which can be avoided with early anticoagulant therapy, for which clinical suspicion is fundamental, ordering an abdominal Doppler ultrasound and/or abdominal CT in the case of sudden onset of abdominal pain, fever or prolonged ileus after abdominal surgery[89].

Treatment of thromboembolic episodes of IBD is the same as in the general population and is based on the use of anticoagulation, first with heparin (usually low-molecular-weight heparins, LMWH) and then oral anticoagulants which should be sufficient for most patients[90]. Occasionally other measures may be required, such as thrombolysis or placement of an inferior cava filter that can be used as an effective means of preventing pulmonary embolus when anticoagulant therapy is contraindicated or thromboembolism recurs in spite of anticoagulant therapy. These drugs have proven safe in clinical trials where their effectiveness was evaluated as primary treatment. The optimal duration of anticoagulant therapy is unknown, but in general will vary depending on the severity of thrombosis and bleeding risk. In the first episode, 6 mo provided adequate coverage, but will be extended if the risk factor has not disappeared (surgery, immobilization) opting for lifelong anticoagulation in the setting of an inherited hypercoagulable state[89,91]. Despite treatment, up to 13%-26% of patients have a recurrent thromboembolic event[65,92]. Similar rates were found in patients with prior colectomy, thus surgery does not seem to prevent recurrence[65].

Treatment of thromboembolic episodes is important, but so is prevention. Possible measures include the control of disease activity, correcting vitamin and nutritional deficiencies, cessation of smoking, early mobilization after surgery or the use of intermittent pneumatic compression for patients at high risk of bleeding. Drug prophylaxis with LMWH is recommended in patients hospitalized with severe UC[93] or when planning surgery[94]. Outpatients with moderate flares and restricted mobility (old age, motor deficiencies…) are probably also candidates for pharmacologic prevention.

Atherosclerosis and arterial thromboembolic disease

Early atherosclerosis: Early atherosclerosis is a common phenomenon in several immune-based inflammatory diseases, particularly rheumatoid arthritis and systemic

lupus erythematosus[95], and is one of the most important causes of morbidity and mortality in these diseases, justifying the publication of specific recommendations[96]. The inflammatory process is behind the emergence of this phenomenon with a prominent role for the cytokines IL-6 and TNF that are significantly associated with the severity of subclinical atherosclerosis, independent of Framingham risk score[97]. Both cytokines are implicated in the pathogenesis of IBD, making possible the development of early atherosclerosis in these patients. Few data exist on this entity in IBD, although case reports of arterial occlusions in young patients with CD support this possibility[98]. Furthermore, to assess the presence of subclinical atherosclerosis at an early stage, several methods have been proposed, such as assessment of the intima-media thickness of the common carotid artery wall or the measurement of carotid artery stiffness; these have been shown to predict the occurrence of cardiovascular events[99,100]. Both parameters have been found to be altered in IBD patients compared to controls[101,102], although not uniformly in all studies[103].

Cardiovascular risk factors: There are few data on the prevalence of cardiovascular risk factors in IBD, apart from the known relationship with tobacco use[104]. Only in the cohort study by Ha *et al*[105], where the controls were randomly selected, IBD patients had a higher frequency of hypertension and hyperlipidemia, with similar rates of diabetes mellitus. Plasma lipid levels were inversely correlated with inflammatory activity[106], thus do not appear to have a particularly decisive role in predisposition to atherosclerosis in patients with IBD. As mentioned earlier, inflammatory activity *per se* could promote the development of atherothrombotic complications and in relation to this, C-reactive protein has been identified as a risk factor both in chronic inflammatory diseases[107] and in the general population[108,109]; unfortunately there are no specific data for IBD.

Arterial thrombotic events: Only two studies have evaluated the incidence of arterial events in IBD independently of venous thrombosis. The aforementioned study by Ha *et al*[105] found an overall increased incidence compared to the control group, mainly due to a marked increased in the risk of acute mesenteric ischemia (HR = 11.2, $P < 0.001$). The risk of myocardial infarction, conversely, was only discretely increased (HR = 1.6) in women over 40 years; in contrast, stroke was elevated in women below that age. However, Bernstein *et al*[110], found an overall increase in the prevalence of ischemic heart disease (IRR = 1.26) and cerebrovascular disease (IRR = 1.32) regardless of age group, although the latter only applied to patients with CD. In any case, except for acute mesenteric ischemia, in which local factors are probably involved, the rates found were quite similar to those of the control population, and not necessarily clinically relevant.

IBD therapy and cardiovascular diseases

The deleterious effects of glucocorticoids on the cardiovascular system are well known[111,112]: among their adverse effects are hypertension, hyperglycemia, hyperinsulinemia and hyperlipidemia, determining in some contexts increased cardiovascular morbidity, as in renal transplantation[113]. In other diseases, such as rheumatoid arthritis[114], inflammatory activity control can reduce cardiovascular complications. In spite of this, there is no direct evidence that IBD treatments alter the thrombotic tendency of the disease; however, some drugs show a favorable profile on some of the factors involved. For example, aminosalicylates reduce platelet activation and azathioprine inhibits formation of platelet-leukocyte aggregates[62]. There are no specific data for IBD, but methotrexate therapy in rheumatoid arthritis has been shown to decrease the prevalence of metabolic syndrome[115] in this disease and, more particularly, cardiovascular morbidity and mortality[114]. Regarding anti-TNF drugs, the results are somewhat contradictory: initially, endothelial function and insulin resistance transiently improve. On the other hand, infliximab in particular, shows a potential adverse effect on the lipid profile[116]. Likewise, thrombotic events associated with these drugs in patients without other risk factors have been described, although this needs to be confirmed[117].

Finally, it has to be noted, that some of the drugs used in the management of cardiovascular risk factors may be beneficial for IBD. Thus, the anti-diabetes drug rosiglitazone has been proven effective in the treatment of UC in two clinical trials[118,119], atorvastatin could have an antiinflammatory effect in CD[120] and ACE inhibitors have an antifibrogenic effect[121,122], not yet explored in CD.

PSYCHIATRIC COMORBIDITY

Anxiety and mood disorders have been extensively studied in IBD patients, whereas data on other conditions, such as psychoses, are scarce. However, there may be some connection, because some of the drugs used in the management of IBD, such as steroids[123], can precipitate psychotic manifestations and, on the other hand, the treatment of IBD may be followed by improvement of psychiatric illness[124].

As in other chronic diseases, the prevalence of anxiety and depression is higher in patients with IBD than in controls, both in hospital[125-128] and population cohorts[129-132]; their frequency is variable but approaches 24%-27%[129,133], which is two to three times higher than in a control population[129,131]. There are no great differences between UC and CD[130], or with other chronic diseases such as rheumatoid arthritis or diabetes[134].

Psychiatric comorbidity in IBD has been considered a risk factor for the onset of IBD itself, because it can precede its diagnosis[129,132]. However, the relative risks are low, and are limited to the year prior to diagnosis, which could represent the presence of symptoms of an undiagnosed somatic illness[135]. Moreover, the frequency of anxiety and depression increases after diagnosis of IBD,

suggesting that it is a consequence rather than a cause of the disease[132].

The role of daily stress and major life events in the precipitation of flares has also investigated, mainly because patients with higher perceived stress have a greater chance of disease reactivation[136,137]. However, there are several potential factors which may have contributed to this finding. In many studies, the sample size is not enough, and on the other hand, these results may be influenced by the fact that the influence of stress on disease activity is what patients, and probably many physicians, expect to be true[138]. Furthermore, anxiety and depressive symptoms predicted an increased likelihood of functional symptoms[139], and have a decisive influence on variables such as abdominal pain and overall well-being, used in the calculation of indices for most common activity indices. In addition, episodes of recurrence are limited to a relatively restricted period following the initial outbreak[137], which could be attributed to an incomplete improvement of IBD. Finally, several studies did not find such an association[130,140,141] and the results of trials of psychological interventions in IBD have been negative[140]. Thus, although anxiety and depression are more frequent around the periods of IBD activity, they did not seem to be risk factors for flares; also, more importantly, to wrongly assume that stress is responsible for disease exacerbation, may contribute in some way to induce unjustified and harmful feelings of guilt in some patients.

Psychiatric comorbidity has a marked impact on the management of IBD because it is, together with disease activity, the main determinant of quality of life in these patients[142]. Additionally, it is one of the factors associated with poorer adherence to treatment[41] and determines a greater use of health resources[139]. Thus, given the particular importance of these observations, and the frequent association of psychiatric symptoms with IBD, it is essential to identify and properly manage these conditions. In this sense, the use of screening tests with a good balance between sensitivity and specificity, such as the Anxiety and Depression Detector[143,144] or the Goldberg Anxiety and Depression Scale, could be recommended as an initial screening tool[134]. Treatment of psychiatric comorbidity in IBD does not differ from the general approach to these disorders, and the options include different types of psychotherapy[145] or second-generation antidepressants such as selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitor, with fewer side effects than traditional drugs (tricyclics and MAO inhibitors) and that may be initiated by the gastroenterologist pending evaluation by the appropriate specialist.

CONCLUSION

Throughout the evolution of a patient with IBD, these diseases are frequently associated with other non-related diseases which may change management and prognosis. On the one hand, decision making is complicated because the available evidence does not always apply, as in most clinical trials such patients are excluded. On the other hand, their existence entails taking into account the possible consequences of treatment on other comorbidities, both by the possibility of interactions and by the facilitation of potential adverse effects. Prognosis also changes, especially in the presence of cardiovascular comorbidity, which is associated with a greater overall morbidity and mortality, especially in the surgical context. Finally, the concomitant presence of several diseases requires collaboration and coordination among professionals for joint decision making, and implementation of the proper clinical circuits to facilitate medical attention.

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