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Review Article

Hyposplenism and gastrointestinal diseases: significance and mechanisms

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Short Title: Hyposplenism and bowel diseases

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Abstract

Background

Functional hyposplenism is a recognised complication of several gastroenterological disorders, including coeliac and inflammatory bowel diseases, and is believed to contribute to the increased infection risk seen in these disorders.

Summary

The mechanisms of hyposplenism are poorly understood. In this article, we review possible mechanisms underlying development of functional hyposplenism and discuss implications for its management.

Key messages

Identifying functional hyposplenism is important, as it may permit earlier recognition and treatment of serious infections through patient education and vaccination.

Introduction

Historically, the spleen has been variably regarded as the seat of compassion, melancholia, laughter or anger. It was then deemed unnecessary for life once splenectomy started being performed as a surgical procedure in the 1800s [1]. However, it was not until the mid-20th century that the long-term risks of splenectomy became evident and the true significance of the spleen began to be understood [1]. It is now established that the spleen plays a vital role in filtering and immunological processes, failure of which are thought to underlie the main hazard of asplenia: bacterial infections, notably overwhelming post-splenectomy infection (OPSI) (**Box 1**). The relative risk of significant infections in splenectomised patients compared to matched controls is 2.0-3.5 [2], with an absolute risk of 0.5% per year [3]. Although the rates are highest immediately post-splenectomy, infections can occur up to 20 years later [4, 5]. Asplenia can also lead to venous, and possibly arterial, thromboembolic events [6], and has also been associated with higher rates of certain malignancies, although a causal link has yet to be established [2].

Box 1: Overwhelming post-splenectomy infection (OPSI)

OPSI is a syndrome of fulminating sepsis characterised by a marked bacteraemia, usually with encapsulated organisms such as *Streptococcus pneumoniae* or *Neisseria meningitidis.* There is usually no obvious primary source of infection. Patients present with an acute non-specific prodrome and can deteriorate rapidly, with death ensuing within 24 to 48 hours. Mortality rates are around 50 to 70% [7].

In addition to asplenic states, several diseases have been associated with anatomically intact yet hypofunctional spleens. These include several gastrointestinal disorders (**Fig. 1**) such as coeliac and inflammatory bowel diseases (IBD) [7]. In this article, we review the evidence for functional hyposplenism in bowel diseases and its clinical significance. We also discuss the possible underlying mechanisms and implications for management.

Main Text

Coeliac disease

Coeliac disease (Box 2) is the gastrointestinal disorder most frequently associated with functional hyposplenism [7]. The prevalence of hyposplenism depends on the diagnostic tests used, but is generally lower in paediatric than adult coeliac disease [8, 9]. Functional hyposplenism is more common in coeliac disease with complications: in one study it was found in 59% with associated autoimmune diseases and in 80% with enteropathy-associated T-cell lymphoma and ulcerative jejunoileitis, but in only 19% of uncomplicated adult coeliac patients [10]. These findings were supported by a recent study that reported prevalences of functional hyposplenism in patients with untreated (43.7%) and refractory (88.2%) coeliac disease [11]. Duration of pre-exposure to gluten and older age at diagnosis were identified as prognostic variables for functional hyposplenism in a multivariate analysis [12].

Box 2: Coeliac disease terminology (adpated from references [91-93])

- **Classical:** coeliac disease with signs and symptoms of malabsoprtion.
- **Paediatric classical:** paediatric equivalent of classical coeliac disease.
- **Non-classical:** coeliac disease without signs and symptoms of malabsorption, but other features such as anaemia.
- **Refractory coeliac disease (RCD):** persistent symptoms and villous atrophy despite a strict gluten free diet for more than 12 months. Sub-classified as RCD1 (increased phenotypically normal intra-epithelial T lymphocytes) and RCD2 (increased phenotypically abnormal intra-epithelial T-lymphocytes).
- **Ulcerative jejunoileitis:** pre-malignant small bowel ulcerative disorder that can cause strictures. This shares immunological features with RCD2.
- **Enteropathy-associated T-cell lymphoma:** a T-cell bowel lymphoma associated with accumulation of abnormal, clonal, intra-epithelial lymphocytes; the most feared complication of coeliac disease.

Three recent large studies have highlighted the potential significance of functional hyposplenism in coeliac disease. Ludvigsson and colleagues used Swedish national health registers to assess the long-term risks of >15,000 coeliac patients [13]. They reported significantly higher risks of sepsis, particularly from *S. pneumoniae*, in coeliac patients compared to both an in-patient reference group and the general population [13]. The relative risk of sepsis in coeliac disease (2.6) was higher than that of more commonly recognised complications such as fractures (1.5) [14]. Similar data were reported by Thomas [15] and Tjernberg [16], and supported by a recent meta-analysis [17].

The increased risk of infection in coeliac disease is likely multifactorial. Causes might include increased gut permeability allowing bacterial translocation, and associated diseases that predispose to infections such as type 1 diabetes mellitus [14]. Nevertheless, the observation that infections with encapsulated bacteria, like *S. pneumoniae,* are particularly common in these patients indicates that hyposplenism plays an important role. How hyposplenism causes susceptibility to these pathogens is still not fully understood. One potential mechanism involves defective splenic reticuloendothelial cells, which fail to entrap circulating pathogens. The spleen is also important in generating and maintaining IgM memory B-lymphocytes [18], which produce natural IgM antibodies against carbohydrate antigens, including those with anti-pneumococcal specificity [19].

It is thought that hyposplenism in coeliac disease is the result of two distinct mechanisms: functional hyposplenism and splenic atrophy. Evidence to support these distinct mechanisms comes from the association between splenic atrophy and mesenteric lymph node cavitation (MLNC) syndrome. MLNC occurs in advanced coeliac disease and indicates a poor prognosis [20]. Major infections have been reported in several case reports

and small series of coeliac patients, variably associated with splenic atrophy and MLNC [21]. In addition, studies have shown that gluten-free diets can reverse functional hyposplenism but not splenic atrophy [22-24]. Notably, different assays for detecting functional hyposplenism were used in these studies – namely erythrocyte pitting versus heat-damaged erythrocyte uptake – making direct comparisons challenging.

Inflammatory bowel disease (IBD)

The prevalence of hyposplenism reported in IBD depends on the splenic function test used, but rates of 30% in ulcerative colitis (UC) and 26% in Crohn's disease were claimed in early series using blood films and splenic scans [25-27]. Using pitted erythrocyte counting, subsequent studies reported rates of 9% in Crohn's disease and 20% in UC [28], while a more recent prevalence study, also using pitted erythrocytes, found functional hyposplenism in around 54% of UC patients [11].

Patients with IBD are significantly more likely to develop opportunistic infections. One recent American study of around 280,000 IBD patients, found the prevalence of opportunistic infections to be 17.8% in Crohn's disease and 19.2% in UC compared to 7% in non-IBD controls [29]. These increased infection rates are likely a reflection of several interacting factors including the use of immunosuppressive medication [30], malnutrition, increased gut permeability, chronic inflammation and co-morbidities [31]. However, recent data have highlighted the potential importance of functional hyposplenism in IBD as another cause of these increased infection rates.

A Danish study of 74,156 IBD patients reported a significantly increased risk of invasive pneumococcal disease in patients with IBD [32]. This propensity for infections with encapsulated bacteria suggests that hyposplenism is an important contributing factor. Importantly, based on conditional logistic regression, the risk of invasive pneumococcal disease was deemed unrelated to the underlying IBD medications and was present up to four years before diagnosis [32, 33]. Similarly, Goren and colleagues analysed the rates of bacteraemia in hospitalised patients with IBD. Using logistic regression modelling, they found age, and not IBD-related medications, to be associated with increased rates of bacteraemia [34].

Strategies to normalise this infection risk have been assessed through effects on putative mechanisms of predisposition. In a study of 61 IBD patients, a depletion of peripheral IgM memory B-lymphocytes, important in the immune response to encapsulated bacteria, correlated with splenic impairment assessed by pitted erythrocyte counts [35]. Treatment with infliximab, an anti-tumour necrosis factor alpha (TNFα) monoclonal antibody, restored this pool of lymphocytes and splenic function in the majority of Crohn's patients [36]. It is of interest to note that a multivariate analysis of Crohn's patients found that the increased risk of infections in patients on infliximab is related to disease severity and use of prednisolone [37], rather than infliximab itself.

Hyposplenic IBD patients may also be at risk of other complications such as post-operative pneumococcal sepsis, septic shock and disseminated intravascular coagulation [27, 38]. Smaller spleen length at the time of surgery correlated with more aggressive IBD and complications such as perforation, fistulas, abscesses and bleeding in an early case series of 116 patients [39]. Furthermore, IBD patients are at increased risk of thrombosis and treatment guidelines advise prophylactic anticoagulation [40]. This pro-thrombotic and hypercoagulable state in IBD is thought to be secondary to active inflammation [41], and one that splenic dysfunction may well contribute to. One study reports a case of ischaemic stroke in a patient with Crohn's disease associated with splenic atrophy [42], suggesting that hyposplenism may be contributory to the thrombotic risk in IBD. Studies assessing spleen size and function in IBD patients with or without thrombotic complications are awaited.

Other gastrointestinal disorders

Case reports have demonstrated features of hyposplenism in various malabsorptive and inflammatory bowel disorders including tropical sprue, Whipple's disease, eosinophilic gastroenterological disorders, collagenous colitis and intestinal lymphangiectasia [43-47] and in various hepatic disorders [7]. The extent and significance of hyposplenism in these bowel disorders have not been extensively studied. A recent study, although limited by small numbers, also reported a high prevalence of hyposplenism in various autoimmune gastrointestinal disorders including autoimmune atrophic gastritis (55%), autoimmune enteropathy (66.6%) and autoimmune liver disease (87.5%) [11].

Mechanisms of hyposplenism in bowel disease

The aetiology of hyposplenism in bowel diseases remains largely unknown, but several theories exist (**Table 1** and **Fig. 2.**). A better understanding of these mechanisms might permit rational therapeutic approaches to optimise splenic function and minimise infection risk.

Reticuloendothelial atrophy

Immune defects in hyposplenism may be quantitative rather than reflecting a specific defective splenic function. Hyposplenic individuals have less lymphoid tissue than control subjects [48]. Lymphocyte depletion from thoracic duct drainage in animals leads to splenic appearances similar to those seen in coeliac disease [49]. In digestive disorders, lymphocyte depletion may occur through the enteric route [50], potentially disrupting lymphocyte recirculation within the spleen and subsequent reticuloendothelial atrophy. However, this theory has not been fully supported experimentally [51]. Splenic immune cell egress may also occur after intestinal manipulation (for example laparotomy) [52]. Whether this can also cause hyposplenism is yet to be assessed and effects are likely short-lived and limited to the peri-operative period.

In experimental murine models of *Leishmania donovani* infection, TNFα was particularly important in lymphocyte traffic and splenic marginal zone remodelling [53]. Mice that lacked TNFα, or those mice that received anti-TNFα antibodies, had preserved marginal zone macrophages. In one study, patients with Crohn's disease given infliximab restored their pool of peripheral IgM-memory B-lymphocytes [36]. There has been no study assessing whether restoration of this pool of lymphocytes reduces the rates of infection in patients with gastrointestinal diseases. However, reduction in IgM-memory B-lymphocytes post-splenectomy was not associated with increased rates of infection [54].

Splenic atrophy

Another quantitative defect that may contribute to hyposplenism is splenic atrophy. While splenic atrophy in sickle cell disease is thought to occur through multiple episodes of splenic infarctions [55], the mechanisms of splenic atrophy in gastrointestinal disorders remain poorly understood. The suggestion that an autoimmune process is important is suggested by the various immunological abnormalities demonstrated in splenic atrophy [56, 57]. Further evidence for an autoimmune aetiology in splenic atrophy comes from a study of chronic lymphocytic choriomeningitis virus clone 13 (LCMV13) infection in mice [58]. While acute LCMV13 infection leads to a temporary disruption of splenic architecture, chronic LCMV13 infection leads to irreversible splenic atrophy with predominant loss of B-lymphocytes [58]. The authors demonstrated that $NK1.1^+$ and $CD8^+$ cells were at least partly responsible for this splenic atrophy and that inhibiting these cells mitigated some of the destruction [58]. Splenic atrophy can occur in coeliac disease and specifically affects the size of the marginal zone and white pulp B-lymphocyte compartment [59], possibly via an autoimmune mechanism. This could lead to IgM memory B-lymphocyte depletion and contribute to hyposplenism.

Reticuloendothelial block

The reticuloendothelial function of the spleen may be blocked by circulating substances such as immune complexes or pathogens. For example, functional hyposplenism in rheumatoid arthritis can occur secondary to circulating immune complexes interfering with reticuloendothelial function [60]. Plasma exchange can reverse impaired splenic function in patients with nephritis and vasculitis by removing circulating complement-binding immune complexes [61]. There is evidence for raised levels of complement-binding immune complexes in coeliac disease and IBD [62], but whether these reduce splenic function is unclear [51].

Damage to the intestinal barrier may also be important and perhaps explains why many different gastrointestinal disorders are associated with hyposplenism. A dysfunctional intestinal barrier results in increased permeability and translocation of bacteria and bacterial products into the systemic circulation [63]. Subsequent splenic uptake [64] may cause a reticuloendothelial block leading to hyposplenism. This also suggests that controlling the underlying bowel disease may ameliorate hyposplenism. In keeping with this, mice treated with probiotics attenuated gut permeability and reduced splenic pro-inflammatory cytokine production [65]. Although not specifically assessed, treatment of Crohn's patients with infliximab improved splenic function [36].

Emerging research suggests that gut microbiota influences many areas of human health and disease [66]. Notably, development of the spleen is modulated by gut microbiota diversity. Rosado and colleagues demonstrated that gut colonisation within the first two weeks of life promotes the development of secondary lymphoid structures and expands B-lymphocyte compartments within the spleen [67]. A subtype of splenic IgM expressing B-lymphocyte is important in generating IgA responses in the gut [68]. Recent work demonstrates that spleen associated IgM B-lymphocytes may migrate to the gut to generate localised secretory IgA mucosal immune

responses [69]. Reduction in IgM-memory B-lymphocytes in hyposplenic patients may therefore lead to reduced local IgA responses and increased susceptibility to infection. Although unproven, an altered gut microbiome in bowel disorders may also influence the maintenance of these lymphocytes and contribute toward splenic dysfunction.

Investigating hyposplenism

Mammalian spleens have two main structural elements, white and red pulp, corresponding to the two main functions of the spleen. The white pulp is concerned with adaptive immune responses against blood-borne antigens. Despite extensive knowledge of these immune responses [70], none are yet characteristic or measurable enough to be considered tests of splenic function. For example, while splenic function is inversely correlated with circulating IgM memory B-lymphocytes in coeliac disease [10] and IBD [35], measurement of this immunological biomarker has not been validated in clinical practice. The red pulp acts as a filter for blood – mechanically through venous slits and physiologically via phagocytic activity - removing infectious agents, colloidal particles, effete red cells and platelets. In addition to the removal of whole cells, it also has an 'editing' function, whereby oxidatively damaged membranes are removed from erythrocytes.

Apart from direct splenic imaging, all current 'splenic function tests' are measures of red cell clearance or editing. Most techniques are not routinely available outside research settings or are not sensitive enough to be used as screening tests in clinical practice. Thus, identifying functional hyposplenism is challenging and a robust and easily applied test remains an unmet need.

The original method of assessing hyposplenism relied on counting Howell-Jolly bodies (basophilic red blood cell inclusions) on peripheral blood smears [55]. Although simple, repeatable and widely available, it was not sensitive enough to detect milder degrees of hyposplenism [71]. One recent prospective study demonstrated that detection of Howell-Jolly bodies may be used as an initial screening test for functional hyposplenism [72].

Scintigraphic methods were developed to assess splenic function by monitoring the rate of clearance of technetium-99m-labelled substances or heat-damaged, autologous erythrocytes [73]. These methods can be combined with imaging tools to allow a reliable and simultaneous assessment of spleen function and volume. However, they are time-consuming, expose patients to radiation and are not widely available.

The most widespread method for assessing splenic function is counting of "pits" on the surface of erythrocytes using differential interference contrast microscopy [74]. These pits are vacuoles beneath the erythrocyte plasma membrane, which are visible as crater-like depressions. A pitted erythrocyte count of >4% has been associated with hyposplenism in various conditions, including coeliac disease [73, 75]. Since counting pits is repeatable, quantitative and learned through brief training, it has been regarded as the standard for assessing splenic function. The equipment for pit counting is more commonly available in research rather than clinical settings. However, conventional microscopes can be converted into interference phase contrast mode through Nomarski optics in an inexpensive manner. Some experts have suggested that counting pitted erythrocytes could be used to screen patients, who could then undergo scintigraphic scanning to confirm hyposplenism [73].

Management of hyposplenism

Hyposplenism is not currently assessed in individuals with gastrointestinal diseases and there are no specific considerations for management in current guidelines. Testing for hyposplenism through haematological blood analysis should be considered and general management guidelines applied, if there is clinical suspicion. Infection remains the main hazard of hyposplenism and several strategies of prevention can be employed.

Education and early treatment of infections

Hyposplenic patients should be identified as being at risk of infection. National guidelines advocate that both patients and healthcare professionals should be educated about these risks so that potentially life-threatening infections can be treated promptly [76, 77]. Patients should be taught about when to seek medical care and the importance of vaccinations. Increased awareness may be achieved through information leaflets, alert bracelets and the systematic development of registries. Spleen Australia, a national spleen registry, has recently been shown to significantly reduce the rates of invasive infections in asplenic and hyposplenic patients [78]. Arguably the main benefit of registries is their educational value, encouraging vaccination and prompting earlier recognition of infections [79]. They also act to identify patients who have not been adequately dealt with by routine clinical care.

Vaccinations

The British Society of Gastroenterology (BSG) recommends that adults with coeliac disease be vaccinated against *S. pneumoniae* [80] and that all IBD patients on immunomodulatory or biologic therapies should receive pneumococcal vaccination with a booster after 5 years [40]. Unfortunately, the uptake of vaccination is poor. In one large study of at-risk individuals, only 3.7% of the 3584 patients with either sickle cell or coeliac disease had been vaccinated in the past 12 months and 13.5% in the past 5 years [81]. Spleen registries and better patient education may increase uptake.

The choice of vaccine in potentially hyposplenic individuals is important since protection against encapsulated bacteria is dependent on T-independent IgM memory B-lymphocytes, which are impaired in hyposplenism. Impaired immune responses to various vaccines have been seen in hyposplenic individuals [82, 83]. Conjugated vaccines, which elicit T-cell dependent immune responses, can restore the pool of anti-pneumococcal IgG memory B-lymphocytes in asplenic patients [84]. Patients with Crohn's disease developed higher antibody responses to certain pneumococcal serotypes when given the conjugated vaccine [85]. Vaccination strategies tailored to hyposplenic populations should include conjugated vaccines.

The timing of vaccination is another important issue. Immunosuppressive medications impair vaccine responses in IBD patients [85]. Some authors have argued that IBD patients should be vaccinated at the time of diagnosis, rather than prior to initiating immunosuppressive drug regimens [33].

Antibiotics

The role of antibacterial prophylaxis in hyposplenism remains unclear and is not universally recommended. The evidence supporting use of antibacterial prophylaxis in functional hyposplenism emerges from the sickle cell disease literature, where the associated hyposplenism is more profound than that observed in gastrointestinal diseases. In a meta-analysis evaluating 457 children with sickle cell disease and hyposplenism, daily penicillin prophylaxis reduced the incidence of pneumococcal infection by three-fold [86]. British Society for Haematology guidelines advocate lifelong penicillin prophylaxis in high-risk cases [76].

There is insufficient evidence to support the routine use of antibiotic prophylaxis in hyposplenic patients with bowel disorders. While the possible benefits of preventing severe infections with antibiotic prophylaxis are self-evident, there are potential significant harms to this approach. These include emergence of multi drug-resistant organisms, especially since adherence to daily antibiotics is poor [87]. Antibiotic exposure can disrupt the symbiotic relationship between host and gut microbiome leading to dysbiosis [88] and microbiota dysbiosis plays a part in the pathogenesis of gastrointestinal diseases. There is a reported association between antibiotic exposure and development of coeliac disease [89] and perhaps even IBD [90]. Finally, adverse drug-related effects such as hypersensitivity can occur.

Conclusions

Functional hyposplenism is a complication of many gastroenterological disorders, although poorly understood and seldom assessed. There is increasing evidence suggesting that functional hyposplenism contributes to the increased infection risk in patients with coeliac disease and IBD. Although counting pitted erythrocytes can accurately assess splenic function, the test is not routinely used. Infectious complications of functional hyposplenism can be minimised through education and vaccination. However, there is currently insufficient evidence to recommend antibiotic prophylaxis.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Contributions

AM wrote the first draft of the manuscript. All authors reviewed and contributed to the writing of the article.

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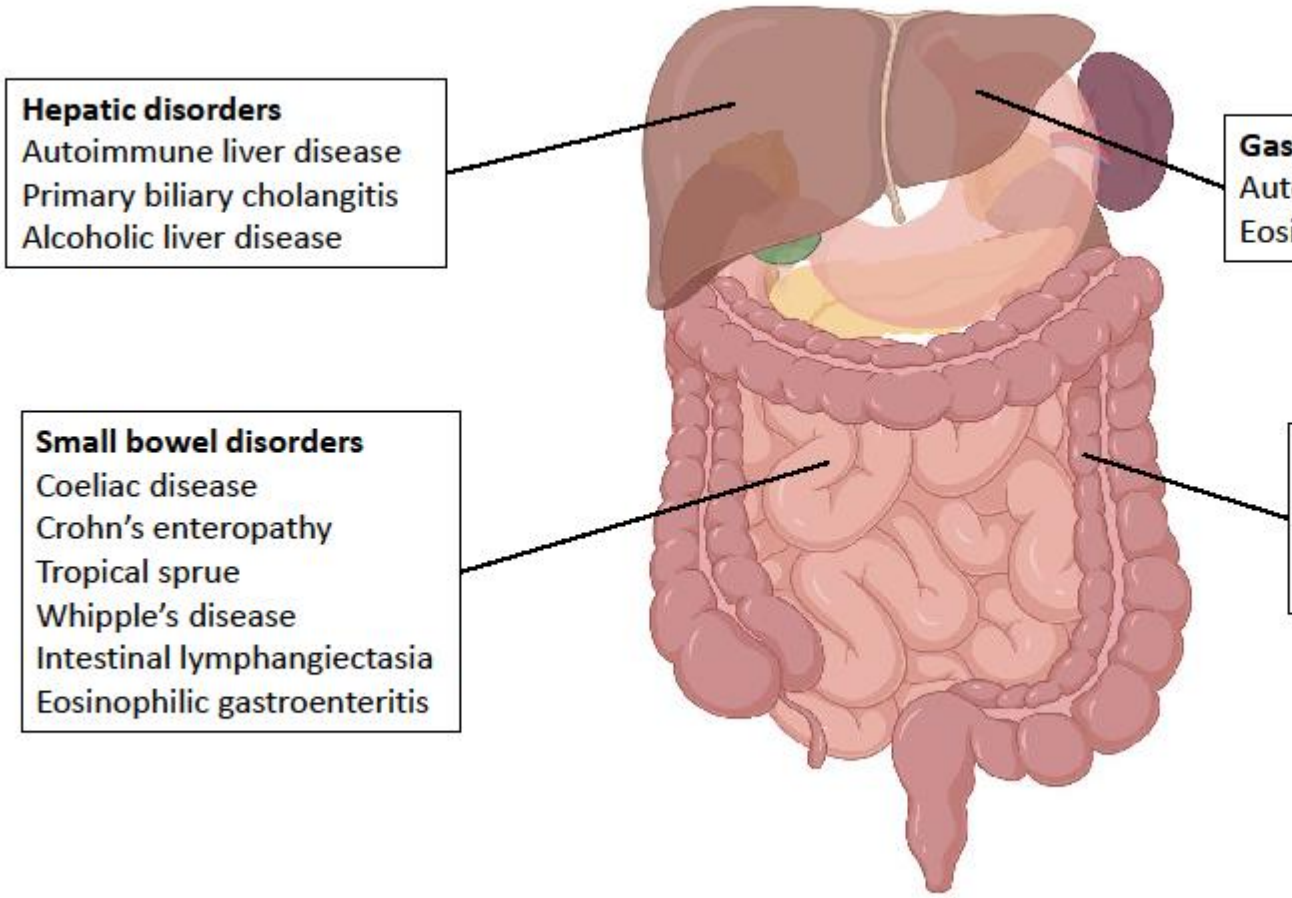
Figure legends

Fig. 1. The range of gastroenterological and hepatic disorders associated with functional hyposplenism.

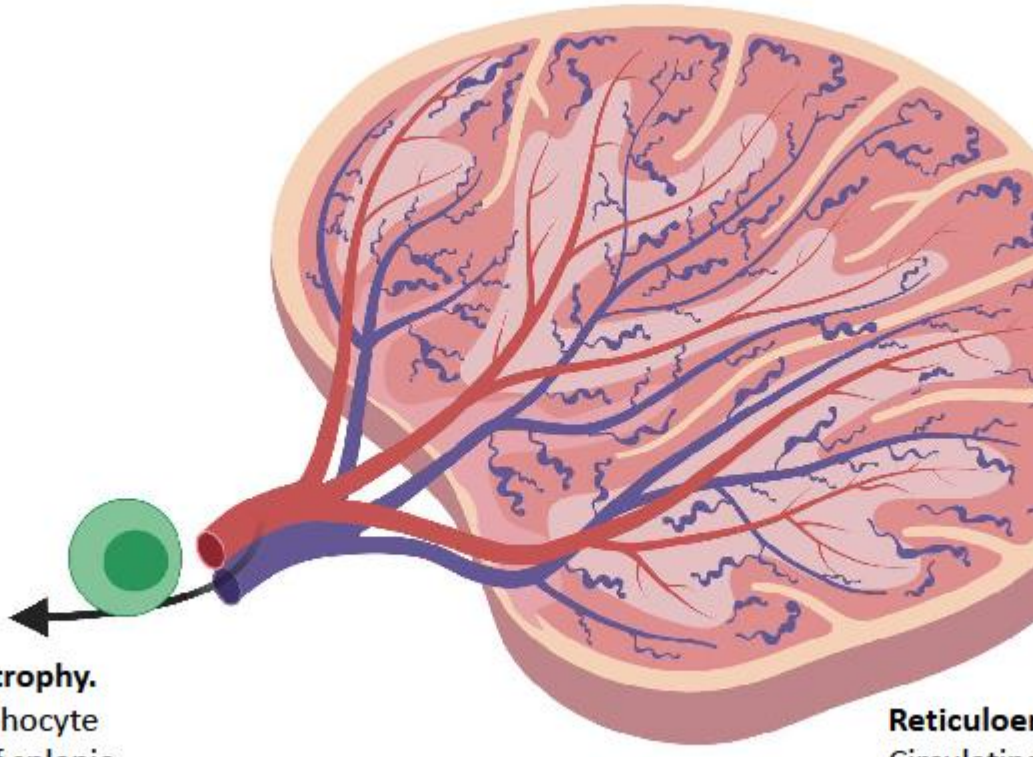
Fig. 2. Proposed mechanisms underlying hyposplenism in bowel disorders.

Table legends

Table 1. Proposed mechanisms of hyposplenism in bowel diseases.


Hepatic disorders
Autoimmune liver disease
Primary biliary cholangitis
Alcoholic liver disease
Small bowel disorders
Coeliac disease
Crohn's enteropathy
Tropical sprue
Whipple's disease
Intestinal lymphangiectasia
Eosinophilic gastroenteritis

Splenic atrophy.
Possible autoimmune phenomenon
to loss of specific splenic regions



Reticuloendothelial atrophy.
Caused by either lymphocyte
egress or the failure of splenic
lymphocyte recirculation

Reticuloen
Circulating
cells interf

Table 1. Proposed mechanisms of hyposplenism in bowel diseases.

Proposed mechanism	Description
Reticuloendothelial atrophy	A quantitative splenic function defect consisting of disrupted splenic lymphocyte re-circulation likely secondary to intestinal lymphocyte egress.
Splenic atrophy	A quantitative splenic function defect linked to immune dysfunction. In coeliac disease the marginal zone and white pulp B-lymphocyte compartments are depleted.
Reticuloendothelial blockade	Disruption of splenic function by circulating substances such as complement-binding immune complexes or pathogens that limit binding of other substances leading to reduced splenic activity.