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EXPERT
REVIEWS

Jejunioileal bypass as the main procedure in the onset of immune-related conditions: the model of BADAS

Expert Rev. Clin. Immunol. 9(5), 441–452 (2013)

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Bariatric surgery represents a common approach for the control of severe morbid obesity, reducing caloric intake by modifying the anatomy of the gastrointestinal tract. Following jejunioileal bypass, a large spectrum of complications has been described, with rheumatic manifestation present in up to 20% of cases. Although bowel bypass syndrome, also called blind loop syndrome, is a well-recognized complication of jejunioileal bypass, the same syndrome was recognized in patients who had not had intestinal bypass surgery, and the term the 'bowel-associated dermatosis–arthritis syndrome' (BADAS) was coined. The pathogenesis of BADAS is as yet poorly understood and only few data concerning this issue have been published in the literature. The aim of the present paper is to review the literature and to discuss putative pathogenic mechanisms of BADAS, focusing on the immune system.

KEYWORDS: bariatric surgery • blind loop syndrome • bowel-associated dermatosis–arthritis syndrome • bowel bypass syndrome

Bariatric surgery represents a common approach for the control of severe morbid obesity, reducing caloric intake by modifying the anatomy of the GI tract. These surgical procedures are classified as either restrictive, malabsorptive or a combination of both. Restrictive approaches limit caloric intake by creating a small gastric reservoir with a narrow outlet to delay emptying. Malabsorptive procedures, also called intestinal bypass surgery (IBS), bypass varying portions of the small intestine where nutrient absorption occurs [1]. The initial effects of profound metabolic changes are thought to ensue directly from the bypass of the small intestine's absorptive surface. As a consequence, the remaining surface adapts to such a change with hypertrophy of the residual functional units, leading to increased villus height and consequently an increased rate of absorption, which are both hallmarks of this condition [2].

Unfortunately, bariatric surgery is burdened by several complications, with no clear evidence of one procedure being the standard of care [3]. In general, restrictive approaches have a lower mortality and a decreased rate of surgical and nutritional complications compared with the malabsorptive or combined procedures [4].

After bariatric surgery, a large spectrum of complications has been described (outlined in Box 1). Some complications occur early, such as thromboembolism, pulmonary or respiratory failure, hemorrhage, peritonitis and wound infection, and some late, such as gastrointestinal (GI) obstruction, marginal ulceration near the stomach–small intestine anastomosis, incisional hernias, nutritional deficiencies of micronutrients and dumping syndrome, which refers to a complex of neurohormone-mediated symptoms including facial flushing, lightheadedness, palpitations, fatigue and diarrhea [2,5].

Liver disease is the most common complication to follow jejunioileal bypass (JIB). Obese individuals show an increased incidence of fatty liver disease (nonalcoholic fatty liver disease) and this is worsened by IBS in a third of patients. In this group of patients, nonalcoholic fatty liver disease may evolve to fibrosis and cirrhosis, culminating in death [5,6]. Besides the most common complications, patients undergoing IBS, and in particular JIB, may subsequently develop rheumatic manifestation in up to 20% of cases [2]. In 1979, Dicken and Seehafer reported a condition named bowel bypass syndrome (BBS)

Box 1. Complications of bariatric surgery.**Immune-related complications**

- Articular complications: arthralgias, nonerosive arthritis, erosive arthritis, inflammatory back pain and tendinitis
- Myalgias
- Panniculitis
- Erythema nodosum
- Cutaneous complications: skin pustules, ecchimoses, urticaria and psoriasis
- Necrotizing vasculitis
- Retinal vasculitis
- Raynaud's phenomenon
- Serositis: pericarditis and pleural effusion
- Peripheral nervous system complications: paresthesias and carpal tunnel syndrome
- BADAS

Nonimmune-related complications

- Thromboembolism
- Pulmonary insufficiency
- Wound infection
- Electrolyte imbalance: hypocalcaemia, hypokalemia and hypomagnesemia
- Anemia
- Hypoalbuminemia
- Metabolic acidosis
- Hypoglycemia
- Vitamin deficiency
- Bowel complications: anastomotic leak, stricture, obstruction, diarrhea, malabsorption, pseudo-obstruction, intussusception, volvulus, bypass enteritis, proctitis, granulomatous enteritis, megacolon, pneumatosis cystoides intestinalis, hemorrhage, peritonitis, incisional hernias and marginal ulceration near the stomach–small intestine anastomosis
- Dumping syndrome
- Liver disease: abnormal liver function tests, fatty infiltration, fibrosis, cirrhosis and granulomatous hepatitis
- Cholelithiasis
- Kidney complications: oxalate calculi, interstitial nephritis, glomerulonephritis and Bartter's syndrome
- Metabolic bone disease
- Encephalopathy, neuritis, burning feet syndrome, meralgia paresthesia, posterolateral myelopathy, myotonic syndrome, optic neuropathy, Wernicke–Korsakoff encephalopathy and lumbosacral plexopathy
- Infection
- Psychological disturbance

BADAS: Bowel-associated dermatosis–arthritis syndrome.

characterized by recurrent episodes of fever, malaise, nonerosive polyarthralgia or arthritis, and the development of skin lesions. Moreover, Raynaud's phenomenon, paresthesias, pericarditis, lower limb numbness and hepatic disease are additional manifestations reported by patients with BBS. Symptom onset is rather variable, ranging from 3 months to 5 years postoperatively, and this syndrome may be self-limiting or recurrent [7].

Although BBS (also known as blind loop syndrome) is a well-recognized complication of JIB, in particular of the malabsorptive or combination operations, the same syndrome was recognized in patients who had not had IBS, and Jorizzo *et al.* coined the term

the 'bowel-associated dermatosis–arthritis syndrome' (BADAS) [8].

In fact, BBS has also been observed in association with the small stomach and Roux-en-Y jejunectomy, jejunocolic bypass [7], ileocolic bypass [8], ileoanal pouch anastomosis [9], biliopancreatic diversion [10], in patients with gastric phytobezoar [11], diverticulitis with sigmoid stenosis [12], appendectomy [13], Billroth II gastrectomy, Crohn's disease and ulcerative colitis without history of bowel surgery [8].

Although several triggers have been postulated, associated risk factors are yet to be identified. However, rheumatologic manifestations following bowel bypass surgery seem to be more common in females and in those who have undergone JIB. There is no correlation between the amount of weight loss ensuing and incidence of symptoms [2,6,7]. Therefore, the interaction between surgeon and clinician and a careful evaluation of patients might define possible risk factors.

Pathogenesis

The pathogenesis of BADAS is still poorly understood and only limited data have been published so far. Some authors have raised different hypotheses about the development of BADAS as a consequence of bariatric surgery. The aim of the present paper is to review the literature and to discuss putative pathogenic mechanisms of BADAS, focusing on the immune system (FIGURES 1 & 2).

The authors postulate that the wide clinical spectrum of BADAS and other immune-related conditions after bariatric surgery is the consequence of immune system activation at different levels. In particular, a continuous and abnormal stimulation of both the innate and adaptative immune systems, which begins at the GI tract, together with vitamin and mineral deficiencies, in particular vitamin D, may be the cause of these clinical conditions.

One of the most likely hypotheses is that since IBS creates a blind loop of small bowel, this may be colonized by intestinal bacterial flora. Stasis and bacterial overgrowth are facilitated by the postoperative lack of peristalsis, the great length of the defunctionalized loop and the diversion of digestive juices and food [14]. In normal subjects, jejunal bacteria are typically aerobic and rarely exceed 10^5 organisms/ml. On the contrary, in bypassed jejunum, up to 10^6 organisms/ml have been isolated, both aerobes and anaerobes. *Bacteroides fragilis* represents the most

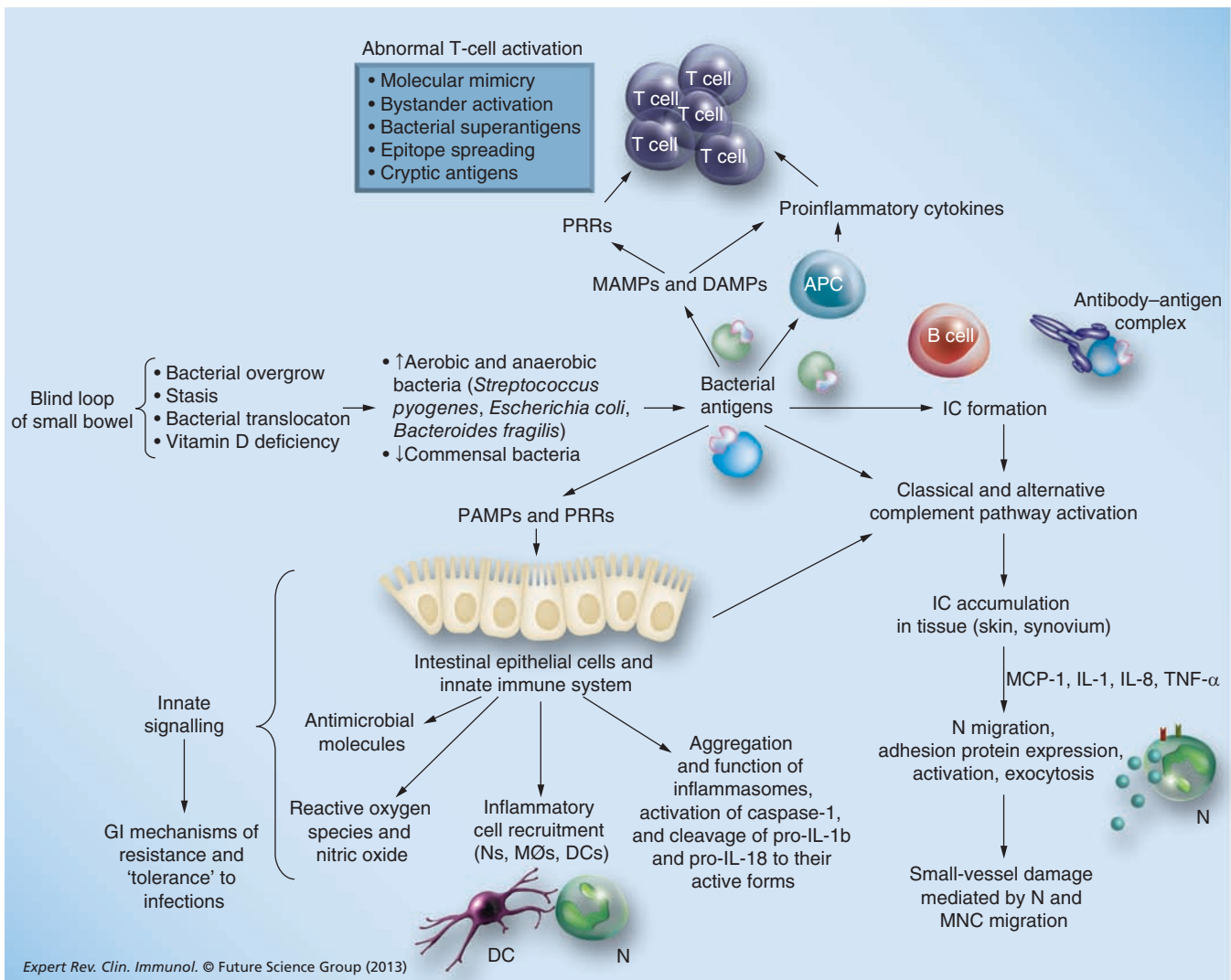


Figure 1. Bacterial immune complexes originating from the blind loop reach the circulatory system, accumulate in the skin and synovium, and lead to small-vessel damage mediated by Ns and mononuclear cells. Disturbed expression of proinflammatory mediators may deeply affect N rolling and migration properties and explain N activation, exocytosis and infiltration of the tissue. The complement system is activated by antigen–antibody complexes and through PRRs. PRRs are capable of discriminating between self- and nonself-antigens based on repeating PAMPs present on pathogen surfaces. PRRs are often found embedded within host cell membranes, either on the cell surface, on intracellular vesicles or found in the cytoplasm. PRRs are also involved in the immediate response to infection mediated by the innate immune system. It is generally believed that innate response to an infection aims to directly resist or prevent pathogen colonization by the secretion of several antimicrobial molecules, complement activation or inflammatory cell recruitment; this is so-called ‘innate signaling’. If a pathogen cannot be easily eradicated through the innate immune response, the host may act to at least limit the severity of the infection with a strategy termed ‘tolerance’. Several mechanisms have been described to explain how pathogens induce activation and expansion of autoreactive T cells and trigger autoimmune responses (molecular mimicry, bystander activation, bacterial superantigens, epitope spreading and cryptic antigens). Molecules derived from pathogens or commensal microorganisms and endogenous stress-induced molecules can activate T cells. In particular, DAMPs and MAMPs can induce inflammatory T cells either directly by binding to PRRs on T cells or indirectly through the induction of proinflammatory cytokine production by innate immune cells. APC: Antigen-presenting cell; DAMP: Damage-associated molecular pattern; DC: Dendritic cell; GI: Gastrointestinal; IC: Immune complex; MAMP: Microorganism-associated molecular pattern; MØ: Macrophage; N: Neutrophil; PAMP: Pathogen-associated molecular pattern; PRR: Pattern recognition receptor.

common pathogen among the anaerobes, while *Escherichia coli* predominates among the aerobes [15,16].

Gut injury and gut barrier failure have been considered to be contributors to the development of systemic inflammation and distant organ injury. These conditions are secondary to loss of gut

barrier function and the eventually ensuing translocation of bacteria and endotoxins from the gut to the portal and systemic circulations [17]. Several authors have proposed bacterial translocation as a major contributor to the development of systemic infection, multiple-organ dysfunction syndrome and systemic inflammatory

have shown that the mesenteric LN is the first and, frequently, only tissue that contains translocating bacteria, suggesting that the intestinal lymphatic vessels are the major route by which gut-derived proinflammatory or toxic factors reach the systemic circulation [21].

The GI mucosa is an important immunologic center, holding 80% of the leukocyte population, and is absolutely required for host homeostasis, with an estimated 100 trillion bacteria residing in the intestine. The dysregulation of gut homeostasis results in several diseases such as inflammatory bowel diseases and could also play a pivotal role in the pathogenesis of BADAS.

The mucosal immune system can be divided into inductive sites, where antigens sampled from mucosal surfaces stimulate naive T and B lymphocytes (present in organized mucosa-associated lymphoid tissue and regional draining LNs), and effector sites, where after extravasation and differentiation the effector cells are able to exert their function, including the formation of secretory IgA antibodies [22,23]. The effector sites consist of distinct histological compartments, including surface epithelia, the stroma of exocrine glands and lamina propria of various mucosae.

A single epithelial cell layer separates enteric flora and environmental antigens from the sterile host and subepithelial lymphoid tissue is segmentally organized in follicular-associated epithelium. These lymphoid sites are represented by both Peyer's patches (PPs) and isolated lymphoid follicles (ILFs). The lamina propria compartment is particularly enriched in plasma cells, macrophages and dendritic cells. Mesenteric LNs provide a draining secondary lymphoid compartment for the intestinal environment. These compartments cooperate for the induction and organization of effector phases of immunity [24].

In these compartments, leukocytes are key players to maintain tolerance to the enteric flora and food antigens, and a defense to foreign infectious agents. In particular, B lymphocytes are crucial in maintaining homeostasis and immunity, mainly through differentiation into IgA-producing plasma cells. Moreover intestinal plasma cells derive from B cells initially activated in gut-associated lymphoid tissue [22,25].

ILFs are constituted of B cells organized into a central follicle that may contain a germinal center, representing a unique compartment of B lymphocytes found at the host–bacterial interface of the bacteria-laden intestine. Notably, ILFs, but not PPs and LNs, contain only minimal numbers of T cells, dendritic cells and macrophages, suggesting a novel mode of B-cell activation at this site. These findings highlight the role of the mucosal B-cell response in controlling the commensal bacterial population, which to a certain extent is due to B-cell receptor-mediated antigenic stimulus [24,26,27].

After induction, ILFs induce the maturation of IgA-producing cells and the resulting antibodies bind and inhibit potentially harmful flora. Therefore, while PPs and mesenteric LNs are also capable of inducing B-cell differentiation into IgA plasmablasts, ILFs, in normal conditions, may represent the major source of IgA secretion [22,24].

When flora or infectious agents compromise mechanical and innate barriers, the failure of the appropriate maturation and

responsiveness of ILF B cells may lead to dysregulation of homeostasis. In the same way, the failure of ILF formation may result in insufficient antibody responsiveness, allowing infections by opportunistic pathogens or enteric flora [26,27].

Recent studies on ILF B cells highlight the importance of B-cell subsets in mediating gut homeostasis; therefore, it is conceivable that these cell subsets may play a pivotal role in BADAS pathogenesis. In the course of BADAS, the blind loop of small bowel is colonized by intestinal bacterial flora. The innate immune system tries to control this bacterial overgrowth, leading to ILF B-cell hypertrophy. Unfortunately, in these individuals, some conditions that cause a failure of appropriate ILF B cells maturation and responsiveness may coexist, leading to dysregulation of immune system homeostasis.

Further studies investigating the molecular mechanisms of homing, retention and activation of these B-cell subsets in the gut mucosa will prompt us to modulate their presence and activity for therapeutic purposes.

Furthermore, it is conceivable that in BADAS an abnormal and continuous activation of the complement system (CS), could lead to an aberrant activation of B cells. Indeed, the importance of the CS in inflammation is well established and evidence supports its role in the regulation of B lymphocytes, identifying a link between innate and adaptive immunity. A key event in humoral immunity is the recognition of foreign antigens, leading to covalent binding of C3d. This event enhances B-cell memory and effector functions by inducing B-cell survival within germinal centers, retention of antigen on follicular dendritic cells and transport of immune complexes to the follicular dendritic cells by B cells via complement receptors [24,26,27].

CS molecules are ideal candidates to coordinate both earlier events that occur as a consequence of the induction of innate immunity, and those that appear later during the adaptive immune reaction, representing the link between innate and adaptive immunity [28,29].

Because of bacterial overgrowth, bacterial antigens, especially peptidoglycans, act as antigenic triggers for immune complex formation [30]. The pathogenic role of bacteria is also supported by the possible improvement of the disease following antibiotic therapy [6]. Wands *et al.* evaluated five patients who developed arthritis after IBS to investigate whether it was associated with circulating cryoproteins. Only three patients displayed cryoprotein complexes while others displayed complexes containing IgG, IgM, IgA, complement components C3, C4 and C5, and IgG antibodies against *E. coli* and *Bacteroides fragilis*. These observations supported the hypothesis that systemically absorbed intestinal bacterial antigens may lead to the formation of circulating cryoprotein complexes that can activate both the classical and alternate complement pathways [31]. Therefore, activation of the alternate pathway of the CS may also play a role in the pathogenesis of BADAS [32]. In this setting, it has also been reported that six out of 17 patients who displayed complement abnormalities 1–9 years after IBS experienced recurrent arthritis. The assessment of classic and alternate complement pathway was carried out through the levels and the ratio of complement components (C3:C4, C3:C3PA, C3PA:C4) in sera. Two

out of those six patients also displayed activation of the alternate complement pathway (C3:C3PA ratio elevated) [33].

Taking into account the abnormal clearance of bacterial products, such as lipopolysaccharides, which occurs in the bypassed bowel loop, it has been claimed that this clearance of bacterial products may be a contributing factor in the development of complement abnormalities. In addition, it has been reported that cutaneous injection of *Streptococcus pyogenes* antigen was able to induce skin lesions, arthritis and other signs resembling that of BADAS in an animal model after IBS and in patients with BBS [34].

Indeed, bacterial immune complexes originating from the blind loop reach the circulation, accumulate in the skin and synovium, and lead to small-vessel damage mediated by neutrophils and mononuclear cell migration [31]. In particular, immunofluorescence analysis revealed the deposition of immune complexes in the dermal–epidermal junction of the skin, renal glomerulus and alveolar walls [35,36].

Moreover, histologic studies of blind loops in patients with BADAS demonstrated changes consistent with a nonspecific chronic inflammatory process [14], whereas the abnormal recruitment of neutrophils in the skin and synovium may reflect a more specific process characterized by the release of proinflammatory mediators, chemoattractants such as macrophage chemoattractant protein 1, and inflammatory chemokines such as IL-1, IL-8 and TNF [37]. Disturbed expression of these proinflammatory mediators may deeply affect neutrophil rolling and migration properties and explain neutrophil exocytosis and infiltration of the skin. Therefore, it is reasonable that these molecules cause activation of neutrophils with an upregulation of the expression of adhesion proteins of dermis endothelial cells favoring an abnormal diapedesis with skin infiltration [14,32].

According to previous studies, the authors hypothesize that CS plays a central role in the pathogenesis of BADAS. CS is activated by antigen–antibody complexes and through pattern recognition receptors (PRRs). PRRs are able to discriminate between self- and nonself-antigens based on repeating patterns of molecular structure (pathogen-associated molecular patterns) present on the surface of pathogens. Complement-activating PRRs include mannose-binding lectin, ficolins, C-reactive protein, C1q and natural IgM. PRRs are often found embedded within host cell membranes, either on the cell surface or on intracellular vesicles or found in the cytoplasm. The contribution of PRRs to complement activation ensures the rapid triggering of the complement cascade within the early immune and inflammation response, and it occurs immediately, with high efficiency [28].

PRRs are also involved in the immediate response to infection mediated by the innate immune system. It is generally believed that the innate response to an infection aims to directly ‘resist’ or prevent pathogen colonization by the secretion of several antimicrobial molecules, complement activation or inflammatory cell recruitment; this is the so-called ‘innate signaling’.

In this setting, growing evidence suggests that if a pathogen cannot be easily eradicated through the innate immune response, the host may act at least to limit the severity of the infection with a strategy termed ‘tolerance’ [38]; in this context, the use of this

term reflects an attempt by the host to survive the infection and limit tissue damage. Such mechanisms particularly occur in the GI tract [39].

Toll-like receptors (TLRs) and Nod-like receptors (NLRs) represent two families of PRRs that mediate innate responses to GI bacterial pathogens. In particular, NLRP1 and NLRP3 have a role in the aggregation and function of inflammasomes, the activation of caspase-1 and the subsequent cleavage of pro-IL-1 β and pro-IL-18 to their active forms [39].

Host resistance in response to enteric bacterial infections is a complex process that requires several steps. First of all, commensal bacteria and the mucus layer provide protective barriers against GI bacterial pathogens. After recognition of bacterial products by TLRs, complex intracellular pathways are activated, leading to the release of antimicrobial peptides, reactive oxygen species and nitric oxide by intestinal epithelial cells. Intestinal epithelial cells, via PRR activation, release chemokines that recruit neutrophils, macrophages and dendritic cells to the site of infection. TLR2 signaling along with IL-1 β and IL-18 may promote cell restitution/regeneration to replace injured epithelial cells; moreover, IL-11 production by subepithelial myofibroblasts, via TLR2 activation, promotes epithelial tight junction integrity [40]. The host has developed several strategies to control the potentially negative impact of inflammation and resistance mechanisms to enteric infections. On this basis, tolerance may act in order to limit tissue damage resulting from host resistance to infections of the GI tract. Other strategies include spatial regulation of PRR expression, control of coreceptor expression and negative regulation to limit responsiveness to microbes [40,41].

Taking this evidence together, it is reasonable to hypothesize that in the blind loop of small bowel colonized by intestinal bacterial flora there are alterations of these mechanisms of resistance and tolerance, and consequently of the innate immune response. Further studies to identify the peculiar role of innate immunity during enteric infections will surely facilitate the understanding of BADAS pathogenesis.

Molecules derived from pathogens or commensal microorganisms and endogenous stress-induced self-molecules activate T cells. In particular, damage-associated molecular patterns and microorganism-associated molecular patterns can induce inflammatory T cells either directly by binding to PRRs on T cells, or indirectly through the induction of proinflammatory cytokine production by innate immune cells [40,41].

This mechanism was widely described concerning both the association between infection and autoimmune diseases (e.g., multiple sclerosis, systemic lupus erythematosus and rheumatoid arthritis), which develop following the activation of autoreactive B and T cells, and between infection and chronic inflammatory diseases (such as Crohn’s disease), which result from uncontrolled innate and adaptive immune responses to normal constituents of the gut flora [37,39].

Several mechanisms have been described to explain how pathogens induce activation and expansion of autoreactive T cells and trigger autoimmune responses. Molecular mimicry has been linked to the pathogenesis of several rheumatic diseases [42], and hence may also be involved in the pathogenesis of BADAS. Such a

mechanism is based on the hypothesis that an exogenous substance may mimic self-antigens by triggering an abnormal autoimmune response. Interestingly, among several environmental factors, infectious agents have been implicated in the induction and/or promotion of autoimmunity, due to their capacity to elicit strong immune activation [42,43]. However, after activation in response to these pathogens, T cells may also become crossreactive to self-antigens, eventually leading to abnormal autoimmune responses. Similarly, circulating antibodies were found to recognize both microbial and self-antigens, suggesting a crossreactivity of B-cell receptors [44].

T cells with a low affinity for a self-antigen, and which have escaped thymus negative selection, can become activated with a microorganism containing an identical antigen, which provides appropriate innate immune signals, resulting in autoimmune disease. According to the observation that specific T cells that have been primed by pathogens and crossreact with self-antigens can cause autoimmunity in animal models, the self-reactive lymphocytes observed at high levels in patients with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis may be those triggered by microorganisms [44–46].

Another mechanism, called bystander activation, describes an indirect nonspecific activation of autoimmune cells caused by the inflammatory environment present during infection. In particular, the inflammatory setting and the paracrine secretion of T-cell growth factors are able to induce the expansion of activated autoreactive T cells [47,48].

Antigen-presenting cells, activated within the inflammatory milieu of a pathogenic infection, can stimulate the activation and proliferation of autoreactive B or T cells; antigen-presenting cells present self-antigens obtained following tissue destruction and/or uptake of local dying cells to autoreactive cells [47,48].

Notably, viral and bacterial superantigens that bind a variety of MHC class II molecules can activate T cells, independent of their specificity. In addition, activation of autoreactive B or T cells may be also achieved by another mechanism called ‘epitope spreading’. Epitope spreading is a condition in which an immune response, which is initiated by various stimuli, including microbial infection, trauma, transplanted tissue or autoimmunity, spreads to include responses directed against a different portion of the same protein (intramolecular spreading) or a different protein (intermolecular spreading) [49]. Notably, autoimmune diseases potentially arise when spreading crossreacts with self-proteins, leading to the destruction of self-tissue [40,41].

It is generally accepted that different peptide/MHC complexes can lead to cross reactivity by the same T-cell receptor (TCR); this flexibility of TCR recognition is crucial to many immunological processes including thymic selection and the ability to recognize nearly all pathogen-derived peptides. At the same time, the activation of TCRs by microbial antigens might lead to autoimmunity [50].

Finally, infections might also lead to autoimmunity through the processing and presentation of cryptic antigens. Cryptic antigens are normally invisible to the immune system, in contrast to dominant antigenic determinants. According to this theory, susceptible individuals acquire an infection by a microbial agent that has antigenic

similarity to self-antigens resulting in pathogen-specific antibody binding to the host structures displaying crossreactive self-antigens and eventually leading to tissue damage and disease [51,52].

It can be postulated that bacterial overgrowth in the blind loop after IBS might favor activation of the immune system through molecular mimicry and other related mechanisms contributing to BADAS pathogenesis.

Another intriguing mechanism investigated as a potential environmental trigger for the induction of autoimmunity is vitamin D deficiency. Bariatric surgery may also cause long-term morbidity due to vitamin and mineral deficiencies. Morbidly obese patients often display vitamin D deficiency prior to surgery because of poor sunlight exposure, less bioavailability of the vitamin when sequestered in fat cells and inhibited hepatic vitamin activation. Bariatric surgery may then worsen vitamin D and calcium deficiencies due to malabsorption, reduced food intake and poor compliance to treatment [53].

Indeed, a high dose of vitamin D supplementation could be preventive and therapeutic, as shown in experimental autoimmune diseases such as autoimmune encephalomyelitis, collagen-induced arthritis, Type 1 diabetes mellitus, inflammatory bowel disease, autoimmune thyroiditis and systemic lupus erythematosus [54,55]. Vitamin D and its active hormonal metabolite, 1,25(OH)₂D₃, are able to regulate innate and adaptive immunity; in particular, it potentiates the innate response (monocytes/macrophages with antimicrobial activity and antigen presentation) but suppresses adaptive immunity (T- and B-lymphocyte functions) [56].

Several immune cells including monocytes, macrophages, dendritic cells and activated T and B cells express vitamin D receptors and are provided with the enzymatic pool to convert vitamin D into its active form. Concerning the adaptive immune response, vitamin D downregulates Th1-dependent responses and directly reduces the production of the Th17 cytokines IL-17A, IL-17F and IL-22 by memory T cells [57]. It has been demonstrated that vitamin D is able to reduce lymphocyte proliferation, Ig production, induce apoptosis of activated B cells, induce regulatory B-cell development and inhibit the generation of plasma cells *in vitro* [56]. Moreover, it is widely accepted that vitamin D affects monocyte/macrophage responses to bacterial infections via TLRs [54–57].

Taken together, all the evidence allows us to speculate that vitamin D deficiency might also contribute to BADAS pathogenesis. In conclusion, our current knowledge of BADAS pathogenesis is too poor to be conclusive. Moreover, according to previous observations, the clinical spectrum of BADAS is protean and, after bariatric surgery, immune-related conditions other than BADAS have been described. On this basis, the authors are not able to identify a single pathogenetic mechanism described above in this paragraph as the most probable or the most important mechanism in the development of the disease.

Nonetheless, all these pathways may cooperate at different levels, with different modalities and intensities. Moreover, the wide clinical spectrum of BADAS and other immune-related conditions after bariatric surgery is complex. Further studies aiming to shed light on BADAS pathogenesis and eventually to develop selective therapeutic approaches are needed.

Clinical patterns

Skin

IBS has been performed since 1956 but the first report of skin lesion development after IBS was described in 1981 [58]. Lesions were described as erythematous papules or vesiculopustules resembling insect bites, or as necrotic lesions similar to those seen in gonococemia. At the beginning, lesions appear as round erythematous macules with a 2–10-mm diameter preferentially located on the upper trunk and extremities, which progress toward indurated pink swellings usually less than 1 cm in diameter. Later the induration increases and develops a small vesicle with a 2–4-mm diameter and eventually evolves to a pustule [59]. Overall lesion duration ranged from 2 to 8 days with recurrence approximately every 1–6 weeks. BADAS belongs to noninfectious neutrophilic dermatoses, which includes Sweet's syndrome, pyoderma gangrenosum, Behçet's disease, rheumatoid neutrophilic dermatosis, familial Mediterranean fever and neutrophilic eccrine hidradenitis [60].

As described by Ely *et al.*, these skin manifestations reproduce the progression through different cutaneous histologic patterns [35]. Indeed, the microscopic appearance of skin biopsy specimens changes with disease progression stage: the early manifestation is congestion of dermal venules with neutrophils and a perivascular mononuclear cell infiltrate; the macular stage produces a perivascular mononuclear cell infiltrate too; the papular stage produces edema of the papillary and reticular dermis. Neutrophil infiltration also shows a different location related to disease stage; in the early stage they are concentrated around dermal venules, but they are widely present in the dermis in the later stage. In older papules and vesicles, the neutrophilic infiltrate increases, incorporating nuclear debris and few eosinophils. Vesicle formation is secondary to massive edema of the papillary dermis, while pustule formation is secondary to expulsion of neutrophilic debris through the epidermis. Although vascular dilatation and accumulation of neutrophils may be seen, there is no endothelial necrosis, infarction or fibrinoid degeneration [58–60].

Joints

Joint manifestations are highly variable in terms of onset time, duration, severity and distribution [61]. Arthritis is more common in females and no correlation between the amount of weight lost and the incidence of arthritis was observed. In most cases, arthritis occurs within the first 3 years following IBS. It is usually episodic, migratory and polyarticular, with peripheral joints more commonly affected than axial joints [61,62].

Knees, ankles, shoulders, wrists and metacarpophalangeal joints represent the sites most affected while axial skeleton involvement has been rarely described and tendonitis and myalgias have also been reported [62,63]. Articular symptoms are typically remittent and intermittent, and episodes can last for days to weeks followed by spontaneous resolution. In some patients, symptoms may become persistent from a few days to several months, thus mimicking rheumatoid arthritis or ankylosing spondylitis [61–64].

Objective findings are often mild, but joint effusions, synovial thickening and joint swelling are present in many patients. Synovial fluid has been reported to display both inflammatory and

noninflammatory features and within the synovium, a chronic synovitis with prevalent lymphocytic infiltrate is the most common histological finding [61,65]. Radiographic joint changes are not significant and usually do not include erosions, even if chronic erosive polyarthritis has also been described [66].

Laboratory findings

Routine blood analysis is usually normal. However, it is possible to observe rheumatoid factor and antinuclear antibody positivity, γ -globulin increase, complement reduction, circulating immune complexes and cryoglobulins. In most patients, HLA haplotypes are not consistent with an underlying rheumatic disorder and in patients who showed *HLA*B27* had presented with spondylitic symptoms earlier [61,64].

Treatment

Treatment of patients with BADAS is largely empiric and the use of drugs is based on the results of case reports or small case series [61–66]. Although the treatment of BADAS consists of antibiotics such as tetracycline, metronidazole or clindamycin to overcome bacterial overgrowth, relief is generally only temporary. In this regard it may be useful to rotate antibiotics, in a dose of antibiotics for 1 week each month, or prokinetic agents such as cisapride that help to clear the small intestine [63,67]. NSAIDs may alleviate arthralgias and daily prednisone can control articular symptoms.

Patients with BADAS may benefit from treatment with systemic corticosteroids, cyclosporine or other drugs affecting the function of neutrophils, such as colchicine, sulphones or sulfasalazine, similar to those patients with neutrophilic disorders [12]. A novel therapeutic option might be the use of antibodies against TNF, which affects the recruitment of neutrophils in the skin [12].

Bypass reversal is curative in the majority of patients partially responding to pharmacological therapy [63,68,69]. In patients without bowel bypass, treatment of the underlying GI disease has contributed to remission [8].

Unusual rheumatic manifestations after bariatric surgery

Over the years, several cases of BADAS have been described in substantial numbers of patients after IBS but rheumatic manifestations other than this syndrome have also been reported. In 1971, Shagrin *et al.* reported that seven out of 31 patients (23%) treated with jejunocolostomy for obesity developed articular symptoms. Most of the articular manifestations were transient, lasting only 2 months, but in two patients they were more severe and lasted over 24 months. In one patient, severe articular symptoms required reconstitution of her bowel to the normal anatomical sequence. Complete relief and resolution of symptoms were immediately observed [62].

In 1979, Goldman *et al.* described two patients with JIB who subsequently developed leukocytoclastic vasculitis. The authors report two cases in which necrotizing vasculitis with tenosynovitis arthralgia/arthritis syndrome developed after IBS. Each of these patients had jejunoileostomies, and the excluded segment was placed in an ileal–colonic anastomosis [70].

In 1979, Zapanta *et al.* described 13 patients with arthritis related to JIB. These patients had a symmetrical polyarthritis, and eight also had extra-articular connective tissue disease manifestations such as alopecia, pleurisy, Achilles tendinitis, carpal tunnel syndrome and erythema nodosum-like lesions. The incidence of antinuclear antibodies and rheumatoid factor positivity, the presence of immune complexes and antibodies to intestinal flora, and the numbers of circulating T and B lymphocytes were comparable to those of patients who did not develop arthritis following IBS [71].

In 1982, Fagan *et al.* reported three patients with systemic inflammatory complications following JIB surgery for morbid obesity. They experienced asymmetrical polyarthritis, tenosynovitis, sterile skin pustules, mucous membrane ulceration and retinal vasculitis resembling Behçet's syndrome. Antibiotic therapy failed, whereas dapsone produced a sustained remission. Bacterial overgrowth was not observed in all patients, suggesting that bacteria may be required to initiate, but not to perpetuate, inflammatory complications [72].

In 1983, Delamere *et al.* reported that 38 out of 107 patients who underwent JIB developed episodic polyarthralgia and arthritis affecting both large and small joints, with a similar incidence of preoperative joint symptoms in those who did and in those who did not consequently develop the postoperative arthropathy. Reversal of the intestinal bypass was always associated with an immediate, complete and permanent remission of symptoms [73].

In 1985, Clegg *et al.* studied 13 patients after JIB surgery. All patients developed circulating immune complexes containing IgG and IgA and seven patients developed arthritis. IgA complexes were shown to contain secretory component, a protein predominantly associated with intraluminal IgA, in significantly higher levels in patients with arthritis [74].

In 1997, Caux *et al.* described the fifth reported case of panniculitis associated with BBS. These five patients had tender nodules, nodules with discharge of necrosis or erythema nodosum-like lesions. A biopsy specimen revealed septal and lobular panniculitis and a glucose hydrogen breath test was consistent with bacterial overgrowth. The authors postulated that these rheumatic manifestations might have the same immunologic mechanism of BBS [61,75,76].

In 2003, Cox and Palmer reported a case of BBS associated with ileoanal pouch anastomosis that required high-dose prednisolone to control disease [9]. Since mycophenolate mofetil was known to be useful in pyoderma gangrenosum [77], it was as an effective steroid-sparing agent for this patient [9].

In 2006, Kawakami *et al.* described a case of fulminant BADAS characterized by necrotizing fasciitis-like severe skin and systemic manifestations that required differential diagnosis with cellulites and necrotizing fasciitis and was treated with high doses of corticosteroids [78].

In 2007, Kevans *et al.* described a patient who developed hand, wrist, elbow, hip and foot arthritis and diarrhea 3 weeks after a partial gastrectomy and vagotomy (Roux-en-Y gastrojejunostomy with jejunojejunostomy) for a chronic nonhealing prepyloric gastric ulcer. Six weeks after the surgery diarrhea, abdominal pain and arthritis had completely resolved without medical therapy [79].

Expert commentary

Immune-related complications after JIB are underestimated; indeed, only scarce literature reports regarding these conditions are available to date, and it limits the possibility of defining the real incidence of the disease spectrum. BADAS represents a model in which surgical procedures trigger immune disorders, revealing a more complex scenario than initially thought and identifying a link between the surgeon and clinician. Here we have highlighted several mechanisms suggested to explain the pathogenesis of immune-related complications after JIB, showing the complexity and the wide clinical spectrum of the disease presentation.

Despite the increasing burden of immune-related conditions after bariatric surgery, a commonly accepted algorithm for treating patients is currently lacking, mostly because the adequate management of these patients has not yet been identified. The treatment of BADAS consists of antibiotics, but generally relief is only temporary. Reversal of bypass may be curative in the majority of patients, pointing out the role of the blind loop in disease pathogenesis. Patients with BADAS may benefit from treatment with systemic corticosteroids or other immunosuppressive agents, including monoclonal antibodies against TNF.

Until now, published literature has reported large cohorts of patients still treated with JIB in selected patients in which different procedures are not available or, alternatively, on the basis of new suggested indications, such as patients affected by unresponsive Type 2 diabetes [68,80]. Thus, it is still possible that patients could undergo these surgical procedures and consequently develop immune-related diseases. From a rheumatologic point of view, it could be useful to remember, in the differential diagnosis of chronic arthritis, the clinical pattern of BBS.

Despite the fact that some surgical procedures are no longer performed, immune-related conditions may represent a mid- to long-term complication. Therefore, patients who underwent bariatric surgery may be referred to a rheumatologist several years later. On this basis and according to the authors' experience, in the last 5 years more than 15 patients were admitted to our rheumatologic clinic with immune-related symptoms. These patients underwent JIB or other bariatric procedures many years before the onset of any immune-related symptoms, and due to their clinical manifestations and lack of any other symptoms or biomarkers suggestive of chronic arthritis different from BADAS, we finally diagnosed BADAS. In this setting, we recommend considering BADAS in the differential diagnosis, particularly in those patients surgically treated decades ago.

The fact that surgical procedures other than JIB are not associated with bacterial stasis and bacterial overgrowth suggests that other pathogenetic mechanisms might determine the development of BADAS. Moreover, the low incidence of the disease after such procedures suggests that a favoring background such as genetic predisposition may be required to see the full disease.

Only a close interaction between the surgeon and clinician, and a careful evaluation of patients before and after surgical procedures, will allow a precise and accurate definition of these immune-related conditions and will help us to understand the underlying pathogenic mechanisms.

Five-year view

Although bariatric surgery is constantly evolving in an attempt to prevent complications, BADAS is still observed. One possible explanation is that while metabolic complications are well characterized, BADAS pathogenesis has not yet been fully clarified. Hence, it would be difficult to achieve primary prevention unless the underlying mechanism is elucidated. In this setting, several groups have raised different hypotheses to explain the aberrant immune response that occurs after bariatric surgery but conclusive results are lacking. For example, the intriguing hypothesis that recognizes the intestinal flora of the blind loop as the abnormal activator of the immune response may also clarify the link between systemic autoimmunity and infections. On the other hand, it is of note that the CS appears to be a key player in the induction and perpetuation of BADAS and BADAS-like syndromes.

However, although bariatric surgery could represent a trigger factor to develop rheumatic/autoimmune disorders in non-pre-disposed subjects, it could also unmask an underlying subclinical process. In addition, the lack of validated preventive strategies as well as predictors of BADAS development points out the need for

cooperation between surgeons and clinicians to perform an early diagnosis. In this context, it might be inappropriate to consider BADAS as a rheumatologic disease requiring only antirheumatic treatment. Since surgery is the trigger event for disease development, a 'window of opportunity' to apply a prophylactic and surveillance program aimed to avoid immune-related complications is already available.

Indeed, the wide application of bariatric surgery in subjects with lower BMI increases the target population for such procedures and, consequently, for immune complication. Therefore, besides surgical, nutritional and metabolic follow-up, an immunological follow-up should also be performed in treated patients, particularly those with a familial history of autoimmune disorders.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- After jejunioleal bypass, and occasionally other bariatric bypass procedures, a large spectrum of complications have been described, with rheumatic manifestation in up to 20% of cases.
- Although bowel bypass syndrome, also called blind loop syndrome, is a well-recognized complication of bariatric surgery, the same syndrome was recognized in patients who had not had intestinal bypass surgery, and the term 'bowel-associated dermatosis–arthritis syndrome' (BADAS) was coined.
- The pathogenesis of BADAS is currently poorly understood and only few data concerning this issue have been published in the literature; the intestinal flora of the blind loop and bacterial translocation could be the abnormal activator of the immune response, with a link between systemic autoimmunity and infections.
- Symptom onset is variable, ranging from 3 months to 5 years postoperatively, and this syndrome may be self-limiting or recurrent. Differences in symptoms have been explained by a complexity of pathogenetic mechanisms.
- The treatment of BADAS consists of antibiotics, but generally relief is only temporary. Reversal of bypass may be curative in the majority of patients. Patients with BADAS might benefit from treatment with systemic corticosteroids or other immunosuppressive agents, including antibodies against TNF.

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