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Bidirectional Study of Oral Recurrent Aphthous Ulcers and Inflammatory Bowel Disease

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Abstract: Objective: To investigate the etiological mechanisms, treatment and oral manifestations of inflammatory bowel disease (IBD) in relation to recurrent aphthous ulcer (RAU). Materials and Methods: By summarizing and reviewing the research in the literature on the etiological mechanisms and treatment of RAU and IBD in the past decade in China and abroad. By summarizing and reviewing the research in the literature on the etiological mechanisms and treatment of RAU and IBD in the past decade in China and abroad. To explore the interaction between oral and intestinal lesions. Results: Some specific bacteria in the oral cavity may translocate and colonize the intestine, affecting the microecological balance of the gut and interfering with the disease process of IBD. Also, in patients with IBD, their oral salivary microbiome is altered and may show extraintestinal manifestations such as oral mucosal lesions. The occurrence of RAU may aggravate the dysbiosis and immune abnormalities of the intestinal mucosal flora that will be indirectly caused by patients with IBD, as well as malnutrition. Conclusion: Patients with IBD and RAU can affect the microecology of the oral-intestinal axis. patients with IBD are at increased risk of oral mucosal disease and oral symptoms and are associated with the activity of IBD. Due to the complex pathogenic interactions between RAU and IBD. It is recommended that dentists and gastroenterologists should be aware of the bidirectional association between the two diseases for early recognition and multidisciplinary medical management.

Keywords: Recurrent Aphthous Ulcers, Inflammatory Bowel Disease, Dysbiosis, Immune Dysregulation

1. Introduction

As a common oral mucosal disease, recurrent aphthous ulcer (RAU) are also known as "aphtha". RAU is an oval ulcer about the size of a mung bean, usually located in the mucosa of the mouth, cheek and tongue, and upper palate. It is often accompanied by pain. At present, previous studies have concluded that the potential pathogenesis of RAU includes infection, immune abnormalities, food and drug factors, nutritional factor deficiency, etc., but there is no unified conclusion [1]. As a frequent disease of the digestive system, inflammatory bowel disease (IBD) is also a chronic inflammatory disease. The main clinical features are intestinal mucosal inflammation and recurrent inflammation, often accompanied by abdominal pain and diarrhea. Ulcerative colitis (UC) and Crohn's disease (CD) are the two main types of IBD. Both oral mucosa and intestinal mucosa belong to digestive tract mucosa. Domestic and foreign studies have confirmed that oral cavity and intestinal tract can influence each other to cause disease [2]. Oral and intestinal mucosal cells are digestive tract epithelial cells from different parts developed from the same embryonic layer [2]. Since both oral mucosa and gastrointestinal mucosa come from the ectoderm, they have many similarities, such as structure, function,

physiology and pathology. So they may share a common pathogenesis. The similarities are: (1) the epithelial cells are tightly connected to each other; (2) there is a basement membrane between the epithelial cells and the lamina propria [3]. Studies have shown that people with IBD have a greater chance of developing RAU compared to healthy people. Up to 10% of UC patients and up to 20%-30% of CD patients are accompanied by RAU [4]. The oral manifestations of IBD may appear before the intestinal imaging manifestations. According to relevant studies, oral manifestations of IBD may appear before intestinal disease in up to 60% of patients [5]. Based on clinical statistics of oral manifestations in patients with IBD, a high prevalence of specific oral lesions was found. Especially during the active phase of IBD, there is a high chance of oral mucosal lesions, and RAU has been shown to be a disease type that has a significant association with the active phase of IBD [6]. When RAU is combined with IBD, symptoms are usually more extensive and persistent [7]. IBD and RAU influence each other's progress through a bidirectional relationship. However, the pathogenesis of the association between IBD and RAU remains to be further explored.

2. Oral-Intestinal Axis

As the entrance of digestive tract, oral cavity affects the health of the whole digestive tract. When RAU occurs in the mouth, it will indirectly affect gastrointestinal health. When patients are prone to RAU, the oral microbiota is often accompanied by oral microbiota disorder and the disturbance of the oral microbiota will also affect the homeostasis of the intestinal microbiota through saliva and eating, which is likely to cause IBD. In addition, immune system dysregulation in RAU patients also disrupts the epithelial barrier and promotes the progression of IBD.

2.1. Dysbiosis of Oral Microbiota

The oral epithelium is the first barrier against pathogenic invasion in the oral cavity. In many cases, systemic diseases in other sites are manifested in the oral cavity. The oral cavity is a microecological environment with a large number of microorganisms [8]. The role of the oral microbiota in oral diseases is clearly characterized. Oral dysbiosis is one of the pathogenesis of RAU. Studies have shown that H. pylori infection is strongly associated with the development of RAU [9].

Indeed, the relative abundance of Enterobacteriaceae is highest in the oral cavity compared to other lesion sites. Alterations in the oral microbiota may cause dysbiosis of the intestinal flora and the development of chronic inflammation of the intestinal tract. Segata et al. reported that the oral microbiome may have a considerable effect on the distal digestive tract group [11]. Since some systemic diseases are associated with oral and intestinal dysbiosis, it is reasonable to hypothesize that swallowing oral bacteria through saliva may be a possible mechanism for systemic diseases of oral junction. In the oral and intestinal microenvironment, the existence of microorganisms is necessary, but the ingested oral bacteria are not easy to colonize in the healthy intestinal tract, which is not enough to cause diseases [8]. However, some oral bacteria can be transmitted from the oral cavity under pathological conditions and transferred to the digestive tract via the non-intestinal route and the intestinal route [12]. In addition, saliva affects microbial growth in the GI tract because it is a buffering agent and affects pH, while its high mucin content promotes nutrient absorption. In patients with intestinal lesions, abnormal colonization of oral microorganisms is often detected at the tissue lesions. It has been found that many microbiota of oral origin occur in the intestine of patients with IBD. Indeed, oral bacteria, such as Clostridium, Prevotella, Porphyromonas, and Actinobacter, are often found in the intestine of patients with gastrointestinal diseases [13]. Nucleobacteria are extremely abundant in the oral cavity and can also be found in the intestinal mucosa of patients with IBD. It acts as a bridge during oral dysbiosis, allowing other key bacteria to bind to it through adhesins and play a role in oral inflammation [14]. Yeasts in the gut originate from the oral cavity, and their levels in the gut are closely related to oral hygiene [14]. In the last decade, for the analysis of the gut microbiota, information about the dysbiosis of the intestinal flora in IBD patients was found and certain oral microorganisms in the gut microbiota of IBD patients were identified. Although these communities had different compositions, species richness levels were similar in the two environments [15-18]. Both oral and intestinal microbiota are influenced by feeding practices and medications. The development of the gut microbiota, on the other hand, is heavily influenced by diet. Sugar intake has an even greater impact on the oral microbiota. It has been shown that Veillonella and Malassezia can cause oral lesions in IBD patients via the oral-intestinal axis. This phenotype may make the oral cavity an evaluative indicator for diagnosing and monitoring the outcome of patients with IBD [19].

2.2. Immune System

Studies have shown that RAU patients have imbalanced subsets and functional defects of immunocompetent cells. Specific antigens, non-specific wounds, food and other stimuli can trigger the imbalance of lymphocyte subsets, leading to the disorder of immune regulation and the uncontrolled regulation between immunocompetent cells. This immune dysregulation eventually leads to local necrosis of the oral epithelium and the formation of oral ulcers [20, 21]. Bacterial components induce inflammation by stimulating inflammatory cells and pattern recognition receptors that reside on them, such as lipopolysaccharides, peptidoglycans, and proteases. For example, after the occurrence of RAU in oral infection with Helicobacter pylori (HP), the cells in the oral cavity of the patient are mutated, which can change the antigenicity of the cells in the lesion, and then cause autoimmune reaction [8]. According to the relevant experiments, the morphology and pathogenic principle of HP cultured in saliva and plaque of human mouth are very similar to that of HP bred in gastrointestinal tract. After oral infection

with HP, HP settles into the gastrointestinal mucosa at an appropriate time. And the metabolites and enzymes produced by HP can aggravate the local inflammation of patients and cause damage to the gastrointestinal mucosa. thus triggering the production of antibodies against gastric parietal cells. This antibody will have a certain effect with the anti-RAU antibodies that induce oral mucosal lesions, resulting in cross-immunity [22]. It has been hypothesized that genetically susceptible individuals can undergo immune-mediated oral mucosal damage in response to susceptible environmental factors. The oral mucosa is involved in immune tolerance to oral antigens. RAU can present as both primary and secondary disease, the latter of which may be associated with systemic disease. RAU has been reported to represent an increased risk of underlying gastrointestinal immune inflammatory diseases, such as IBD [5]. In addition, local pro-inflammatory factors including TNFαand IL6 cause low-grade systemic inflammation in RAU by entering the systemic circulation [23]. The destruction of intestinal epithelial barrier caused by immune dysregulation leads to the increase of intestinal epithelial permeability, which further induces systemic inflammation and immune dysregulation.

3. Intestinal-Oral Axis

The intestinal microenvironment may influence oral conditions. Patients with IBD are often accompanied by oral diseases. Clinical statistics show that IBD patients are more likely to be associated with RAU. It is a widely accepted hypothesis that the intestinal microenvironment affects the oral microenvironment due to the dysregulation of gut microbiota and immune disorders. In addition, malnutrition secondary to IBD may affect oral health and induce RAU. Therapeutic drugs may also indirectly affect oral microenvironment homeostasis and promote the occurrence and development of RAU.

3.1. Dysbiosis of the Flora

The oral microbiota is thought to be an important factor contributing to altered susceptibility to RAU in IBD patients. The intestinal mucosal epithelium is the second largest physical barrier in the body, after the skin [24]. The intestinal mucosal epithelial barrier selectively absorbs nutrients, prevent pathogen invasion as well as the loss of water and electrolytes, and expel metabolites [25]. The dysregulated immune response of gut microbiota is one of the accepted hypotheses for the pathogenesis of IBD. A related study found that patients with IBD showed dysbiosis of the intestinal flora compared to the normal group. Increased mucosal bacterial load was observed in patients with IBD. the inflammatory state of IBD may make the gut more tolerant to air-tolerant oral bacteria than the steady-state gut. In saliva microbiome testing experiments in IBD patients，Said [26] et al. found significant changes in oral microbiome composition in both CD and UC patients, with higher levels of prevotella and veillonella, as well as decreased levels of streptococcus and haemophilus. In addition, Xun et al. [27] also examined the variant microbiome of IBD patients and found significant changes in oral microbiome components as well. These studies point to the fact that patients with IBD also have dysbiosis of the oral flora. Most studies agree that prevotella, haemophilus, and veillonella are affected in the oral cavity of IBD patients and that these gut microbes are enriched in CD patients. At the same time, the transport of these bacteria can trigger a pathobiology-specific systemic response to induce oral inflammatory response, leading to the oral manifestations of RAU in IBD. These systemic responses may also explain the altered microbiome composition in the oral cavity of IBD patients [20]. When pathogen interactions are out of balance, sustained host inflammation can lead to the destruction of oral mucosal tissue.

3.2. Immune System

According to statistics, the intestine contains a high population of lymphocytes, accounting for 70% of the whole body. Intestinal mucosal epithelial cells are also considered to be a central axis in the regulation of mucosal immunity. In terms of immune mechanisms, the pathogenesis of RAU is similar to that of IBD, covering mainly the association between oral or intestinal pathogens and the host immune and inflammatory response. Long-term pathogen imbalance and persistent host inflammatory response lead to the destruction of oral mucosal integrity. The production of RAU has a certain correlation with the immune status of patients. Many digestive system diseases in the human body are caused by the abnormal immune status of relevant parts, such as IBD. One of the parenteral expressions of these diseases is the production of RAU. Patients with IBD and other parenteral manifestations may be more susceptible to RAU than other patients [28-29]. RAU is not a true autoimmune disease, but a dysregulated local immune response to various irritants [30]. It is the manifestation of multiple interrelated networks that contribute to ulceration independently or together. When a system in the network is significantly damaged, it may manifest as a unique disease and oral ulcer [31]. It was found that the absence of peripheral immune tolerance and the Th1 or Th2 polarization of the immune response are the main features of chronic inflammatory diseases [32]. Increased Th1-type immune responses favoring RAU occurrence, while increased Th2 responses reducing RAU occurrence [33]. CD is associated with an increase in TH1-type cytokines and manifests as an aphthous lesion. UC is associated with Th2 cytokines [34]. Mechanistically, we know very little about the immunological basis of oral CD, but it appears to be a further manifestation of the whole gastrointestinal pathological process. This may be caused by impairment of the innate immune system in CD patients as well as other factors that promote oral inflammation. Several types of antibodies have been found in the sera of RAU patients, indicating the immune-mediated nature of RAU. When the oral mucosal barrier is defective in tight junctions, the levels of antibodies against gliadin, TG and yeast are also elevated in RAU patients, a manifestation similar to that of inflammatory bowel disease [35].

The results of relevant studies showed that Th1 immune response participated in the immunopathology of RAU. And CD4+T cells were present in all RAU patients [36]. In contrast to UC patients, high levels of TNF-α and IL-6, as well as high IL-6/TGF-β and IL-17/TGF-β ratios were found in the serum of CD patients, suggesting that CD patients have significant pro-inflammatory effects and Th-1 and Th-17 immune responses [37]. The antioxidant capacity of patients' saliva is reduced in the active phase of CD patients [38]. In patients with IBD, the inflammatory response is not limited to the intestinal tract, but also involves extraintestinal sites, such as: the oral cavity. Therefore, some changes in saliva may reflect not only oral conditions but also the severity of IBD [39]. Salivary levels of IL-1β and TNF-a were significantly higher in patients with active CD compared to the healthy group and patients with inactive CD. It has been noted that elevated expression of TNF-a in saliva is closely associated with certain specific oral lesions [40]. Therefore, when there are alterations in the expression of cytokines throughout the GIT in patients with active IBD, it is likely that patients will also have concomitant oral lesions. Thus, salivary proinflammatory cytokine levels and oxidative stress parameters may be useful biomarkers of IBD.

3.3. Malnutrition

Malnutrition is considered to be an important risk factor for IBD, and children are particularly affected. According to existing studies and literature, another major cause of RAU is the lack of various trace elements in the body of patients, especially the lack of vitamin B12. IBD patients with long-term parenteral nutrition may suffer from digestive diseases resulting in micronutrient deficiency and malnutrition. Chronic nutritional deficiencies can lead to cellular immune changes, increase the chance of infection, prevent the renewal of inflammatory tissue cells and prolong wound healing time, etc. [41]. There are many malnutrition factors associated with IBD, including those that affect the intake, digestion, absorption and metabolism of nutrients required [42]. Dysphagia is the most common symptom reported in IBD, which is more common in the active stage of the disease [6]. Especially when CD has a tendency to involve the small intestine, it can cause serious nutritional problems. Inflammation, surgical resection, fistulas, or dysbiosis can reduce the area of intestinal absorption in IBD patients, resulting in damage or malabsorption.

The anabolic activity of oral epithelium is very active, significantly higher than that of most tissue cells in the body. This high rate of cell regeneration requires continuous replenishment of raw materials needed for protein synthesis to satisfy cell growth, reproduction and metabolism. Once there is a lack of nutrients, the growth, reproduction and metabolism of its cells will be affected. Oral tissue is one of the most sensitive parts to malnutrition, and the symptom of malnutrition is first manifested in oral tissue. Malnutrition due to IBD is significantly associated with the progression of oral disease. It can alter tissue homeostasis and reduce resistance to microbial biofilms and tissue repair thereby affecting oral health [43]. Numerous micronutrient deficiencies often occur in IBD. Vitamin absorption may be affected by enteritis [44]. Nonspecific oral lesions may be the result of malnutrition and malabsorption syndromes, including glossitis, ulceration of the mouth, and cheilitis. RAU may be caused by nutritional deficiencies such as vitamin B and iron deficiency [5]. Vitamin B deficiency results in a burning sensation in the mouth, which is especially noticeable on the tongue. Other oral manifestations are cracked and red lips, mouth ulcers, broken corners of the mouth, and sore throat. The manifestations of iron deficiency have some similarities to vitamin B deficiency.

3.4. Drug Therapy

Treatment for IBD includes corticosteroids, immunomodulators, non-steroidal anti-inflammatory drugs, biologics, and antibiotics, all of which have been associated with RAU-like lesions [45]. Non-specific oral lesions may also be the result of medical treatment. RAU symptoms are more extensive and persistent in IBD patients, and IBD and its treatment are believed to exacerbate these ulcers [43]. If RAU develops after adolescence and IBD after adulthood, it is highly likely that the presence of RAU is an accompanying mucosal lesion. Treatment for IBD includes anti-inflammatory medications, hormonal drugs. For topical steroid therapy, oral inflammatory and granulomatous lesions associated with IBD may be associated with certain adverse effects such as mucosal atrophy and risk of systemic resorption and should not be used indefinitely [4].

4. Conclusion

For the direction of the oral-intestinal axis, the dysbiosis of oral flora and the abnormal immune system in RAU patients will further induce IBD. In the direction of the intestinal-oral axis, the occurrence and aggravation of RAU in IBD patients will be indirectly caused by the dysregulation of intestinal mucosal flora and immune abnormalities. In conclusion, this paper explores the interaction between oral and intestinal lesions, and suggests that stomatologists and gastroenterologists should pay attention to the bidirectional association between the two diseases, and conduct multidisciplinary medical management.

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