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Phosphatidylcholine for the treatment of Ulcerative Colitis

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Ulcerative colitis is a chronic inflammatory disease affecting the colon, that causes diarrhea, bleeding and cramping pain. Although the exact cause of the disease is not known, a deficiency of the phospholipid phosphatidylcholine can be detected in the intestinal mucus of those affected. Phosphatidylcholine occurs naturally in the mucus layer and accumulates on its surface. The phospholipid forms a hydrophobic fatty film that represents an essential factor for the integrity of the barrier function of the mucus layer. Supplemental phosphatidylcholine with delayed release showed promising results in clinical trials for the treatment of ulcerative colitis. Phosphatidylcholine stands out by the fact that side effects are not to be expected.

Colitis ulcerosa is a chronic inflammatory disease affecting the bowel, that typically begins in the rectum and spreads continuously from there into the colon. In contrast to Crohn's disease, only the large intestine is usually affected by the inflammation, that is limited to the upper wall layers (mucosa and submucosa). Depending on the pattern of attack, proctosigmoiditis (inflammation of the rectum and sigmoid colon) is distinguished from left-sided colitis (inflammation of the left flexure). Infection of the entire colon, on the other hand, is referred to as pancolitis (Fig. 1). In Germany, 412 out of

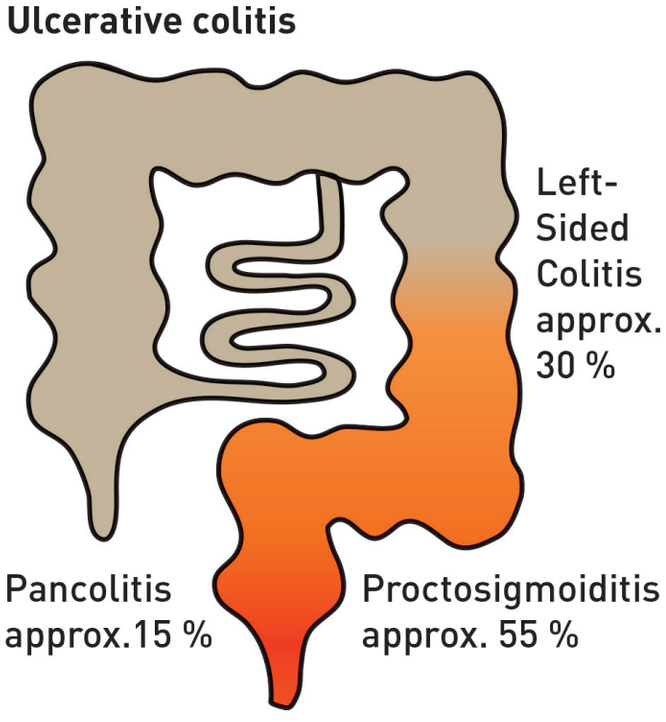

Fig. 1: Ulcerative colitis begins in the rectum and spreads from there into the colon. In about 55 % of patients, the disease is restricted to the proctosigmoid, 30 % have left-sided colitis and 15 % have pancolitis [2].

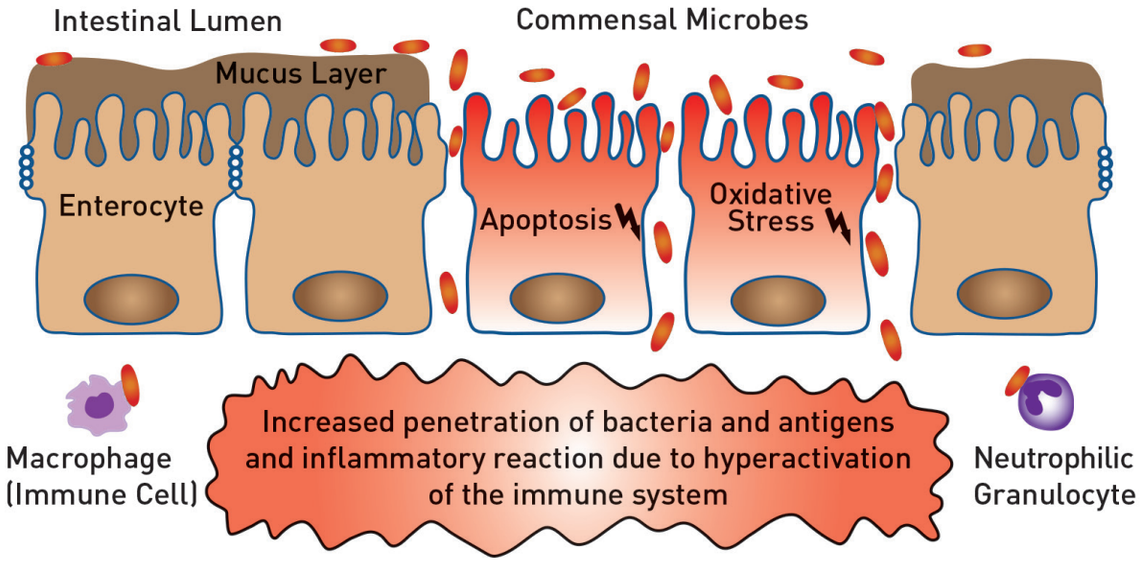

Fig. 2: The intestinal epithelium is overlaid with a mucus layer, which prevents the invasion of bacteria and antigens. In ulcerative colitis, changes in the mucus layer lead to increased permeability and increased uptake of antigens. The activation of the immune system leads to an inflammatory process with increased oxidative stress and damage to the intestinal mucosa. [3]

every 100,000 inhabitants are affected by ulcerative colitis, which represents the most common chronic inflammatory bowel disease before Crohn's disease (322 out of 100,000) [1].

Pathogenesis of ulcerative colitis

The intestinal mucosa with its large surface of about 300 m^2 ensures that nutrients and water from the intestinal lumen can be sufficiently absorbed. To protect against inflammation caused by commensal microbes, a tight-fitting mucus layer adheres to the large intestine, that effectively prevents the direct contact of bacteria, bacterial toxins and digestive enzymes to the intestinal epithelial cells. In ulcerative colitis, there are changes in the mucus layer that lead to a loss of barrier function. Due to the defective barrier, bacteria and antigens from the intestinal lumen increasingly enter the intestinal mucosa. This leads to activation of immune cells, to an increased release of pro-inflammatory cytokines, to a chronic inflammatory process and ultimately to damage affecting the intestinal epithelium (Fig. 2). [3]

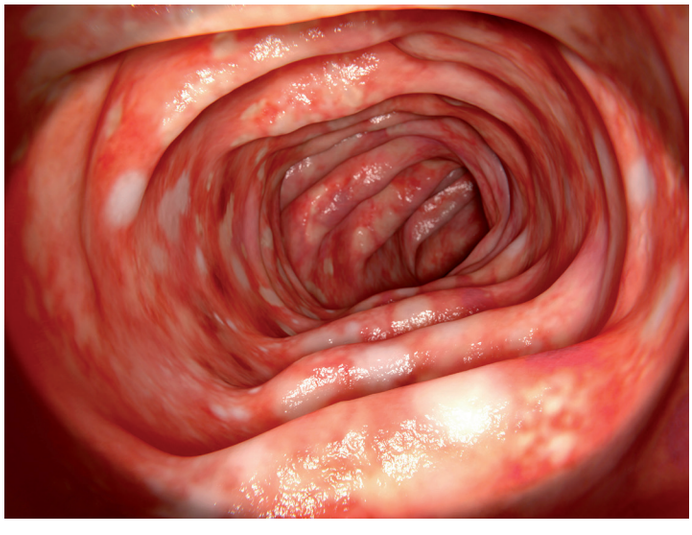

Fig. 3: Endoscopic image of a section of the colon affected by ulcerative colitis. The inner surface is characterized by confluent mucosal damage. (Photo®: Juan Gaertner, shutterstock.com)

As a result of the inflammatory reaction, erosions and ulcers develop in the course of the disease, which then confluence in the area of mucosal damage (Fig. 3). Ulcerative colitis usually occurs intermittently with periods of no symptoms between flares. The main symptoms are bloody diarrhea, imperative urgency and colic, the severity of which often correlates with the severity of the endoscopic pattern of infestation. [4] The course of the disease is unpredictable. It can lead to severe acute symptoms and to serious complications such as the so-called toxic mega colon or a perforation of the intestinal wall, which require intensive care treatment as an emergency situation. According to current guidelines, glucocorticoids and immunosuppressants are recommended for the treatment of ulcerative colitis in addition to anti-inflammatory drugs (so-called aminosalicylates).[5] A promising therapeutic option is also the phospholipid phosphatidylcholine, which forms a natural component of the intact mucus layer of the intestine.

Phosphatidylcholine for the treatment of ulcerative colitis

Although the etiology of ulcerative colitis is not fully understood, a deficiency of the phospholipid phosphatidylcholine in the mucus layer is discussed as the causative factor of the disease. Phosphatidylcholine, the quantitatively most prominent phospholipid in leci-

thins, has amphiphilic ("both loving") properties, with a polar headgroup (phosphocholine) and a non-polar hydrocarbon tail (fatty acids). In an aqueous environment, the non-polar, lipophilic ("fat-loving") tail groups orient themselves to each other, while the polar, hydrophilic ("water-loving") head groups align themselves towards the water. The resulting bilayers form the backbone of the cellular membranes of plant and animal cells, in which phosphatidylcholine is an important structure-forming component.

Phosphatidylcholine is also an essential component of the intestinal mucus, which forms a protective, hydrophobic barrier on the surface of the mucus layer (Fig. 4) [6]. In the case of patients with ulcerative colitis, approximately 70 % lower phosphatidylcholine contents were detected in the mucus compared to healthy individuals, irrespective of whether the mucus membrane was inflamed or not. It is therefore believed that deficiency of phosphatidylcholine leads to softening and loss of mucus layer barrier function. The penetration of bacteria then leads to an activation of the reactive immune system with an inflammatory response and apoptotic reactions (collateral damage).

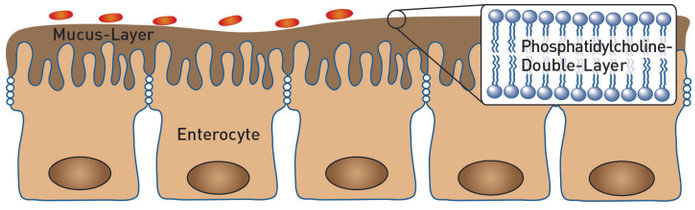

Fig. 4: The phospholipid phosphatidylcholine is secreted from the intestinal mucosa into the mucus layer. Phosphatidylcholine accumulates on the surface of the mucus layer and forms a protective bilayer that binds the mucus to the mucosa and maintains its integrity. [6]

Phosphatidylcholine is secreted by the ileal mucosa, the mucosa of the small intestine, and migrates to the surface of the mucus through the colon. It is assumed that the concentration of the phospholipid decreases continuously and the lowest levels are found in the mucus layer of the rectum. This would explain the onset of the disease in the rectum and the continuous spread proximally, according to the degree of reduction in phosphatidylcholine content in the mucus. Therefore, a recent treatment approach for ulcerative colitis is to compensate for the lack of phosphatidylcholine in the mucosa by substitution therapy. However, in order to prevent the phospholipid from being enzymatically hydrolyzed and absorbed already in the upper digestive tract after oral intake, it must be "packaged" in such a way that it is released only in a retarded manner in the lower intestinal sections and is available there. [7]

The positive effect of delayed release phosphatidylcholine supplementation has been confirmed in clinical trials. In one study, 60 patients with chronic active ulcerative colitis received either 1.5 g of a corresponding formulation or placebo four times daily over a period of three months. As the primary endpoint of the study, a remission of the disease, ie the temporary or permanent easing of the disease symptoms was determined. While only three participants from the placebo group (10 %) achieved a clinical response during the treatment period, 16 participants from the phosphatidylcholine group (53 %) responded. Only in this group could a significant improvement of the disease activity be detected endoscopically. In phosphatidylcholine therapy, 19 out of 30 patients showed a significant shortening of the bowel area affected. No significant side effects were reported during treatment. [8]

In another investigation, 60 participants with steroid refractory ulcerative colitis were recruited and treated with phosphatidylcholine or placebo for 12 weeks. Regarding these patients, the symptoms of the disease can no longer be controlled despite glucocorticoid treatment. During the study period, only three (10 %) of the participants in the placebo group experienced a significant improvement in disease activity, enabling them to discontinue steroid therapy. In contrast, the symptoms in 24 participants (80 %) of the phosphatidylcholine group improved so much that they were able to stop glucocorticoid therapy. [9]

In a dose-finding study, 40 patients with chronic active ulcerative colitis were divided into four groups. Subjects were treated over 12 weeks with either 0.5 g, 1 g, 3 g, or 4 g of sustained-release phosphatidylcholine per day. During the study period, no patient from the 0.5 g group achieved clinical remission, compared with three patients (30 %) from the 1 g group, five patients (50 %) from the 3 g group and six patients (60 %) from the 4 g group. There was a marked improvement in disease activity in all groups with a response to treatment after an average of five weeks. No serious side effects were reported. [10]

Lecithin-Type	Content of Phosphatidylcholine, PC [g / 100 g]
Liquid Lecithin	12
Deoiled Lecithin	20
Purified Lecithin	50
Purified Phosphatidylcholine	90

Table 1: Content of phosphatidylcholine of different lecithins with raising degree of purification.

Conclusion

Ulcerative colitis is characterized by an inflammation of the colon, that leads to recurrent diarrhea, intestinal bleeding and colic. The cause of the disease is attributed to changes in the mucus layer that rests on the intestinal mucosa. It is believed that a deficiency of the phospholipid phosphatidylcholine leads to a softening of the mucus layer, which subsequently loses its barrier function. The penetration of bacteria and antigens leads to an immune reaction that damages the epithelial cells and causes the corresponding symptoms. The supplementation with delayed-release phosphatidylcholine is being investigated in clinical trials for the treatment of the disease. This new treatment approach is characterized by a favorable side effect profile and shows promising results in the investigations. However, the course of the disease is unpredictable. It can lead to serious complications requiring immediate intensive care treatment. Regarding patients with ulcerative colitis, the risk of colorectal cancer is increased. Regular surveillance colonoscopy is recommended. [5]

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