1. As suggested by the reviewer some details regarding to CD40/CD40L pathway have been provided.

   "The CD40-CD40L pathway has a dual role, directly stimulating mucosal angiogenesis and activating CD40L-expressing T cells, which in turn stimulates intestinal fibroblasts to release angiogenic cytokines[31]. CD40 is upregulated by several cell types in patients with IBD, including antigen-presenting cells, monocytes, and endothelial cells. CD40L is overexpressed by T cells and platelets, and plasma CD40L levels are particularly high in patients with active IBD[31,32]. The CD40-CD40L pathway promotes mucosal inflammation and triggers increased production of various cytokines and cell adhesion molecules[31]. CD40 binding stimulates the production of TNF-α, and TNF-α increases CD40 expression[32]".

2. The part regarding to the CV risk in IBD has been downgraded in the paper, abstract and cor tip.

   Abstract:

   Endothelial dysfunction is considered one of the etiological factors of inflammatory bowel disease (IBD). An inflammatory process leads to functional and structural changes in the vascular endothelium. An increase of leukocyte adhesiveness and leukocyte diapedesis, as well as an increased vascular smooth muscle tone and procoagulant activity is observed. Structural changes of the vascular endothelium comprise as well capillary and venule remodeling and proliferation of endothelial cells. Hypoxia in the inflammatory area stimulates angiogenesis by up-regulation of vascular endothelial growth factor, fibroblast growth factor and TNFα. Inflammatory mediators also alter the lymphatic vessel function and impair lymph flow, exacerbating tissue edema and accumulation of dead cells and bacteria. The endothelial dysfunction might be diagnosed by the use of two main methods: physical and biochemical. Physical methods are based on the assessment of large arteries vasodilatation in response to an increased flow and receptors stimulation. Flow-mediated vasodilatation (FMD) is the method that is the most widely used; however, it is less sensitive in detecting early changes of the endothelium function. Most of the studies demonstrated a decrease of FMD in IBD patients but no changes in the carotic intima-media thickness. Biochemical methods of detecting the endothelial dysfunction are based on the assessment of the synthesis of compounds produced both by the normal and damaged endothelium. The endothelial dysfunction is considered an initial step in the pathogenesis of atherosclerosis in the general population. In IBD patients, the risk of cardiovascular diseases is controversial. Large, prospective studies are needed to establish the role of particular medications or dietary elements in the endothelial dysfunction as well to determine the real risk of cardiovascular diseases.

Cor tip:

Endothelial dysfunction seems to play an important role in the pathogenesis of IBD. Inflammatory process leads to functional and structural changes in the vascular endothelium and in consequence its activation. It may contribute to cardiovascular complications, however, in IBD patients, the risk of cardiovascular disease is still controversial. Some of immunomodulatory medications used in IBD treatment may decrease the risk of endothelial dysfunction. In this review article, we present the role of the endothelium in the inflammatory process, diagnostic methods of its dysfunction and current knowledge of the cardiovascular disease risk in IBD.

3. Information about new possibilities of treatment in IBD has been provided.

"New therapeutic options for patients with IBD include anti-adhesion molecules, such as vedolizumab, etrolizumab, and PF-00547659[94]. Vedolizumab targets α4-β7 integrins and blocks interactions between α4-β7 integrins and MAdCAM-1. Etrolizumab targets the β7 subunit, and PF-00547659 is a monoclonal antibody against MAdCAM-1[94]. Anti-chemokine receptor CCR 9 interferes with the activation of inflammatory cells in the intestine. Other medications, such as laquinimod and tofacitinib, reduce the synthesis of pro-inflammatory cytokines[94]".

"Danese *et al*.[32] showed that anti-TNF-α downregulates the CD40/CD40L pathway".

"some evidence suggests that cyclosporine A inhibits angiogenesis targeting VEGF-A[85,92]"

4. The summary and take home message has been changed.

"In conclusion, endothelial dysfunction plays a pivotal role in the development of IBD. Some immunomodulatory medications used to treat IBD affect endothelial function; however, large studies on the interactions between the gut microvasculature, cytokines, chemokines, cell adhesion molecules, inflammatory growth factors, and platelets are needed to create new therapeutic strategies for patients with IBD"

The manuscript has been revised by two native speakers.