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Hemorrhoids: pathophysiology and risk factors

by V. Lohsiriwat, *Thailand*

Varut LOHSIRIWAT, MD, PhD
Associate Professor of Surgery
Division of Colorectal Surgery
Department of Surgery
Faculty of Medicine Siriraj Hospital
Mahidol University, Bangkok
THAILAND

Hemorrhoids are a very common anorectal condition defined as the symptomatic enlargement and distal displacement of the normal anal cushions. However, the exact pathophysiology of hemorrhoids remains unknown. The current theories surrounding hemorrhoid development involve mechanical injury to the anal mucosa, vascular abnormalities and the hypervascularization of anorectal region, rectal redundancy, tissue inflammation, and any combination thereof. The different pathophysiologies may result in different approaches to hemorrhoids. Nevertheless, an improvement in our understanding of the pathophysiology of hemorrhoids will prompt the development of better pharmacological and nonpharmacological approaches to hemorrhoids in the future. This article comprehensively reviews the current pathophysiology and risk factors of hemorrhoids.

Medicographia. 2019;41:52-55

Introduction

Some patients with hemorrhoids presented with anal bleeding without prolapsing symptoms, while others had severe prolapsed hemorrhoids without any bleeding or manifested with both prolapsing and bleeding symptoms. So what is the exact pathophysiology of hemorrhoids? Hemorrhoids are generally referred to as abnormally congested and/or descended anal cushions.[1] The anal cushions are a well-vascularized thickening of anal submucosal tissue that helps the anal sphincter complex maintain complete fecal continence at rest. During defecation, the contraction of the anal submucosal muscle flattens the cushions and holds them up against the internal anal sphincter.[2] Typically, there are three major anal cushions located in the right anterior, right posterior, and left lateral aspect of the anal canal, with a various number of minor cushions lying between them.[1] When these cushions have some pathologic changes, they can cause symptoms, such as bleeding and prolapsing.

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Pathophysiology of hemorrhoids

◆ *Mechanical injury to the anal cushions*

Today, the theory of mechanical injury to the anal cushions is widely accepted. It proposes that hemorrhoids develop when the supporting tissues of the anal cushions

Address for correspondence:
Varut Lohsiriwat, MD, PhD, Division of Colorectal Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand
(email: bolloon@hotmail.com)

www.medicographia.com

disintegrate or deteriorate. During defecation, the Valsalva effect, especially with excessive straining, leads to an engorgement of the anal cushions that could significantly protrude into the lumen of the anal canal. They are then subjected to the shearing effect of the passing stool.[2] Apart from excessive or prolonged straining, the engorgement of anal cushions may be caused by pregnancy and conditions related to increased intra-abdominal pressure, such as chronic cough and heavy lifting. Passing hard and lumpy stools without straining could cause the same injury to the anal cushions. The destructive changes in the supporting connective tissue of the anal cushions result in the downward displacement of anal cushions (known as sliding anal cushions), which subsequently interferes with the venous drainage of the hemorrhoidal plexus, leading to symptomatic hemorrhoids.

Destructive or degenerative changes in the elastin and collagen tissue of the anal cushions could also be a result of aging, a high level of supporting tissue degradation, or a decrease in dense and mature collagen fibers. An increased expression of matrix metalloproteinase, a proteinase capable of degrading extracellular matrix proteins, including elastin and collagen, was evident in hemorrhoidal tissue[3] and in the serum of patients with hemorrhoids,[4] especially in those with high-grade hemorrhoids. Several investigators reported that hemorrhoidal tissue contained fewer type I collagen fibers (mature and strong fibrils), but more type III collagen fibers (immature and thinner fibrils) than normal anal tissue,[5,6] suggesting that abnormalities in collagen composition may contribute to the development of hemorrhoids.

◆ *Vascular abnormalities*

Based on the study of anorectal manometry and ultrasonography in normal individuals and those with hemorrhoids, patients with hemorrhoids had a significantly higher resting anal pressure, but a comparable thickness of the anal sphincter. These results suggested that the high anal pressure in patients with hemorrhoids is of vascular origin.[7] A more recent study of the anorectal vascular plexus using transperineal color Doppler ultrasound with spectral wave analysis between healthy volunteers and patients with hemorrhoids found that the latter had significantly higher peak velocities and acceleration velocities of the afferent vessels.[8] The diameter and arterial blood flow of the terminal branches of the superior rectal artery markedly increased in subjects with hemorrhoids,[9] indicating that there is hyperperfusion of the anal canal in patients with hemorrhoids. Moreover, an intrinsic vascular sphincter mechanism involving coordinated filling and drainage of the hemorrhoidal venous plexus by sphincter-like constrictions of venous vessels was found to be destroyed or dysregulated in patients with hemorrhoids.[8]

The correlation between the development of hemorrhoids and its vascular abnormalities or the dysregulation of blood supply to, from, and within the anal cushions has been studied with great interest because the understanding of these pathological changes could lead to a novel pharmacological or surgical approach to treating hemorrhoids. An imbalance between vasoconstrictor and vasodilator substances, either by intrinsic or extrinsic factors, can cause abnormal vasodilatation and venodilatation of the hemorrhoid plexus.[1] An increase in potent vasodilatory substances, such as nitric oxide, was evident in hemorrhoids. Using immunohistochemistry and western blot analysis, hemorrhoidal tissue had significantly higher protein levels of nitric oxide synthase, an enzyme that catalyzes the production of nitric oxide from L-arginine, than normal anorectal tissue. The vascular endothelium of hemorrhoids was shown to have more positive immunoreactivity to nitric oxide synthase than normal anorectal tissue, suggesting that blood vessels in hemorrhoids could be exposed to higher nitric oxide concentrations than those in normal tissue.[10] This finding was confirmed by another immunochemical study in which the investigators found an overexpression of inflammatory-related nitric oxide synthase in hemorrhoidal tissue.[3]

Venous hypertension could be another etiology of hemorrhoid formation. Venous reflux and insufficient venous drainage by increased intra-abdominal pressure and pregnancy cause high outflow pressure in the hemorrhoidal venous plexus. Long-standing venous hypertension leads to some pathological changes in the vein, including microangiopathy, leukocyte adhesion to the endothelium, and perivascular tissue inflammation.[11] It was evident that, using transvaginal duplex ultrasonography, over one-third of female patients with leg or vulvar varicose veins had hemorrhoids via direct tributaries from the internal iliac veins. The prevalence of hemorrhoids increased with the number of internal iliac vein reflux or incompetence.[12] In addition to the high arterial blood flow and venous hypertension of the hemorrhoidal arteriovenous plexus, angiogenesis was seen in hemorrhoidal tissue and could be one of the important phenomenas of hemorrhoids. Compared with normal anorectal tissue, hemorrhoids had higher microvascular density, higher immunoactivity of markers for neovascularization or newly formed microvessels, and high expression of angiogenesis-related proteins, such as vascular endothelial growth factor.[3,13]

◆ *Tissue inflammation*

Although the main histologic findings of hemorrhoids are abnormal dilatation and distortion of the vascular channel and destructive changes in the supporting connective tissue within the anal cushion, an inflammatory reaction may be evident in hemorrhoids.[1] It was shown that there was a minimal inflammatory reaction in the hemorrhoids if the overlying mucosa was intact, but there were marked inflammatory changes if superficial ulceration was present. Notably, ulceration was commonly found in cases of prolapsed or thrombosed hemorrhoids.[14] Interestingly, hemorrhoids were reported to be a cause of high ^{18}F-fluorodeoxyglucose (FDG) uptake on position emission tomography (PET) scans in the rectum,[15] thus

indicating an existing inflammatory reaction in hemorrhoidal tissue. Another histological investigation demonstrated a severe inflammatory reaction in hemorrhoids, especially at the vascular wall and its surrounding tissue suggesting that tissue inflammation may play an important role in the pathogenesis of hemorrhoids or in the aggravation of acute symptoms of hemorrhoids.[16] However, it cannot be ruled out that inflammatory changes in hemorrhoids may be a result of inflammatory responses to thrombosis, prolapsed tissue, or mechanical injury to the anal cushions or venous stasis.

It was also suggested that venous stasis or the engorgement of the hemorrhoidal venous plexus led to an increase in carbon dioxide and a decrease in oxygen in the vascular channels to cause ischemic injury to the blood vessel wall. Should this condition continue, veins and venules within the hemorrhoidal plexus will be weakened, stretched, and tortuous.[17] If venous stasis persists, perivascular inflammation will be evident and further lead to swelling and congestion of the anal cushions. Since venopathy and perivascular tissue inflammation have been evident in hemorrhoids, they could be a target for pharmacological approaches to symptomatic hemorrhoids. In fact, micronized purified flavonoid fraction, an oral flavonoid-based venoactive drug, has been shown to improve the overall symptoms of acute hemorrhoidal attacks, such as bleeding and pain, which is due to its anti-inflammatory effects and venoprotective actions.[18]

◆ *Rectal redundancy*

Another theory of hemorrhoid development is rectal redundancy, suggesting that prolapsing hemorrhoids are a result of an internal rectal prolapse since the redundant and mobile distal rectal mucosa push the anal cushions through the anus, ie, rectal redundancy interferes with the proper fixation of the supporting tissue within the anal cushions to the rectal wall.[1] However, there is still some controversy surrounding this theory because not all hemorrhoids prolapse circumferentially in daily practice.

Risk factors for hemorrhoids

Since the development of hemorrhoids is multifactorial, several risk factors have been reported to be associated with hemorrhoids. Constipation was identified to be one of the most important risk factors for hemorrhoids.[19-21] Individuals experiencing constipation are more likely to have prolonged and excessive straining together with passing hard and lumpy stool, which causes structural damage to the anal cushions. Using a multicenter database of screening colonoscopy in the US, constipation and low fiber intake increased the prevalence of hemorrhoids.[19] Meanwhile, a population-based study of 8.8 million Medicare patients in the US found strong associations between hemorrhoids and diarrheal disorders.[22] These findings highlight the correlation between the formation of hemorrhoids and excessive straining from defecation disorders – either constipation or diarrhea.

Strong risk factors (odds ratio >2)
Constipation
Diarrhea
Modest risk factors (odds ratio, 1.1-2.0)
A history of childbirth
Depression
Low fiber intake
Obesity
Nonsedentary behavior
Pregnancy

Table I. *Risk factors* for hemorrhoids.*

**Note: The designation of risk categories is arbitrary and regarded as semiquantitative.*

A more recent population-based study of Korean adults reported that obesity, self-reported or physician-diagnosed depression, and a history of pregnancy were risk factors for hemorrhoids.[23] However, there was no correlation between the presence of hemorrhoids and education level, alcohol consumption, diabetes mellitus, hypertension, fat intake, fiber intake, or physical activities. A link between the occurrence of hemorrhoids and obesity in the Asian population was supported by other studies in Western countries.[24,25] It was estimated that an increase of 1 in the body mass index would increase the risk of hemorrhoids by 3.5%.[25]

Pregnancy and a history of childbirth were constantly shown to be significant predictors of hemorrhoids.[21,23] However, the association between the presence of hemorrhoids and lifestyle factors is less clear because the studies on this matter are sparse and often have weak designs. Based on the available literature, it appeared that high fiber intake and sedentary behavior could reduce the risk of hemorrhoids.[19,20] Meanwhile, spicy diet, alcohol intake, and physical activities could trigger an acute hemorrhoid crisis in young individuals.[20] *Table I* summarizes factors associated with the development of hemorrhoids published in the literature.

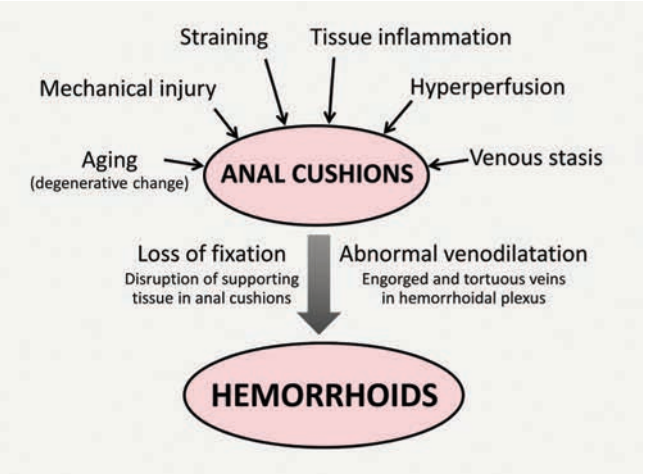

Figure 1. *Schematic diagram of hemorrhoid development.*

Conclusions

The exact pathophysiology of hemorrhoid development remains unknown, but it is most likely to be multifactorial *(Figure 1).* The different pathophysiologies may result in different approaches to treating hemorrhoids. Having a better understanding of the development of hemorrhoids could guide physicians and surgeons to treat hemorrhoidal diseases more precisely and to prevent the recurrence of hemorrhoidal symptoms more appropriately. ■

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Keywords: hemorrhoid disease; inflammation; pathophysiology; risk factors