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Hemorrhoids: Epidemiology, Clinical Evaluation, Management of Hemorrhoidal Disease

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Abstract: This review discusses the pathophysiology, epidemiology, risk factors, classification, clinical evaluation, and current non-operative and operative treatment of hemorrhoids. Hemorrhoids are defined as the symptomatic enlargement and distal displacement of the normal anal cushions. The most common symptom of hemorrhoids is rectal bleeding associated with bowel movement. The abnormal dilatation and distortion of the vascular channel, together with destructive changes in the supporting connective tissue within the anal cushion, is a paramount finding of hemorrhoids. It appears that the dysregulation of the vascular tone and vascular hyperplasia might play an important role in hemorrhoidal development, and could be a potential target for medical treatment. In most instances, hemorrhoids are treated conservatively, using many methods such as lifestyle modification, fiber supplement, suppositorydelivered anti-inflammatory drugs, and administration of venotonic drugs. Non-operative approaches include sclerotherapy and, preferably, rubber band ligation. An operation is indicated when non-operative approaches have failed or complications have occurred. Several surgical approaches for treating hemorrhoids have been introduced including hemorrhoidectomy and stapled hemorrhoidopexy, but postoperative pain is invariable. Some of the surgical treatments potentially cause appreciable morbidity such as anal stricture and incontinence. The applications and outcomes of each treatment are thoroughly discussed.

Keywords: Hemorrhoids; Pathophysiology; Treatment; Management; Outcome.

INTRODUCTION. Hemorrhoids are a very common anorectal condition defined as the symptomatic enlargement and distal displacement of the normal anal cushions. They affect millions of people around the world, and represent a major medical and socioeconomic problem. Multiple factors have been claimed to be the etiologies of hemorrhoidal development, including constipation and prolonged straining. The abnormal dilatation and distortion of the vascular channel, together with destructive changes in the supporting connective tissue within the anal cushion, is a paramount finding of hemorrhoidal disease[1]. An inflammatory reaction[2] and vascular hyperplasia[3,4] may be evident in hemorrhoids. This article firstly reviewed the pathophysiology and other clinical backgrounds of hemorrhoidal disease, followed by the current approaches to non-operative and operative management

PATHOPHYSIOLOGY OF HEMORRHOIDAL DISEASE. The exact pathophysiology of hemorrhoidal development is poorly understood. For years the theory of varicose veins, which postulated that hemorrhoids were caused by varicose veins in the anal canal, had been popular but now it is obsolete because hemorrhoids and anorectal varices are proven to be distinct entities. In fact, patients with portal hypertension and varices do not have an increased incidence of hemorrhoids[5]. Today, the theory of sliding anal canal lining is widely accepted[6]. This proposes that hemorrhoids develop when the supporting tissues of the anal cushions disintegrate or deteriorate. Hemorrhoids are therefore the pathological term to describe the abnormal downward displacement of the anal cushions causing venous dilatation. There are typically three major anal cushions, located in the right anterior, right posterior and left lateral aspect of the anal canal, and various numbers of minor cushions lying between them[7] (Figure 1). The anal cushions of patients with hemorrhoids show significant pathological changes. These changes include abnormal venous dilatation, vascular thrombosis, degenerative process in the collagen fibers and fibroelastic tissues, distortion and rupture of the anal subepithelial muscle (Figure 2). In addition to the above findings, a severe inflammatory reaction involving the vascular wall and surrounding connective tissue has been demonstrated in hemorrhoidal

specimens, with associated mucosal ulceration, ischemia and thrombosis[2]. Several enzymes or mediators involving the degradation of supporting tissues in the anal cushions have been studied. Among these, matrix metalloproteinase (MMP), a zinc-dependent proteinase, is one of the most potent enzymes, being capable of degrading extracellular proteins such as elastin, fibronectin, and collagen. MMP-9 was found to be over-expressed in hemorrhoids, in association with the breakdown of elastic fibers[8]. Activation of MMP-2 and MMP-9 by thrombin, plasmin or other proteinases resulted in the disruption of the capillary bed and promotion of angioproliferative activity of transforming growth factor β (TGF-β) [9]. Recently, increased microvascular density was found in hemorrhoidal tissue, suggesting that neovascularization might be another important phenomenon of hemorrhoidal disease. In 2004, Chung et al[4] reported that endoglin (CD105), which is one of the binding sites of TGF-β and is a proliferative marker for neovascularization, was expressed in more than half of hemorrhoidal tissue specimens compared to none taken from the normal anorectal mucosa. This marker was prominently found in venules larger than 100 μm. Moreover, these workers found that microvascular density increased in hemorrhoidal tissue especially when thrombosis and stromal vascular endothelial growth factors (VEGF)

were present. Han et al[8] also demonstrated that there was a higher expression of angiogenesis-related protein such as VEGF in hemorrhoids. Regarding the study of morphology and hemodynamics of the anal cushions and hemorrhoids, Aigner et al[3,10] found that the terminal branches of the superior rectal artery supplying the anal cushion in patients with hemorrhoids had a significantly larger diameter, greater blood flow, higher peak velocity and acceleration velocity, compared to those of healthy volunteers. Moreover, an increase in arterial caliber and flow was well correlated with the grades of hemorrhoids. These abnormal findings still remained after surgical removal of the hemorrhoids, confirming the association between hypervascularization and the development of hemorrhoids. Using an immunohistochemical approach, Aigner et al[3] also identified a sphincter-like structure, formed by a thickened tunica media containing 5-15 layers of smooth muscle cells, between the vascular plexus within the subepithelial space of the anal transitional zone in normal anorectal specimens Unlike the normal specimens, hemorrhoids contained remarkably dilated, thin-walled vessels within the submucosal arteriovenous plexus, with absent or nearly-flat sphincter-like constriction on the vessels. These investigators concluded that a smooth muscle sphincter in the arteriovenous plexus helps in reducing the arterial inflow, thus facilitating an effective venous drainage. Aigner et al[3] then proposed that, if this mechanism is impaired, hyperperfusion of the arteriovenous plexus will lead to the formation of hemorrhoids. Based on the histological findings of abnormal venous dilatation and distortion in hemorrhoids, dysregulation of the vascular tone might play a role in hemorrhoidal development. Basically, vascular smooth muscle is regulated by the autonomic nervous system, hormones, cytokines and overlying endothelium. Imbalance between endothelium-derived relaxing factors (such as nitric oxide, prostacyclin, and endotheliumderived hyperpolarizing factor) and endothelium-derived vasoconstricting factors (such as reactive oxygen radicals and endothelin) causes several vascular disorders[11]. In hemorrhoids, nitric oxide synthase, an enzyme which synthesizes nitric oxide from L-arginine, was reported to increase significantly[8]. Several physiological changes in the anal canal of patients with hemorrhoids have been observed. Sun et al[12] revealed that resting anal pressure in patients with nonprolapsing or prolapsing hemorrhoids was much higher than in normal subjects, whereas there was no significant change in the internal sphincter thickness. Ho et al[13] performed anorectal physiological studies in 24 patients with prolapsed hemorrhoids and compared with results in 13 sex- and age-matched normal subjects. Before operation, those with hemorrhoids had significantly higher resting anal pressures, lower rectal compliance, and more perineal descent. The abnormalities found reverted to the normal range within 3 mo after hemorrhoidectomy, suggesting that these physiological changes are more likely to be an effect, rather than the cause, of hemorrhoidal disease.

EPIDEMIOLOGY AND RISK FACTORS OF HEMORRHOIDS. Although hemorrhoids are recognized as a very common cause of rectal bleeding and anal discomfort, the true epidemiology of this disease is unknown because patients have a tendency to use self-medication rather than to seek

proper medical attention. An epidemiologic study by Johanson et al[14] in 1990 showed that 10 million people in the United States complained of hemorrhoids, corresponding to a prevalence rate of 4.4%. In both sexes, peak prevalence occurred between age 45-65 years and the development of hemorrhoids before the age of 20 years was unusual. Whites and higher socioeconomic status individuals were affected more frequently than blacks and those of lower socioeconomic status. However, this association may reflect differences in healthseeking behavior rather than true prevalence. In the United Kingdom, hemorrhoids were reported to affect 13%-36% of the general population[1,15]. However, this estimation may be higher than actual prevalence because the community-based studies mainly relied on selfreporting and patients may attribute any anorectal symptoms to hemorrhoids. Constipation and prolonged straining are widely believed to cause hemorrhoids because hard stool and increased intraabdominal pressure could cause obstruction of venous return, resulting in engorgement of the hemorrhoidal plexus[1]. Defecation of hard fecal material increases shearing force on the anal cushions. However, recent evidence questions the importance of constipation in the development of this common disorder[14,16,17]. Many investigators have failed to demonstrate any significant association between hemorrhoids and constipation, whereas some reports suggested that diarrhea is a risk factor for the development of hemorrhoids[16]. Increase in straining for defecation may precipitate the development of symptoms such as bleeding and prolapse in patients with a history of hemorrhoidal disease. Pregnancy can predispose to congestion of the anal cushion and symptomatic hemorrhoids, which will resolve spontaneously soon after birth. Many dietary factors including low fiber diet, spicy foods and alcohol intake have been implicated, but reported data are inconsistent[1].

CLASSIFICATION AND GRADING OF HEMORRHOIDS. A hemorrhoid classification system is useful not only to help in choosing between treatments, but also to allow the comparison of therapeutic outcomes among them. Hemorrhoids are generally classified on the basis of their location and degree of prolapse. Internal hemorrhoids originate from the inferior hemorrhoidal venous plexus above the dentate line and are covered by mucosa, while external hemorrhoids are dilated venules of this plexus located below the dentate line and are covered with squamous epithelium. Mixed (interno-external) hemorrhoids arise both above and below the dentate line. For practical purposes, internal hemorrhoids are further graded based on their appearance and degree of prolapse, known as Goligher's classification: (1) Firstdegree hemorrhoids (gradeI): The anal cushions bleed but do not prolapse; (2) Second-degree hemorrhoids (grade II): The anal cushions prolapse through the anus on straining but reduce spontaneously; (3) Third-degree hemorrhoids (grade III): The anal cushions prolapse through the anus on straining or exertion and require manual replacement into the anal canal; and (4) Fourthdegree hemorrhoids (grade IV): The prolapse stays out at all times and is irreducible. Acutely thrombosed, incarcerated internal hemorrhoids and incarcerated, thrombosed hemorrhoids involving circumferential rectal mucosal prolapse are also fourth-degree hemorrhoids[18]. Some authors proposed classifications based on anatomical findings of hemorrhoidal position, described as primary (at the typical three sites of the anal cushions), secondary (between the anal cushions), or circumferential, and based on symptoms described as prolapsing and non-prolapsing[19]. However, these classifications are in less widespread use.

CLINICAL EVALUATION OF HEMORRHOIDS. The most common manifestation of hemorrhoids is painless rectal bleeding associated with bowel move ment, described by patients as blood drips into toilet bowl. The blood is typically bright red as hemorrhoidal tissue has direct arteriovenous communication[3]. Positive fecal occult blood or anemia should not be attributed to hemorrhoids until the colon is adequately evaluated especially when the bleeding is atypical for hemorrhoids, when no source of bleeding is evident on anorectal examination, or when the patient has significant risk factors for colorectal neoplasia[18]. Prolapsing hemorrhoids may cause perineal irritation or anal itching due to mucous secretion or fecal soiling. A feeling of incomplete evacuation or rectal fullness is also reported in patients with large hemorrhoids. Pain is not usually caused by the hemorrhoids themselves unless thrombosis has occurred, particularly in an external hemorrhoid or if a fourth-degree internal hemorrhoid becomes strangulated. Anal fissure and perianal abscess are more

common causes of anal pain in hemorrhoidal patients. The definite diagnosis of hemorrhoidal disease is based on a precise patient history and careful clinical examination. Assessment should include a digital examination and anoscopy in the left lateral position. The perianal area should be inspected for anal skin tags, external hemorrhoid, perianal dermatitis from anal discharge or fecal soiling, fistula-in-ano and anal fissure. Some physicians prefer patients sitting and straining in the squatting position to watch for the prolapse. Although internal hemorrhoids cannot be palpated, digital examination will detect abnormal anorectal mass, anal stenosis and scar, evaluate anal sphincter tone, and determine the status of prostatic hypertrophy which may be the reason for straining as this aggravates descent of the anal cushions during micturition. Hemorrhoidal size, location, severity of inflammation and bleeding should be noted during anoscopy. Intrarectal retroflexion of the colonoscope or transparent anoscope with flexible endoscope also allow excellent visualization of the anal canal and hemorrhoid, and permit recording pictures[20].

MANAGEMENT OF HEMORRHOIDAL DISEASE. Therapeutic treatment of hemorrhoids ranges from die tary and lifestyle modification to radical surgery, depending on degree and severity of symptoms[21,22]. The current management of internal hemorrhoids is illustrated in Table 1. In addition, selected meta-analyses showing various treatment options of hemorrhoidal disease are shown in Table 2[23-32].

Dietary and lifestyle modification. Since shearing action of passing hard stool on the anal mucosa may cause damage to the anal cushions and lead to symptomatic hemorrhoids, increasing intake of fiber or providing added bulk in the diet might help eliminate straining during defecation. In clinical studies of hemorrhoids, fiber supplement reduced the risk of persisting symptoms and bleeding by approximately 50%, but did not improve the symptoms of prolapse, pain, and itching[26]. Fiber supplement is therefore regarded as an effective treatment in non-prolapsing hemorrhoids; however, it could take up to 6 wk for a significant improvement to be manifest[13]. As fiber supplements are safe and cheap, they remain an integral part of both initial treatment and of a regimen following other therapeutic modalities of hemorrhoids. Lifestyle modification should also be advised to any patients with any degree of hemorrhoids as a part of treatment and as a preventive measure. These changes include increasing the intake of dietary fiber and oral fluids, reducing consumption of fat, having regular exercise, improving anal hygiene, abstaining from both straining and reading on the toilet, and avoiding medication that causes constipation or diarrhea. Medical treatment Oral flavonoids: These venotonic agents were first described in the treatment of chronic venous insufficiency and edema. They appeared to be capable of increasing vascular tone, reducing venous capacity, decreasing capillary permeability[24], and facilitating lymphatic drainage[25] as well as having anti-inflammatory effects[26]. Although their precise mechanism of action remains unclear, they are used as an oral medication for hemorrhoidal treatment, particularly in Europe and Asia. Micronized purified flavonoid fraction (MPFF), consisting of 90% diosmin and 10% hesperidin, is the most common flavonoid used in clinical treatment[27]. The micronization of the drug to particles of less than 2 μm not only improved its solubility and absorption, but also shortened the onset of action. A recent meta-analysis of flavonoids for hemorrhoidal treatment, including 14 randomized trials and 1514 patients, suggested that flavonoids decreased risk of bleeding by 67%, persistent pain by 65% and itching by 35%, and also reduced the recurrence rate by 47%[27]. Some investigators reported that MPFF can reduce rectal discomfort, pain and secondary hemorrhage following hemorrhoidectomy[27]. Oral calcium dobesilate: This is another venotonic drug commonly used in diabetic retinopathy and chronic venous insufficiency as well as in the treatment of acute symptoms of hemorrhoids[28]. It was demonstrated that calcium dobesilate decreased capillary permeability, inhibited platelet aggregation and improved blood viscosity; thus resulting in reduction of tissue edema[29]. A clinical trial of hemorrhoid treatment showed that calcium dobesilate, in conjunction with fiber supplement, provided an effective symptomatic relief from acute bleeding, and it was associated with a significant improvement in the inflammation of hemorrhoids[20]. Topical treatment: The primary objective of most topical treatment aims to control the symptoms rather than to cure the disease. Thus, other therapeutic treatments could be subsequently required. A number of topical preparations are available including creams and

suppositories, and most of them can be bought without a prescription. Strong evidence supporting the true efficacy of these drugs is lacking. These topical medications can contain various ingredients such as local anesthesia, corticosteroids, antibiotics and anti-inflammatory drugs[21]. Topical treatment may be effective in selected groups of hemorrhoidal patients. For instance, Tjandra et al[12] showed a good result with topical glyceryl trinitrate 0.2% ointment for relieving hemorrhoidal symptoms in patients with low-grade hemorrhoids and high resting anal canal pressures. However, 43% of the patients experienced headache during the treatment. Perrotti et al[43] reported the good efficacy of local application of nifedipine ointment in treatment of acute thrombosed external hemorrhoids. It is worth noting that the effect of topical application of nitrite and calcium channel blocker on the symptomatic relief of hemorrhoids may be a consequence of their relaxation effect on the internal anal sphincter, rather than on the hemorrhoid tissue per se where one might anticipate a predominantly vasodilator effect. Apart from topical medication influencing tone of the internal anal sphincter, some topical treatment targets vasoconstriction of the vascular channels within hemorrhoids such as Preparation-H® (Pfizer, United States), which contains 0.25% phenylephrine, petrolatum, light mineral oil, and shark liver oil. Phenylephrine is a vasoconstrictor having preferential vasopressor effect on the arterial site of circulation, whereas the other ingredients are considered protectants. Preparation-H is available in many forms, including ointment, cream, gel, suppositories, and medicated and portable wipes[14]. It provides temporary relief of acute symptoms of hemorrhoids, such as bleeding and pain on defecation. Non-operative treatment Sclerotherapy: This is currently recommended as a treatment option for first- and second-degree hemorrhoids. The rationale of injecting chemical agents is to create a fixation of mucosa to the underlying muscle by fibrosis. The solutions used are 5% phenol in oil, vegetable oil, quinine, and urea hydrochloride or hypertonic salt solution[22]. It is important that the injection be made into submucosa at the base of the hemorrhoidal tissue and not into the hemorrhoids themselves; otherwise, it can cause immediate transient precordial and upper abdominal pain[15]. Misplacement of the injection may also result in mucosal ulceration or necrosis, and rare septic complications such as prostatic abscess and retroperitoneal sepsis[16]. Antibiotic prophylaxis is indicated for patients with predisposing valvular heart disease or immunodeficiency because of the possibility of bacteremia after sclerotherapy[17] Rubber band ligation: Rubber band ligation (RBL) is a simple, quick, and effective means of treating first- and second-degree hemorrhoids and selected patients with third-degree hemorrhoids. Ligation of the hemorrhoidal tissue with a rubber band causes ischemic necrosis and scarring, leading to fixation of the connective tissue to the rectal wall. Placement of rubber band too close to the dentate line may cause severe pain due to the presence of somatic nerve afferents and requires immediate removal. RBL is safely performed in one or more than one place in a single session[18] with one of several commercially available instruments, including hemorrhoid ligator rectoscope[29] and endoscopic ligator[30] which use suction to draw the redundant tissue in to the applicator to make the procedure a one-person effort. The most common complication of RBL is pain or rectal discomfort, which is usually relieved by warm sitz baths, mild analgesics and avoidance of hard stool by taking mild laxatives or bulk-forming agents. Other complications include minor bleeding from mucosal ulceration, urinary retention, thrombosed external hemorrhoids, and extremely rarely, pelvic sepsis. The patients should stop taking anticoagulants for one week before and two weeks after RBL. Infrared coagulation: The infrared coagulator produces infrared radiation which coagulates tissue and evaporizes water in the cell, causing shrinkage of the hemorrhoid mass. A probe is applied to the base of the hemorrhoid through the anoscope and the recommended contact time is between 1.0-1.5 s, depending on the intensity and wavelength of the coagulator[31]. The necrotic tissue is seen as a white spot after the procedure and eventually heals with fibrosis. Compared with sclerotherapy, infrared coagulation (IRC) is less technique-dependent and avoids the potential complications of misplaced sclerosing injection[22]. Although IRC is a safe and rapid procedure, it may not be suitable for large, prolapsing hemorrhoids.

Operative treatment An operation is indicated when non-operative approaches have failed or complications have occurred. Different philosophies regarding the pathogenesis of hemorrhoidal disease creates different surgical approaches

CONCLUSION Therapeutic treatment of hemorrhoids ranges from dietary and lifestyle modification to radical surgery, depending on degree and severity of symptoms. Although surgery is an effective treatment of hemorrhoids, it is reserved for advanced disease and it can be associated with appreciable complications. Meanwhile, non-operative treatments are not fully effective, in particular those of topical or pharmacological approach. Hence, improvements in our understanding of the pathophysiology of hemorrhoids are needed to prompt the development of novel and innovative methods for the treatment of hemorrhoids.

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