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REVIEW ARTICLE

Postoperative Abdominal Adhesions: Clinical Significance and Advances in Prevention and Management

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Abstract Postoperative adhesions remain one of the more challenging issues in surgical practice. Although peritoneal adhesions occur after every abdominal operation, the density, time interval to develop symptoms, and clinical presentation are highly variable with no predictable patterns. Numerous studies have investigated the pathophysiology of postoperative adhesions both in vitro and in vivo. Factors such as type and location of adhesions, as well as timing and recurrence of adhesive obstruction remain unpredictable and poorly understood. Although the majority of postoperative adhesions are clinically silent, the consequences of adhesion formation can represent a lifelong problem including chronic abdominal pain, recurrent intestinal obstruction requiring multiple hospitalizations, and infertility. Moreover, adhesive disease can become a chronic medical condition with significant morbidity and no effective therapy. Despite recent advances in surgical techniques, there is no reliable strategy to manage postoperative adhesions. We herein review the pathophysiology and clinical significance of postoperative adhesions while highlighting current techniques of prevention and treatment.

Keywords Peritoneal · Adhesions · Review · Complications

Introduction

Postoperative adhesions remain one of the more challenging issues in surgical practice. Although peritoneal adhesions occur after every abdominal operation, the density, time interval to develop symptoms, and clinical presentation are highly variable with no predictive patterns.[1,2] Adhesion formation following an invasive intervention was first recognized more than 1500 years ago, when lung adhesions were described as an injury response to lung puncture.[3] In 1889, von Dembrowski published the first data on induction of adhesions in an animal model. Since then, numerous studies have investigated the pathophysiology of postoperative adhesions both in vitro and in vivo.[4] However, factors such as type and location of adhesions, as well as timing and recurrence of adhesive obstruction remain unpredictable and poorly understood. Furthermore, only minimally invasive surgical techniques have been shown to reduce adhesion formation and associated morbidity and mortality.[5]

Although the majority of postoperative adhesions are clinically silent, the consequences of adhesion formation can represent a lifelong problem including chronic abdominal pain, recurrent intestinal obstruction requiring multiple hospitalizations, and infertility.[6,7] Moreover, adhesive disease can become a chronic medical condition with significant morbidity and no effective therapy. As an unavoidable consequence of any abdominal operation, discussion of these adverse outcomes should be part of preoperative informative consent.[8] Adhesions are a particular bane of pelvic surgery and a major cause of complications following gynecological surgeries.[9] In addition, despite recent advances in surgical techniques, there is no reliable strategy to manage postoperative adhesions.[10]

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Herein, we review the pathophysiology and clinical significance of postoperative adhesions while highlighting current techniques on prevention and treatment.

Pathogenesis of Peritoneal Adhesions

The uncertainty in the biologic processes involved with adhesion formation is a main hindrance to identifying effective treatment strategies. By definition, peritoneal adhesions are pathologic bands connecting adjacent structures. The physical properties of these bands can vary significantly from a thin membrane of connective tissue to a thick fibrous band that may contain blood vessels and nerves, or a tight connection between two organ surfaces.[5,11] Typically, tissue injury initiates an inflammatory response, and the subsequent healing process stimulates fibrous tissue formation. However, frequently the inflammatory process involves organs that may not have been directly injured.[11] Several investigators have tried to explain why the normal healing process creates adhesions in some patients, but not in others. One theory postulates that adhesion formation is a result of the disequilibrium between fibrin deposition and degradation (Fig. 1). Fibrin formation is the end product of the coagulation cascade in the peritoneal cavity, when thrombin triggers conversion of fibrinogen into fibrin.[12] The systemic coagulopathy results in the fibrin deposits, which are a matrix for development of fibrocollagenous tissue and formation of an extracellular matrix (ECM).[12] The ECM may stay in place even after degradation of the fibrin deposits.

The activation of the fibrinolytic system during first 5–7 days following peritoneal injury is critical to prevent adhesion formation. The conversion of plasminogen into plasmin is the main trigger of fibrin degradation into fibrin-split products. The tissue-type (tPA) and urokinase-type (uPA) plasminogen activators are the most well-known stimulators of plasminogen conversion into plasmin, which are produced and stored in endothelial cells, mesothelial cells, and macrophages.[13] tPA, a serine protease, is the most potent plasminogen activator with a high affinity for fibrin. The presence of fibrin markedly enhances the activation rate of plasminogen.[13,14] In turn, there is typically higher plasminogen activation at sites at risk of adhesions. In the peritoneal cavity, tPA is responsible for up to 95% of the plasminogen activity.[15] uPA also is equally effective in the degradation of the fibrin matrix.[16] However, due to lower fibrin affinity, uPA stimulates lower levels of plasminogen activation compared with tPA. uPA also appears to have an alternative role in fibrinolysis, while it plays a more important role in tissue remodeling.[17]

Plasminogen activation is inhibited by plasminogen activator inhibitors (PAI)-1 and PAI-2, through formation of inactive complexes. The glycoprotein PAI-1 is the most potent inhibitor of both tPA and uPA, while PAI-2 seems to be less effective. Nevertheless, PAI-2 still plays a role in peritoneal tissue repair.[18] Both PAI-1 and PAI-2 are produced by various cell types, including endothelial and mesothelial cells, monocytes, macrophages, and fibroblasts. PAI-3 and protease nexin 1 are two other plasminogen activator inhibitors, yet their biologic role requires further investigation. Furthermore, plasmin might be inhibited directly by several protease inhibitors such

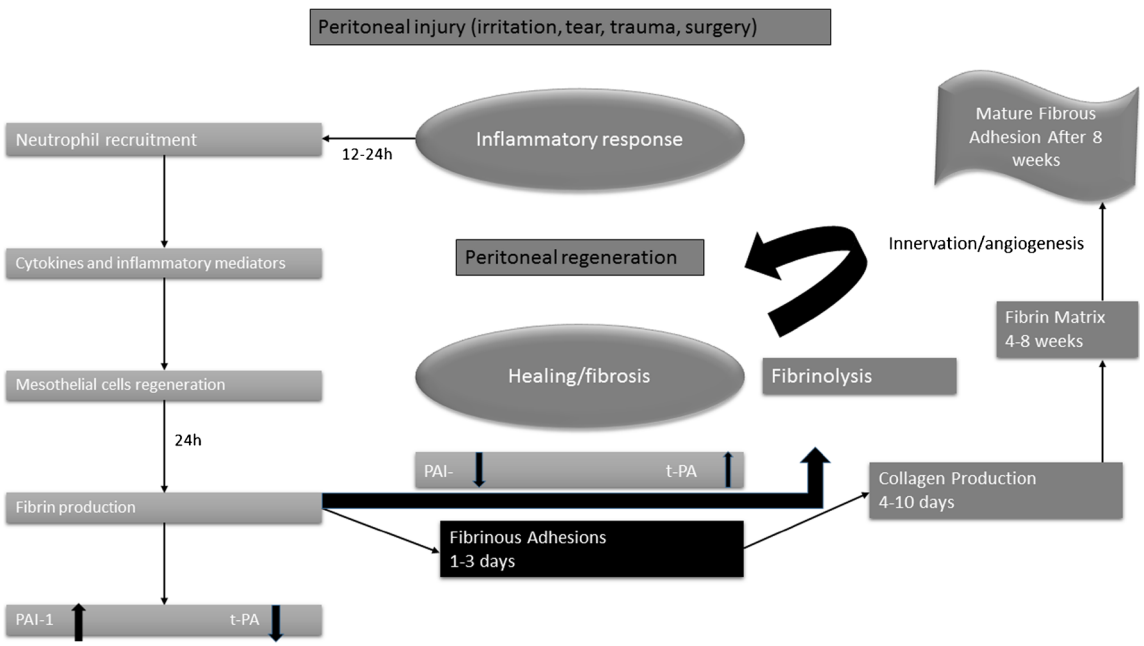

Fig. 1 Illustration of a plausible pathogenesis model of postoperative adhesions

as α2-macroglobulin, α1-antitrypsin, and α2-antiplasmin. The role of direct plasmin inhibitors in peritoneal fibrinolysis are, however, also not well defined.[5] Of note, the levels of PAI-1 and tPA/PAI complex are increased in peritoneal samples from patients with higher propensity to form severe adhesions, and hence might be used as biomarkers to identify high-risk patients.[12]

The balance between plasminogen activators and inhibitors appears to be the major determinant of peritoneal tissue repair process (normal healing vs. adhesion formation). When fibrinolysis fails to occur, the initially formed temporary fibrin matrix persists and can progressively become organized with collagen-secreting fibroblasts. Additionally, the secretion of angiogenic factors by fibroblasts creates new blood vessels.[19] Peritoneal adhesions are formed after these newly vascularized tissues are covered with a layer of peritoneum.[20,21]

Epidemiology

Adhesions occur in nearly all patients undergoing intra-abdominal operations.[22–24] Postoperative adhesions are the primary cause for small bowel obstruction (SBO) and comprise 70% of admissions for bowel obstruction.[1,5,25,26] Approximately 3% of all laparotomies and 1% of all surgical admissions are related to adhesions.[26] The majority of epidemiologic data regarding adhesive bowel obstruction is derived from data of national registries and retrospective cohorts of elective abdominal surgery. Because of the nature of these studies, it is difficult to determine specific operative factors that may influence the development of bowel obstruction. The epidemiological data of the Surgical and Clinical Adhesions Research (SCAR) group reported that adhesions were more common following procedures that involve small intestine, colon, appendix, or the uterus.[19,27–29] The procedures with highest risk of adhesion-related hospital readmission were total proctocolectomy (15.4%), total colectomy (8.8%), and ileostomy (10.6%).[29] In contrast, procedures in the upper abdomen involving the stomach, gallbladder, or pancreas were associated with lower rates of adhesion formation.[30] Similarly, age was inversely correlated to adhesion-related readmissions with individuals younger than 60 years to be at highest risk. Inflammation due to peritonitis, Crohn's disease, and colon procedures performed for colon cancer also have been demonstrated to increase adhesion-related complications.[29]

The LAPAD (LAParotomy or LAParoscopy and ADhesions) trial was the largest study designed to investigate risk factors associated with adhesive SBO. Patients who underwent elective open or laparoscopic abdominal surgery for either benign or malignant conditions were included in the study. Intra-operative factors such as incision type, the presence and severity of adhesions, and adhesiolysis time were among numerous variables that were assessed. The results demonstrated that procedures of the lower gastrointestinal tract (odds ratio 4.57, $P < 0.01$), as well as severity of adhesions in the operative area (odds ratio 2.37, $P = 0.04$) were independent risk factors for adhesive SBO.[31] The presence of midline incision at the index procedure was correlated with iatrogenic bowel injury, whereas the number of previous laparotomies was irrelevant. Using these data, Broek et al. developed a nomogram to predict iatrogenic bowel injury during adhesiolysis.[32] Emergency surgery has also been identified as a risk factor for adhesion formation. Sisodia et al. reported that patients who have had an emergent operation demonstrated higher incidence of adhesion-related complications compared with patients who underwent elective surgery.[33]

Postoperative adhesions may present within a wide clinical spectrum of disease, from a single band causing a closed loop obstruction to asymptomatic extensive dense adhesions. Therefore, the size of the adhesion bands is not a good predictor of their sequela. Identification of factors associated with adhesion formation and, more importantly, adhesion-related complications are pivotal to distinguish high-risk patients (Table 1). Considering highly variable and sometimes contradictory results of the current data, future studies with rigorous methodology are required.

Economic Burden of Peritoneal Adhesions

Several studies have evaluated the economic burden of postoperative adhesions on the healthcare system. The major limitation of most studies has been the lack of standard definitions for adhesion-related complications. Moreover, there is no consistent recording of many complications in health records. This is partly attributed to the fact that a different surgeon than the index procedure often treats patients suffering adhesion-related complications. As a result, usually the primary surgeon is unaware of the complication.[2]

Ellis et al. estimated that 33% of patients, who underwent abdominal or pelvic surgery, were readmitted for adhesion-related complications with an average of 2 admissions during a 10-year follow-up.[19] In another study over a 24-year period, intestinal obstruction was responsible for 0.9% of all admissions, 3.3% of major laparotomies, and 28.8% of large or small bowel obstructions.[27] In 1988 in the USA, admissions

Table 1 Risk factors for adhesion formation

Risk factors for adhesion formation
Emergency surgery[33]
Pelvic surgery[19,27–29]
Lower gastrointestinal procedures[19,27–29,31]
Age <60 years[29]

for adhesiolysis accounted for nearly 950,000 days of inpatient care.[25,34] Updated data in 1994 indicated that more than 300,000 admissions took place for complications of peritoneal adhesions.[35] Furthermore, lysis of adhesions was associated with a prolonged operative time, 6% incidence of iatrogenic bowel injury, and increased risk of postoperative complications.[5,26,30] Likewise, the length of hospital stay following surgery for peritoneal adhesions was increased, mainly due to a prolonged recovery period.[36,37] In the USA, the total cost of hospital and surgical expenditures for the management of adhesion-related complications has increased from $1.3 billion in 1994 to $5 billion in 2001 (Table 2).[29] Efforts to decrease the incidence of postoperative adhesive disease would likely have a dramatic economic influence. In fact, it has been estimated that anti-adhesion agents, with an average cost of $200 and potential effectiveness of less than 25%, might reduce the healthcare expenditures by approximately $55 million over 10 years.[38]

Prevention of Peritoneal Adhesions

The best approach to limit the morbidity and decrease the economic burden of adhesion-related complications is prevention of the formation of postoperative adhesions. Current preventative measures can be categorized into two main strategies: alterations in surgical technique to minimize tissue injury and physical barriers (Table 3).[42,43] These strategies are summarized in Fig. 2.

Technical Measures

Appropriate surgical technique is an important factor in helping to avoid adhesion formation. Gentle handling of tissues and delicate dissection technique are crucial for limiting tissue injury, inflammation, and preventing serosal damage.[39] Furthermore, minimizing exposure and desiccation of bowel surface as well as removal of debris can reduce the risk of adhesion formation.[39,44] It is important to avoid unnecessary introduction of foreign bodies such as talc, lint, or fibrinogenic suture materials. For instance, suture materials such as silk or chromic catgut stimulate more tissue reactivity than polyglactin.[45,46] Another experimental study demonstrated that absorbable sutures such as polyglactin and mixes of lactic and glycolic acids were associated with a lower incidence of postoperative adhesion formation compared with non-absorbable fixation methods such as polypropylene sutures and titanium tackers.[47] Similarly, polyglactin sutures were associated with a lower incidence of peritoneal adhesions in both sterile and contaminated settings compared with other absorbable sutures such as Polydioxanone and Poliglecaprone 25, a benefit that was less profound in the contaminated setting, perhaps suggesting the crucial role of inflammation in adhesion formation.[48] Finally, several factors related to the surgical environment such as air-handlers, powder-free gloves, and "lint-free" surgical supplies have also been reported to reduce peritoneal adhesion formation.[39]

Table 2 Economic burden associated with adhesions

Incidence of adhesion-related admissions
300,000 admissions each year in the USA[35]
1% admissions for surgery[35]
3% admissions for emergency laparotomy[35]
33% readmission rate for related conditions twice in 10 years[19]
Adhesion-related healthcare expenditures
1.3 billion dollars in 1994[35]
5 billion dollars in 2001[29]

The closure of the parietal peritoneum during closure of the abdominal wall was previously thought to prevent adhesion formation. However, a recent systematic review demonstrated conflicting evidence regarding the long-term benefits of peritoneal closure on adhesion reduction among patients undergoing cesarean section.[49] In a prospective cohort of 173 patients who underwent repeat cesarean delivery, Lyell et al. reported that peritoneal closure was associated with increased risk of postoperative adhesions. The closure of the rectus muscles resulted in fewer combined filmy and dense adhesions overall (27.5 vs. 46%; $P = 0.04$).[41]

Abdominal wall reconstruction with synthetic or bioprosthetic mesh also carries a significant risk of adhesion formation. While bioprosthetic mesh appears to elicit fewer and lower-grade adhesions compared with synthetic mesh, further studies are required.[50] Prostheses coated with permanent anti-adhesive barriers (Bard™ Composix™ E/X, Bard™ Composix™ L/P, and DUALMESH (®) Biomaterial) have been correlated with improved adhesion characteristics compared with uncoated meshes, likely attributed to the inflammatory reaction that is caused by the chemical composition of the barrier or the conditions required for resorption and metabolism of the barrier components.[51] Moreover, on repeated laparotomies, the adhesions were easier to separate, translating into less operative time and effort.[52]

In a meta-analysis of 17 studies, Ten Broek et al. demonstrated that no specific open surgical technique significantly reduced the incidence of adhesion-related complications.[39] Leaving the peritoneum open with the abdominal closure (relative risk (RR) 0.36; 95% CI 0.21–0.63) and laparoscopy (RR 0.14; 95% CI 0.03–0.61) were associated with reduced incidence of adhesions.[39] Several studies have validated the benefit of laparoscopy in reduction of postoperative adhesions.[40,53,54] Furthermore, laparoscopic adhesiolysis may result in a reduction, but not elimination, of the frequency, extent, severity, and type of abdominal adhesion reformation between organs and the abdominal wall. Of note, the

Table 3 Preventive measures for adhesion formation

Technical measures[39–41]	Commercially available physical barriers[5]
Handle tissues gently	Seprafilm® Adhesion Barrier (Cambridge, MA; Genzyme Corporation)
Minimize bowel exposure and desiccation	Gynecare Interceed™ Absorbable Adhesion Barrier (Somerville, NJ; Johnson & Johnson)
Minimize use of foreign bodies	Gore Preclude Surgical Membrane® (Flagstaff, AZ; W.L. Gore and associates Inc.)
Debridement of necrotic tissue	Repel-CV® (Iselin, NJ; SyntheMed Inc.)
Use "powder-free" gloves and "lint-free" supplies	Adept® Adhesion Reduction Solution (Deerfield, IL; Baxter Healthcare Corporation)
Laparoscopic or robotic techniques	
Avoiding closure of the peritoneum during wound closure	

incidence of visceral adhesions is not minimized by laparoscopy.[55,56] In addition, some investigators have failed to note an advantage of laparoscopy over open surgery in the prevention of adhesive SBO (Table 4).[6,57–60] For example, in one retrospective study of 700 patients who underwent laparoscopic or open colorectal surgery, SBO occurred in 11.2% of patients in the laparoscopic group versus 9.8% in the open surgery arm.[53] Although the difference between the two groups did not reach statistical significance, conversion to an open procedure and stoma formation were independent risk factors for SBO development.

Minimally invasive (MIS) radical prostatectomy is another procedure that has been studied with regard to its relation to adhesion formation. MIS prostatectomy is performed within the peritoneal cavity and hence may have an increased incidence of SBO compared with open radical extra-peritoneal prostatectomy. In a retrospective study performed by Loeb et al., 14,147 patients with prostate cancer were treated with either open extra-peritoneal (n = 10,954) or MIS (n = 3193) radical prostatectomy.[61] With a median follow-up of 45 and 76 months, respectively, the overall incidence of SBO was 3.7% for minimally invasive and 5.3% for open radical prostatectomy (p = 0.0005). Adhesiolysis occurred in 1.1 and 2.0% of MIS and open prostatectomy patients (p = 0.0003).[61] However, multivariable analysis did not show any significant difference in the incidence of SBO or adhesiolysis between MIS and open prostatectomy.[61]

In women undergoing gynecological surgery, 60–90% develop adhesions and adhesions can be the etiology of 15–20% of secondary infertility.[42] Comparing the incidence of adhesions between gynecological laparotomy and laparoscopic surgery, patients incur similar risk of adhesion-related readmissions.[43] In contrast, an early randomized controlled trial including 105 patients with tubal pregnancy reported that patients who had a laparotomy formed significantly more adhesions than patients undergoing laparoscopy (p < 0.001); however, tubal patency did not differ between groups.[62] Among patients with adhesions and infertility, adhesiolysis can be an important infertility treatment leading to improved ability to become pregnant and decreased pregnancy loss.[63]

Physical Barriers

Despite recent advances in the development of adhesion barriers, major drawbacks have limited the effectiveness of these products. Solid or liquid physical barriers are applied to cover the injured peritoneal tissues and keep the tissues separated until completion of the reepithelialization process.[64,65] However, these barriers are unable to cover all visceral and peritoneal surfaces, limiting their efficacy. Although studies

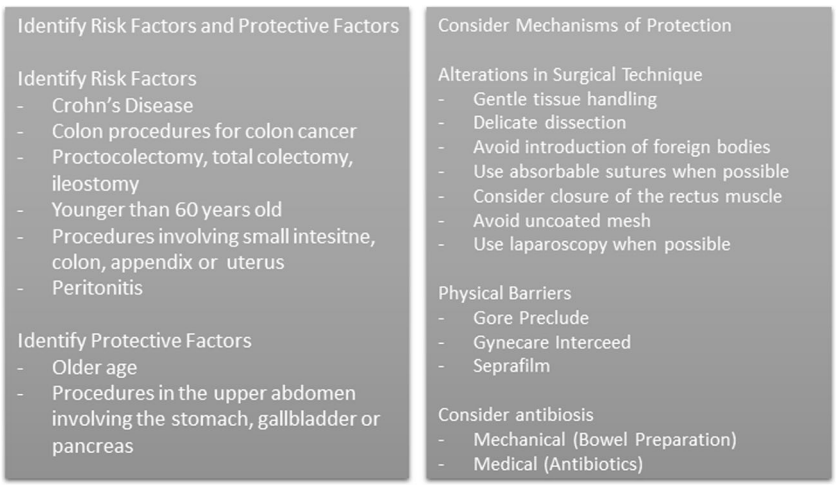

Fig. 2 Summary of key pathobiology and prevention strategies associated with postoperative adhesions

Table 4 Studies evaluating the role of laparoscopy in adhesion formation

Study, year	Type of study	*N*	Fewer adhesions than open surgery	No difference in adhesion-related admissions
Burns et al., 2013[40]	Retrospective	187,148	+	
Lower et al., 2004[57]	Retrospective	24,046		+
Taylor et al., 2010[6]	Prospective	411		+
Scholin et al., 2011[58]	Retrospective	786		+
Smolarek et al., 2016[53]	Retrospective	707	+	
Sidana et al., 2012[55]	Retrospective	151	+	

N number of patients in each study

have shown that physical barriers minimize the formation of postoperative adhesions, there is no significant improvement in clinical outcomes of patients due to adhesion-related complications (e.g., reoperation rates, chronic abdominal pain, or infertility).[66] Increased risk of intraabdominal abscesses and anastomotic leak, particularly if the barriers are used near anastomosis, prolonged operative time, and higher cost are some of the disadvantages of physical barriers.[66–68]

A range of physical barriers have been approved for clinical application in the USA (Table 3).[5] Gore Preclude is a polytetrafluoroethylene membrane that prevents the development of pelvic adhesions, especially after second look surgeries. However, a strip of Gore-Tex remains within the pelvis permanently.[69] Gynecare Interceed is an oxidized regenerated cellulose that precludes formation of de novo and recurrent adhesions. The major drawback of this barrier is that it becomes ineffective in the presence of blood.[67] Both Gore Preclude and Gynecare Interceed barriers have been reported to reduce the incidence and extent of adhesions compared with good surgical technique alone.[67,70] Oxidized regenerated cellulose is not inferior to polytetrafluoroethylene membrane in terms of safety and efficacy.[67,69]

Seprafilm is a chemically modified sodium hyaluronate/carboxymethylcellulose absorbable barrier. Seprafilm reduced the incidence of adhesions and adhesive SBO requiring reoperation, but it did not change the overall SBO incidence.[71,72] A prospective, randomized controlled study of patients who underwent abdominopelvic surgery due to inflammatory bowel disease demonstrated that Seprafilm was safe and efficient in decreasing adhesion formation.[73] Application of Seprafilm on the suture or staple line of a fresh intestinal anastomosis should be avoided, as it may increase the risk of anastomotic leak and fistula formation.[72,73] In a long-term follow-up of 35 patients who underwent Hartman's procedure, van der Wal et al. reported that Seprafilm placement did not prevent SBO. The incidence of chronic abdominal complaints were, however, lower in the Seprafilm group compared with controls (35.3 vs. 77.8%, respectively; $P = 0.018$).[73–75] In contrast, a multicenter randomized controlled trial reported that Seprafilm did not prevent adhesion formation following cesarean delivery.[76] Finally, a multicenter study of patients undergoing colectomy and ileal pouch-anal anastomosis with diverting-loop ileostomy demonstrated that Seprafilm peritoneal placement before closure was related with macroscopically less adhesion formation.[77]

At the time of laparoscopic surgery, the use of barriers alone has led to a 50–60% macroscopic improvement in adhesion formation. The combination of broad peritoneal cavity protection, by insufflating a low-temperature and humidified gas mixture of CO_2, N_2O, and O_2, with local application of a barrier has been demonstrated to be almost 100% effective in preventing postoperative adhesion.[60]

Application of liquid barriers such as polyethylene glycol (Spraygel), which is approved only in Europe, have also been proven to be effective in reducing adhesion formation.[78]

Intestinal Inflammation

As noted, activation of the inflammatory cascade plays an important role in the pathogenesis of postoperative adhesion formation. In turn, intestinal microflora may play a role in adhesion formation. Specifically, bacterial intestinal colonization has been associated with a fourfold decrease in peritoneal and peri-anastomotic adhesion formation risk.[79,80] A possible underlying mechanism of the inflammatory contribution of bacterial translocation is the activation of the cell-mediated immune response. More specifically, bacterial translocation activates the expression of macrophages and interleukin-6 (pro-inflammatory cytokine),[81] that in turn can lead to exacerbation of peritoneal adhesion formation.[82]

Intestinal bacterial burden reduction, either medically (antibiotics) or mechanically (bowel preparation), may have an impact on the incidence of postoperative adhesions. More specifically, intravenous administered of broad-spectrum antibiotics to decrease the bacterial burden may also reduce the risk and severity[83] of postoperative peritoneal adhesions, as has been demonstrated in experimental animal models.[84] Similarly, bowel preparation may induce long-acting changes in intestinal microbiota homeostasis, a potential mechanism to

reduce bacterial burden and translocation that in turn could exacerbate peritoneal adhesion formation.[85,86]

Ongoing Research

Despite promising results in animal studies, new systemic agents have not shown similar efficiency in humans.[42] Nonsteroidal anti-inflammatory drugs, corticosteroids, calcium channel blockers, antihistamines, antibiotics, fibrinolytic agents (streptokinase and urokinase), colchicine, and vitamins have had disappointing results in human trials.[87–90] Pioglitazone, a PPAR-γ agonist, has been demonstrated to reduce postoperative adhesion formation without compromising anastomotic healing in a mouse model. However, the safety and efficacy of PPAR-γ agonists in humans has yet to be determined.[91] The local administration of simvastatin in a rat model also was reported to reduce the incidence and severity of peritoneal and small bowel adhesions.[92]

Currently, products that utilize the barrier method for separating traumatized tissues represent the only successful strategy in postoperative adhesion prevention. Brochhausen et al. introduced scanning electron microscopy (SEM) and subsequent morphometry as a useful tool to analyze the performance of barrier materials. Striking morphological differences in the peritoneal lesion surface organization was observed between the different barriers, depending on the degree of barrier colonization by mesothelial cells.[93] Chaturvedi et al. reported that an ultrapure alginate-based antiadhesive barrier gel decreased the incidence of postoperative adhesion formation in a rat model with cecal abrasion and peritoneal sidewall excision.[94] Recently, Fredriksson et al. demonstrated that using carbazate-activated polyvinyl alcohol (PVAC)-impregnated sutures in a rat model was associated with reduced intraperitoneal adhesions compared to controls ($P = 0.04$). However, intra-peritoneal instillation of PVAC had no effect.[95]

Conclusion

Adhesions are an inevitable consequence of intra-abdominal surgeries. Complications associated with postoperative adhesions continue to challenge the health care system, without any single, implementable solution. Meticulous and minimally invasive surgical techniques as well as physical barriers are currently the only widely accepted methods of postoperative adhesion prevention. Although the understanding of the pathogenesis of peritoneal adhesions has undoubtedly grown over the past decade, much more research needs to be done. In particular, innovation of novel adhesion-reducing adjuvants, further high-quality studies with better methodology and larger number of patients are required.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflicts of interest.

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