Tissue adhesion after surgical interventions (Review)

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Received October 14, 2024; Accepted February 28, 2025

DOI: 10.3892/etm.2025.12847

Abstract. Tissue adhesion after surgical procedures is a common postoperative complication that affects a significant number of patients across all surgical disciplines. In pelvic surgical procedures, second-look surgeries have revealed adhesions in more than half of all patients weeks to several months after surgery. Adhesions can be asymptomatic, but they can also cause a wide range of complications, such as severe pain, nausea, vomiting, constipation, ileus and reproductive dysfunction. Undetected adhesions that lead to problems in subsequent surgical interventions are also of high clinical importance. Lysis of these adhesions before the actual surgery leads to loss of time and possible additional complications, such as trocar injuries in laparoscopies or inadvertent enterotomies during adhesiolysis, during the originally planned intervention. The health care associated with adhesion-related problems are significant. Because of the widely varying manifestations of symptoms, the already concerning figure of patients with significant adhesions is likely to increase. Outpatient healthcare expenditures are further increased because of undetected adhesions. Adhesions therefore represent a major surgical and health economic problem; however, yet there are currently few options for prophylaxis and treatment.

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Abbreviations: CAM, cell-adhesion molecules; CO_2, carbon dioxide; ECM, extracellular matrix; HIF, hypoxia-induced factor; H_2O_2, hydroxygen peroxide; MMP, matrix metalloproteinase; MMT, mesothelial-to-mesenchymal transition; NIPP, Non-Invasive Physical Plasma; PAI, plasminogen activator inhibitor; ROS, reactive oxygen species; TIMP, tissue inhibitors of metalloproteinases; TNF-α, tumor necrosis factor α; tPA, tissue-type plasminogen activator; uPA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor

Key words: postoperative complications, adhesion prophylaxis, adhesion therapy, peritoneum, surgery

Contents

1. Introduction

One of the most common complications associated with the peritoneum is the formation of abdominal adhesions after surgery. Adhesions are bands of connective tissue that form between organs or between organs and the abdominal wall, typically in response to inflammation or (surgical) trauma. Such adhesions can remain symptom-free for life, but they can lead to organ dysfunction. These include restricted movement, pain, intestinal obstruction or infertility. The formation of adhesions is a significant problem after abdominal operations such as caesarean sections, appendectomies or hysterectomies.

As aforementioned, adhesions are significant regarding frequent issues faced in many surgical disciplines. They are associated with chronic pelvic pain, infertility, and intestinal obstruction, which lead to significant clinical challenges, as noted across multiple studies (1,2). In 2004, one in 20 gastrointestinal procedures was primarily indicated for adhesion lysis according to US Health System analyses. This has resulted in 900,000 days of hospitalization as well as annual adhesion-related costs of $2.3 billion (3).

The subsequent problems caused by adhesions have not diminished (4,5). Capmas *et al* (6) describe that adhesions are widespread in abdomino-pelvic surgery, particularly in gynecological and colorectal procedures. The study was conducted in France and demonstrated costs for hospitalization and surgery due to adhesions of approximately €4 million in 2019. In this time period, more than 25.000 surgeries were performed in France with either the primary or secondary goal of adhesiolysis. The adhesion-dependent economic burden on the healthcare system arises primarily from the direct costs of readmissions and repeat operations (6). The costs associated with loss of productivity and long-term patient morbidity are also considerable. However, these indirect costs are usually

not even considered, but would significantly increase the impact (5). Moreover, the process of adhesiolysis itself was a part of one in three laparoscopic surgeries, as detailed per diagnosis-related group codings. A 2023 systematic review concerning the health care costs of adhesion-related small bowel obstruction in different countries found national costs reaching up to $1.77 billion (7). The literature review included 7 clinical trials conducted worldwide between 1999 and 2016. The mean total cost of the 39,573 patients was $1,814-$2,568 with medical treatment vs. $4,914-$25,321 in the surgical treatment group. The mean length of stay was 3.0-7.0 days for conservative treatment and 8.0-16.3 days for surgical treatment. On average, the length of stay for patients who underwent surgery was about three times longer than for patients who received conservative treatment, which explains the significantly higher treatment costs.

2. Adhesion types and diagnostics

Adhesions are attachments of tissue areas, which are not physiologically connected to each other. They consist of fibrous bands of scar tissue and thus connect areas of tissue or organs that were originally not connected to each other. Adhesions often arise as a result of surgery, inflammation or trauma. As such, they are part of the body's natural healing process, but can form abnormal connections that lead to medical complications (8,9). In surgical context, one usually refers to adhesions involving abdominal and pelvic organs as well as the peritoneum.

Fig. 1 shows that adhesions can form between almost any intra-abdominal surface, such as the intestines or the greater omentum. These surfaces are then connected to either each other or the abdominal wall via such adhesions. Adhesions are generally classified into three main types according to their location, structure and functional effect.

One type of adhesion may occur during embryonic organogenesis. This form of adhesion is congenital and is the result of abnormal embryonic development. These adhesions usually involve the gastrointestinal tract, e.g. the persistence of a congenital band causing small bowel obstruction. However, they tend to be more isolated and less extensive than acquired adhesions. This happens comparatively rarely and is usually only incidentally diagnosed. In most cases, such adhesions remain asymptomatic and do not require therapy (8).

Adhesions can also be formed post-inflammatorily as a consequence of acute or chronic underlying diseases. These adhesions arise as a reaction to pathological processes such as infections, endometriosis or chronic inflammation. Such pathological adhesions tend to form dense and highly vascularized fibrous bands. The clinical presentation is often asymptomatic or mild in these cases. However, they can also occur with certain diseases such as pelvic inflammatory disease or intra-abdominal sepsis. In the clinical presentation, this can lead to chronic pelvic pain, infertility and complications during surgical interventions (9,10). A post-mortem study revealed adhesions in 28% of all cases in probands who had never undergone surgery (9). Etiologically, such adhesions can be attributed to intra-abdominal inflammatory processes (such as peritonitis, Crohn's disease, endometriosis, and radiotherapy-induced inflammation) (2,10).

The largest adhesion group consists of clinically significant postoperative adhesions (Fig. 1). Here, the peritoneum has been damaged, which is estimated to occur in 70-100% of patients (11,12). These adhesions are the result of surgical trauma and are by a wide margin the most common adhesions. The formation of such acquired adhesions is a response to injury and subsequent inflammation of the peritoneum. The adhesions can vary greatly in density and extent and range from very fine to extremely strong and dense fibrous bands (10,12).

Although adhesions can also be completely asymptomatic, all three main types can also lead to a variety of complications. These range from the mildest symptoms to very serious complications. For one thing, unclear symptoms such as chronic abdominal or pelvic pain can occur. In many cases, however, there are also defined clinical manifestations such as inflammatory diseases or functional limitations of the affected organs, e.g. peritonitis, intestinal obstruction or infertility (13). As a diagnosis of adhesions is nearly impossible without directly seeing them, adhesions are mostly detected incidentally during surgical procedures. The patient's medical history may provide indications. When the displaceability of organs and organ areas in relation to each other is restricted, further evidence can sometimes be found with the use of imaging techniques.

Modern imaging techniques enable very accurate clarification of anatomical abnormalities. The use of a cine magnetic resonance imaging (MRI) device makes it possible to analyze the abdominal cavity with a high image sequence. It was seen that adhesions could be detected with a sensitivity of 86.0% and a specificity of 80.0% (14). In addition, the non-invasive procedure also made it possible to assess the localization and extent of adhesions as well as the mobility of affected organs. Another advantage of MRI is that patients are not exposed to ionizing radiation. However, the method has its limitations with extremely thin adhesion bands and in areas where only very low organ dynamics are naturally present. However, MRI-based mapping of adhesions facilitates better planning of a surgical procedure and reduces potential surgical risks and thus also postoperative complications. Future advances in suitable imaging techniques could significantly improve the diagnosis and subsequent treatment of adhesions. However, routine adhesion diagnostics using such devices is hampered by the high technical and financial requirements.

3. Peritoneum

The peritoneum plays a crucial pathophysiological role in the development of adhesions. Intra-abdominal adhesions are mostly adhesions of the peritoneum itself, resulting from damage during the surgical procedure. The larger the surface of an organ covered by peritoneum and the denser the intra-abdominal position of each organ in relation to each other, the higher the risk of adhesions. This risk is particularly high during ovarian interventions, which achieve adhesion rates of 90% in gynecologic adnexal surgery (15,16).

The peritoneal membrane has two sheets that line the peritoneal cavity in humans. The parietal sheet covers the abdominal wall from the inside, while the visceral sheet envelops the abdominal organs located intraperitoneally (17). The peritoneum is derived from the mesoderm and develops

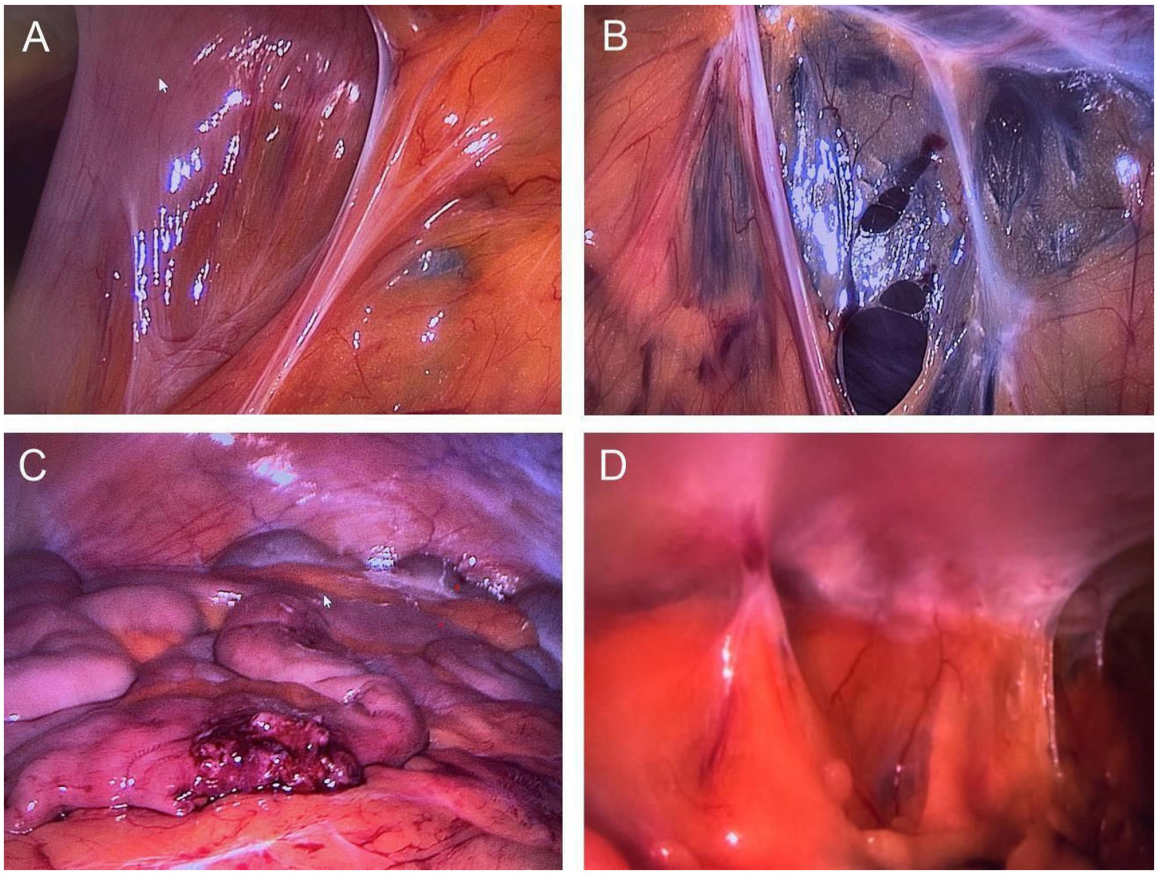

Figure 1. Tissue adhesions in the abdominal cavity. (A) Adhesion of small intestine to the abdominal wall. (B) Adhesion of the greater omentum to the abdominal wall. (C) Dissolving adhesions of the small intestine. (D) Adhesion of the greater omentum to the abdominal wall. All photos are from standard surgery performed in 2023 and 2024 at the Department of General, Visceral and Thoracic Surgery (Bundeswehr Hospital Berlin, Berlin, Germany). The two patients have signed a consent form and have agreed to the anonymized publication of the images.

from the lateral squamous mesoderm during early embryogenesis. During embryogenesis, the peritoneum forms a continuous membrane that lines the abdominal cavity and covers most of the visceral organs. It later develops into the abdominal cavity, which allows the abdominal organs to move. Structurally, the peritoneum can be divided into two layers (18). Histologically, the peritoneum possesses an outer single-layered mesothelial cell layer that carries microvilli. In humans, this brush border increases the secretory surface area by approximately 1.8 m^2 (19). Under the mesothelium, there is a basement membrane and further below there is a connective tissue layer with nerves, blood, and lymph vessels (20).

The primary functions of the peritoneum include regulation of the fluid balance within the abdominal cavity, maintaining organ mobility within the abdominal cavity and recruitment and modulation of immune cell actions and. Intra-abdominal homeostasis is sustained by secreted or resorbed peritoneal fluid (19,20). This allows the mesothelial cells to provide 50-75 ml of peritoneal fluid on the surface, which enables low-friction displacement of the intraperitoneal organs (21). Finally, the peritoneum functions as an immunologically active tissue. The peritoneal mesothelial cells respond to infections or injuries and can release cytokines and other inflammatory mediators. Cell-free areas of the stroma contain fat-associated lymphoid clusters (macula lactea) with lymph node-like functions (22,23). Neutrophilic granulocytes and various lymphocyte types are located here for local immune defense against infection and inflammation (24,25).

The adhesion formation is one of the most common complications associated with the peritoneum, but there are also other diseases of the peritoneum that can significantly restrict its function. Peritonitis is an inflammation of the peritoneum and can occur after infections, trauma or surgical interventions in the abdominal cavity. The increased secretion of immunomodulators leads to an increase in vascular permeability. This intensifies local inflammatory effects and disrupts peritoneal fluid homeostasis (18,20). Furthermore, fibrotic and sclerotic processes can harden the peritoneum and thus impair its functionality (19). Finally, the peritoneum is also frequently affected by abdominal cancers. Peritoneal carcinomas can occur in particular in stomach, colon and ovarian cancer. Malignant cells penetrate the peritoneal mucosa, causing inflammation and worsening the oncological prognosis (15,19).

4. Cell biology of adhesion tissue formation

As in wound healing, the pathophysiological processes involved in adhesion formation include exudation, resorption, and repair. At the cell biological level, complex interactions between mesothelial cells and the extracellular matrix (ECM) are involved, which are orchestrated by different signaling pathways (26). Following abdominal surgery, these biological

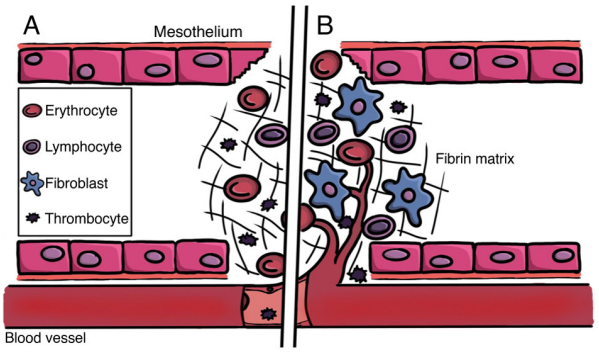

Figure 2. Process of adhesion formation on a cellular level. (A) Activation of the coagulation and fibrin system. Fibrin matrix formation is followed by the migration of erythrocytes, lymphocytes and thrombocytes. (B) Fibroblasts migrate into the precursor scaffold of fibrin as well as blood and immune cells and change their functionality from mesothelial to mesenchymal cell type (mesothelial-to-mesenchymal transition). A connective tissue-like adhesion tissue forms, which finally becomes vascularized.

events also take place leading to the repair of the damaged tissue (Fig. 2).

The reparative processes begin with activation of the fibrin system, accompanied by local inflammation. As tissue repair progresses, hypoxia occurs and redox-regulated signaling and effector cascades are stimulated in the affected tissue. Revascularization occurs in the late phase of repair. Dysregulation in these complex and finely orchestrated mechanisms, e.g. imbalances of fibrin synthesis and degradation, leads to abnormalities in tissue formation and ultimately to tissue adhesions (27,28).

The formation of tissue adhesions begins with the activation of the coagulation cascade. Injury to the mesothelial layer leads to the release of permeability-increasing substances, such as histamine or different cytokines and increases vascular permeability (29). Moreover, activation of the coagulation cascade occurs in areas of trauma. In the extrinsic pathway, tissue factor (tissue thromboplastin, factor III) localized in the subendothelial tissue activates factor VII in the blood. In parallel, the intrinsic pathway is stimulated. Collagen of the endothelium, exposed due to trauma, leads to contact activation of additional coagulation factors (factor XIII, factor IX, factor XI, factor XII). Both pathways lead to the activation of factor V and factor X, and subsequently to proteolytic cleavage of fibrinogen to fibrin by the enzyme thrombin. Polymerization and cross-linking of the fibrin monomers results in building a fibrin matrix (30,31).

Inflammatory reactions also play an important role in adhesion formation. Following injury, immune cells infiltrate the site and release cytokines and growth factors such as tumor necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-β), which promote fibrosis and activate mesothelial cells. Activation of inflammatory pathways also induces the expression of adhesion molecules on the surface of mesothelial cells, which facilitates interaction with ECM components and neighboring cells (30,32).

Peritoneal mesothelial cells undergo a so-called mesothelial-to-mesenchymal transition (MMT). During this process, these cells largely lose their epithelial properties and take on a fibroblastic or myofibroblastic phenotype (33). MMT leads to an increased release of ECM components such as collagen and fibronectin. The pivotal regulator of MMT is TGFβ1 (34,35). As a result, fibrous components form, which can be regarded as the initial adhesion tissue.

During the process, the ECM continues to be extensively modified. Most commonly, collagen, fibronectin and hyaluronic acid are upregulated and integrated into the ECM in excess at injury sites. This remodeling is primarily mediated by matrix metalloproteinases (MMP) and their regulators Tissue Inhibitors of MMP (TIMP). After MMT, the fibroblasts and myofibroblasts secrete alpha-smooth muscle actin (α-SMA), a marker for myofibroblastic differentiation. Furthermore, the cells produce additional ECM proteins, which increases the mechanical stiffness of the adherent tissue. (32).

The formation of new blood vessels (angiogenesis) in the adherent tissue is another important characteristic of adhesion formation. Reactive oxygen species (ROS) and signaling molecules such as vascular endothelial growth factor (VEGF) are essential factors in angiogenic initiation and progression (34,35). The adhesion becomes irreversible when the adhesion tissue is vascularized (36).

As in wound healing, redox processes are seemingly involved in adhesion formation. ROS, such as hydroxyl radical, hydrogen peroxide (H_2O_2), superoxide anion, and singlet oxygen, serve as cofactors for cellular proteins and as second messengers. Nitric oxide controls ECM production and is released from adhesion-associated fibroblasts (37). H_2O_2 is an important signaling molecule for the activation of VEGF-dependent vascularization processes (38). Furthermore, it controls various processes regarding pro-inflammatory and anti-inflammatory cell responses including immunomodulation. Immune cells, such as monocytes and macrophages, migrate into the tissue and further contribute to an adhesive microenvironment through immune modulatory protein factor secretion (18,20,39).

Thus, a strategy of using specific therapeutics in order to suppress ROS levels seems a promising way to intervene in the process of adhesion formation. Several recent publications regarding chronic wound healing discuss the use of anti-oxidant-incorporating hydrogels for wound management (40,41). Some of the incorporated anti-oxidant substances include gallic acid-conjugated gelatin, Lignin, and Pseurotin A (42-44).

5. Cellular misregulations leading to adhesion formation

There are two auto-regulated processes in which dysregulation may primarily occur during the formation of adhesive tissue. These are fibrinogenesis/fibrinolysis and ECM synthesis/degradation (30). A disturbed balance of synthesis and degradation of the fibrin matrix during coagulation is primarily responsible for adhesion formation. The extent of the coagulation pathway activation correlates with the degree of inflammation in the area of trauma.

The mesothelial cells making up the outermost layer of the peritoneum express cell adhesion-molecules (CAM), e.g. intercellular adhesion molecule 1 or vascular cell adhesion molecule 1. CAM, cytokines and growth factors (TGF-β, VEGF) stimulate the invasion of granulocytes and lymphocytes as part of the pathogenic process (45). Important

cytokines involved in adhesion formation include interleukin 1 (IL-1), IL-6 and TNF-α (46). Further insight may be provided by modulating these cytokines using molecular strategies such as small molecules in future experiments may. Cytokine levels also correspond to the local inflammation status and reflect the risk of adhesion formation. Cytokine monitoring after surgical interventions would therefore potentially also be a biomarker for adhesion formation.

VEGF, which induces angiogenesis, is important in adhesion formation as vascularization precludes reversal of adhesions. VEGF inhibitors (i.e. humanized monoclonal antibodies against VEGF such as Bevacizumab) are especially used in the treatment of oncologic diseases. VEGF inhibitors could also inhibit the proliferation of adhesive tissue and, in particular, reduce the formation of adhesion-associated blood vessels. Their use could therefore also be promising in adhesion prevention. (47).

On the other hand, complications have also been described following the use of VEGF inhibitors. In a study of cancer patients receiving bevacizumab, wound healing complications were observed (48). The more closely a surgical incision was made after bevacizumab administration, the greater the wound healing complications. Since VEGF contributes significantly to growth and vascularization, it is an important factor in wound healing. This is in contrast to its use as an adhesion inhibitor, as this application is intended to suppress the adhesion-associated growth and wound healing processes. These side effects significantly limit VEGF blockade for adhesion prophylaxis and must be investigated further.

Fibrinogenesis is regulated by fibrinolysis, in which fibrin is enzymatically digested. Sufficient degradation of fibrin polymers usually leads to healing of the traumatized peritoneal area. Plasmin, a serine protease formed from the enzymatically inactive precursor plasminogen, is responsible for this degradation (49). During surgery, the fibrinolytic capacity of the peritoneum decreases significantly. The enzymatic activation of plasmin occurs locally in the peritoneum mainly induced by tissue-type plasminogen activator (tPA) and by urokinase-type plasminogen activator (uPA) (36). Fibrin levels induce the activity of tPA/uPA, while plasminogen activator inhibitor (PAI) inhibits it (31,49,50). PAI is secreted by both adhesive tissue cells and migratory immune cells (36). A study of tissue expression of PAI and tPA in the peritoneum showed that in patients with severe adhesions, synthesis of tPA was significantly decreased while synthesis of PAI significantly increased. The resulting reduced fibrinolytic capacity represented a risk factor for the development of adhesions (50,51).

Another critical step in adhesion formation is the synthesis of ECM components. Here, too, there is a balance between ECM synthesis by adhesive myofibroblasts and ECM degradation by extracellular MMP. MMP are in turn inhibited by the MMP inhibitors TIMP in order to prevent an excessive cell response. As with the fibrin-plasmin system, a pathological imbalance of the ECM-MMP-TIMP system leads to impaired wound healing and subsequently to an increased risk of adhesion tissue formation (52,53). Elevated PAI-1 levels in the peritoneum can impair fibrinolysis and promote adhesion formation (50). Accordingly, increased tPA levels have been shown to correlate with a lower risk of adhesion, whereas increased PAI-1 levels correlate with an increased risk of adhesion (51). Another regulator of MMP enzyme activity is the neurokinin receptor-1 (NKR-1). By antagonizing NKR-1, MMP activity could be increased and thus adhesion formation was reduced (53).

6. Adhesion prophylaxis

One has to differentiate between surgical methods and the use of so-called barrier methods when discussing strategies for minimizing adhesion formation.

As far as suitable surgical procedures are concerned, the goal is an option with minimal intraoperative trauma and thorough hemostasis (54). Thus, minimally invasive surgery, such as laparoscopy, seems to have several advantages over laparotomy (55,56).

There are several factors that determine the risk of adhesion formation during laparoscopy. One of these factors is the intraoperative hypoxia caused by carbon dioxide (CO_2) insufflation. In a mouse model, hypoxia was correlated with an upregulation of the hypoxia-induced factor 1a (HIF-1a) and HIF-1b (57). Best results with the intention to minimize this risk could be achieved with a CO_2 insufflation with a concentration of 3% added oxygen (58).

Another factor is the peritoneal insufflation pressure during laparoscopic surgery. Animal studies demonstrated more severe adhesions when higher pressures (6, 9, 12 mmHg) were applied (59). In postoperative analyses, more, larger and more severe adhesions were observed with increasing pressures. The results suggest that higher insufflation pressures may increase both ischemia and trauma to the peritoneum, thus raising the risk of adhesion formation.

Nevertheless, laparoscopic techniques can in principle be used to treat adhesions. The minimally invasive nature causes less tissue trauma and thus reduces the risk of new adhesive tissue formation (60). However, in very complex situations with dense or extensive adhesions, it can be very challenging. It may then be necessary to switch to open surgery for technical reasons. Based on the literature data, the authors assume that laparoscopic procedures offer a small but significant advantage in terms of adhesion prevention.

Several studies have investigated the molecular mechanisms of adhesion formation and gained insights into the possible prophylactic application of fibrinolytics (61). Thus, pharmacological activation of plasmin appears to be a potentially effective application to reduce adhesion. The data were confirmed with recombinant tPA, streptokinase-streptodornase and pepsin/trypsin in clinical studies. Despite promising adhesion-reducing results, however, there are only few clinical data available (61-64). One reason may be that protein/enzyme preparations are expensive to produce and sensitive in clinical use.

Barrier methods are currently the most promising methods for preventing adhesions. They act as spacers between peritoneal wound surfaces and thus reduce the formation of fibrin bridges (65). There is currently a lack of sufficient and systematic clinical evidence on adhesion prophylaxis to adequately assess the effectiveness of the various procedures. Therefore, some medical societies do not yet provide a clear recommendation for the use of adhesion prophylaxis. A consensus article from 2022 explicitly emphasizes that more and coordinated

research activities on adhesion prophylaxis should be encouraged (65). Standardized examination procedures (study design) and evaluation criteria (e.g. second-look laparoscopy) are also important instruments.

Three barrier methods have been approved by the US Food and Drug Administration: 'Interceed', 'Seprafilm' and 'Adept'. The medical product 'Adept' consists of a 4% icodextrin-solution. The resorption of this solution after surgery takes more than 96 h, as the fluid cannot be resorbed directly, but must be removed from the intraperitoneal cavity via the lymphatic system (54,66,67). In comparison, Ringer's solution is resorbed in less than 24 h and thus serves as a poor spacer between individual peritoneal layers (68). The barrier methods called 'Interceed' and 'Seprafilm' are bioresorbable membranes, which are applied intraoperatively, and have a similar purpose and way of functioning as 'Adept.'

There are also gelatinous barrier methods, e.g., 'SprayGel,' which is made of polyethylene glycol (54). These can be applied during laparotomy and endoscopically. Finally, the relatively novel barrier method called '4DryField' is applied in the form of a powder and effects both adhesion formation and hemostasis (69,70). Some studies have also failed to demonstrate sufficient efficacy of anti-adhesion candidates. For example, ibuprofen, dexamethasone and heparin exhibited no prophylactic effects with regard to the formation of adhesions.

Another innovative method for adhesion prophylaxis is the use of non-invasive physical plasma (NIPP), also known as cold atmospheric plasma. NIPP treatment is on the threshold between preclinical investigations including clinical trials and routine use in everyday clinical practice, e.g. in tissue repair and wound management (71,72). The main biomedical effect factors are ROS including free oxygen radicals. These locally modulate the immunological environment of the tissue area and can therefore reduce postoperative adhesions (73-76). NIPP inhibits both cell growth and cell-cell contacts of proadhesive peritoneal fibroblasts (77). Such anti-adhesive effects have already been described in connection with the treatment of keloid-forming fibroblasts (78). This treatment does not necessarily require the direct intraoperative use of a NIPP device, but it is also possible to apply physiologic saline solution that has itself been treated with NIPP. Such indirect treatment with NIPP has been reported to be successful in various *in vitro* cell models (79,80). Therefore, postoperative irrigation of the abdominal cavity with NIPP-treated physiologic saline could be a promising concept for adhesion prophylaxis.

7. Adhesion therapy

The primary treatment for adhesions is adhesiolysis, a surgical procedure to remove or separate the adhesions. This procedure, like any surgical intervention, carries risks, including the possibility of recurrence of adhesions. However, clinical studies on non-invasive, pharmacological and physiotherapeutic procedures have not yet revealed any significant effects in adhesion patients (81-83).

The results of clinical studies show that laparoscopic adhesiolysis significantly reduces the risk of morbidity, mortality and postoperative infections. Furthermore, serious complications and incisional complications are significantly reduced. These clinical data suggest that laparoscopic adhesiolysis, when feasible, may offer better short-term outcomes compared to open surgery (84,85). Due to their minimally invasive nature, laparoscopic procedures are considered the adhesiolysis method of choice (60).

However, surgical adhesiolysis does not always lead to a reduction in adhesion-related symptoms. In the case of adhesion-associated chronic abdominal pain, adhesiolysis did not lead to any pain relief in 33% of patients (10). In another clinical study, no improvement in pain was observed at all (86). A meta-analysis showed initial pain relief in about two-thirds of laparoscopically treated adhesion patients. However, the results did not allow any conclusions to be drawn about long-term effects (87). Abdominal pain in particular is more difficult to correlate with specific clinical pathophysiology.

In reproductive medicine, surgical adhesiolysis is evaluated much more positively. In the case of diagnosed adhesion-related infertility, surgical adhesiolysis leads to a postoperative one-year pregnancy rate of 61%. In patients with severe adhesions, however, this rate drops to In the case of diagnosed adhesion-related infertility, surgical adhesiolysis leads to a postoperative one-year pregnancy rate of 61%. In patients with severe adhesions, however, this rate drops to 20% (88).

The use of robot-assisted surgery, e.g. with the da Vinci robotic surgery system, to combat adhesions is particularly interesting with regard to innovative new procedures in surgery (89). In gynecological patients with extensive adhesions, robotic surgery showed more favorable results compared to laparoscopy, both in terms of operative time and intraoperative blood loss (90). In addition, literature analysis showed that the rate of conversion from laparoscopic surgery to open surgery due to complicated adhesions is lower when a robotic approach is used (91).

However, it should be borne in mind that curative surgical adhesion therapy carries the risk of causing new adhesions. As with adhesion prophylaxis, this underlines the unsatisfactory situation with regard to therapeutic options for tissue adhesions.

8. Conclusion

The formation of tissue adhesions is a major medical and health economic problem. Adhesions can remain asymptomatic, but they can also cause unpleasant to severe symptoms such as abdominal pain, obstruction and sterility. Furthermore, the anatomical consequences of adhesions often lead to longer and additional surgical interventions as well as longer postoperative hospital stays. This ultimately increases the healthcare costs of the treatment (92-94).

Adhesions are often diagnosed by chance during the originally planned operation. It would be possible to identify areas of adhesion prior to surgery using imaging techniques such as MRI. This can even be done with relatively good accuracy, so that such findings could be incorporated into surgical planning. However, imaging is complex and expensive and has not yet been able to establish itself in routine practice. Adhesion-minimizing prophylactic procedures are only available to a limited extent. The only effective procedures are barrier methods. These involve introducing agents into the operated area that delay contact between traumatized tissue areas in the abdominal cavity for as long as possible and thus

reduce the adhesion rate. Innovative molecular approaches relate to fibrin turnover. This can be regulated by means of fibrin-associated factors, which reduces fibrin synthesis and subsequent adhesion events. There is also initial data on using physical plasma to affect the ROS biology of the wound area, which can also inhibit adhesive processes. However, both approaches have not yet been integrated into everyday clinical practice. The treatment of identified adhesions is currently only possible surgically. Attempts with pharmacological agents have failed as ineffective. However, surgical interventions carry the risk of renewed adhesions. This can be countered to a certain extent by using minimally invasive procedures. Minimizing traumatological influences also reduces the formation of new adhesions. It has also been shown that robotic-assisted surgery can have positive and anti-adhesive effects.

As the clinical data situation is still very heterogeneous overall and there is a lack of comprehensive systematic clinical studies, there are only a few clear and guideline-based recommendations for diagnosis, prophylaxis and treatment of adhesions. The medical associations and health and science policy are called upon to take action here. In terms of the medical treatment of such tissue defects, a clear awareness of the dangers but also of the medical care options must be created. In addition, it is essential in the current situation that the political framework conditions are created that place the problem of adhesions more at the center of structured research approaches in accordance with its enormous medical and health economic significance. There are some promising approaches for the prophylaxis and treatment of adhesions, but there is still a long way to go before they can be used clinically.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

MCKS, AA and MBS were responsible for conceptualization. AA and MCKS provided the resources for the figures included. MCKS prepared the original draft. MCKS, AA and MBS reviewed and edited the manuscript. MBS supervised the project. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patients for the use of the images in Fig. 1.

Competing interests

The authors declare that they have no competing interests.

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