Chirurgia (2023) 118: 113-126
No. 2, March - April

http://dx.doi.org/10.21614/chirurgia.2840

Mechanisms and Therapeutic Approaches for Peritoneal Adhesions: A Comprehensive Review

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Abbreviations:
BCH: Bacterial cellulose hydrogel;
CMC: Carboxymethylcellulose;
SCAR: Clinical Adhesions Research;
CTGF: Connective tissue growth factor;
COX-2: Cyclooxygenase 2;
ePTFE: Expanded polytetrafluoroethylene;
FHG: Ferric hyaluronate gel;
FGF: Fibroblast growth factor;
HA: Hyaluronic acid;
HA-CMC: Hyaluronic acid and carboxymethylcellulose;
IL-1: Interleukin-1;
IL-6: Interleukin-6;
MMPs: Matrix metalloproteinases;
MCP-1: Monocyte chemoattractant protein-1;

Received: 14.02.2023
Accepted: 12.04.2023

Rezumat

Mecanismele și abordările terapeutice ale aderențelor peritoneale: un review de literatură

Aderențele peritoneale sunt responsabile pentru numeroase şi uneori severe, fenotipuri clinice, şi reprezintă o problemă majoră pentru mulți pacienți. Aderențele se formează în cavitatea peritoneală ca urmare a unei intervenții chirurgicale, inflamații sau leziuni şi pot provoca o serie de simptome, inclusiv dureri abdominale, obstrucție a intestinului subțire, infertilitate şi alte complicații. Incidența aderențelor peritoneale rămâne ridicată deoarece se estimează că peste 50% dintre pacienții care suferă o intervenție chirurgicală abdominală vor dezvolta aderențe. Deşi tehnicile chirurgicale şi managementul perioperator au progresat, riscul de formare a aderențelor nu poate fi eliminat şi, astfel, dezvoltarea unor strategii de prevenire şi a unor tratamente eficiente rămâne o prioritate în domeniul chirurgiei. În acest review de literatură rezumăm mecanismele celulare şi moleculare implicate în formarea aderențelor peritoneale, dar tratamentele experimentale care au fost studiate ca soluție anumite fenotipuri clinice.

Cuvinte cheie: peritoneu, aderențe peritoneale, biologia peritoneului, factori antiaderenți, strategii de prevenire

NAC: N-acetylcysteine;
NSAIDS: Non-steroidal anti-inflammatory drugs;
ORC: Oxidized regenerated cellulose;
PAI-1: Plasminogen activator;
PDGF: Platelet-derived growth factor;
PRP: Platelet-Rich Plasma;
PE/PC: Polyester/porcine collagen;
PET: Polyethylene terephthalate;
PP: Polypropylene;
PP/PGCL: Polypropylene/polyglecaprone;
PTFE: Polytetrafluoroethylene;
TIMPs: Tissue inhibitors of metalloproteinases;
tPA: Tissue-type plasminogen activator;
TGF-β: Transforming growth factor-beta;
TNF-a: Tumor necrosis factor-alpha;
VEGF: Vascular endothelial growth factor.

Abstract

Peritoneal adhesions are responsible for several and sometimes severe clinical phenotypes remaining a major problem for many patients today. Adhesions are formed within the peritoneal cavity as a result of surgery, inflammation, or injury and can cause a range of clinical symptoms, including abdominal pain, small bowel obstruction, infertility, and other complications. The incidence of peritoneal adhesions remains high as it is estimated that more than 50% of patients who undergo abdominal surgery will develop adhesions. Although advancements in surgical techniques and perioperative management have been developed, the risk of adhesion formation cannot be eliminated, and thus, the development of effective prevention strategies and treatments remains a priority in the field of surgery. In this review, we summarize the cellular and molecular mechanisms involved in the peritoneal adhesions, but also the experimental therapy approaches that have been investigated toward a solution to their possible clinical phenotypes.

Key words: peritoneum, peritoneal adhesions, biology of peritoneum, anti-adhesive factors, prevention strategies

Introduction

The peritoneum is the continuous serous membrane that lines the inner wall of the abdomen and covers most of the abdominal organs, including the stomach, intestines, liver, and spleen. It is considered the largest membrane in the body and its main role is to separate the abdominal from the pelvic cavity providing a smooth surface that allows the organs to move and glide against each other without friction (1,2). It plays an important role in regulating fluid balance as it secrets and absorbs fluid, which helps prevent the organs from becoming dehydrated and helps to prevent fluid build-up in the abdominal cavity. In addition to its functional role, it also has a protective function, serving as a barrier that helps to prevent infections from spreading from one part of the abdomen to another (3,4).

Disruption or injury of the peritoneum leads to peritoneal abdominal adhesion formation which is a frequent complication after abdominal or pelvic surgery, resulting from an inflammatory response and the formation of fibrous tissue (5,6). Except for surgery, a variety of factors contribute to peritoneal adhesion formation, like radiation therapy, endometriosis, peritoneal dialysis, or even more infections such as peritonitis, appendicitis, or bacterial infections common after laparotomy (7-9). Recently, it has been found that the presence of intestinal microbes within the peritoneal cavity leads to the activation of mesothelial EGFR signaling and increased formation of adhesions (10). The study provides new insights into the mechanisms behind post-surgical peritoneal adhesions and highlights the importance of proper surgical techniques and infection control measures in preventing complications (10).

The exact prevalence of peritoneal adhesions is not known, but it is estimated to affect a large percentage of people worldwide, almost 67%-93% of patients who have undergone abdominal surgery. Although the formation of adhe-

sions is a normal part of the healing process after surgery, excessive or abnormal adhesions can lead to various clinical phenotypes, such as chronic pain, bowel obstruction, infertility, and others leading to a deterioration of patients' lives, and sometimes could lead to death (5,11,12). The exact number of deaths due to adhesions is not well established, however, it could vary depending on several factors such as the population, the health care system, and the surgical procedures performed.

It is noteworthy that the Surgical and Clinical Adhesions Research (SCAR) Group conducted a study to investigate the impact of postoperative adhesions in patients who underwent abdominal and pelvic surgeries in Scotland. The study, which was conducted over a period of ten years, found that gynecological laparoscopic and open surgical procedures had a higher risk of readmissions due to complications directly associated with adhesions. Specifically, about 15% of readmissions occurred within the first year after surgery (13,14). Moreover, Ellis et al. showed that 6% of over 20,000 cases or about one-third of patients who underwent surgery were reoperated almost twice due to adhesion-related complications (15). This highlights the significant impact that adhesions can have on patient outcomes, quality of life, and healthcare utilization. Overall, in the literature, the incidence of readmissions directly related to adhesions varies from 5-20% (16,17).

The development of peritoneal adhesions remains a significant challenge in the field of abdominal surgery, and efforts are continuously being made to improve surgical techniques and perioperative management to prevent adhesion formation. An improved understanding of the molecular and cellular mechanisms involved in adhesion formation may lead to the development of novel therapies that target specific aspects of the pathogenesis of peritoneal adhesions. Herein, we aim to provide an overview of the biology of peritoneal adhesion formation and summarize the current prevention strategies to minimize the formation of peritoneal adhesions.

The Biology of Peritoneal Adhesions

The peritoneum is an important structure in biology as it plays many vital roles in the body, and its functions are essential for maintaining the health and well-being of an organism. In fact, it is a complex and dynamic system that can change in response to various stimuli. It mainly consists of mesothelial cells that are supported by a delicate connective tissue matrix, while there are two types of the peritoneum: the parietal and the visceral peritoneum (18,19). The parietal covers the inner surface of the abdominal wall, whereas the visceral is part of the peritoneum that covers the organs within the abdominal cavity (1,2). The role of mesothelial cells is to produce a lubricating fluid including glycosaminoglycans and surfactants that help to reduce friction between the organs and the peritoneal surface whereas the connective tissue matrix is composed of extracellular matrix components, including collagen fibers, glycoproteins, and proteoglycans, that provide mechanical support to the peritoneum. The matrix also contains a network of small blood vessels and lymphatic vessels, which provides the peritoneum with a rich blood supply (20-23) (*Fig. 1*).

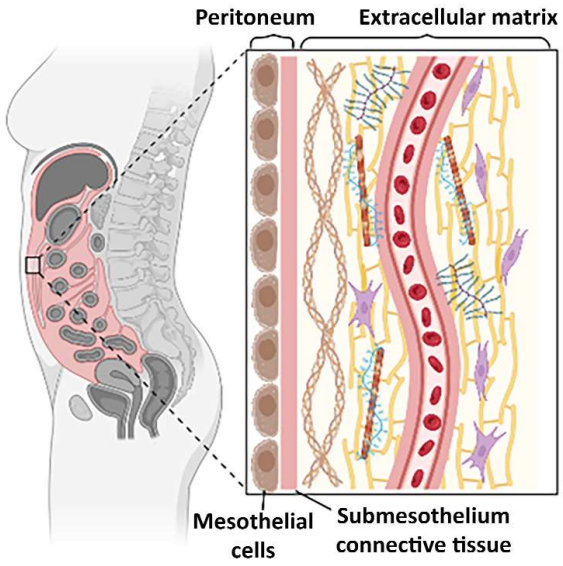

Figure 1. Schematic representation of the peritoneum which consists of a layer of mesothelial cells and connective tissue associated with the extracellular matrix.

The peritoneal fluid contains a mixture of cells, proteins, and other biological molecules like plasma proteins, sugars such as glucose, enzymes such as amylase, and inflammatory cells such as macrophages and lymphocytes, which help to protect against infection and injury, but it also contains cytokines and chemokines (24,25). Moreover, it is also rich in nerve fibers which maintain the health and function of the abdominal organs and the entire body. As nerve fibers are part of the sympathetic and parasympathetic nervous systems, they are responsible for transmitting signals from the abdominal cavity to the central nervous system providing sensory input to the abdominal cavity (18,26). The composition of cells and the volume of the peritoneal fluid could be altered under different pathological conditions. For example, in peritonitis (an inflammation of the peritoneum), the peritoneal fluid may contain increased numbers of white blood cells and other inflammatory cells (27). In other conditions, such as cirrhosis or nephrotic syndrome, the volume of peritoneal fluid can increase due to changes in pressure and fluid dynamics within the abdominal cavity (28,29), while women with endometriosis have been reported to have higher levels of peritoneal fluid, as compared to healthy women, which may be due to the presence of an inflammatory response and an increase in cytokine levels (30).

Although the delicate layer of mesothelial cells functions as a barrier preventing the formation of adhesions, its delicacy is one of the unique properties of the peritoneum that makes it highly susceptible to trauma and inflammation and thus in the formation of adhesions. Adhesions are developed through a complex and dynamic process that involves multiple factors and pathways, similar way to that described for skin wound healing (22,31). During peritoneal injuries, the mesothelial cells are detached triggering an inflammatory response attracting immune cells and the release of cytokines, chemokines such as monocyte chemoattractant protein-1 (MCP-1), and growth factors that help to promote tissue regeneration. These factors include transforming growth factor-beta (TGF-β), interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) (*Table 1*) (4,19,20). Moreover, there is an increased deposition of fibrin due to the activation of the coagulation cascade. The balance between tissue-type plasminogen activator (tPA) and plasminogen activator (PAI-1) can be disrupted, resulting in decreased fibrinolysis and an increase in fibrin deposition, which can contribute to the formation of adhesions. Studies in mice showed that these two factors are critical in regulating fibrinolysis and adhesion formation Inhibition of PAI-1 can promote fibrinolysis and reduce adhesion formation, while deficiency of tPA can lead to decreased fibrinolysis and increased adhesion formation (32-36). These findings highlight the importance of targeting specific components of the fibrinolytic system in the development of therapies for preventing or treating adhesions.

The inflammatory response also triggers the migration and proliferation of cells but also angiogenesis, which involves the formation

Table 1. Key factors involved in different stages of tissue regeneration

Process	Factors involved
Inflammation	IL-1, IL-6, TNF-α, TGF-β, PDGF, FGF, VEGF, MCP-1, MIP-1α, MIP-2, CXCL10, ICAM-1, VCAM-1
Fibrin deposition	Fibrinogen, thrombin, tPA, uPA, PAI-1, PAI-2
Cell proliferation/ migration and angiogenesis	Integrins, cadherins, selectins, chemokines, growth factors (e.g., PDGF, TGF-β, FGF)
Cell proliferation	Growth factors (e.g., TGF-β, PDGF, FGF, VEGF), EGF, insulin, IGF-1
Extracellular matrix remodeling	MMPs (e.g., MMP-2, MMP-9), TIMPs (e.g., TIMP-1, TIMP-2), plasminogen, plasmin, uPA, uPAR, PAI-1, PAI-2

of new blood vessels in the injured area. This process is important for delivering oxygen and nutrients to the injury site. Factors like VEGF, PDGF, and FGF, stimulate the proliferation and migration of endothelial cells, leading to the formation of new blood vessels (37). In addition, TGF-ß and connective tissue growth factor (CTGF) have been implicated in angiogenesis and fibrosis that may play a role in adhesion formation as well (4,36,38).

In addition, extracellular matrix turnover is also a critical component of the peritoneal response to injury. Cells migrate to the injury site to help rebuild tissue, and the extracellular matrix is reorganized to help stabilize and reinforce the new tissue (20,39). The newly formed granulation tissue mainly consisting of collagen is organized and remodeled to form permanent adhesions. This process is mediated by enzymes such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), which can be upregulated in response to injury and contribute to the formation of adhesions (24). Specifically, it has been shown that there is an increase in MMP expression and activity in the peritoneal tissue during adhesion formation. This leads to excessive ECM degradation and impaired wound healing. At the same time, there is a decrease in TIMP expression and activity, which further exacerbates the effects of MMPs. Together, these factors contribute to the formation of dense, fibrous adhesions (20,22).

It is evident that various cellular and molecular processes play an important role during peritoneal injury, repair, and regeneration and the exact mechanism is not yet completely understood. A deeper understanding of the complex and dynamic interactions between the various cell types and signaling pathways involved in the peritoneal response to injury is crucial for developing effective strategies to prevent and treat peritoneal adhesions

Current Prevention Strategies for Peritoneal Adhesions

Studies regarding the pathogenesis of adhesions have led to the development of new preventive and therapeutic strategies, which hold promise for reducing the frequency and intensity of postoperative adhesions. The prevention of peritoneal adhesions has been the subject of extensive research, and various strategies such as surgical precautions, barrier methods, and pharmacological agents have all been investigated for their potential to reduce the formation of adhesions (5,40-42) (*Fig. 2*).

Surgical precautions

Surgical precautions techniques were considered the main method that can be used to reduce the formation of peritoneal adhesions. Laparoscopic surgery is a minimally invasive technique that is associated with a lower

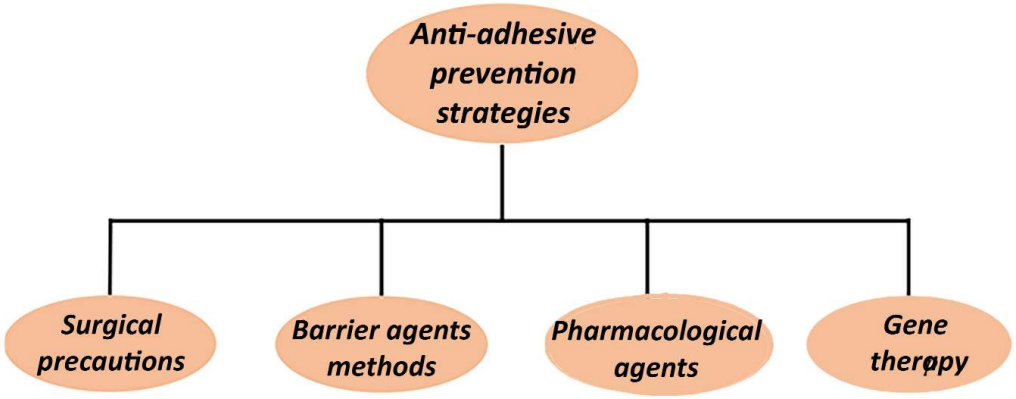

Figure 2. Classification of prevention strategies for peritoneal adhesions

incidence of peritoneal adhesions compared to open surgery. The use of smaller incisions and the ability to visualize the peritoneal cavity in high definition allow for more precise dissection and tissue preservation (43-46). The laparoscopic approach is an effective treatment for recurrent small bowel obstruction and chronic abdominal pain caused by adhesions (47). For example, the success rate of laparoscopic adhesiolysis in managing small bowel obstruction resulting from adhesions is approximately between 70% and 90% (8,48).

Moreover, robotic surgery is a relatively new surgical approach that has gained popularity in recent years due to its many advantages, including reduced blood loss, shorter hospital stays, and faster recovery times (49). Robotic surgery is also associated with a lower incidence of peritoneal adhesions compared to traditional open surgery. This is because robotic surgery involves making smaller incisions and using more precise movements, which minimizes the trauma to the peritoneum and reduces the risk of adhesion formation. While there is limited research on the specific impact of robotic-assisted surgery on the formation of peritoneal adhesions, recently, it has been found that it may have a lower risk of conversion, almost 1.5 times lower compared to traditional laparoscopic surgery (49-52). On the other hand, hybrid surgery which involves switching from laparoscopic or robotic surgery to open surgery is used in high-risk cases, such as excessive bleeding or an unclear view of the surgical site. However, the effectiveness of this approach remains unclear and requires further investigation and there is no evidence to suggest that it is specifically useful in preventing peritoneal adhesions (49,53).

Although robotic surgery is a safe and effective option with a lower incidence of adhesion-related complications and conversion rate compared to laparoscopic surgery (52), ultimately, the choice of surgical approach between robotic, laparoscopic, or hybrid surgery for the prevention of peritoneal adhesions could be made on a case-by-case basis, taking into account individual patient factors and the surgeon's expertise.

In addition to surgical techniques, other factors like gentle tissue handling, the use of delicate tools and careful dissection can help to minimize tissue trauma and lower the likelihood of developing adhesions (40). Additionally, intraoperative irrigation with warm saline or lactated Ringer's solution can help prevent adhesions by reducing tissue desiccation and minimizing ischemia-reperfusion injury (54). The use of warm fluids helps to maintain tissue temperature, the irrigation also helps to wash away any blood or tissue debris that may be present in the surgical site whereas the use of saline or lactated Ringer's solution can help to maintain tissue hydration, which is important for preventing tissue damage and promoting healing (45).

Peritoneal adhesions can form as a result of surgical procedures, particularly those involving the abdominal cavity. The risk of adhesion formation following any surgical procedure can vary depending on multiple factors, including the extent of tissue manipulation, the type and duration of the procedure, and individual patient factors such as age and medical history. Contaminated surgeries are also more likely to result in adhesion formation, regardless of the surgical technique used (10,55). Strict adherence to aseptic techniques during surgery and thorough cleansing of the surgical site can help reduce the risk of contamination and subsequent adhesion formation.

Therefore, a critical analysis of the propensity for adhesion formation is essential when planning and performing surgical procedures. Surgeons must evaluate the individual patient's medical history, surgical context, and other factors to determine the best approach and minimize the risk of adhesion formation.

Barrier agents methods

While surgical precautions techniques remain the mainstay in reducing peritoneal adhesion formation, other approaches have also been explored. Barrier agents are a common strategy used during surgery to physically

separate injured tissues and prevent their contact during the healing process (56). Some common surgeries that barrier agents may be used include bowel resections, hysterectomies, and cesarean sections, as well as surgeries in the thoracic and pelvic regions (57-59). In all cases, it has been found that these agents prevent the formation of adhesions by reducing the extent of inflammation and fibrin deposition. Different types of barrier agents have been developed, including absorbable and non-absorbable materials (41,60). Absorbable agents like oxidized regenerated cellulose, carboxymethylcellulose, or hyaluronic acid have been extensively studied in animal models and clinical trials, whereas non-absorbable materials including expanded polytetrafluoroethylene and polyethylene glycol, have also shown promise in reducing adhesion formation (40,41).

Cellulose-based barrier agents, such as oxidized regenerated cellulose (ORC) or carboxymethylcellulose (CMC), are thought to act as inert and biocompatible barriers that physically separate tissues and prevent adhesions from forming. Common commercially available products based on cellulose and used in surgery are Seprafilm and Surgicel (61). ORC does not appear to directly affect the signaling behavior of mesothelial cells, instead, it works by absorbing fluid and forming a physical barrier that prevents mesothelial cells and other tissues from coming into contact with each other, thereby reducing the risk of adhesion formation (62,63). A review of several clinical trials found that the use of oxidized regenerated cellulose agents during surgery resulted in a significant reduction (almost 60%) in the incidence of postoperative adhesions (5,45). Several other studies have also reported similar findings. For example, in a randomized controlled trial of patients undergoing laparoscopic surgery, researchers found that the use of an ORC barrier significantly reduced the incidence and severity of adhesions, as well as the need for adhesion-related reoperations, compared to a control group (45,64-66).

Similarly, CMC is a water-soluble polymer that is widely used as an excipient in the pharmaceutical industry, food, cosmetics, and biomedicine (67). However, due to its biocompatibility, biodegradability, and low toxicity, CMC has been utilized as a component of adhesion prevention barriers as it forms a gel-like barrier when placed between the peritoneal surfaces (67,68). Several studies with several randomized patients have investigated the efficacy of CMC-based barriers in reducing peritoneal adhesion formation in both animal models and human patients (61,69). Another agent which is based on cellulose is bacterial cellulose hydrogel (BCH). BCH is a biodegradable and promising material that has been found to participate in the prevention of peritoneal adhesions in animal models. Limited pre-clinical studies have investigated the use of BCH and further experimental studies are necessary to fully understand its potential benefits and limitations (70,71).

In addition, the use of a natural linear polymer, hyaluronic acid (HA), HA has been identified as a promising agent for reducing post-surgical adhesions in both animal models and clinical trials (72–75). Studies on animal models have shown the effectiveness of HA following various types of surgeries, such as abdominal, colorectal, orthopedic, and cardiac surgeries (40). The exact way in which HA reduces the formation of adhesions is not entirely known, but it is thought to protect the surfaces of mesothelial cells (76). Moreover, a clinical trial has demonstrated the efficacy of HA in preventing post-surgical adhesions, particularly in gynecological surgeries (77). This study involved 397 women who were randomized to receive either ferric hyaluronate gel (FHG) or not and the results showed that the frequency and severity of adhesions were significantly reduced in the FHG group compared to the group with no serious adverse events associated with the use of FHG (77). These findings suggest that HA may be a valuable tool in reducing the incidence of post-surgical adhesions and improving patient outcomes.

In addition, a combination of hyaluronic

acid and carboxymethylcellulose (HA-CMC) was used in patients undergoing laparoscopic appendectomy indicating the effectiveness of this membrane in reducing adhesion formation (78). Moreover, HA-CMC has also been investigated in postoperative bowel adhesions in patients undergoing laparoscopic urologic pelvic surgery. This randomized controlled trial with half receiving HA-CMC membrane and half acting as the control group, showed that the HA-CMC group had a significantly lower incidence of postoperative bowel adhesions (79). Recently, another study of patients undergoing laparoscopy for fertility-related indications found that the application of HA reduced the incidence of adhesions and improved fertility outcomes suggesting that HA may have beneficial effects on fertility (80).

It is noteworthy to mention that another promising barrier agent is the Platelet-Rich Plasma (PRP) gel. PRP is created by processing a sample of a patient's blood to concentrate the platelets, which are then combined with a gel or fibrin matrix (82). The resulting PRP gel is rich in growth factors, cytokines, and other substances that are involved in the healing process of the body. In the field of surgery, PRP gel is used to promote healing and reduce the risk of adhesion formation (81). It is believed that the growth factors and cytokines in PRP can stimulate the healing process, reduce inflammation, and promote tissue regeneration. In some cases, PRP gel is applied directly to the surgical site during or after surgery to help promote healing and reduce the risk of adhesion formation. In other cases, PRP is injected into the tissue surrounding the surgical site to promote healing and reduce inflammation (82). It is important to note that the use of PRP gel in surgery is still considered experimental, and more research is needed to fully understand its effectiveness and safety.

Except for absorbable materials, non-absorbable materials have been used as adhesion barriers as well. Examples of non-absorbable materials include polytetrafluoroethylene (PTFE), expanded polytetrafluoroethylene (ePTFE), and polyethylene terephthalate (PET) films (56,83). Studies have shown that these materials can be effective in mitigating the development of adhesions in animal models and some clinical settings, such as during spinal surgeries (84). However, there are concerns about the long-term safety of these materials and their potential to cause foreign body reactions or infections. Thus, their use is typically limited to specific surgical procedures and patient populations where the benefits are believed to outweigh the risks (41). A comparative analysis in rats following the implantation of three types of mesh materials: polypropylene (PP), polypropylene/polyglecaprone (PP/PGCL), and polyester/porcine collagen (PE/PC) showed that the PP/PGCL and PE/PC meshes caused significantly fewer adhesions than the PP. Additionally, the degree of inflammation was lower in the PE/PC group compared to the other two groups suggesting that the different mesh materials may have varying effects on the formation of peritoneal adhesions, with some materials causing less inflammation and fewer adhesions (85).

The use of both absorbable and non-absorbable materials has been shown to be effective in reducing the incidence of adhesions. However, the success of these methods depends on several factors such as the type of surgery, the patient's overall health, and the proper post-operative management.

Pharmacological agents

In addition to barriers, pharmacological agents can also be used to reduce the formation of peritoneal adhesions. These agents include fibrinolytic agents, antioxidants, anti-inflammatory drugs, and other compounds that can modulate the cellular and molecular processes involved in adhesion formation. Examples of these agents include nonsteroidal anti-inflammatory drugs (NSAIDs), and tumor necrosis factor (TNF)-alpha inhibitors (40,41).

Fibrinolytic agents, such as tPA and uPA have been investigated as potential methods for preventing postoperative adhesions (86).

Fibrinolytic agents work by promoting the breakdown of fibrin, which is a key component of adhesions (87,88). Clinical trials have shown that the use of tPA can reduce the incidence of postoperative adhesions while its efficacy has produced alternative results, with some studies showing a reduction in adhesion formation and others showing no significant difference compared to control groups. Streptokinase is a fibrinolytic agent that can dissolve fibrin clots and adhesions. However, it can lead to bleeding complications and severe hypotension symptoms due to allergic reactions (89,90). Moreover, antioxidants, such as N-acetylcysteine (NAC), have also been investigated for their potential to reduce the formation of adhesions. Oxidative stress is a key factor in the formation of adhesions, and antioxidants may help to reduce this stress. NAC can have anti-adhesive effects when applied locally to the surgical site (91). In a rabbit model, NAC applied with a sponge was effective in preventing post-operative pericardial adhesions, and the sponge was then removed from the surgical site (92). However, the efficacy of NAC in preventing adhesions in humans has not been well-established.

Tumor necrosis factor (TNF)-alpha inhibitors have been investigated for their potential to prevent postoperative peritoneal adhesions as well (93). TNF-α is a pro-inflammatory cytokine that is involved in the inflammatory response to injury and infection. It has been implicated in the pathogenesis of postoperative adhesions, as it promotes the recruitment and activation of inflammatory cells and the production of extracellular matrix proteins (4). TNF-α inhibitors, such as infliximab, adalimumab, rosuvastatin, or even more corticosteroids such as dexamethasone and methylprednisolone, triamcinolone have been demonstrated to decrease adhesion formation in animal models of peritoneal adhesions while clinical trials of TNF-α inhibitors for the prevention of postoperative adhesions have not yet been performed (94). Recently, Purandare et al. showed the effect of triamcinolone on the formation of postoperative adhesions in a rat model. The results suggest that the administration of triamcinolone significantly reduces the formation of post-operative adhesions, possibly by altering mitochondrial function (95). Despite the promising results of preclinical studies, and the use of TNF-α inhibitors the potential benefits of these agents need to be weighed against their potential side effects, including an increased risk of infections, malignancies, and reactivation of latent tuberculosis but also TNF-α inhibitors can be very expensive, which limits their widespread use.

NSAIDs are commonly used to reduce inflammation and pain. NSAIDs including ibuprofen, celecoxib, naproxen, and aspirin, may help reduce the formation of postoperative adhesions by inhibiting the production of prostaglandins, which are involved in the process of adhesion formation (96-99). Studies have been performed in rabbit, hamster, guinea pig, and porcine models and showed that NSAIDs reduce the severity and extent of peritoneal, pelvic, and tendon adhesions particularly when administered locally to the surgical site (40,100-102). The exact mechanism by which NSAIDs reduce adhesions is not fully understood, but it is believed to be due to their inhibition of cyclooxygenase 2 (COX-2), which leads to decreased production of prostaglandins in the inflammatory cascade (83). NSAIDs also block the production of thromboxanes, which are involved in the biochemical pathways leading to adhesion formation (98). However, systemic administration of NSAIDs can cause various side effects, so local delivery of NSAIDs in inert physical barriers has become a more recent approach for adhesion prevention. There have been no in-human trials to examine the efficacy of NSAIDs in reducing post-surgical adhesions.

Moreover, natural anti-inflammatory agents, such as green tea extract, and Turkish galls extract, have also been investigated for their potential anti-adhesion effects in rats (103,104). Additionally, the treatment with a traditional Chinese herbal medicine known as 'HuoXueTongFu formula' has been recently found to prevent peritoneal adhesions in

a rat model by regulating macrophage polarization and the SOCS/JAK2/STAT/PPAR-γ signaling pathway (105). Specifically, the formula reduced the expression of pro-inflammatory cytokines and chemokines while increasing anti-inflammatory cytokines, leading to a shift towards an M2 macrophage phenotype. This was associated with the downregulation of the SOCS/JAK2/STAT signaling pathway and upregulation of PPAR-γ, which has anti-inflammatory effects. Overall, this study provides evidence that 'The HuoXueTongFu formula' is a potential therapeutic agent for preventing post-surgical peritoneal adhesions through modulation of macrophage polarization and the SOCS/JAK2/STAT/PPAR-γ signaling pathway (105). Moreover, the potential of ligustrazine, a natural compound derived from the Chinese herb Ligusticum chuanxiong Hort, in preventing the formation of postoperative peritoneal adhesions has been studied (106). Using a rat model, the ligustrazine treatment significantly reduced the incidence and severity of peritoneal adhesions and revealed the underlying mechanism of action, showing that ligustrazine inhibits inflammation and fibrosis by down-regulating the expression of TGF-ß1 and Smad3 (106). While these natural agents have shown promise in reducing adhesion formation in animal models, further research is needed to determine and evaluate the safety and efficacy of this traditional medicine in human patients.

Gene therapy

Gene therapy is an emerging field of research that holds great promise for the development of new therapeutic approaches, and it could be considered a potential treatment option for peritoneal adhesions, although research in this area is still in its early stages. Several genes could be identified as potential targets for gene therapy in the prevention and treatment of peritoneal adhesions, such as TGF-ß, TIMP-1, and IL-10 (107). Viral vectors could efficiently deliver genes to cells in the peritoneum, and they can provide sustained expression of the therapeutic protein over an extended period. This sustained expression can help to prevent adhesion formation by blocking the activity of genes and molecules that promote adhesion formation, or by promoting the activity of genes and molecules that prevent adhesion formation. While traditional pharmacological therapies have limitations in terms of their efficacy and safety profile, gene therapy could have the potential to provide targeted, long-term effects that can prevent the formation of adhesions following surgery.

One approach could involve the use of anti-inflammatory genes to reduce the inflammatory response that occurs after a peritoneal injury, for example, the gene of IL-10 which is a potent anti-inflammatory cytokine and has been indicated to mitigate the formation of peritoneal adhesions in animal models (108). In addition, the use of genes promotes fibrinolysis and prevents the formation of fibrin clots. For example, the gene of the tPA, which promotes the breakdown of fibrin clots, has been shown to reduce the formation of peritoneal adhesions in animal models (107). Additionally, genes that promote the differentiation of fibroblasts into myofibroblasts, which are the main cell type responsible for the formation of peritoneal adhesions, could be used to reduce their numbers and prevent adhesion formation.

However, there are still significant challenges that need to be addressed before gene therapy can become a viable clinical option for adhesion prevention. These include the need to develop safe and effective gene delivery methods, as well as to identify the optimal target genes and doses for gene therapy. The use of gene therapy for adhesion prevention is still in the experimental stage and requires further investigation.

Conclusions

To date, despite the current knowledge that is constantly evolving, abnormal peritoneal adhesions remain a challenging clinical problem. While significant progress has been made in understanding the underlying

mechanisms of adhesion formation, the exact mechanisms are still not fully understood, thus a comprehensive understanding of the involved cellular and molecular processes could help to identify novel targets for therapy, allowing for more effective prevention and treatment of peritoneal adhesions. The development of various preventive and therapeutic strategies is crucial to improve patient outcomes and reducing healthcare costs. Several prevention strategies, including physical barriers, pharmacological agents, and gene therapy, have been developed for adhesion prevention. Physical barriers are the most commonly used method for adhesion prevention, while NSAIDs are the most investigated pharmacological agents for their anti-adhesive effects. On the other hand, although gene therapy is still in the experimental stage and requires further investigation is a promising technique. Despite this, recent studies have shown that the combination of two or more preventive strategies can provide better outcomes compared to single-agent therapies. Nonetheless, the continued search for safe and effective pharmacological agents to prevent peritoneal adhesions remains an important area of research, with the potential to significantly improve patient outcomes following abdominal surgery. Despite these approaches, the prevention of peritoneal adhesions remains a challenging problem with no single solution. Further research is needed to better understand the underlying mechanisms of adhesion formation and to develop more effective prevention strategies.

In conclusion, this review may highlight potential emerging therapies for preventing and treating peritoneal adhesions. It could also identify areas where further research is needed to better understand the mechanisms underlying adhesion formation and identify new therapeutic targets. Additionally, the review may provide insights into strategies for improving surgical techniques and minimizing the risk of adhesion formation. Overall, the review could serve as a valuable resource for clinicians and researchers working in this field, providing a comprehensive overview of the current state of knowledge and highlighting future directions for research and clinical practice.

Competing Interests

The authors declare that they have no competing interests for this article.

Author's Contributions

KS designed the review outline and wrote the first draft. KS, KE, AT, GG, EGK and SR coordinated the subsequent revisions and updated the manuscript and the figure design. KS, KE, AT, GG, SR, GR, NN and KK and DP commented and revised the manuscript. All authors read and approved the final manuscript.

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