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Pathophysiology of Adhesions

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Rezumat

Fiziopatologia aderenţelor

Formarea unor aderenţe intraperitoneale după chirurgia abdominală sau pelvină este un fenomen foarte frecvent. Deşi nu există o definiţie unanim acceptată, ele reprezintă punţi de ţesut cicatricial între diferite organe din cavitatea peritoneală ca rezultat al unui proces excesiv de reparare locală. Aderenţele pot fi congenitale sau câştigate după un proces local inflamator. Unele aderenţe pot fi asimptomatice, dar multe dintre ele pot determina complicaţii severe, cum ar fi dureri abdominale sau pelvine, intertilitate feminină, ocluzia intestinală. Medicii şi pacienţii trebuie informaţi despre posibilitatea apariţiei postoperatorii a aderenţelor intraperitoneale şi această posibilitate trebuie menţionată în consimţământul informat semnat de pacient. În formarea aderenţelor sunt implicate multiple mecanisme proinflamatorii, multe cu o fiziopatologie încă incomplet cunoscută. Procedurile laparoscopice nu diminuă cu mult posibilitatea de apariţie a aderenţelor postoperatorii. Diagnosticul imagistic este destul de nesigur, iar posibilităţile de prevenire modeste ca rezultat final. Folosirea unor tehnici chirurgicale corecte şi evitarea unor manevre traumatizante pentru organele intraperitoneale pot ajuta la scăderea procentului de aderenţe postoperatorii.

Cuvinte cheie: complicaţii postoperatorii, aderenţe intraperitoneale, fiziopatologie, inflamaţie, dureri abdominale, cicatrizare, laparoscopie

Abstract

Formation of intraperitoneal adhesions after abdominal or pelvic surgery is a very common phenomenon. Although there is no universally accepted definition, they are bridges of scar tissue between the various organs of the peritoneal cavity as a result of a local repair process excessively. Adhesions can be congenital or acquired as a local inflammatory process. Some adhesions can be asymptomatic, but many of them can cause severe complications such as abdominal or pelvic pain, female infertility, and intestinal obstruction. Physicians and patients should be informed of the possibility of postoperative intraperitoneal adhesions and this possibility should be mentioned in the informed consent signed by the patient. The formation of adhesions has multiple proinflammatory mechanisms involved, many with a pathophysiology still incomplete understood. Laparoscopic procedures do not diminish much the possibility of developing postoperative adhesions. Diagnostic imaging is quite uncertain, and the possibilities of preventing with a poor final result. The use of correct surgical technique and avoidance of traumatic intraperitoneal organs maneuvers may help reduce postoperative adhesions incidence.

Key words: postoperative complications, intraperitoneal adhesions, pathophysiology, inflammation, abdominal pain, scarring, laparoscopy

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Prelude

Postoperative adhesions represent a common consequence in patients who underwent abdominal or pelvic surgery. Such adhesions can be asymptomatic, but they can cause complications such as chronic abdomino-pelvic pain, secondary infertility, an increase in bowel obstruction risk and more complexity for future surgery, including longer surgery times and an increase in morbidity. (1) Even though all of these complications may occur shortly after the operation, the manifestation of these complaints several years after operation is not unprecedented. (2) Adhesions may act as vascular grafts between healthy organs and areas of ischemic tissue, reflecting the body's attempt to overcome the local damage. (3)

Definition

The literature contains neither an official definition of adhesions nor a recognized standardized classification for objective assessment of their extent and severity. There is a lack of clinically oriented guidelines for the diagnosis, treatment and options for reduction of adhesions. (4)

Adhesions are fibrous bands of scar tissue, often result of surgery, that form between internal organs and tissues, joining them together abnormally. (5) Peritoneal adhesions may be a thin film of connective tissue, a thick fibrous bridge containing blood vessels and nerve tissue, or a direct contact between two organ surfaces. (6)

Adhesions may be classified as either congenital or acquired. The majority of adhesions are postsurgical. Congenital adhesions are a consequence of embryological anomaly in the development of the peritoneal cavity. Acquired adhesions result from the inflammatory response of the peritoneum that arises after intra-abdominal inflammatory processes, radiation and surgical trauma. (7) Postoperatively, they have been classified as de novo (type 1) or reformed (type 2). (8)

The problem of postsurgical adhesions increases with the patient's age, the number of laparotomies, and the complexity of surgical procedures. The number of prior episodes a patient has experienced is the strongest predictor of recurrence.

Only 10% of patients had documentation of postoperative adhesions on their consent forms. There is a failure to inform patients about this important postoperative problem. (9)

In contrast to most surgical complications, the risk of adhesion-related morbidity remains for many years and complications are often not followed up by the primary surgeon. Thus, it is essential to discuss adhesions as a possible complication during the informed-consent process. In addition, in case of any reoperation, a high risk of inadvertent organ damage exists and should be discussed prior to surgery as well. These recommendations apply also for laparoscopic procedures. (10)

Frequency

It is estimated that peritoneal adhesions develop after 93-100% of upper abdominal laparotomies and after 67-93% of lower abdominal laparotomies. Nevertheless, only 15-18% of these adhesions require surgical reintervention. The laparoscopic approach appears to decrease the risk of adhesion formation by 45%. (11)

Post-mortem examination of patients who had not undergone surgery identified postinflammatory adhesions in 28% of cases. These are caused by intra-abdominal inflammation or can be attributed to endometriosis, peritonitis, radiotherapy, or long-term peritoneal dialysis. (4)

Diagnosis

It is generally considered that some people are more prone to develop postoperative adhesions than are others. Unfortunately, there is no available marker to predict the occurrence or the extent and severity of adhesions preoperatively. Additionally, there are no available serum markers or imaging studies that are generally considered to be able to predict the incidence, severity, or extent of adhesions. (8) Post-surgically, many adhesions may be asymptomatic or can lead to a broad spectrum of clinical problems, including intestinal obstruction, chronic pelvic or abdominal pain and female infertility, requiring re-admission to hospital and often additional surgery, while at the same time they can complicate future surgical procedures. (7)

The patients' symptoms include meteorism, irregular bowel movements, chronic abdominal pain, digestive disorders, intestinal occlusions and often fail to be associated with their cause. (4)

Intra-abdominal adhesions are predominantly diagnosed intraoperatively. Careful history taking can substantiate the suspicion of adhesions. Evidence pointing to adhesions may be yielded by high-resolution ultrasonography and functional cine MRI, both of which detect limited movement relative to one another of organs joined by adhesions. However, neither of these modalities is established in routine clinical practice. (4)

Complications

Adhesion-related reoperations are a common consequence of surgical procedures and adhesiolysis is followed by a high incidence of adhesion reformation and de-novo adhesion formation. (7)

The incidence of adhesive small bowel obstruction after oncologic gynecological surgery is about 11%. The incidence of adhesions can increase with postoperative radiation therapy.

Adhesions are the leading cause of secondary female infertility worldwide, and an important cause of chronic pelvic pain. Fifteen to 20% of female infertility is caused by adhesions. In addition, adhesiolysis during reoperation is time-consuming and exposes the patient to the risk of unintended injury such as enterotomy. (12)

Small bowel obstruction has a 10% risk of mortality. Inadvertent enterotomy at adhesiotomy occurs in 19% of patients undergoing reoperation.(13)

Chronic lower abdominal pain severely impairs the quality

of life of those affected and forms the indication for 30% to 50% of all laparoscopies and 5% of hysterectomies. It is difficult to advise those suffering from such pain whether an operation will reveal the cause and whether laparotomic or laparoscopic adhesiolysis may relieve their symptoms. (4)

It is possible that a common mechanism for pelvic pain exists and that adhesions are only associated features. Bradykinin, histamine and other autacoids are able to stimulate pain receptors. Although adhesions are thought to cause pain indirectly by restricting organ motion, thus stretching and pulling smooth muscle of adjacent viscera or the abdominal wall, adhesions themselves are capable of generating pain stimuli. Nerve fibres, identified histologically, ultrastructurally, and immunohistochemically, were present in all examined peritoneal adhesions. Furthermore, fibres expressing the sensory neuronal markers calcitonin gene-related protein and substance P were present in all adhesions irrespective of reports of chronic abdominopelvic pain. (6)

Overall, approximately one-third of patients who underwent open abdominal or pelvic surgery were readmitted an average of two times over the subsequent 10 years for conditions directly or possibly related to adhesions. (6)

The rate of recurrence after adhesiolysis is 85%. (1)

Costs

A number of studies have shown that the economic burden of adhesiolysis is significant. (12) The clinical consequences of peritoneal adhesions have a significant relevance for the health insurance companies and the social system. (14)

The exact cost of adhesion- related complications is much higher, if the costs for outpatient medical care, infertility treatment and absence from work are also considered. (7)

In the USA, adhesive small bowel obstructions led to over 2,200 deaths in 2001 and more than 67,000 hospital admissions with the length of hospital stay averaging 9.8 days. The financial burden to the US healthcare system of these adhesion-related hospital admissions is estimated to be greater than $5 billion dollars annually. (15)

Physiology

The peritoneum is a serous membrane covered by a monolayer of flat, microvilli-rich mesothelial cells, which are anchored to a basement membrane. The submesothelial, vascularised connective tissue consists mainly of a thin layer of loose collagen fibres including some fibroblasts and nerve fibres. (14)

Physiologically, mesothelial cells are responsible for the frictionless gliding of intraperitoneal organs by secreting substantial amounts of phosphatidylcholine. Mesothelial cells also create an antithrombotic surface and possess fibrinolytic activity. They are also involved in the immunological response of the peritoneum by activating lymphocytes and monocytes. (16)

Activated mesothelial cells are able to synthesize biologically active mediators such as nitrogen monoxide, plasminogen activator inhibitor and tissue plasminogen activator. Mesothelial cells are actively involved in serosal wound healing and in the regulation of peritoneal inflammation. (14)

Etiology

Adhesions develop after an injury to the normal peritoneal tissue. This injury can result from surgery, trauma, inflammation, infection, or foreign body placement in the peritoneal cavity. Ischemia has been proposed as the most important injury that leads to adhesion development. Another possible underlying mechanism may be a deficient, suppressed, or overwhelmed natural immune system. (8)

Surgical trauma, i.e., the combined impact of cutting, coagulation, and pressure-induced ischemia – particularly from excessively tight knots – may bring about peritoneal damage. Equally, mesothelial injury results from bacterial inflammation processes, from contact, from bright surgical lights, or from use of dry drapes. The greater omentum is involved in 80% of cases of postoperative intra-abdominal adhesions, the bowel in only around 50%. (4)

Microarray analysis of adhesions identified specific genes with increased and decreased expression when compared with normal peritoneum. Knowledge of these genes and ontological pathways with altered expression provides targets for new therapies to treat patients who have or are at risk for postoperative adhesions. (17)

Pathophysiology

The pathophysiology of adhesion formation remains poorly defined, and a uniformly effective method of adhesion prevention does not exist. (18)

After damage of the serosal membrane as a result of physical, chemical, biochemical or biological influences, wound healing occurs within 5 to 10 days. This time frame is independent of the size of the damaged surface. (14)

The dynamic sequences of cellular events within peritoneal wound healing are regulated by various cytokines and mediator substances. In fact, the processes of wound healing in the serosa show molecular similarities to that in the dermis, which represent an important model for wound healing. The first morphological reaction after serosal injury is the exudation of a dense fibrin layer which is then infiltrated by polymorphonuclear granulocytes within the first 12 h. (14)

After 24–36 h, the main cellular component is dominated by numerous macrophages. Already 2 days after injury the wound is almost completely covered by a monolayer of macrophages embedded in a scaffold of fibrin. In addition, primitive mesothelial cells are detectable in deeper regions of the lesion. Furthermore, groups of mature mesothelial cells, which are already connected via desmosomes and tight junctions, can be found on the surface of the lesion. (14)

After 5 days, the process of wound healing is already partially completed as shown by a single cell layer of mesothelial cells covering the wound surface. On day 7, a

discontinuous basement membrane is present. At day 8, the entire traumatized area is lined by a monolayer of mesothelial cells, which are anchored with a continuous basement membrane on day ten. In the wound bed, fibroblasts arrange their longitudinal axis parallel to the wound surface and bundles of collagen are present between the fibroblasts. (14)

Wound healing is a dynamic process in which the interplay between mediators, blood cells and extracellular matrix leads to the regeneration of the inner or outer body surface. (14)

After 24–36 h the fibrin clot is infiltrated by macrophages and granulocytes. The following reparative phase comprises the formation of granulation tissue by the sprouting of capillaries and fibroblasts. Subsequently, the granulation tissue is altered by further resorption of the exudate and distinct collagen synthesis into mature scar tissue. This process can last for weeks to months.

If the wounded serosal area is connected with a neighboring surface (e.g. bowel or abdominal wall) by the fibrin clot, repair via fibroblasts will lead to the formation of a permanent adhesion consisting of fibrous and fat tissue with nerve fibres and blood vessels, which is responsible for clinical symptoms such as obstruction. In the case of lack of contact with a neighboring structure, a newly formed surface containing a monolayer of mesothelial cells will be created. (14)

After injury to the normal mesothelial cells vasoactive substances such as histamines and kinins are released by the disruption of stromal mast cells, increasing vascular permeability, which contributes to the collection of a fibrin-rich exudates that covers the injured area. Two processes occur essentially simultaneously. In one, the fibrin polymers in this exudate interact with fibronectin to form the fibrin gel matrix, which consequently produces fibrin bands between the injured areas. At the same time, fibrinolysis starts. Fibrinolysis dominates at sites where healing occurs without adhesions. In contrast, if fibrinolysis is impaired, this imbalance may result in the persistence of the fibrinous mass. (8)

Subsequently, proliferating fibroblasts invade this area and deposit extracellular matrix material including collagen that contributes to the formation of adhesion. After elicitation of angiogenesis factors such as vascular endothelial growth factor (VEGF), proliferation of endothelial cells initiates the development of vascular structure within the adhesion tissue. Thus, different mechanistic steps regulate the healing process, with imbalances in any of these potentially contributing to adhesion development. Furthermore, it is likely that these activities are more pronounced at sites with prior fibrosis, such as those undergoing adhesiolysis. (8)

It has been demonstrated that fibroblasts in the adhesion tissues have different phenotype (myofibroblasts) than do the normal peritoneal tissue fibroblasts. More importantly, it has been shown that conversion of these cells from the normal phenotype to the adhesion phenotype can be induced by hypoxia. Compared with peritoneal fibroblasts, adhesion fibroblasts have a significant increase in the basal mRNA levels for collagen I, fibronectin, matrix metalloproteinase-1 (MMP-1), tissue inhibitor of metalloproteinase-1 (TIMP-1), transforming growth factor (TGF)-β1, (TGF)-β1, cyclooxygenase-2 (COX-2), and interleukin (IL)-10. (8)

Tissue plasminogen activator (tPA) and plasminogen activator inhibitor type-1 (PAI-1) are intracellular enzymes found in the peritoneal mesenchymal cells. These constitute the intrinsic protective fibrinolytic activity of fibroblasts. The tPA/PAI-1 ratio has been shown to be 80% higher in normal peritoneal fibroblasts than in adhesion fibroblasts. Under hypoxic conditions, this ratio significantly decreases in normal fibroblasts (90%), with an even more exaggerated decrease observed in adhesion fibroblasts (98%).(8)

COX-2 enzyme has been shown to have an important role in the regulation of inflammatory and angiogenesis steps of postoperative adhesions development. In adhesion fibroblasts, the expression of COX-2 is significantly increased compared with that of the normal fibroblasts. Hypoxia enhances the level of COX-2 expression in normal fibroblasts whereas there is no change in adhesion fibroblasts. (8)

Both normal peritoneal and adhesion fibroblasts expressed IL-6 and TNF-α. Adhesion fibroblasts exhibited significantly higher levels of IL-6 and TNF-α mRNA as compared to normal peritoneal fibroblasts. Both IL-6 and TNF-α mRNA levels were up-regulated in response to hypoxia in both normal peritoneal and adhesion fibroblasts. The increase in IL-6 and TNF-α mRNA level of normal fibroblasts reached the levels observed in adhesion fibroblasts. Hypoxia promotes the development of the adhesion phenotype by the induction of inflammatory markers, which may contribute to the development of postoperative adhesions. (19)

The process of adhesion formation might be regarded as an ischemic disease. Under hypoxic conditions, metabolic enzymes are regulated via hypoxic responsive elements by the hypoxia-inducible factor 1 (HIF-1). (20)

Thrombin is formed by activated complement and coagulation cascades and breaks fibrinogen down to fibrin, which then combines with fibronectin from the peritoneal connective tissue to form a temporary wound bed, into which peritoneal cells and fibroblasts migrate. Within the next 72 h local mesothelial fibrinolysis begins. This physiological fibrinolytic activity is based on synthesis of urokinase-like plasminogen activator (u-PA) and tissue plasminogen activator (t-PA), which release plasmin, a local protease with broad substrate specificity, from plasminogen. Plasmin degrades fibrin polymers, components of the extracellular matrix and basal membrane, and activates other proteases, e.g., matrix metalloproteinases. This depletion of fibrin deposits then results in complete healing. (4)

Molecular pathways involved in fibrinolysis inhibition, inflammation, and tissue hypoxia crosstalk and potentiate the effect of each. The principal molecular aberrations included in this crosstalk are the reduction of tissue plasminogen activator (tPA) and up-regulation of TGF-β1 and HIF-1α. (21)

Laparoscopy

It is generally accepted that laparoscopy, compared with

open surgery, reduces adhesion formation.

Open surgery has more additional traumatic effects related with the midline incision line (MIL) giving access to the operated organs, tissue drying, direct hand-manipulations, accumulation of foreign bodies and severe tissue ischemia by MIL extension, ligations and suturing of the abdominal wound. Most of these tissue traumatic factors are reduced or excluded during laparoscopy with subsequent beneficial outcome such as fast postsurgical recovery, less morbidity, pain decrease etc. (22)

However, laparoscopic surgery entails other, specific effects due to the use of gas media to extend the abdomen. (22) In an animal model, CO2 laparoscopic surgery did not decrease the formation of postoperative adhesion, compared with open surgery. (23)

Most mammalian cells can respond to oxygen level alterations by increasing or decreasing the expression of specific genes. The hypoxic regulation of many of these genes, such as plasminogen activator inhibitor (PAI) and vascular endothelial growth factor (VEGF), takes place at both transcriptional and posttranscriptional levels. The transcriptional regulation is mediated by transcription factors known as hypoxia inducible factors (HIFs). (24)

No new adhesion formation occurs after postoperative day 7. Theoretically, optimal prevention of adhesion formation requires intervention throughout the critical 7-day period of peritoneal healing. (25)

There is no difference between peritoneal healing and adhesion formation for the first 3 days after peritoneal injury. The fibrinolytic activity normally begins three days after peritoneal injury and increases to a maximum by day 8. Therefore, those adhesions that will be formed are in place by day 8, when mesothelial regeneration has been completed. (7)

VEGF expression is crucial for the vascularisation of the fibrous tissue bands. (14)

Substance P released at sites of tissue injury, in addition to promoting inflammation, is thought to stimulate proliferation of epithelial, vascular, and connective tissue cells as part of the wound healing process. Substance P may induce tissue fibrosis via augmentation of cytokine-induced fibroblast proliferation, effects on collagen organization, and regulation of matrix metalloproteinase expression. (26)

Laparoscopy induces peritoneal acidosis and the intense illumination of the peritoneum may affect the peritoneum, either directly or indirectly, by causing local desiccation. Local TGF-b levels were affected by the intensity of light. Other components are intraabdominal pressure, duration of procedure, choice of dissection devices, desiccation, and the insufflation gas. (27)

It does not appear that laparoscopic adhesiolysis results in a greater reduction of postoperative adhesion reformation than is able to be achieved by laparotomy. De novo adhesion formation after operative laparoscopy has been reported to occur in only 12% of the cases versus 50% after laparotomy. However, laparoscopic reproductive pelvic surgery as compared with laparotomy procedures has been shown in various animal and clinical studies to result in less recurrent and de novo adhesion formation. (28)

Peritoneal adhesions may be seen as a chronic inflammatory process. Peritoneal adhesions reflect a continual dysfunction in cell differentiation and cell proliferation in an ongoing inflammatory process. (29)

Epidermal growth factor (EGF) facilitates peritoneal membrane healing by augmenting cell adhesion and migration. EGF has important roles in DNA synthesis, cell proliferation, and wound healing. (30)

Generally, adhesion formation may be regarded as defective wound healing and as disturbed in situ regeneration of the peritoneal surface. (3) There is no association between the morphology of peritoneal adhesions and the number of previous abdominal surgeries. (31)

Elder and mature adhesions reveal less collagen bundles than younger adhesions, whereas the amount of adipose tissue increases over time. (31)

Conclusions

The prevention of postoperative adhesions is an important public health goal, particularly in light of the frequency of this complication. The routine use of anti-adhesion products is not recommended given the lack of studies with a high level of evidence concerning their efficacy and safety of use. (11)

Every step in the pathophysiology of adhesions formation may be an opportunity to intervene and to stop the cascade of events.

Avoiding injury to the peritoneum should be the most important premise to prevent peritoneal adhesions following intraperitoneal surgery. Influencing the inflammatory response to the peritoneal injury seems to be necessary in preventing peritoneal adhesions. (29)

All patients should be informed about the consequences induced by adhesion formation.

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