REVIEW ARTICLE

Intra-abdominal Adhesions

Definition, Origin, Significance in Surgical Practice, and Treatment Options

Dörthe Brüggmann, Garri Tchartchian, Markus Wallwiener, Karsten Münstedt, Hans-Rudolf Tinneberg, Andreas Hackethal

SUMMARY

Background: Intra-abdominal adhesions arise after more than 50% of all abdominal operations and are an important source of postoperative complications. They attach normally separated organs to each other and can cause major problems for the affected patients by giving rise to small bowel obstruction, chronic pelvic pain, dyspareunia, infertility, and higher complication rates in subsequent operations. They are also a frequent source of medicolegal conflict. Thus, every physician should be familiar with their mechanism of origin, their consequences, and the methods by which they can be prevented.

Methods: A selective PubMed/Medline search from 1960 onward as well as articles to which these publications referred. The expert consensus position of the European Society for Gynaecological Surgery is also taken into consideration.

Results: Adhesions arise through aberrant wound healing after peritoneal injury with further influence from a variety of other factors. Preventive measures include minimizing peritoneal injury intraoperatively through the meticulous observance of basic surgical principles, moistening the mesothelium to keep it from drying out, irrigating the peritoneal cavity to remove blood and clot, and keeping the use of intra-abdominal foreign material to a minimum.

Conclusion: Adhesions are an inevitable consequence of intra-abdominal surgery. They can be prevented to some extent with meticulous surgical technique and certain other measures. For operations carrying a high risk of postoperative adhesions, e.g., surgery on the adnexa or bowel, commercially available peritoneal instillates or barrier methods can be used to limit adhesion formation.

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Intra-abdominal adhesions following surgery represent a major unsolved problem (1). They occur after 50% to 100% of all surgical interventions in the abdomen and can complicate future surgery considerably (2). Dembrowski published the first data on induction of adhesions in an animal model in 1889 (3), and the intervening 120 years have seen extensive studies in vitro and in vivo. Nevertheless, the literature contains neither an official definition of adhesions nor a recognized standardized classification for objective assessment of their extent and severity. Accordingly, study findings are often imprecise and do not lend themselves to adequate interpretation. By the same token, there is a lack of clinically oriented guidelines for the diagnosis, treatment and options for reduction of adhesions.

The severe consequences of intra-abdominal adhesions for patients, physicians, and healthcare systems stand in stark contrast to the low level of awareness and knowledge—due not least to the lack of standardization and the patchy data—among doctors. Against that backdrop, this article sets out to:

- Increase clinicians' awareness of adhesions and their consequences
- Offer an overview of the pathogenesis of adhesions
- Describe universally applicable and readily implemented strategies to reduce the occurrence of adhesions
- Introduce commercial products for reduction of adhesions.

Material and methods

We performed the literature search for this review with the aid of our working group's existing database. This database, comprising articles published in PubMed/Medline since 1960, is updated monthly by addition of all articles found using the search terms "adhesions", "intraperitoneal adhesions", "intraabdominal adhesions", "adhesion reduction", "adhesion prophylaxis", and "adhesion formation". It also contains relevant publications found in the reference lists of the articles identified. The expert consensus position of the European Society for Gynaecological Endoscopy was taken into consideration.

Types of adhesions

Intra-abdominal adhesions may be congenital or acquired. Congenital adhesions arise during physiological

BOX 1

Overview of factors that influence the formation of adhesions*[1]

- Complexity of operation (e1)
- Extent of peritoneal trauma (e2, e3)
- Previous illness (e.g., diabetes) (4)
- Poor nutritional status (4)
- Intra-abdominal placement of foreign bodies (e.g. meshes) (4)
- Excessive coagulation with tissue necrosis (e4)
- Accompanying bacterial infection (4)
- Laparoscopy
  - Dehydration owing to high insufflation pressure and compression of capillary flow (e5, e6)
- Laparoscopy
  - Dehydration owing to dry gas (e7)
- Laparoscopy
  - Mesothelial hypoxia owing to use of CO_2 (e8)
- Laparotomy
  - Dehydration owing to light and heat (e4)
- Laparotomy
  - Exposure to foreign material (e.g., glove powder) (e9, e10)
- Laparotomy
  - Mesothelial dehydration and abrasion from use of dry abdominal drapes (e2, e3)

*[1]The numbers in parentheses are reference citations

organogenesis—like the frequently observed attachment of the sigmoid colon to the left pelvic wall—or can be traced back to abnormal embryonal development of the abdominal cavity. They are usually asymptomatic and are diagnosed incidentally (4).

Postmortem examination of patients who had not undergone surgery identified postinflammatory adhesions in 28% of cases (5). These are caused by intra-abdominal inflammation or can be attributed to endometriosis, peritonitis, radiotherapy, or long-term peritoneal dialysis (4, 6, 7).

Postoperative adhesions form after 50% to 100% of all abdominopelvic interventions (2). They develop as a result of wound healing and are influenced by various factors (7) *(Box 1)*.

The greater omentum is involved in 80% of cases of postoperative intra-abdominal adhesions, the bowel in only around 50% (8). Ovarian adhesions can be demonstrated in over 90% of patients after gynecological adnexal surgery (9); this is explained by the high sensitivity of the ovarian epithelium and its proximity to other peritoneal surfaces (10). Patients at high risk of already having or developing adhesions are those with previous or planned adnexal interventions, ablation of endometriosis, or bowel surgery involving large peritoneal defects, together with all those who have undergone previous abdominal surgery with pronounced formation of adhesions.

Diagnosis

Intra-abdominal adhesions are predominantly diagnosed intraoperatively. Careful history taking can substantiate the suspicion of adhesions; no other clinical investigations or imaging procedures enable a confident diagnosis. 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 (e11, e12). However, neither of these modalities is established in routine clinical practice.

Complications of adhesions

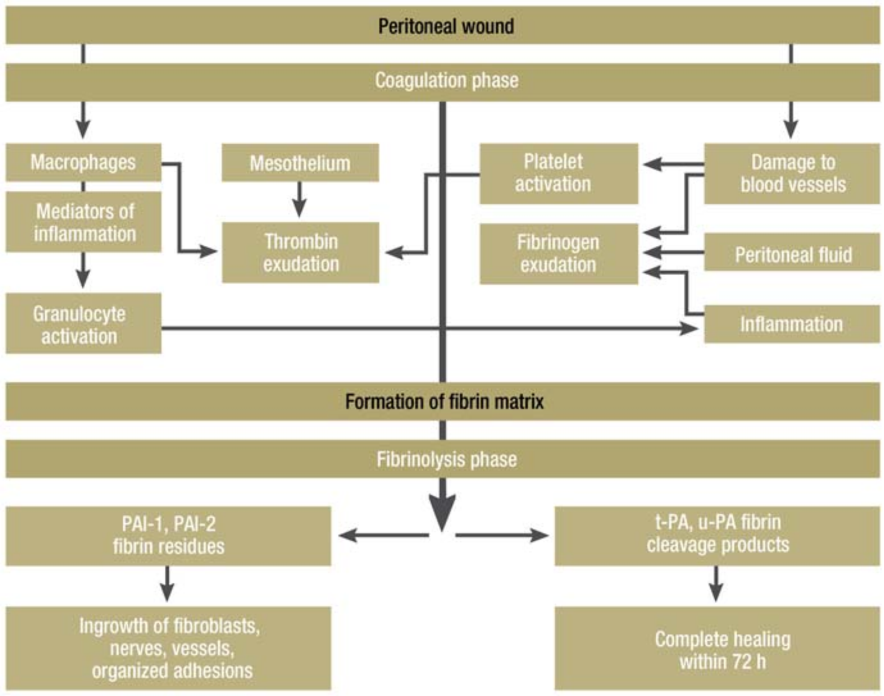
The intra-abdominal adhesions that arise from the beginning of the surgical procedure can cause complications decades later (8, 11). The patients' symptoms include meteorism, irregular bowel movements, chronic abdominal pain, digestive disorders, infantility, and intestinal obstruction, and often fail to be associated with their cause (12). In contrast to congenital or postinflammatory adhesions, which are mostly asymptomatic, postoperative adhesions cause 40% of all cases of intestinal obstruction. Stenoses of the large intestine are produced principally by malignancies and only rarely by adhesions, but adhesions cause 65% to 75% of small bowel obstruction—the most serious of all adhesion-induced complications (8). Particularly colectomy, involving a large peritoneal incision, carries an 11% cumulative risk of intestinal obstruction within the first year after operation (13).

Adhesions are responsible for 15% to 20% of all cases of secondary female infertility (14). Paraovarian, peritubal adhesions can lead to follicular entrapment and reduced mobility and mechanical blockade of the fallopian tubes. This may limit oocyte transport, increasing the risk of ectopic pregnancy (14, 15).

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 (16). In his review of 11 studies, DiZerega showed that adhesions had been responsible for the chronic lower abdominal pain in only 40% of the women who had undergone surgery (17). In 25% of cases the cause remained unclear. Accordingly, 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. In a prospective study, Keltz et al. observed a significant reduction in chronic abdominal pain after right-sided paracolic adhesiolysis (18). In contrast, Swank et al. found no amelioration of pain after laparoscopic release of adhesions not constricting the bowel (19).

Patients who have undergone surgery previously should be thoroughly informed about possible adhesiolysis and its potential complications and required to give their informed (or written) consent. Discussion

FIGURE



Overview of pathophysiological interrelationships and factors thought to be involved in the origin of adhesions (modified from e16)

points should include extension of the operation and anesthesia time, the increased blood loss and the significantly higher risk of injury to the omentum, bladder, ureters and vessels (20). Reoperations have a 20% rate of enterotomy—often associated with poorer patient outcome and longer hospital stay (20). Particularly in the case of known extensive intra-abdominal adhesions, the indication for any further operation should be considered very carefully because of the up to 85% likelihood of reformation or de novo formation of adhesions (21). If this occurs, future minimally invasive surgery may be difficult or even impossible (20, e2). Adhesion-related changes in pelvic anatomy can also complicate or prevent:

- Diagnostic ultrasonography
- Oocyte harvesting in the context of IVF treatment
- Performance of intraperitoneal chemotherapy or peritoneal dialysis (6, 7, e2).

Pathogenesis

Since intra-abdominal adhesions arise from aberrant peritoneal wound healing processes, any mesothelial damage by surgical trauma or bacterial inflammation can lead to their formation (22). Damage to the peritoneum is followed by capillary bleeding and increased vascular permeability with consequent exudation of fibrinogen (6, 22, e2). After cleavage of fibrinogen to fibrin and its bonding with fibronectin the defect is closed and a temporary wound bed forms (22, e13). Within the ensuing 72 h endogenous fibrinolytic activity of the mesothelial cells leads to breakdown of these fibrin deposits and thus to complete regeneration (e15).

A key role in the origin of adhesions is attributed to a pathological reduction in peritoneal fibrinolysis capacity (e16). This may result from destruction of mesothelia, from their insufficient supply with blood, from increased synthesis of fibrinolysis antagonists following trauma, from hypoxia, from radical formation, or from bacterial infection (22, e14, e16–e18). In the course of the subsequent organization processes the persisting fibrin matrix gives rise to a mesothelialized tissue structure that is stabilized by connective tissue and may contain arterioles, venules, capillaries, and nerve fibers (e14). An overview of the identified pathophysiological associations and the factors thought to be involved in the origin of adhesions is provided by the *Figure*, *Table 1* and the *eBox*.

Prevention of postoperative adhesions

Strategies for reduction of adhesions are based on their pathophysiological mechanisms of origin *(Box 2)*.

Damage to the serosa and the use of intra-abdominal foreign bodies should be kept to a minimum (4). Blood and clot in association with a peritoneal wound constitute a potentiating factor, because additional fibrin has to be degraded by the fibrinolytic activity of the peritoneum (e24). Before closure of the abdominal wall, therefore, it is advisable to perform careful—though not excessive, to avoid necrosis—hemostasis and irrigate repeatedly with saline and Ringer solution. There is no consensus in the literature as to whether

TABLE

Overview of the principal factors affecting the fibrinolytic capacity of the mesothelium

Factor	Fibrinolytic activity	Reference
Urokinase-like plasminogen activator (u-PA)	↑	(e15)
Tissue plasminogen activator (t-PA)	↑	(e15)
Matrix metalloproteinases (MMP)	↑	(6)
Tissue-derived inhibitors (TIMP)	↓	(6)
Plasminogen activation inhibitors (PAI 1/ 2)	↓	(e14, e19)
Mechanical destruction of mesothelium	↓	(e16)
Mesothelial ischemia	↓	(e16)
Hypoxy	↓	(e18, e20)
Radical formation	↓	(e18)
Bacterial lipopolysaccharide	↓	(e18, e21)
Interleukins (e.g., IL-1, IL-6)	↓	(18)
Neurokinin-1 receptor (NK-1)	↓	(e20)
Substance P (SP)	↓	(e16, e20)
Tumor necrosis factor α (TNFα)	↓	(e17, e22)
Transforming growth factor β (TGFβ)	↓	(e17, e23)
Intracellular adhesion molecule (ICAM 1)	↓	(4, e17)
Vascular cell adhesion molecule (VCAM)	↓	(4, e17)

laparoscopy is associated with fewer de novo and recurring adhesions than laparotomy (8, e26). A lower rate of adhesion development in laparoscopic interventions could be related to reduction of peritoneal trauma as a result of more exact preparation under magnification (e3). Moreover, contamination of the abdominal cavity and adhesion-potentiating foreign-body reactions are reduced (e9). Further advantages include a minimized incidence of postoperative infections and a tamponade effect of the pneumoperitoneum in the event of hemorrhage. A disadvantage of laparoscopy, related to the longer operating time and the high insufflation pressure, is the risk of mesothelial injury; this can be reduced by using humidified and warmed gases (e25). With regard to development of adhesions, minimally invasive access via natural orifices (Natural Orifice Transluminal Endoscopic Surgery, NOTES) seems to be superior to both laparoscopy and laparotomy. In an animal study, Dubcenco found the lowest number and severity of adhesions in the group in which endoscopy was carried out by the orogastric route (e27).

In those at high risk the use of adhesion-reducing adjuvants can be considered independent of the extent and location of the mesothelial defect. The widely used, commercially available adjuvants licensed for use in Germany include:

- Humidified and warmed insufflation gases for laparoscopy
- Medicinal agents
- Colloid and crystalloid solutions
- Separators: fluids for peritoneal instillation or site-specific mechanical barriers.

Attempted drug treatment can involve local and systemic anti-inflammatory agents, fibrinolytics, or antibiotic solutions. Moreover, colloids (dextran) and crystalloid solutions (Ringer lactate or saline) have been used, alone or with corticosteroids or heparin, to separate peritoneal surfaces. No clinical study has yet demonstrated a clear adhesion-reducing benefit of these substances (25).

The 4% glucose polymer icodextrin is an adhesion-inhibiting peritoneal instillate. Besides its application for intraoperative moistening of peritoneal surfaces it is instilled into the abdominal cavity (e28). By virtue of its osmotic activity it is thought to retain fluid in the peritoneal cavity for 3 to 4 days and keep organs and injured peritoneal surfaces separated from each other until it is eliminated via the kidneys. Randomized, double-blind multicenter studies have confirmed the adhesion-reducing properties of icodextrin after surgery. Comparison of icodextrin and Ringer lactate revealed an advantage for the former with regard to the reduction of incidence (52% vs. 32%), extent (52% vs. 47%), and severity (65% vs. 37%) of adhesions. Clinical improvement was observed in 49% of patients following treatment with icodextrin, against 38% after Ringer lactate (e28–e30). Data from the European registry on the use of icodextrin (adept™ Registry for Clinical Evaluation, ARIEL) demonstrate high

BOX 2

Practical tips: general strategies for reduction of adhesions*[1]

- Preference for tissue-sparing and microinvasive surgical techniques
- Minimization of operating time and of heat and light
- Avoidance of peritoneal trauma by superfluous contact and coagulation
- Limited placement of intra-abdominal foreign bodies such as patches, meshes, and suture material
- Use of moistened abdominal drapes and swabs and occasional application of saline solution to minimize dehydration of mesothelial surfaces
- Irrigation of the abdominal cavity to remove residual intra-abdominal blood depots
- Reduction of infection risk by ensuring sterile working conditions and giving antibiotics as required
- Laparotomy: preferential use of latex- and powder-free gloves
- Laparoscopy: use of humidified gases at appropriately low insufflation pressure
- High-risk patients: use of barrier techniques or peritoneal instillates after appropriate explanation

*[1]Modified from (4, 23, e3, e9, e24, e25)

user-friendliness and high patient safety. Complications described after icodextrin instillation are septic and inflammatory states, anastomotic insufficiency, and labial swelling (e31).

Cross-linked esters of hyaluronic acid form a viscous gel that is applied to traumatized peritoneal surfaces after abdominopelvic surgery to help keep them separate during the healing process. Few studies have been conducted on the efficacy of hyaluronic acid esters in preventing adhesions. In a group of 52 patients in a randomized multicenter study, application of hyaluronic acid gel was shown to reduce formation of adhesions after laparoscopic enucleation of myoma. Following treatment 62% of these patients were free of adhesions, compared to 41% of those who did not receive the gel. Application of the gel significantly lowered the difference in severity of intra-abdominal adhesions between first and subsequent operations (0.3 ± 0.9 vs. 0.8 ± 1.0, $p<0.05$) (e32). Furthermore, Pellicano et al. documented an increase in the rate of pregnancy from 38.8% to 77.8% in previously infertile women 12 months after laparoscopic enucleation of myoma with application of gel (e33).

Carboxymethylcellulose (CMC) and polyethylene oxide (PEO) form a gel-like resorbable barrier for sealing peritoneal surfaces and prevention of future adhesions. In a randomized study, 37 high-risk patients received a CMC/PEO barrier in the course of laparoscopic ablation of endometriosis. Follow-up laparoscopy documented a significant adhesion-reducing effect of this measure as assessed using the American Fertility Society score, with a decrease from 8.4 ± 3 points to 6.2 ± 2 points. In the non-treated control group there was increased growth of adhesions and thus a rise in the score from 10 ± 2.5 points to 14 ± 3 points (e34).

A barrier membrane consisting of hyaluronic acid and CMC can separate peritoneal surfaces for around 7 days (10). Because of its high fragility this membrane is predominantly used in laparotomies (e35). The efficacy of such membranes in reducing intra-abdominal adhesions after enucleation of myoma and colectomy has been investigated in a number of randomized studies. With regard to the gynecological data, the Cochrane analysis by Ahmad et al. notes that the positive findings reported by Diamond et al. (e35) have to be interpreted with caution owing to statistical deficiencies (24). Follow-up laparoscopy 8 to 12 weeks after use of the barrier membrane on abdominal wall closure in patients undergoing colectomy and creation of an ileal pouch showed that 51% of treated patients were free of adhesions, against 6% in the control group (e36, e37). This barrier membrane is the only agent which has been specifically investigated for the reduction of the incidence of small bowel obstructions as a complication of adhesions: In a multicenter study conducted by Fazio et al. (e38), the membrane resulted in a 1.6% absolute and 47% relative reduction in the occurrence of this complication. It should be pointed out, however, that application of the membrane directly onto to the anastomosis sutures increased the risk of anastomotic insufficiency (e38).

Another type of adhesion barrier, applied as a spray, comprises a pair of polyethyleneglycols in a two-component system. The barrier is sprayed onto injured serosal surfaces and seals them for 7 to 14 days. Early clinical pilot studies showed an adhesion-preventing benefit of the spray, but this effect was not confirmed in subsequent, more extensive trials (e39, 23). Evaluation of the next-generation product in a porcine model showed a reduction in number (ca. 46%) and extent (ca. 83%) of the adhesions formed (e40).

Oxidized regenerated cellulose can be applied to injured surfaces as a resorbable membrane, following careful hemostasis. Moistening of the membrane stops it slipping and provides a physical barrier between tissues until the membrane is resorbed after 4 weeks. In their Cochrane analysis, Ahmad et al. conclude that oxidized regenerated cellulose leads to a reduction in the occurrence of pelvic adhesions after gynecological laparotomy and laparoscopy (24). It is advised, however, that this finding be interpreted with caution.

Perspective

Since surgical treatment of adhesions is highly likely to be associated with the induction of new adhesions, reduction or prevention of adhesions should be every surgeon's primary goal. In this regard, the Clinical Adhesion Research and Evaluation Group (CARE Group) has been founded at Giessen University Hospital. This interdisciplinary group aims to optimize patient care by integrating existing strategies into routine clinical practice and conducting research into new techniques for reducing adhesions. The general measures described in this review can readily be put into practice and comprise minimization of peritoneal injury by the following means: meticulous observance of established surgical principles, moistening of the mesothelium to keep it from drying out, reduction of the use of intra-abdominal foreign materials to a minimum, and irrigation of the abdominal cavity to remove blood and clot. Adhesion-reducing agents differ, sometimes considerably, in their indications and area of surgery. Their use is particularly advisable in high-risk patients.

Conclusive interpretation of the partially controversial study findings on adhesion-reducing adjuvants is hampered by the limited number of studies, the small numbers of patients, the large variety of factors influencing adhesion development, and the lack of a standardized classification of adhesions. The result is skepsis among clinicians and low acceptance of adhesion-reducing products. Moreover, it is often difficult to arrange for these products to be used because there is no provision for their reimbursement under the diagnosis-related groups system. Further high-quality studies are therefore required.

KEY MESSAGES

- Adhesions result from peritoneal trauma and aberrant wound healing processes and can therefore develop after any intra-abdominal operation.
- Intra-abdominal adhesions occur in 50 to 100% of patients with previous surgery.
- Particularly in patients with previous surgery, adhesion-related complications can occur at any time.
- The possibility of adhesions and the associated risk must always be documented in writing in the course of preoperative explanation of the planned procedure for purposes of consent.
- General strategies for preventing adhesions should be integrated into routine clinical practice. The use of commercially available peritoneal instillates or barrier techniques is particularly advisable in patients at high risk of developing adhesions.

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Conflict of interest statement
Prof. Tinneberg has received reimbursement of travel costs and lecture fees from Baxter. Dr. Hackethal has received reimbursement of travel costs from Baxter und has consultancy contracts with NordicPharma und Fischer&Paykel. Dr. Tchartchian has a consultancy contract with and has received reimbursement of travel costs from Covidien.
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REVIEW ARTICLE

Intra-abdominal Adhesions

Definition, Origin, Significance in Surgical Practice, and Treatment Options

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eBOX

Supplementary information on pathogenesis of adhesions

Surgical trauma, i.e., the combined impact of cutting, coagulation, and pressure-induced ischemia – particularly from excessively tight knots – may bring about peritoneal damage (22, e2). Equally, mesothelial injury results from bacterial inflammation processes, from contact, from bright surgical lights, or from use of dry drapes (22). Capillaries at the trauma site leak blood containing complement and coagulation factors. Local peritoneal macrophages and mesothelial cells start to secrete proinflammatory cytokines, histamine, prostaglandins, and kinins, leading to potentiated influx of further inflammation-related cells, increased vascular permeability, and subsequent fibrinogen exudation (6, 22, e2). 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 migrate peritoneal cells and fibroblasts (22, e13, e14). 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 (e15, e16). Plasmin degrades fibrin polymers, components of the extracellular matrix and basal membrane, and activates other proteases, e.g., matrix metalloproteinases (6). This depletion of fibrin deposits then results in complete healing (e15).

A key part in the origin of adhesions is played by pathological reduction of peritoneal fibrinolysis capacity (e16). This results from:

- Reduced release of plasminogen activators following loss of or insufficient supply of blood to mesothelia (e16)
- Reduction in the activity of plasminogen activators by a local and systemic increase in protease antagonists – plasminogen activator inhibitors PAI 1 and 2 – after surgical trauma (e14).

As shown by in-vitro and in-vivo studies at molecular level, this disequilibrium between plasminogen activators and protease antagonists is based on increased expression of inflammation mediators (e.g., substance P) – particularly of cytokines (e.g., tumor necrosis factor), growth factors (e.g., transforming growth factor), and adhesion molecules (intercellular adhesion molecule-1 and vascular adhesion molecule-1). (25, e4, e5).