Human Reproduction Update, Vol.21, No.4 pp. 536–551, 2015
Advanced Access publication on May 1, 2015 doi:10.1093/humupd/dmv021

human reproduction update

Predisposing factors to post-operative adhesion development

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Submitted on April 26, 2014; resubmitted on March 31, 2015; accepted on April 7, 2015

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BACKGROUND: Adhesion development is the most common sequelae of intra-abdominal and pelvic surgery and represents a significant, yet poorly understood, cause of morbidity among post-operative patients. It remains unclear, for example, exactly why adhesions form more frequently in certain tissues and/or patients, or at specific locations within them, as opposed to others. This review contributes to the growing knowledge pool by elucidating factors that potentially predispose to the development of adhesions. Given the strong correlation between a hypofibrinolytic state and adhesion formation, this review article will examine not only those factors that have been shown to directly predispose to adhesion development, but also those that are likely do so indirectly by means of altering the coagulation/fibrinolytic profile.

METHODS: A literature search was performed using the PubMed database for all relevant English language articles up to February 2014. All of the identified articles were reviewed with particular attention to predisposing factors to post-operative adhesion development. In addition, the reference lists of each article were reviewed to identify additional relevant articles.

RESULTS: Various factors have been shown to directly increase the risk of post-operative adhesion development; namely, certain genetic polymorphisms in the interleukin-1 receptor antagonist, increased estrogen exposure, and endometriosis. In addition, numerous factors are known to increase the risk of fibrosis, therefore likely increasing the risk of adhesion development indirectly. These factors include genetic polymorphisms in plasminogen activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor, diabetes mellitus, metabolic syndrome, hyperglycemia, obesity, depression, binge alcohol consumption, anti-Parkinsonian medications, oral hormone therapy, pregnancy, and cancer.

CONCLUSIONS: The literature reviewed in this paper will help to direct future research aimed at understanding the mechanisms that underlie the association of certain factors with adhesion development. This information will be crucial in the creation of adequate preventative and treatment strategies.

Key words: post-operative adhesions / predisposing factors / hemostasis / fibrosis / hypoxia

Introduction

Adhesion development is the most common sequelae of intra-abdominal and pelvic surgery (Diamond, 1993), and represents a significant cause of morbidity among post-operative patients. The most severe complication associated with post-operative adhesions is small bowel obstruction (SBO). Over 40% of all SBO cases are attributable to post-operative adhesions (Ellis, 1971, 1982; Menzies, 1993) and carry a mortality rate of ~3–13% (Nieuwenhuijzen *et al.*, 1998; Fevang *et al.*, 2000; Margenthaler *et al.*, 2006). SBO results when adhesive bands distort and subsequently result in obstruction of a loop of bowel. In their systematic review and meta-analysis of adhesion-related complications, ten Broek *et al.* (2013) report that the incidence of SBO from any cause following abdominal surgery was 9%, whereas the incidence of adhesive SBO was 2%. Among patients with a known cause of SBO, adhesions were the single most common cause.

Adhesion formation following pelvic surgery is also common, and is a major cause of infertility in women. The mechanism by which adhesions cause infertility includes distortion of the normal ability of the Fallopian tube to achieve ovum pickup following ovulation, which can be due to ovarian encapsulation by adhesions or limitations in tubal/fimbral potential for movement. It has been estimated that 22% of all infertility cases are attributable to adhesions (Cates *et al.*, 1985; Trimbos-Kemper *et al.*, 1985). In one study, adhesions were found in 37% of infertile patients. In 15% of these cases, adhesions were the only factor identified as the cause of infertility (Milingos *et al.*, 2000). The meta-analysis by ten Broek *et al.* (2013) found that, among patients undergoing colorectal surgery for inflammatory bowel disease, the pregnancy rate was 50%. This was significantly lower than the pregnancy rate in patients who were treated medically (82%). Interestingly, pregnancy rates have been shown to increase by 38 to 52% among previously infertile patients following laparotomy with adhesiolysis (diZerega, 1997), demonstrating the potential value of adhesiolysis.

Another major consequence of adhesion development is chronic pelvic or abdominal pain, likely the result of increased tension on internal organs at sites stretched as a consequence of anomalous attachments (Liakakos *et al.*, 2001). In an analysis of eleven studies, it was found that adhesions were the most common pathology in patients with chronic pelvic pain (CPP) (diZerega, 1997). Further, another study demonstrated that 82% of patients with chronic abdominal pain had only adhesions and no other disease. Upon laparoscopic adhesiolysis, 74% of these patients had either a reduction or a complete resolution of their pain, indicating that adhesions were the sole contributor to their pain (Swank, 2003). Other authors estimate that 60–90% of patients with adhesions experience pain relief or reduction after adhesiolysis, once again reinforcing the association between adhesions and chronic pain (Duffy and diZerega, 1996), however, interpretation of this descriptive study is limited by the lack of a control group.

Caution must be exercised, however, before making any firm conclusions regarding the effectiveness of adhesiolysis for CPP. In their Cochrane review, Stones *et al.* (2005) concluded that there is still uncertainty about the role of adhesiolysis in women presenting with CPP, and that there is 'no evidence of benefit, rather than evidence of no benefit.' To date, only three RCTs have examined the role of adhesiolysis in pain, none of which are without limitations. Peters *et al.* (1992) examined the effectiveness of adhesiolysis on pelvic pain in 48 women with known pelvic adhesions. They found that although adhesiolysis may benefit those with severe adhesions involving the intestinal tract, it is not indicated in women with mild or moderate adhesions. Similarly, Swank *et al.* (2003) investigated the effectiveness of laparoscopic adhesiolysis on patients with chronic abdominal pain in a sample of both men ($n = 29$) and women ($n = 87$). While laparoscopic adhesiolysis was found to relieve chronic abdominal pain, it was no better than diagnostic laparoscopy. However, this study was not designed to specifically examine CPP. Furthermore, no data were reported on the condition of the pelvis; therefore these results do not necessarily apply specifically to women with CPP. In the most recent study, Cheong *et al.* (2014) examined whether laparoscopic adhesiolysis significantly improves pain and quality of life in women with CPP and adhesions ($n = 92$). At 6-month follow-up, significant improvements were seen in self-report ratings of pain intensity/quality, measure of subjective health status, measure of emotional status and self-report of quality of life in the adhesiolysis group when compared with the control group. The authors concluded that in a selected population of women with CPP, adhesiolysis may improve pain and quality of life, though the study was stopped before recruitment reached a statistically powered sample size due to difficulty with enrollment and funding. Of note, each of these three studies employed a relatively small sample size, highlighting the need for further large trials in this area.

In addition to the impact that post-operative adhesions have on patient well-being, adhesions also have an overall impact on the healthcare system and the economy. One reason for this is that the presence of previous adhesions impedes subsequent surgical access (Holmdahl, 1997). In effect, dissection of adhesions causes longer operating times and increased complications, both intraoperatively (e.g. bleeding and damage to the bladder, bowel, or ureters (Cheong *et al.*, 2001)), and up to 10 years post-operatively (Lower *et al.*, 2000; Parker *et al.*, 2001). Meta-analyses show an increase in operative time by 15 min in patients with previous surgery, as well as a reduction in operative time with the placement of an anti-adhesion barrier (ten Broek *et al.*, 2013). Post-operative adhesions are associated with a significant post-operative readmission rate. It is estimated that up to 34% of post-operative patients are readmitted for reasons related to adhesions within the next decade (Lower *et al.*, 2000; Parker *et al.*, 2001). The end result is an enormous financial burden attributable to post-operative adhesions—an estimated annual total of $2.3 billion for the cost of hospitalizations for adhesiolysis in the USA (Sikirica *et al.*, 2011). Figure 1 summarizes the common clinical sequelae of post-operative adhesions.

Pathophysiology

The peritoneum is an extensive layer of mesothelial cells that functions to protect the abdominal organs and reduce friction between their viscera (diZerega, 1993). The peritoneum is exquisitely delicate and highly susceptible to trauma due to the loose interconnection between mesothelial cells (Mutsaers and Wilkosz, 2007). Damage to the peritoneum can be secondary to inflammatory or surgical causes. Inflammatory damage occurs as a result of intra-abdominal inflammatory processes, including pelvic inflammatory disease, appendicitis, acute cholecystitis, acute diverticulitis and possibly past use of an intrauterine contraceptive device. There are a handful of factors that can damage the peritoneum perioperatively. These include trauma, ischemia, infection, exposure to intestinal contents and foreign bodies (e.g. talcum and powders from gloves, fibers from disposable paper items, and lint from abdominal

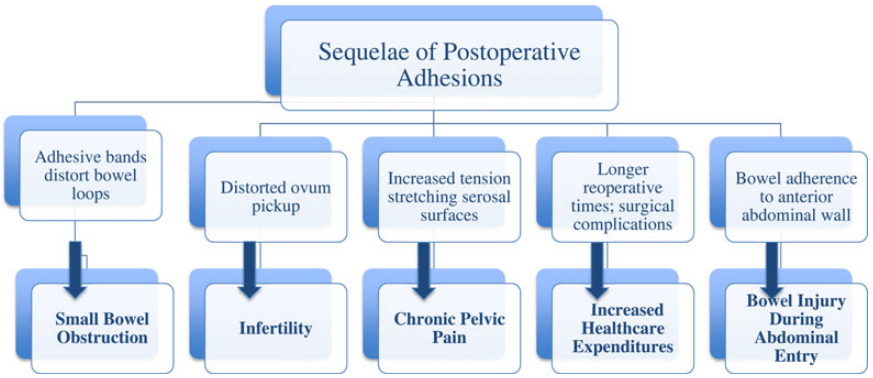

Figure 1 Common clinical sequelae of post-operative adhesions.

packs) (Liakakos *et al.*, 2001). Postsurgical adhesions are the most common subtype of adhesions, and will be the focus of this review.

Over the past decade we have collected an immense amount of compelling evidence to support the hypothesis that hypoxia, as a result of tissue injury, is the initiating factor leading to post-operative adhesion development. Hypoxia triggers critical adaptations that enable cell survival, including apoptosis suppression, altered glucose metabolism and an angiogenic phenotype, which collectively cause the development of the adhesion phenotype (Saed and Diamond, 2002, 2003; Saed *et al.*, 2002, 2003, 2004; Alpay *et al.*, 2007, 2008; Fruehauf and Meyskens, 2007; Jiang *et al.*, 2008, 2009). Hypoxia and the subsequent oxidative stress is believed to play a significant role in the pathogenesis of post-operative adhesions. In support of this concept, studies suggest that acute oxidative stress in the peritoneum subsequently induces mesothelial cell loss or dysfunction, peritoneal fibrosis, and intra-abdominal adhesion formation (Reed *et al.*, 2007). During the first 5 min of ischemia, there is already a significant production of free radicals, either through an increase in reactive oxygen species (ROS) formation or by decreasing ROS scavengers (Taskin *et al.*, 1998, 1999; Souza *et al.*, 2003; Pelicano *et al.*, 2004; Ara *et al.*, 2005). The enhanced production of ROS is associated with phenotypic changes (Fletcher *et al.*, 2008), such as enhanced expression of cytokines, growth factors and extracellular matrix (Saed and Diamond, 2004, 2006; Saed *et al.*, 2004; White *et al.*, 2011; Shavell *et al.*, 2012), as well as genotypic changes such as alterations in DNA sequence of NAPH oxidase (Fletcher *et al.*, 2014).

Once the peritoneum is damaged, the coagulation cascade is set in motion. The coagulation cascade involves the conversion of a series of inactive proenzymes to active enzymes, ultimately resulting in the formation of a clot. Intrinsic and extrinsic pathways lead to the activation of factor X, which then triggers the conversion of prothrombin (factor II) to thrombin (factor IIa). Thrombin serves as the final enzyme of this cascade and converts fibrinogen into fibrin monomers. These fibrin monomers then polymerize to form an insoluble fibrin clot (Hellebrekers and Kooistra, 2011).

This cascade is a normal hemostatic response to tissue injury and is targeted at repair of the damage. However, if two damaged peritoneal surfaces come in contact with each other, the healing process can in essence result in 'fusion' to form a connection, e.g. an adhesion (Davey and Maher, 2007). The role of fibrin in the healing process is meant to be a temporary one, and as such, in healing without adhesions, it must be degraded by the fibrinolytic system for restoration of normal tissue structure and function (Collen, 1980). In the fibrinolytic system, plasminogen is converted to its active form, plasmin, by tissue plasminogen activator (tPA) or urokinase-type plasminogen activator (uPA). Plasmin's role is to degrade fibrin into fibrin degradation products (FDPs). To counteract this process, plasminogen activator inhibitor-1 (PAI-1) and PAI-2 serve as inhibitors of tPA. Additionally, thrombin-activatable fibrinolysis inhibitor (TAFI) inhibits the conversion of plasminogen to plasmin, and α2-antiplasmin inactivates plasmin. Another key player, antithrombin III (AT-III), acts as an anticoagulant by inhibiting the action of thrombin. Failure of the fibrinolytic system to break down fibrin into FDPs results in perpetuation of the scaffolding into which fibroblasts can migrate with subsequent deposition of collagen and other forms of extracellular matrix material, with subsequent formation of permanent fibrous connective tissue (Hellebrekers and Kooistra, 2011).

Research indicates that the coagulation cascade is altered in response to tissue hypoxia. Studies have demonstrated a marked reduction of the tPA/PAI-1 mRNA expression ratio as well as decreased tPA activity in response to tissue hypoxia (Saed and Diamond, 2003). Thus the likelihood that fibrinous collections at surgical sites would undergo fibrinolysis is markedly reduced. Subsequent fibroblast migration into the fibrinous mass and deposition of extracellular matrix results in adhesion development.

The inflammatory system also plays a significant role in the regulation of hemostasis and, as such, inflammation secondary to surgery or any other tissue injury is a key player in the pathogenesis of postsurgical adhesion formation. The proinflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor-α increase expression of PAI-1 and decrease expression of tPA, which explains an increased tendency to fibrin deposition in surgical patients (Hellebrekers and Kooistra, 2011). This relationship has been further solidified by research that found a significant correlation between extent of adhesion formation and preoperative plasma levels of both PAI-1 and C-reactive peptide (CRP) (Hellebrekers *et al.*, 2009). Seeing that PAI-1 and CRP are acute-phase reactants and markers of systemic inflammation, the authors postulate that this correlation indicates a role of chronic inflammation in the process of adhesion formation and that inflammatory state is predictive of extent of adhesion formation. Hellebrekers *et al.* (2009) also identified a negative correlation between tPA concentration and adhesion formation, which further supports the idea that adhesions are caused by insufficient

peritoneal fibrinolytic activity (Hellebrekers *et al.*, 2009). Figure 2 depicts the interconnected processes of inflammation, hypoxia, coagulation, and fibrinolysis and their role in the development of post-operative adhesion formation.

Animal studies have shown a strong correlation between a hypofibrinolytic state and adhesion formation (Holmdahl, 1997). In fact, anything that hinders the process of fibrinolysis significantly increases the risk of permanent adhesion development (Davey and Maher, 2007). Thus, this review article will examine not only those factors that have been shown to directly predispose to adhesion development, but also those that likely do so indirectly by means of altering the coagulation/fibrinolytic profile. It is important to keep in mind that further research is necessary to identify a direct link between these indirectly associated factors and adhesion formation before these factors can be labeled 'predisposing factors.'

Methods

A literature search was performed using the PubMed database (www.pubmed.org) to identify all relevant internationally published English articles from the inception of PubMed to February 2014. Search terms included 'post-operative adhesions,' 'predisposing factors,' 'risk factors,' 'hemostasis,' 'coagulation,' 'fibrinolysis' and 'genetics.' All of the identified articles were reviewed with particular attention to predisposing factors to post-operative adhesion development. We also reviewed the references from each article to identify additional relevant articles, without restriction.

Results

Various factors have been shown to directly increase the risk of post-operative adhesion formation. In addition, numerous factors are known to increase the risk of fibrosis, therefore plausibly increasing the risk of adhesion formation indirectly. The following section discusses the relevant research supporting each of these factors. A summary of the factors associated with increased or decreased risk of adhesion development, as well as with alterations in fibrosis, is depicted in Table I. These factors have been grouped into five major categories: surgical and medical history (type of surgery, medications, diabetes mellitus, cancer, endometriosis); reproductive milieu (hormones, menstrual cycle, pregnancy); specific demographics (gender, age, genetics); lifestyle and nutritional factors (obesity, exercise, diet, alcohol, smoking); and psychological well-being (stress, mood). Figure 3 depicts the impact that each of these categories has on the coagulation and fibrinolytic systems with its consequential propensity for adhesion development, or for remesotheliazation and healing without adhesion development, respectively

Surgical and medical history

Type of surgery

Unfortunately, no surgical patient is spared from the risk of developing adhesions and the subsequent sequelae, as adhesions frequently develop following any surgical procedure. In one study of 448 adult patients who had undergone at least one previous abdominal surgery,

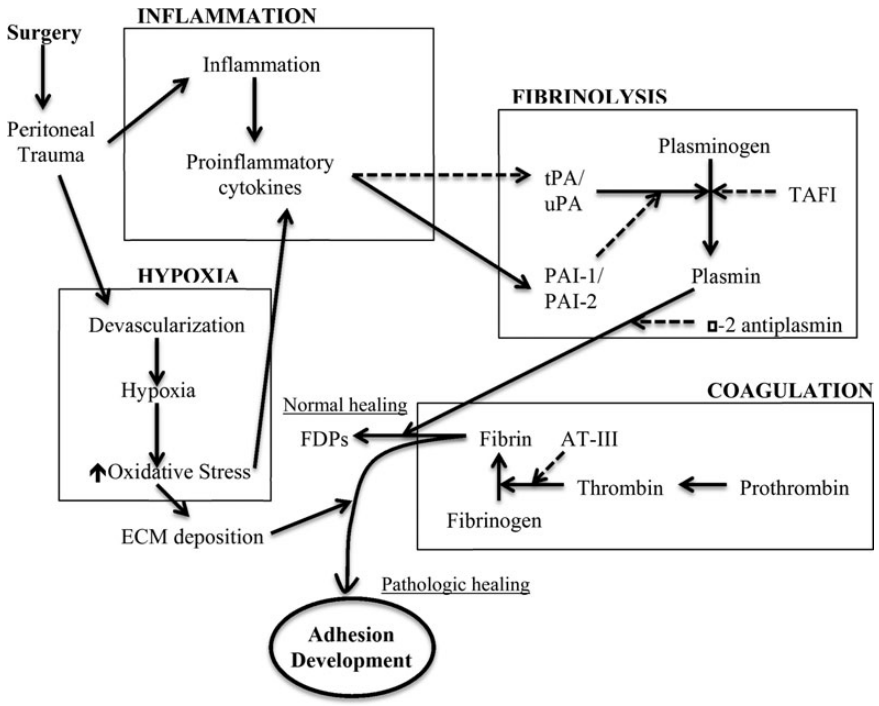

Figure 2 Inflammation, hypoxia, coagulation and fibrinolysis, and their role in the development of post-operative adhesion formation. Dashed lines represent inhibition. AT-III, antithrombin III; ECM, extracellular matrix; FDPs, fibrin degradation products; PAI, plasminogen activator inhibitor; TAFI, thrombin-activatable fibrinolysis inhibitor; tPA, tissue plasminogen activator; uPA, urokinase-type plasminogen activator. Adapted with permission from Hellebrekers and Kooistra (2011).

Table I Factors associated with increased/decreased risk of fibrosis as well as post-operative adhesion formation.

		Hypothesized to increase risk of adhesions	Hypothesized to increase risk of fibrosis	Unclear/ conflicting findings	Hypothesized to decrease risk of fibrosis	Hypothesized to decrease risk of adhesions
Medical/ surgical history	Type of Surgery	Adhesiolysis		Lower GI tract surgery		
	Medications		Anti-Parkinsonian drugs		Statins	Tamoxifen
	Diabetes Mellitus		✓			
	Cancer		✓			
	Endometriosis	✓				
Reproductive milieu	Hormones	Estrogen	Hormone therapy (oral)			
	Menstrual cycle			✓		
	Pregnancy		✓			
Specific demographics	Gender			✓		
	Age			✓		
	Genetics	IL-1RN*2 polymorphism; HLA subtypes A24 and DR1	PAI-1 polymorphisms; TAFI polymorphisms	Fibrinogen polymorphisms		
Lifestyle/ nutrition	Obesity		✓			
	Exercise			✓		
	Diet				Low-saturated-fat diet; coffee; antioxidants	
	Alcohol		Binge consumption		Light to moderate consumption	✓
	Smoking		✓			
Psychological well-being	Stress			✓		
	Mood		Depression			

GI, gastrointestinal; IL, interleukin; PAI, plasminogen activator inhibitor; TAFI, thrombin-activatable fibrinolysis inhibitor; IL-1RN*2: mutant allele of IL-1 receptor antagonist gene.

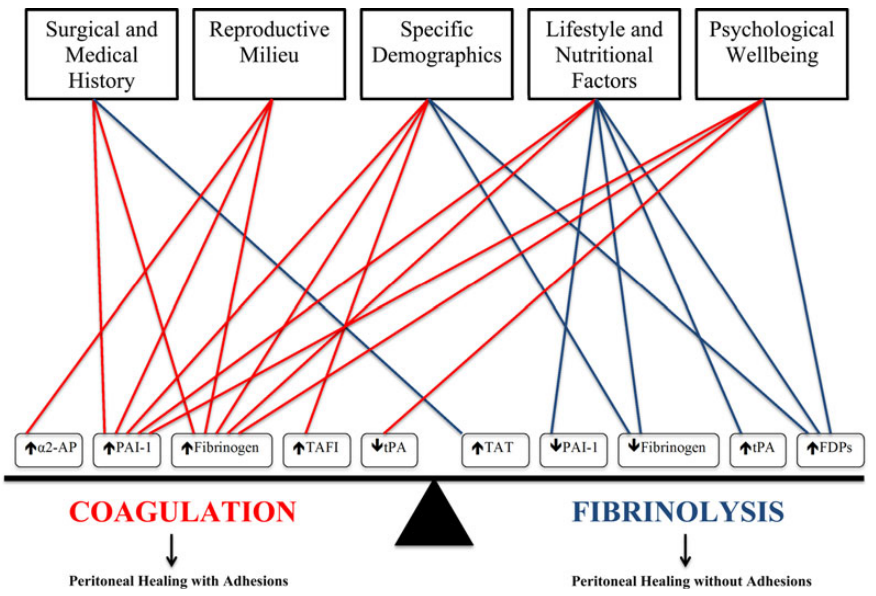

Figure 3 The impact of predisposing factors on key players of the coagulation and fibrinolytic systems. α2-AP, α2-antiplasmin; TAT, thrombin/antithrombin III complex.

100% of these patients developed from 1 to more than 10 adhesions (Luijendijk *et al.*, 1996). Of note, the type of surgery performed is an important determinant of the development of post-operative adhesions. Colorectal surgery has been reported to be the surgery with the highest total number of inpatient episodes, inpatient days, operating time and cost due to post-operative adhesion-related intestinal obstruction (Ellis *et al.*, 1999). Meta-analyses have confirmed that lower gastrointestinal tract surgery has the highest incidence of adhesive SBO (ten Broek *et al.*, 2013).

The risk of adhesion formation is also high following major gynecologic surgery, with 70 to 95% of these patients developing subsequent adhesions (Liakakos *et al.*, 2001). Studies comparing the adhesion risk in laparoscopy versus laparotomy have given mixed results. Despite the fact that there is no definitive evidence that laparoscopy reduces the incidence of post-operative adhesions as compared with laparotomy, it is an attractive option to most surgeons because it offers various advantages. These advantages include smaller size of incision, less bleeding and shorter hospital stay. Additionally, there is likely less contamination by foreign bodies such as gauze particles, glove powder, hair, and lint from drapes, gowns, masks, or laparotomy pads (Alpay *et al.*, 2008).

However, the pneumoperitoneum maintained during laparoscopic surgery is associated with a hypoxic, hyperbaric and acidotic environment, which has the potential to accelerate ischemic injury to the peritoneal mesothelial cells. This injury may contribute to the development of adhesions (Alpay *et al.*, 2008). Studies have shown that insufflation has a detrimental effect on peritoneal architecture (Ott, 2001). Furthermore, it has been demonstrated that insufflation does in fact cause adhesion formation, and it does so in a time- and intra-abdominal pressure-dependent manner (Molinas *et al.*, 2001).

Medications

Many different medications have been associated with an altered coagulation profile. Research indicates that anti-Parkinsonian agents can result in subclinical activation of the coagulation-fibrinolytic system in Parkinson's Disease patients. This effect is most prominent in those patients on a levodopa/dopamine agonist-combination regimen (Sato *et al.*, 2003).

Previous research shows that the cholesterol-lowering drugs, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors—commonly known as statins—have potent antioxidant, anti-inflammatory, and pro-fibrinolytic properties. Both *in vitro* and *in vivo* studies have demonstrated activation of fibrinolysis under the influence of statin drugs, in particular, simvastatin, atorvastatin and lovastatin (Haslinger *et al.*, 2003; Prasad, 2006; Aarons *et al.*, 2007).

A recent study found that when given in supra-therapeutic doses, tamoxifen citrate—an anti-estrogen used in the treatment of breast cancer—can prevent post-operative adhesion development (Karaca *et al.*, 2013). These effects occur in both a dose- and time-dependent manner, and are likely related to the drug's ability to diminish keloid fibroblast proliferation and decrease collagen production (Karaca *et al.*, 2013).

Diabetes mellitus

It has been well established that healing capacity is diminished in individuals with diabetes mellitus. Perhaps the most notable example, the diabetic foot ulcer, is a major cause of morbidity in diabetics and is estimated to occur in up to 15% of these patients (Brem and Tomic-Canic, 2007). There are a multitude of mechanisms that have been implicated in the impaired healing that occurs in diabetic patients, including hypoxia, damage from ROS and advanced glycation end-products (AGEs), diminished immune response, neuropathy, decreased angiogenesis and neovascularization, elevated levels of metalloproteases, and fibroblast dysfunction (Guo and DiPietro, 2010).

Hyperglycemia causes a nonenzymatic reaction to occur between glucose and collagen, resulting in the formation of AGEs. AGE-modified collagen increases matrix thickness, which makes it resistant to hydrolytic turnover and results in accumulation of extracellular matrix proteins (Sharma, 2014). When AGEs interact with the receptor for AGE (RAGE), the AGE/RAGE signaling cascade—a major fibrotic signaling pathway—is activated. Several profibrotic growth factors are subsequently secreted and collagen deposition is increased, ultimately resulting in tissue fibrosis. While this relationship between diabetes and fibrosis has yet to be directly studied in regards to adhesion formation, research has demonstrated that hyperglycemia contributes to fibrosis in the heart and kidneys of diabetic patients (Sharma, 2014; Zhao *et al.*, 2014). It is not implausible to postulate that a similar effect occurs in the peritoneum.

As mentioned, fibroblast dysfunction has been found to be a key player in the poor wound healing seen in diabetic patients (Guo and DiPietro, 2010). Taking things one step further, *in vitro* studies by Rizk *et al.* (2006) demonstrated that adhesion fibroblasts respond abnormally to elevated glucose levels when compared with the response shown by normal fibroblasts. At the normal glycemic level, adhesion fibroblasts were found to have significantly higher mRNA levels of the insulin receptor (IR), insulin-like growth factor-1 (IGF-1) and IGF-1 receptor (IGF-1R), when compared with normal peritoneal fibroblasts. Both insulin and IGF-1 are growth factors and are known to be involved in the regulation of metabolism and growth in almost all tissues in mammals. Furthermore, IGF-1 stimulates mitosis, as well as the production of collagen (Powell *et al.*, 1999). Rizk *et al.* (2006) also found that, when exposed to elevated glucose levels, normal peritoneal fibroblasts compensated for the increase by increasing expression of the IR, IGF-1R and IGF-1. Adhesion fibroblasts, on the other hand, responded to elevated glucose levels by decreasing expression of the IR, IGF-1R and IGF-1. The authors propose that the decreased expression of biomarkers occurred secondary to impaired compensatory mechanisms. These findings suggest that the differential expression and differential response to hyperglycemia of these biomarkers in adhesion fibroblasts might contribute to the tendency toward fibrosis seen in diabetic patients, as well as to the development of post-operative adhesions. The exact mechanisms by which adhesion fibroblasts acquire differences in glucose metabolism, however, have yet to be determined.

In regards to hemostasis, several studies have demonstrated impaired fibrinolysis in patients with type 2 diabetes mellitus (Juhan-Vague *et al.*, 1989; Mansfield *et al.*, 1996, 1997). This impairment is mainly attributed to increased production of PAI-1 by fat-laden insulin-resistant adipocytes (Grant, 2007). Other studies have reported elevated circulating levels of fibrinogen and tPA in insulin-resistant individuals (Juhan-Vague and Vague, 1991; Potter van Loon *et al.*, 1993; Meigs *et al.*, 2000; Raynaud *et al.*, 2000). Similarly, alterations in hemostasis have been reported in individuals with metabolic syndrome (metS)—a syndrome characterized by central obesity, impaired glucose tolerance, dyslipidemia and hypertension. These individuals tend to have significantly higher levels of

plasma PAI-1 and slightly higher levels of plasma fibrinogen (Alessi and Juhan-Vague, 2008). It has been proposed that this elevation in fibrinogen levels is the result of increased IL-6 levels seen in metS (Yudkin *et al.*, 2000; Fain *et al.*, 2004).

Cancer

Just as with diabetes, many publications have also suggested alterations in coagulation and fibrinolysis in cancer patients (Rickles *et al.*, 1992; Zacharski *et al.*, 1992). One study examined specifically patients diagnosed with colorectal cancer. These patients were found to have procoagulant activity and fibrinolytic inhibition, as evidenced by slightly elevated plasma thrombin/antithrombin III complex and PAI-1 levels (Modrau *et al.*, 2001). Another study found coagulation activation in patients with newly diagnosed colorectal cancer as opposed to age-matched controls (Iversen *et al.*, 1996).

The development of post-operative adhesions following radical pelvic surgery is a common problem faced by pelvic surgeons and gynecologic oncologists. In addition to the several aforementioned morbidities associated with post-operative adhesions that can result from any gynecologic procedure (e.g. SBO, infertility, pelvic pain), adhesions occurring secondary to radical pelvic surgery are especially troublesome because they restrict the use of certain treatment modalities (e.g. intraperitoneal chemotherapy, abdominal or pelvic radiotherapy, and intraperitoneal radioactive colloids) (Dedrick *et al.*, 1978; Tewfik *et al.*, 1979).

Past research has examined the use of a barrier device to prevent post-radical pelvic surgery adhesions. The potential benefits of using such a barrier in the gynecological oncology patient are 2-fold. First, separating the surfaces protects the serosal defect, potentially preventing adhesion formation. Second, the barrier acts as a 'pelvic lid' to lift the bowel out of a radiation treatment field, effectively protecting it from subsequent radiation injury and associated fistula formation (Wheeless *et al.*, 1971; Clarke-Pearson *et al.*, 1988; Sener *et al.*, 1989). In an animal study, Montz and colleagues demonstrated that significantly fewer post-radical pelvic surgery adhesions developed when the Gore-Tex Surgical Membrane was employed (Montz *et al.*, 1992).

In a human clinical trial, Bristow and Montz (2005) found that the use of a sodium hyaluronate-carboxymethylcellulose (HA-CMC) barrier (Seprafilm) significantly reduced post-operative pelvic adhesion formation following a radical oophorectomy procedure for locally advanced ovarian cancer. The authors also noted that there was no negative impact on the rate of persistent pelvic disease at second-look surgery. Furthermore, multiple animal studies have shown that utilizing a HA-CMC barrier at the time of primary cancer surgery does not adversely affect oncologic outcome (Hubbard and Burns, 2002; Pucciarelli *et al.*, 2003; Sasaki *et al.*, 2004; Sikkink *et al.*, 2004). In another study of adhesion prevention measures in an ovarian cancer model, Monk *et al.* (1998) found that placement of an expanded polytetrafluoruethylene barrier significantly reduced the number and extent of pelvic adhesion formation at second-look surgery. In their systematic review and meta-analysis of human clinical trials on adhesion barriers for gynecologic and abdominal surgery, ten Broek *et al.* (2014) concluded that oxidized regenerated cellulose and HA-CMC barriers safely reduce clinically relevant consequences of adhesions.

Endometriosis

Endometriosis is yet another disease thought to predispose to adhesion formation. Wiczyk *et al.* (1998) found that the presence of endometriosis strongly but variably predisposes to pelvic adhesion formation. In this report, patients with small foci of endometriosis were found to present with extensive adhesion formation, whereas those with extensive peritoneal studding with endometriotic implants tended to have normal anatomy maintained.

Evidence suggests that the pathogenesis of pelvic adhesions formation in endometriosis involves local inflammatory reactions. Several pro-inflammatory cytokines have been implicated in this process. Barcz *et al.* (2012) have demonstrated increased concentrations of IL-6 and IL-8 in the peritoneal fluid of patients with endometriosis. Furthermore, the increased levels of both cytokines correlated with the severity of disease (Milewski *et al.*, 2008; DZiunycz *et al.*, 2009; Barcz *et al.*, 2012). Additionally, changes in the fibrinolytic system have been reported in patients with endometriosis (Edelstam *et al.*, 1998; Gilabert-Estelles *et al.*, 2003, 2005; Bruse *et al.*, 2004). It has been proposed that the propensity for adhesion formation in endometriosis patients is the result of impaired fibrinolysis. This impairment is believed to mainly be the result of activation of PAI-1 by the pro-inflammatory cytokines (Dong *et al.*, 2003, 2007; Di Filippo *et al.*, 2006).

Reproductive milieu

Hormones

Animal models have demonstrated a direct relationship between estrogen levels and incidence of adhesion development. In one study, Grow *et al.* (1996) studied the effect of estrogen on adhesion formation by assigning primates to one of two groups. In the first group, a hypoestrogenic state was induced by administering GnRH analogue (GnRH-a). The second group received mifepristone (RU486), a well-known antiprogestin and lesser-known anti-estrogenic agent. Primate models have shown significant endometrial thinning following mifepristone administration, demonstrating its potent anti-estrogen effect (Wolf *et al.*, 1989). In humans, chronic administration of mifepristone results in a reduction in uterine leiomyomata (fibroids) by greater than 40%, further supporting this effect (Murphy *et al.*, 1993). Post-operative adhesion development in the control group was significantly greater than either of the treatment groups. It is important to bear in mind, however, that the reduction in fibroid size might also be the result of an antiprogestin effect.

These findings are consistent with previous research, which has shown that pelvic adhesions contain estrogen and progesterone receptors (Wiczyk *et al.*, 1998). Other research has demonstrated that estrogen deprivation results in decreased uterine blood flow (Achiron *et al.*, 1995; Aleem and Predanic, 1995), and that both estrogen and progesterone promote angiogenesis (Hervé *et al.*, 2006). Furthermore, it has been demonstrated that both hormones stimulate growth factor production in the female reproductive tract. In the uterus, the predominant activator of IGF—a hormone known to stimulate mitosis in a variety of tissues—is estrogen. Estrogen-stimulated expression of IGF mRNA has been detected in all compartments of the uterus; however, its expression is greatest in the myometrium, a site that is especially susceptible to adhesion formation during uterine surgery (Murphy and Ghahary, 1990). On the contrary, human clinical trials have suggested that preoperative treatment with GnRH-a does not, in fact, reduce adhesion formation post-open-myomectomy (Diamond, 1996; Coddington *et al.*, 2009).

Research on hormone therapy (HT) has demonstrated an association with increased prothrombotic potential (Połać *et al.*, 2013). Studies have shown that HT actually alters the structure and metabolism of proteins

involved in coagulation and fibrinolysis (Callejon *et al.*, 2005; Norris *et al.*, 2008; Shimomura *et al.*, 2013). In an interesting study, Polac and colleagues demonstrated that, whereas fibrinogen levels increased significantly in patients given the oral form of HT (17-β-estradiol and dydrogesterone), there was no significant change in those that received HT via the transdermal route (17-β-estradiol and 19-norethisterone) (Połać *et al.*, 2013).

Menstrual cycle

On a similar note, several studies have examined the variation of hemostatic factor levels throughout the menstrual cycle. In a recent systematic review of the literature, Knol *et al.* (2012) identified 15 such studies of fibrinolytic parameters (PAI-1, tPA, uPA, D-dimer and α-2-antiplasmin) and 20 studies of fibrinogen levels throughout the menstrual cycle. Overall, the majority of these studies observed no cyclic variation. Those that did report significant differences yielded conflicting results. For instance, two out of the 15 studies of fibrinolytic parameters found cyclic variation in PAI-1 levels. One of these studies reported that levels were lowest during the luteal phase (Giardina *et al.*, 2004), while the other claims they are lowest in the follicular phase (Chung *et al.*, 1998). Thus, while it is possible that the phase of a women's menstrual cycle could predispose to post-operative adhesion development, more research must be done before any definitive conclusions can be made.

Pregnancy

Significant changes in all aspects of hemostasis are seen during normal pregnancy and likely occur secondary to elevated estrogen levels (Sattar *et al.*, 1999; Hellgren, 2003). These changes help to maintain placental function and to decrease bleeding complications during delivery (Brenner, 2004). Overall, there is a tendency toward decreased fibrinolysis and increased propensity for adhesion development during pregnancy (Awonuga *et al.*, 2011). For instance, during pregnancy there is a marked increase in procoagulation factors such as factors VII, VIII, IX, fibrinogen, and von Willebrand factor, and a decrease in the anticoagulants protein S and acquired activated protein C (Szecsi *et al.*, 2010). Also, elevated levels of estrogen induce an increase in α2-antiplasmin and α2-macroglobulin during pregnancy (Petersen, 1993).

Studies by Saed and Diamond (2003) have shown a decreased tPA/PAI-1 ratio produced by adhesion fibroblasts as compared with normal peritoneal fibroblasts. Other research has shown an increase in PAI-1 and a decrease in tPA/PAI-1 ratio in pregnancy (Rehman *et al.*, 2003; Procházková *et al.*, 2010), which is consistent with the idea that there is predisposition toward adhesion development during pregnancy.

Specific demographics

Gender

It remains unclear whether or not one gender is more prone to developing adhesions that the other. In a postmortem study (Weibel and Majno, 1973), it was noted that there was a slightly higher frequency of adhesions among women. Other studies, however, have found a higher incidence among male patients (Beck, 1997). Others have failed to identify any significant differences in post-operative adhesion development between men and women (diZerega, 1993).

When compared with males, it appears that females have a lower fibrinolytic capacity (Siegbahn and Ruusuvaara, 1988). A study by Steptoe *et al.* (2003) found that plasma fibrinogen levels are lower in middle-aged men than women not receiving hormone replacement therapy. Another study found that males exhibit an enhanced stress-induced hemorheological response compared with age-matched females (Veldhuijzen van Zanten *et al.*, 2004).

Age

Overall, no general consensus has been reached in regards to the effect that age has on the development of adhesions, however it is well agreed that there is a high incidence of adhesions at all ages. The Surgical and Clinical Adhesions Research (SCAR) trial examined the burden of adhesions following lower abdominal surgery, and discovered that the risk of adhesion-related readmission in the 5 years following surgery is higher in patients younger than 60 years compared with those aged 60 years or older. Whereas the overall risk for these patients after surgery was estimated to be 5%, the risk was as high as 10% for women under the age of 60 years (Parker *et al.*, 2005, 2007). Interestingly, Weibel and Majno demonstrated that the frequency of spontaneous adhesion development is significantly greater after the age of 60 years (Weibel and Majno, 1973). Experimentally, it has been found that immature rats have quicker peritoneal regeneration when compared with mature rats (Raftery, 1973).

Studies of other fibrotic conditions, such as peritoneal and pulmonary fibrosis, may shed some light on this association. Among peritoneal dialysis (PD) patients, young age is a risk factor for the development of encapsulating peritoneal sclerosis (EPS) (Braun *et al.*, 2011; Korte *et al.*, 2011a, b; De Sousa *et al.*, 2012), independent of length of time on PD or duration of follow-up (Korte *et al.*, 2011a, b). It has been suggested that this finding might be related to the fact that younger patients have a greater capacity for tissue repair, which in the case of peritoneal damage, results in fibrosis and a greater risk for EPS (De Sousa *et al.*, 2012). On the contrary, older age is a risk factor for the development of idiopathic pulmonary fibrosis, a fibrotic condition that is virtually nonexistent in young people (Raghu *et al.*, 2006). An animal study by Selman and Pardo (2014) demonstrated that the ability to resolve lung fibrosis is impaired in aged mice compared with young cohorts.

We must also consider the fact that the age at which scarring of the skin occurs the least is prior to birth. The process of fetal dermal wound healing occurs via scarless repair, with restoration of normal tissue architecture and function, and an inflammatory response that is both diminished and delayed (Burrington, 1971; Rowlatt, 1979; Adzick *et al.*, 1985; Krummel *et al.*, 1987; Longaker *et al.*, 1990). The healing process in the dermis is remarkably similar to that of the mesothelium, and as such, the skin and peritoneum respond very similarly to trauma. Both organs involve an initial, acute inflammatory response, a cellular proliferative phase, and a continuous extracellular remodeling phase (Cheong *et al.*, 2001). Stocker and colleagues (2014) recently demonstrated that, among women undergoing elective laparoscopic gynecologic operations who had previously undergone abdominopelvic surgery, skin scar characteristics were associated with the presence and degree of pelvic adhesions. Women who had more than one abdominal scar, a palpable scar, and/or a longer scar were most likely to have pelvic adhesions. Furthermore, women with the highest mean 'scar scores' (higher score equated to more marked or abnormal scarring) had a greater total adhesion score.

Research has also found that certain factors of the coagulation system vary with age. One study identified a positive correlation between age and PAI-1 (Cosman *et al.*, 2005). Similarly, the Cardiovascular Health

Study found increased activity of both fibrinogen and factor VII in individuals over the age of 65 years (Kop et al., 2002). When considering 20-year old individuals, TAFI levels are generally elevated. This observation might be explained by hormonal changes that occur at the end of adolescence (Peetz et al., 2004).

Another interesting observation is that because of their age, children have a longer lifetime risk for adhesion-related morbidity when compared with adults. Wilkins and Spitz (1986) performed a retrospective chart review of all neonates (defined as ≤28 days old) who had undergone laparotomy in the past 10 years at their hospital, and discovered that 8.3% of these neonates developed SBO secondary to post-operative adhesions.

Genetics

Anecdotal experiences suggest that some individuals are predisposed to post-operative adhesion development; these factors are beginning to emerge. One study examined genotype and allele frequencies of the IL-1RN gene, which encodes the proinflammatory cytokine IL-1RN (IL-1 receptor antagonist). This gene contains a polymorphism and the respective mutant allele is referred to as IL-1RN*2. The presence of this mutant allele is associated with increased monocyte production of IL-1β and a variety of chronic inflammatory diseases. The results showed that IL-1RN*2 allele carriers have an increased risk of adhesion development (Wieser et al., 2002).

Another study examined the relationship between intestinal adhesions causing intestinal obstruction in childhood and HLA subtype. The HLA system constitutes a complex array of genes and gene products related to immune system function in humans. The study found an association of intestinal adhesions with HLA subtypes A24 and DR1 in children. The mechanism linking the HLA system with disease remains unclear, but the authors note that the use of HLA profiles could potentially be used in the future to identify those at risk for intestinal adhesions (Erdogan et al., 2000).

Additionally, the synthesis of many of the elements involved in the coagulation and fibrinolytic systems has been found to have a strong genetic link. This link is related to the presence of polymorphisms in the genes that control the production of these elements. For instance, polymorphisms in the PAI-1 gene are important determinants of plasma PAI-1 levels. A single nucleotide insertion/deletion in the PAI-1 promoter has been identified. Individuals that are homozygous for the deletion allele have been found to have activated PAI-1 gene transcription, increased plasma PAI-1 activity, and decreased fibrinolytic activity (Dawson et al., 1991; Eriksson et al., 1995). The heritability of plasma PAI-1 levels has been reported to be between 30 and 71.4% (Hong et al., 1997; Pankow et al., 1998; Cesari et al., 1999; de Lange et al., 2001; Souto et al., 2001).

Several polymorphisms within the fibrinogen gene locus have been identified and found to be associated with differences in fibrinogen levels (Reed et al., 1994). Research has consistently indicated that one of these polymorphisms, a substitution within the β-fibrinogen gene, is associated with differences in fibrinogen levels (Humphries et al., 1987; Thomas et al., 1991; Green et al., 1993; Scarabin et al., 1993; Heinrich et al., 1995). Overall, however, the association of polymorphisms on the fibrinogen β chain with disease has been inconsistent (Behague et al., 1996). Twin studies have also demonstrated significant heritability of fibrinogen levels, with reports ranging from 20 to 51% heritability (Hamsten et al., 1987; Friedlander et al., 1995). Similarly, a study of weight-concordant monozygotic twins found that most coagulation factor activities and fibrinogen were extremely similar within twin pairs, suggesting a substantial genetic contribution to the variance in the coagulation system (Kaye et al., 2012). Furthermore, the heritability of D-dimer, a FDP, is ∼66% (Ariens et al., 2002).

Research has also identified many single nucleotide polymorphisms within the gene encoding TAFI. Two of these polymorphisms are located in the coding region of the gene and are linked to TAFI levels (Boffa et al., 1999). Around 76 to 82% of the variability of plasma TAFI antigen levels can be attributed to genetic factors (Ariens et al., 2002; Peetz et al., 2004).

We have ongoing research in our laboratory suggesting roles for polymorphisms in NADPH oxidase (Rout et al., 2005). Furthermore, microarray studies from our lab have identified specific genes with increased/decreased expression in adhesion tissues when compared with normal peritoneal tissue (Ambler et al., 2012). In sum, there is a high degree of genetic control over the processes of coagulation and fibrinolysis. Further, there appears to be a significant genetic predisposition to the prethrombotic state in an otherwise healthy individual.

Lifestyle and nutritional factors

Obesity

Similar to diabetic patients, wound healing is also sub-optimal in obese patients. Obesity—defined as a BMI of greater than 30 kg/m^2—has been shown to be associated with an array of wound complications, including infection, hematoma and seroma formation, venous and pressure ulcers, and dehiscence (Wilson and Clark, 2004). Postsurgical wound dehiscence is believed to occur partially as a result of the increased wound tension, which increases tissue pressure, effectively reducing microperfusion and oxygen delivery to the wound (Wilson and Clark, 2004; Anaya and Dellinger, 2006). An impaired immune response secondary to the influence of adipokines has also been implicated in the impaired healing capacity seen in obese individuals. Studies have shown decreased lymphocyte proliferation and peripheral blood mononuclear cell function as well as altered peripheral cytokine levels in obesity (Nieman et al., 1999; Fontana et al., 2007; de Mello et al., 2008).

Obesity is associated with several disturbances in hemostasis, especially impaired fibrinolysis (Lijnen, 2009). The impaired coagulation profile in obese individuals is the result of both environmental and genetic factors (Hamalainen et al., 2005; Balagopal et al., 2008). Fibrinolytic activity is strongly and negatively correlated with both BMI and waist-to-hip circumference ratio (WHR) (Ernst and Resch, 1993; Eliasson et al., 1995; Yarnell et al., 2000). The impaired fibrinolysis seen in obese patients is, in large part, secondary to elevated plasma PAI-1 levels, which may be the result of increased release from visceral adipose tissue (Lundgren et al., 1996; Loskutoff and Samad, 1998) and fatty liver (Cigolini et al., 1996; Alessi et al., 2003). One study found that obese men have 50% higher PAI-1 activity as well as 30% higher tPA antigen compared with men with an ideal BMI (<25 kg/m^2) (Yarnell et al., 2000). In another study, women with a high WHR had significantly higher PAI-1 and fibrinogen levels when compared with both obese women with low WHR and lean women (Landin et al., 1990).

Exercise

An encouraging finding for obese individuals is that there is plenty of evidence that long-term moderate exercise can improve fibrinolytic

capacity. This improvement occurs in the form of decreased PAI-1 levels and increased tPA activity (Juhan-Vague and Alessi, 1996; Charles *et al.*, 1998). While the research supporting changes in tPA in response to moderate exercise have been consistent, findings on PAI-1 have been inconsistent (Eliasson *et al.*, 1996; DeSouza *et al.*, 1997; Womack *et al.*, 2001; Ivey *et al.*, 2003; Morris *et al.*, 2003). Some authors have suggested that intense short-term exercise can also increase fibrinolytic activity (Biggs *et al.*, 1947; Thrall *et al.*, 2007).

Diet

Multiple studies have suggested that the activity of the coagulation and fibrinolytic systems is influenced by nutrition (Nilsson *et al.*, 1990; Schmidt *et al.*, 1990). Dietary intervention with a low-saturated-fat diet can improve fibrinolytic activity (Elkeles *et al.*, 1980). Coffee consumption enhances fibrinolysis in the form of shortened whole blood fibrinolysis time, decreased PAI-1 levels, and increased tPA activity (Samarrae and Truswell, 1977; Wojta *et al.*, 1988). Laboratory studies have demonstrated increased tPA secretion by fibroblast cell cultures upon exposure to methylxanthine, the major active constituent of coffee (Hamilton *et al.*, 1986). Another important consideration is the impact that nutrition has on the healing response. Nutrients that have been reported to contribute to wound healing include proteins, carbohydrates, polyunsaturated fatty acids, arginine, glutamine, vitamin A, vitamin C, vitamin E, magnesium, copper, zinc and iron (Guo and DiPietro, 2010).

Alcohol

There is increasing evidence that alcohol consumption influences fibrinolytic activity. Light-to-moderate alcohol intake is associated with more favorable coagulation and fibrinolytic profiles, seen as lower levels of fibrinogen and higher levels of tPA (Ridker *et al.*, 1994; Yarnell *et al.*, 2000; Mukamal *et al.*, 2001). On the other hand, short-term, heavy alcohol consumption is associated with decreased fibrinolytic capacity, which is believed to occur secondary to elevated PAI-1 levels (Veenstra *et al.*, 1990; Ridker *et al.*, 1994; Lee *et al.*, 1995; Pellegrini *et al.*, 1996; McConnell *et al.*, 1997; Dimmitt *et al.*, 1998; Johansen *et al.*, 1999; van de *et al.*, 2001). One study showed an acute, dose-dependent rise in PAI-1 antigen activity and a prolonged whole blood clot lysis time following consumption of a high dose of red wine (Johansen *et al.*, 1999).

In a recent study, swine that were administered vodka prior to re-operation developed significantly fewer serious pericardial adhesions than both the control group and the swine that were given red wine (Lassaletta *et al.*, 2012). Histologically, the vodka-treated swine demonstrated decreased fibrosis and transmural collagen expression. Interestingly, the blood ethanol levels of the treated animals reportedly fell in the 'moderate consumption' range. As of yet, it remains unknown exactly which compounds in vodka might be responsible for its adhesiolytic properties.

Smoking

Many studies have shown diminished fibrinolysis in chronic smokers when compared with nonsmoking controls (Allen *et al.*, 1985; Meade *et al.*, 1987; Eliasson *et al.*, 1995; Simpson *et al.*, 1997; Newby *et al.*, 2001; Chia and Newby, 2002). One study examined coagulation/fibrinolytic parameters among three groups: current smokers, former smokers and nonsmokers. Although there was no significant association between smoking status and tPA antigen levels or PAI-1 activity, PAI-1 antigen was significantly higher in smokers than nonsmokers, with intermediate levels seen in former smokers. Also, the ratio of tPA to PAI-1 was similar in nonsmokers and former smokers but lower in current smokers, indicating that there may be a partial restoration of fibrinolytic activity after smoking cessation. Thus, it is possible that chronic smoking is associated with decreased fibrinolysis. Furthermore, it is possible that this effect is mediated by the influence of smoking on triglyceride levels and insulin resistance (Simpson *et al.*, 1997).

Similar to several of the previously discussed predisposing factors, smoking is also associated with poor wound healing. Studies have shown that patients who smoke experience delayed wound healing postoperatively as well as a number of other post-operative complications. In a retrospective analysis of 132 patients who had undergone abdominoplasty, Manassa *et al.* (2003) found that the rate of wound problems (defined as dehiscence, skin slough, fat necrosis, or the need for invasive interventions such as wound irrigation, debridement, or secondary closure) and wound dehiscence was significantly greater in smokers when compared with nonsmokers. Other studies have provided support for this association by demonstrating a higher incidence of postoperative infection, wound rupture, anastomotic leakage, wound and flap necrosis, epidermolysis, and decreased tensile strength of wounds among smokers (Chan *et al.*, 2006; Ahn *et al.*, 2008; Guo and DiPietro, 2010).

Psychological well-being

Stress

Interestingly, variations in coagulation and fibrinolysis in response to psychosocial stressors seem to mirror the changes seen in response to exercise. Accordingly, as in short-term, intense exercise, acute mental stress enhances fibrinolysis with increased tPA activity in healthy individuals. The coagulation system is also activated in response to acute mental stress, with increases in fibrinogen, total plasma protein, hematocrit, factor VII and factor VIII (Jern *et al.*, 1989; Urano *et al.*, 1990). On the other hand, long-term psychosocial stressors (e.g. job stress or low socioeconomic status) have the potential to induce a state of 'vital exhaustion,' in which case a hypofibrinolytic picture is favored. For instance, fibrinogen levels are significantly elevated during periods of increased workload compared with calm work periods (Frimerman *et al.*, 1997). Plasma fibrinogen levels have also been found to be inversely associated with socioeconomic status (Steptoe *et al.*, 2003).

Other studies, which have linked increased PAI-1 and decreased tPA activities to long-term psychosocial stressors, have supported these findings (Raikkonen *et al.*, 1996; Vrijkotte *et al.*, 1999). However, some research has reported unchanged fibrinolysis during periods of emotional stress (Sherry *et al.*, 1959). One proposed explanation for this inconsistency is that psychological stress is difficult to define and standardize (Jern *et al.*, 1989). The mechanism underlying the possible impairment in fibrinolysis in individuals with long-term psychosocial stress has not been entirely worked out, but has been linked to insulin resistance, obesity and triglyceride levels (Raikkonen *et al.*, 1996).

Mood

Similarly, many studies have shown significant changes in D-dimer in association with mood factors (von Känel and Dimsdale, 2003; von Känel *et al.*, 2004). One study found a positive correlation between depression (based on scores of the Center for Epidemiologic Studies Depression scale) and D-dimer (Dentino *et al.*, 1999). Other hemostasis variables

have not been significantly tied to mood factors. However, social isolation and low social support are both correlated with elevated fibrinogen levels (Davis and Swan, 1999; Wamala *et al.*, 1999).

Conclusion

Adhesion development is a significant, yet poorly understood cause of morbidity in post-operative patients. To date, it remains unknown exactly why adhesions form more frequently in certain tissues and/or patients, or at specific locations, as opposed to others. This review contributes to the growing knowledge pool by elucidating factors that potentially predispose to the development of adhesions. By identifying those factors shown to directly increase risk (genetic polymorphisms, estrogen exposure and endometriosis) in addition to those that might do so indirectly by way of altering the coagulation/fibrinolytic profile in such a way that increases fibrosis (genetic polymorphisms, diabetes mellitus, metabolic syndrome, hyperglycemia, obesity, depression, binge alcohol consumption, anti-Parkinsonian medications, oral hormone therapy, pregnancy and cancer), this review can be a useful tool for surgeons to identify high-risk patients who might benefit from anti-adhesion agents. Furthermore, this review serves as a useful catalyst for inspiring future areas of investigation. Further research is necessary to understand the mechanisms that underlie the association of the factors identified in this review with adhesion formation. Future research should also investigate whether there exists a direct link between adhesion formation and any of the factors we have identified as potentially doing so indirectly by increasing fibrosis. This information will be crucial in the creation of adequate preventative and treatment strategies.

Authors' roles

C.N.F., G.M.S. and M.P.D. made substantial contributions to the conception, design, analysis, drafting and revision of the article. All authors have approved the final version for submission.

Funding

No funding was received for the completion of this paper.

Conflict of interest

M.P.D. serves on the Board of Directors for Advanced Reproductive Care and is a stockholder in the company. He is also a consultant for Actamax, Auxogyn, Teijin Pharmaceutical, and ZSX Medical, and has received grant support from EMD Serono and AbbVie. C.N.F. and G.M.S have nothing to declare.

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