



## **Samenvatting van het proefschrift**

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*"Abdominal Wall Hernia Repair:  
Intraperitoneal Mesh and Adhesions"*

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Abdominal wall hernia repair is a frequently performed procedure that often requires the management of adhesions and mesh placement. This thesis explored the scope of the problem of adhesions in a clinical setting, then evaluated intraperitoneal adhesion formation to meshes in an experimental setting, and eventually developed a model for translating our experimental results to a clinical setting.

**Part 1: Clinical problem and awareness**

Firstly, we aimed to substantiate the burden of adhesions in abdominal wall hernia repair. In Chapter 2 we evaluated adhesions and related complications through a prospective, observational study of abdominal wall hernia repairs. In uncomplicated hernia repairs, i.e. no fistula or wound infection and no further surgical procedures, 10.3% of all patients experienced an inadvertent enterotomy. When complicated hernia repairs were included, 12.8% of all patients experienced one or more enterotomies. Adhesiolysis time was the most significant risk factor for enterotomy in all patients. As adhesiolysis time exceeded 30 minutes, even without an inadvertent enterotomy, more wound infections, reinterventions, ICU admissions, and episodes of parenteral feeding occurred, together with longer ICU and hospital stay and higher medication costs. With mesh from a previous repair still in place, the risk for an inadvertent enterotomy in uncomplicated repairs increased about 7-fold. Despite the extensive morbidity, surgeons seem to underestimate the problem of adhesions. In Chapter 3 we surveyed all Dutch surgeons and surgical trainees for their knowledge, attitudes and behaviour towards adhesions. Although about two thirds of all respondents indicated that adhesions exert a negative and clinically relevant effect, comparable amounts of respondents significantly underestimated the extent and impact of adhesions. Nevertheless, a more negative perception of adhesions correlated with a more positive attitude regarding adhesion prevention. Also, less know-

ledge about adhesions correlated with more uncertainty about when to use antiadhesive agents which, in turn, correlated with never having used any of these agents. For abdominal wall hernia repair, an extraperitoneal mesh position and the use of coated meshes was agreed to reduce adhesion formation by 85 and 70% of respondents, respectively. Four in 10 respondents indicated that they never inform patients on adhesions preoperatively and only one in 10 indicated to inform patients routinely. Interestingly, knowledge and perception of the clinical relevance of adhesions did not correlate with informed consent behaviour.

#### Part 2: Experimental findings on intraperitoneal mesh related adhesions

After establishing the clinical problem of adhesions, the second part of this thesis studied adhesion formation with intraperitoneal meshes. The first study, presented in Chapter 4, compared adhesion formation against several intraperitoneal meshes in a rat model at 7 and 30 days follow-up. The uncoated polypropylene mesh (Prolene<sup>®</sup>) showed extensive adhesion formation with the mesh at 7 days follow-up. At 30 days, adhesions diminished slightly and inflammation normalized. Comparable results were seen with 2 other meshes (TiMesh<sup>®</sup>, Ultrapro<sup>®</sup>) that had no continuous layer of coating either. The three meshes with an absorbable layered coating (Proceed<sup>®</sup>, C-Qur<sup>®</sup>, Parietex Composite<sup>®</sup>) showed very limited adhesion formation at 7 days follow-up. However at 30 days, adhesions increased significantly as phagocytosis of the absorbable coatings occurred. The fixation points and mesh borders seemed to be preferential sites for adhesion formation. Incorporation into the abdominal wall was insufficient for all meshes. In Chapter 5, four meshes with an absorbable layered coating (Parietene Composite<sup>®</sup>, Parietex Composite<sup>®</sup>, C-Qur Edge<sup>®</sup>, Sepramesh IP<sup>®</sup>) and one with a non-absorbable layered coating (Intramesh T1<sup>®</sup>) were compared at 90 days follow-up. Uncoated polypropylene (Prolene<sup>®</sup>) and collagen meshes (Permacol<sup>®</sup>) served as controls. All coated and collagen meshes performed equally well and significantly better than Prolene<sup>®</sup> in terms of adhesion prevention. Yet, the intensity of inflammation related to the absorbable coating differed highly. Incorporation was again mostly limited to the site of fixation that, together with the mesh borders, proved to be a preferential site for adhesion formation. In addition, the inflammatory reaction of the abdominal wall to the mesh significantly induced adhesion formation. Apart from the meshes, we also compared adhesion formation to several fixation methods at 7 and 90 days follow-up. In Chapter 6, we found that fibrin glue (Tisseel Duo<sup>®</sup>) was resorbed in less than 7 days and provided a strong antiadhesive effect, though mesh fixation was inadequate. Sutures that were resorbed before 90 days follow-up were also associated with a favourable adhesion profile. All other fixation methods (Protack<sup>®</sup> tackers, Absorbatack<sup>®</sup> tackers, Permasorb<sup>®</sup> tackers, Prolene<sup>®</sup> sutures) that were still intact at 90 days showed comparable and less favourable adhesion formation. Fixation methods were also placed without mesh to study the influence of the fixation methods on itself. Interestingly, in these cases adhesion formation was significantly reduced, but in the meantime fixation methods dislocated in up to 72% of tackers placed. Following our observations of adhesion formation associated with

phagocytosis of absorbable coatings, we tested the hypothesis if the addition of a non-absorbable coating could reduce adhesion formation. In Chapter 7 an experimental coating with an increased hydrophilicity was applied to standard polypropylene mesh. The coating was not applied as a continuous layer on one side of the mesh, but rather around every string of mesh. Even though at 7 days a more intense inflammatory reaction was noted than with uncoated polypropylene, adhesions were significantly reduced. Moreover, adhesions were still significantly reduced at 30 days at which point inflammation, and fibroblast numbers in particular, decreased. Finally, some recent breakthroughs in the understanding of adhesion formation and foreign body response were evaluated with regards to intraperitoneal mesh and adhesions. In Chapter 8, mice were treated orally with cromolyn, commonly known as a mast cell stabiliser, and followed up for 7 days after intraperitoneal polypropylene mesh (Prolene®) implantation. As a result, adhesions were reduced by about 50%, but only with cromolyn administered preoperatively. Although the exact method of action remained unclear, we found that the pathogenesis of tissue-biomaterial adhesions differs significantly from intraperitoneal tissue-tissue adhesions. Because oral cromolyn is already available as a registered drug, the adhesion preventive effect is significant and the side effects are second to none, further clinical testing should be attempted.

#### Part 3: A human model for the evaluation of adhesions to meshes

The final chapter establishes a human model to allow for standardized clinical evaluation of adhesions to intraperitoneal meshes. Firstly, in Chapter 9, the abdominal wall of patients who had undergone stoma reversal was examined by ultrasound for the presence of an incisional hernia at the site of the old stoma wound. After a median follow-up of almost 3 years, one in 3 patients had developed an incisional hernia. With obese patients hernias were present in 6 out of 10, compared to one in 4 patients without obesity. Consequently, obesity was identified as the sole risk factor for hernia occurrence. Of note, palpation of the abdominal wall had a limited sensitivity of 58%, so that one in 6 patients with complaints but without a palpable hernia would show a hernia on ultrasound. The high risk for incisional hernia after stoma reversal was reason to consider extra measures of prophylaxis. Therefore, we explored the feasibility and safety of placing a parastomal mesh at the time of temporary stoma creation in Chapter 10. This mesh was placed intraperitoneally and with the intent to prevent incisional hernias after stoma reversal. At the time of stoma reversal, laparoscopy was performed and adhesions scored. Then the stoma was reversed and the mesh defect closed. At a median of 2 years follow-up after stoma reversal no incisional hernias nor mesh infections had occurred. Furthermore, laparoscopy revealed adhesions against all meshes involving a median of 25% of the mesh surface. In more than half of all patients, adhesions could not be lysed bluntly and were appreciated as severe. Altogether, this model allowed for the clinical evaluation of adhesions against intraperitoneal meshes and can be used for translation of our experimental results.