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RESEARCH ARTICLE

# The Pathogenesis of Mesh-induced Inflammatory Response and Pain: Rationale for Development of New Mesh

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## Abstract

Chronic postoperative pain (CPP) in mesh hernia repair (MHR) may complicate the postoperative course. The cause of CPP may be multifactorial - surgical technique, patient-intrinsic factors, and mesh. Polypropylene (PP) mesh is the most widely used material for MHR. Despite its advantages, it has been associated with severe complications in urogynecology leading to a partial mesh ban. PP is not inert and causes foreign body reactions (FBR), corrosion, and loss in biocompatibility. Pain is a hallmark of mesh-induced complications. The pathogenesis of pain is related to an immune response with neutrophils, T cells, and macrophages, major players in mesh-associated fibrosis and pain. Pain may be caused by mesh implantation-induced nerve entrapment, compression, and severe inflammation, relevant for both nociceptive and neuropathic pain. Compression neuropathy has been associated with preoperative pain and chronic postoperative pain in mesh and non-mesh repairs. The mesh may induce FBR changes causing clinical complications and pain. Increased mesh vicinity innervation induced by fibrosis may be responsible for chronic postoperative pain. An aggressive immune response in pelvic floor reconstructive surgery degrades PP. T cells and macrophages may protect against or induce degradation and pain. The main point to eliminate pain is to develop a mesh, that provides long-term corrosion resistance, and biocompatibility. This may be achieved by coating PP mesh with a thin layer of Titanium oxide or meshes of pure titanium. Titanium is considered to be bio-inert providing corrosion resistance and biocompatibility. However, depending on the location and surface of the mesh (roughness, hydrophilicity), there may be a macrophage-neutrophil-induced inflammatory response causing fibrosis and cicatrization. Based on the structure, location, and production Titanium may demonstrate beneficial effects concerning corrosion, oxidation, FBR, and biocompatibility. To improve outcomes in MHR the analysis of cellular immune response concerning mesh properties, composite endpoints, pain, and physical function may be necessary.

**Key Words:** *Hernia repair; Mesh; Chronic postoperative pain; Foreign body reaction; Inflammatory response*

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## Introduction

Inguinal hernia repair (IHR) is one of the most widely performed surgical procedures, with approximately 20 million surgeries performed annually worldwide. Inguinal hernias represent nearly 75% of all abdominal wall hernias. The application of surgical mesh for the repair of various challenging hernias has improved therapeutic results. Unfortunately, however, predominant among postoperative complaints and complications remains the incidence of chronic postoperative pain (CPP). In 1998, mesh inguinodynia, or chronic groin pain was recognized as a new clinical syndrome in correlation with inguinal mesh hernia repair [1]. The predominant cause of inguinodynia is thought to be multifactorial and related to surgical technique, fixation, intrinsic factors of the patient as well as the choice of the mesh [2]. An increased incidence of inguinodynia due to the entrapment of the nerves adjacent to the mesh has long been recognized. In mesh repair, an incidence of up to 21% of inguinodynia has been reported with an overall incidence of clinically significant chronic pain in the 10-12% range [3]. Debilitating chronic pain affecting normal daily activities or work ranges from 0.5 to 6%. Chronic postoperative inguinal pain (CPIP) is defined as bothersome moderate pain impacting daily activities lasting at least 3 months postoperatively and currently, pain is recognized as the leading sign of complication in mesh hernia repair. CPIP risk factors include young age, female gender, high preoperative pain, early high postoperative pain, recurrent hernia, and open repair [4,5]. There are abundant reports of pain associated with the implantation of mesh in hernia repair, however, what exactly causes the pain in mesh repair has not yet been fully elucidated [6]. Mesh-associated pain may be caused by nerve entrapment, compression neuropathy, and inflammatory reaction either by mesh or by the development of fibrosis, both of which of course may be interrelated [7]. While nerve entrapment and compression neuropathy show an obvious relationship to damage caused by surgical mesh implantation, the relationship to inflammatory reaction is less clear. For years the mesh retailing and producing companies led surgeons to believe that PP mesh is inert. Almost 20 years ago, however, it was convincingly demonstrated that distilled water, saline, and blood as *in vivo* implantation cause structural alterations in the size of pores, which may cause shrinkage and expansion of mesh [8]. Recent studies support evidence that the degradation of PP mesh is responsible for reduced biocompatibility and an increase in chronic postoperative pain. Lu *et al.* (2022) analyzed PP mesh explants after 0.5 to 13 years *in vivo*. There were changes in surface chemistry, crystallinity, and mechanical properties, demonstrating mesh degradation correlates with factors like mesh placement, mesh class, and infection [9]. As PP mesh has been associated with long-term complications and pain, it is reasonable to investigate the pathogenesis of mesh-induced pain further [10]. This review paper demonstrates the pathogenesis of mesh-induced pain and its relationship to the foreign material-induced immune response.

## Nociceptive Pain and Neuropathic Pain

"Nociception" provides a means of neural feedback that allows the central nervous system (CNS) to detect noxious and potentially damaging stimuli. "The sensation of pain divides into four large types: acute pain, nociceptive pain, chronic pain, and neuropathic pain". "Acute noxious stimuli (e.g., heat, cold, mechanical force, or chemical stimulation) trigger nociceptors". Acute pain becomes chronic inflammatory pain when the noxious stimulus persists long enough to allow nociceptive neurons to release their pro-inflammatory markers and sensitize or activate responsive cells in their local environment. "Nociceptive pain arises from tissues damaged by physical or chemical agents such as trauma, surgery, or chemical burns, while neuropathic pain arises from diseases or

damage mediated directly to sensory nerves" [11]. Mesh implantation may be accompanied by both nociceptive and neuropathic pain, we may say chronic inflammatory pain.

## Nerve Entrapment

The ilioinguinal nerve may be entrapped by mesh, suture, and tacks or traction spontaneously as it passes through the obliquus internus and transversus abdominis muscles [12]. Nerve entrapment is defined as pressure neuropathy from chronic compression which results in pathophysiologic alterations to all layers of the nerve tissue. Untreated, entrapment can lead to neuropathy and damage to enervated structures and musculature, causing significant morbidity (complex regional pain syndrome) [13,14]. The ilioinguinal nerve is at the greatest risk of entrapment during meshplasty and there may be a greater risk of chronic postoperative pain due to direct or indirect lesions of nerve terminations [15,16]. To minimize these complications a formal understanding of the pertinent anatomy is stressed. Surgeons are taught to respect and pay particular attention to an area termed the "triangle of pain," which contains the femoral branch of the genitofemoral nerve, the lateral cutaneous nerve of the thigh as well as the adjoining "triangle of doom," which contains the external iliac vein and artery as defined laterally by the spermatic vessels and medially by the vas deferens. With the ever-increasing application of laparoscopic and robotic approaches, this new anatomic perspective has required renewed attention and a lengthier learning curve [17,18].

## Compression Neuropathy

Compression neuropathy is related to the incidence of preoperative pain in patients who underwent primary inguinal hernia. This pain occurred near associated anatomical nerve constriction sites evident as an enlargement of the peripheral nerve [19]. On subsequent evaluation, patients who underwent primary open inguinal hernia repair and whose course was complicated by increased pain values were noted to have gross enlargement of the overall diameter and nerve-specific diameter of the ilioinguinal nerve beyond the external inguinal ring, consistent with compression neuropathy [20]. Preoperative pain in the primary inguinal hernia is most commonly associated with ilioinguinal nerve involvement, manifesting as enlargement and fibrosis of the external oblique fascia at the external ring [21]. It is important to appreciate that the association of pain with compression neuropathy has been demonstrated in both primary and secondary inguinal hernia repair, and both mesh and non-mesh repair [6].

## Material Changes - Meshes are not Inert

In low-income countries, commercial meshes are too expensive to use. However, alterations in the mechanical, chemical, and biocompatibility properties of low-cost polyethylene and polyester meshes after steam sterilization do not recommend their use in inguinal hernia repair [22]. PP is the most widely used material for non-resorbable mesh implants. Degradation of PP mesh, which is apparent on the mesh surface as cracking, flaking, and peeling, discovered in the 1990s, may be caused by chronic inflammation [23]. *In vivo* oxidation of PP mesh has been shown to lead to mesh degradation accompanied by chronic inflammatory reactions [24]. Infection, pain, recurrence, and connective tissue are correlated to inflammatory infiltration. Mesh with large pores induces less inflammatory infiltrate, connective tissue, fistula, calcification, and bridging than mesh with small pores [25]. Surprisingly tobacco use is correlated with less oxidation and degradation of polymeric mesh reflection and reduced inflammatory response [26]. Elevated serum level markers associated with an acute inflammatory reaction caused by foreign body reaction (FBR) have been demonstrated after mesh implantation, e.g. IL1, IL-6, IL-10, and fibrinogen. Whether these markers which were

increased in the circulation reflect local activity in the vicinity of mesh is yet to be determined and may differ by compartmentalization and absorption [27,28]. Physical properties of the implant surface have been shown to influence the immune response (e.g., myofibroblast reaction) stimulating fibrosis and scar tissue and inducing pain at the surface and around the mesh [29]. FBR induces changes in the mesh which may be responsible for clinical complications.

## Mesh-induced Inflammation Causes Chronic Pain Syndrome

Several Predictors for chronic pain, the most frequent long-term complication of inguinal hernia repair, have been described. These are female gender, preoperative pain, prior inguinal hernia repair, higher ASA (The American Society of Anesthesiologists) class, and the structure of mesh (multifilament polyester mesh) [30]. Monofilament PP is less frequently removed compared to multifilament polyester PET mesh [31]. Partially absorbable composite mesh is associated with better patient outcomes in terms of less postoperative pain compared to PP [32].

Ilioinguinal neuropathy, a chronic pain syndrome associated with mesh inguinal herniorrhaphy and nerve mesh entrapment, may be caused by damage to sensory nerves, compression, and chronic inflammation [33]. Re-innervation and neo-innervation can be demonstrated after any hernia repair and in the vicinity of the mesh. However, when pain is an overriding issue dictating mesh explant, the degree of mesh innervation is noted to be significantly higher when compared to mesh excised for recurrence [34]. Chronic groin pain after hernia repair can be caused by the entrapment of peripheral nerves in scar tissue formed by the mesh or the incorporation of adjacent nerve fibers in a fibroblastic reaction. Nerve graft contact did not influence nerve motor conduction [35,36]. Inflammatory fibrosis is a wound-healing reaction of the immune system with pain as a hallmark of inflammation. In reaction to the inflammatory response associated with a mesh implant, fibroblasts and potentially myofibroblasts make stiff collagenous tissue that modifies the original healthy tissue causing pain. Should the inflammation persist, there is no reason for the pain to stop [37]. Spinal cord glial cells such as microglia and astrocytes play a critical role in the induction and maintenance of neuropathic pain by releasing powerful neuromodulators such as proinflammatory cytokines and chemokines [38]. Macrophage-nociceptor interactions can interestingly both activate and resolve inflammatory pain. Targeting macrophage-nociceptor interactions in mesh-induced inflammatory response may help to control inflammation and pain [39]. Immune cells are now appreciated as significant contributors to the nervous system. They have been shown to play diverse roles in the initiation, propagation as well and maintenance of disease states, including neuropathic pain. A better understanding and appreciation of neuron and immune cell communication may well lead to the formulation of optimal mesh implants and the avoidance of chronic pain [40]. Whether increased mesh vicinity innervation induced by fibrosis might similarly prove responsible for chronic postoperative pain is currently under investigation.

## PP and Urogynecology

PP mesh has been widely used in pelvic floor reconstructive surgery for prolapse and stress urinary incontinence but tragically its use has often been associated with significant complications including pain. While manufacturers claim that the material is inert and non-degradable, explanted material from patients suffering from clinical complications has shown signs of degradation (fiber cracking, oxidation) after a specific host response. Some women, particularly those treated using transvaginal PP mesh placement for prolapse,

experience intractable pain and mesh exposure or extrusion. Explanted tissue from patients with complications following transvaginal implantation of mesh is typified by a dense fibrous capsule with an immune cell-rich infiltrate-inducing degradation. The "stress-corrosion failure" may be influenced by the inflammatory status of the patient, surgical technique and experience, mesh characteristics (porosity, surface area, and stiffness), and the unique hormonal, immune, and microbial tissue niche of the vagina. In the development process of mesh, host, and biological factors affecting the immune response, mesh registries and long-term surveillance of patients are needed [41-43]. There is evidence that chronic inflammatory reaction (immune cells, T lymphocytes) in the vicinity of mesh is the cause of degradation. T regulatory cells seem to protect the body against fibrosis [44]. Understanding how the adaptive immune response may be responsible for the prevention of complications and pain will be crucial in developing meshes resistant to degradation [45,46]. In women with complications, mesh induces a proinflammatory response that has been shown in some cases to persist years after implantation [47]. Based on available evidence, one can conclude that the PP used for surgical treatment of various structural defects is not inert after implantation in the human body [48]. PP is degraded by an aggressive immune response when used on the pelvic floor in reconstructive surgery for prolapse and urinary incontinence surgery. We need a replacement of PP mesh.

## Alternative Mesh Implants

### Biodegradable metal and non-metal mesh

Ideally, a biodegradable metal implant may provide several advantages over traditional mesh options. Novel materials can be designed with optimized biocompatibility, a controlled degradation rate, antibacterial properties, and desirable mechanical and handling properties [49]. Instead of PP in pelvic organ prolapse surgery, a novel hydrogel-mesh complex may avoid complications [50]. The mesh should be user-friendly, provide corrosion resistance, be affordable, efficacious, potentially removable, and easily monitored improving outcome and quality of life. Biologic mesh use should be avoided when bridging is needed. In inguinal hernia repair, biological and biosynthetic meshes do not have a clear advantage over synthetic meshes [51].

### Titanized mesh

The introduction of surgical meshes made of pure titanium offers a promising alternative. This is the feeling of the authors. Indeed, Titanium's advantage is its corrosion resistance and biocompatibility. In early investigations, the Titanium coating of PP did not improve biocompatibility compared to PP based on short-term data [52]. The addition of glue for the fixation of PP and Titanium (Ti) mesh prolonged the inflammatory reaction causing fibrosis and pain [53]. Silk and Titanium have angiogenic effects in wound healing, in contrast to many other biomaterial sutures which were ultimately associated with adverse events [54,55]. No difference between the Titanium-coated and non-titanium-coated suture material was seen concerning scar quality and wound healing [56]. Chronic pain rate is reduced by Titanium-covered PP mesh [57]. Reducing the material load from 35 to 16 $g/m^2$ biocompatibility could further be improved [58]. The light Titanium-covered PP mesh was associated with less postoperative pain, lower analgesic consumption, and a quicker return to everyday activities than composite medium-weight mesh [59]. An experimental study comparing PP and PP-coated meshes showed that PP + polyglactin mesh implant caused the most intense inflammatory process with lower tissue maturation and collagen deposition. The PP mesh presented a less severe late inflammatory process, with greater tissue maturation and

collagen deposition. The PP + Titanium mesh presented intermediate values between the others [60]. Heavyweight Titanium-coated PP meshes induced a less pronounced foreign body reaction in comparison with identical meshes with no Titanium coating. Titanium coating thus can reduce the inflammatory reaction [61]. In another study, pure Titanium mesh was shown to be the most bio-inert alloplastic material suitable for reinforcement of soft tissue augmentation [62]. The use of Titanium thread mesh implants in the treatment of postoperative ventral hernias is accompanied by a less inflammatory response of the body to the implant and does not lead to an increase in the frequency of postoperative complications [63]. Although the titanized PP lightweight mesh induces slightly less tissue reactivity and has better *in vivo* biocompatibility, further studies should be conducted including the complications and the success rate of pelvic organ prolapse in patients before recommending it in pelvic floor reconstruction [64]. Controversially Titanium has been shown to generate an intense inflammatory reaction in host tissues depending on location, which can cause fibrosis to adjacent structures. Based on short-term results, extraperitoneal mesh does not appear to be superior to intraperitoneal mesh in minimally invasive ventral hernia repair. The choice of mesh location should be based on the current evidence, surgeon, and center experience as well as individualized to each patient [65]. Compared to sublay ventral hernia repair the onlay procedure is associated with a significantly higher risk of seroma. No significant differences were observed when laparoscopic ventral hernia repair was compared with the open surgical procedure. Due to the diversity of surgical techniques reported in included RCTs, it is currently not possible to draw conclusive clinical recommendations [66]. Compared with sublay repair, open IPOM repair appears to pose a higher risk of chronic pain in an incisional hernia [67]. Fibrosis is an essential factor in the repair of fracture sites. However, it can cause cicatrization which may be prevented by a soft tissue barricade, e.g. resorbable collagen [68]. Roughness- and wettability-increasing surface modifications promote osteogenic differentiation of stem cells on Titanium. While these modifications increase the production of osteoblastic factors and bone formation, little is known about their effect on immune cells. The initial host response to a biomaterial is controlled primarily by macrophages and the factors they secrete in response to the injury caused by surgery and the material cues. Surface modifications may influence the activation and production of inflammatory factors by macrophages. It is important to control the surface-induced inflammatory reaction of macrophages and neutrophils which may enhance the success of implanted material [69]. It is worth noting that high levels of Titanium accumulate in humans adjacent to orthopedic implants, and in-vivo and in-vitro studies suggest it may be neurotoxic [70]. Particles may be released into tissues inducing local inflammation. The fact that ongoing Titanium ion release occurs, is evidenced by clinical findings showing the presence of ionic Titanium bound to transferrin in blood and ongoing excretion in the urine of patients with Titanium devices. The degree to which ionic Titanium is released into tissues is unknown. In this context, it is worth mentioning that orthopedic Titanium implants are subjected more to mechanical stress and wear and tear than meshes used for soft tissue reconstruction. There is insufficient information to explain the factors that contribute to the presence of Titanium ions in the serum of humans implanted with Titanium devices. It has been suggested to analyze the role of transferrin and organic acids [71]. Inflammation involves the production of reactive oxygen species that are known to alter the passive layer protecting Titanium implants against the aggressive environment of the human body. Inflammatory processes, therefore, contribute to the deterioration of biomedical

devices [72]. Neutrophils are sensitive to changes in biomaterial surface properties and exhibit differential activation in response to Titanium surface cues. Hydrophilic Titanium surface reduces the neutrophil inflammatory response [73]. Clinicians should carefully evaluate the use of a modified Titanium surface in their practice. Even if no differences in terms of inflammation are present in the short term, these findings need to be validated through long-term studies [74]. Although Titanium mesh is considered to be the most bio-inert mesh material, depending on the location and surface of the mesh (roughness, wettability) there may be a macrophage and neutrophil-induced inflammatory response causing fibrosis and cicatrization, which may be further prevented by coating (collagen). In addition, high levels of Titanium released from specific titanium implants, also in ionic form in Transferrin, may be associated with neurotoxic adverse events. Overall, subject to location and structure, Titanium may demonstrate beneficial effects concerning corrosion, oxidation, and foreign body reaction providing biocompatibility, but there may be adverse events, which need to be explored further through long-term studies.

## Conclusion

To improve outcomes in mesh hernia repair, the analysis of cellular immune response concerning mesh properties, composite endpoints, pain, and physical function may be necessary [75]. The role of surgery for pain treatment and the choice of mesh for pain prophylaxis may be effective in reducing the postoperative pain rate [76]. Alternative materials for mesh implants that offer better stability and biocompatibility require further development to improve the clinical pain outcomes and the patient's quality of life. The introduction of surgical meshes made of pure titanium offers a promising alternative, which needs to be further explored.

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