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Evaluation of Biocompatibility of Alloplastic Materials: Development of a Tissue Culture In Vitro Test System

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ABSTRACT

Optimized biocompatibility is a major requirement for alloplastic materials currently applied in surgical approaches for hernia, incontinence, and prolapse situations. Tissue ingrowth/adherence and formation of connective tissue seem to have important influence in mesh incorporation at the implant site. In an in vitro approach we randomly investigated 7 different mesh types currently used in surgeries with various indications with regard to their adherence performance. Using a tissue culture approach, meshes

were incubated with tissue representative of fibroblasts, muscle cells, and endothelial cells originating from 10 different patients. After 6 weeks, the meshes were assessed microscopically and a ranking of their adherence performance was established.

Tissue culture was successful in 100% of the probes. We did not remark on interindividual differences concerning the growth and adherence performance after incubation with the different meshes in the investigated 10 patients. The ranking was consistent in all patients. In this test system, PVDF Dynamesh® (FEG Textiltechnik, Aachen, Germany) was the mesh with the best growth-in score.

The test system was feasible and reproducible. Pore size seems to be a predictor of adherence performance. The test system may be a helpful tool for further investigations, and the predictive value should be assessed in further in vitro and in vivo investigations.

INTRODUCTION

Alloplastic materials are widely applied in surgical approaches for hernia, incontinence, and prolapse. Development of meshes is an ongoing process characterized by changes in polymer structure, biocompatibility, operative handling, and costs. A good mesh should have negligible foreign body reaction (FBR) with no pathologic fibrosis at a decreased risk of infection.

In 2008, the American Food and Drug Administration (FDA) reported more than 1000 unexpected and severe adverse events, most of the complications were associated with transvaginal placement of surgical mesh to treat pelvic organ prolapse (POP) and stress urinary incontinence (SUI).[1] The docu-

Table I
Meshes

Mesh	Material	Biomechanical Characteristics
Vitamesh®, ProxyBiomedical	large pore monofilament polypropylene	knit polypropylene, pore size 2410μm, thickness (microns) 250, tear resistance (Fmax N) 33.7
Dynamesh®, FEG Textiltechnik	monofilament (PVDF) polyvinylidene fluoride	effective porosity 58 %, reactive surface 1.97 m²/m², suture pullout strength 31 N, tear propagation resistance 28 N, pore size 3000 ?m
TFT Motifmesh®, ProxyBiomedical	micromachined polytetrafluoroethylene	pore size 235μm , thickness (microns) 150 , tear resistance (Fmax N) 15.1
TVT Polypropylene	polypropylene	non-absorbable, permanent polypropylene suture, pore size of 164 x 96 ?m
UltraPro Hernia System Medium UHSM®, Ethicon	polypropylene reinforced with poliglecaprone fibers	filament thickness 0.09 mm, mesh thickness 0.5 mm, (Fmax N) 69N, pore size 300 μm
Proceed surgical mesh®, Ethicon	monofilament polypropylene encapsulated with polydioxanone (PDS)	closely knitted with small pores < 1000 μm size, high tensile strength
Mersilene, Johnson & Johnson	multifilament mesh, polyethylene terephthalate	density 0,19g/cm^3, pore size 120-85 μm

Investigated meshes and their main charact eristics.

mented adverse events resulted from reports of nine surgical mesh manufacturers involved in development of surgical mesh devices used to repair POP and SUI. Besides factors such as overall health of the patient, the surgical technique used, and concomitant procedures undertaken, a particular importance was given to the mesh material and the size and shape of the mesh as causes for those adverse events. However, the search for the optimal mesh for a particular indication with highest functionality and biocompatibility as well as minimized side effect profile in the short-term and long-term follow-up remains difficult.

Biocompatibility is defined as "the ability of a material to perform with an appropriate host response in a specific situation" implying a symbiotic relationship of acceptance between host and the respective implanted material.[2] For a material to perform best it needs to be integrated properly into tissue to generate an appropriate inflammatory response and maintain mechanical integrity (hold shape). These qualities are discussed along with additional and host-related factors that contribute to biocompatibility.

As biocompatibility is described by the foreign body reaction (FBR) at the host-tissue/biomaterial interface, three crucial steps as protein absorption, cell recruitment, and, finally, fibrotic encapsulation and extracellular matrix formation have been identified in order to describe the time course of the FBR. New therapeutic strategies may target cellular and molecular interactions during those phases, influencing the complex cascade of immune modulators, soluable mediators, and different cell types. A considerable influence on the dynamic of the FBR is given by the biomaterial composition, in particular, the type of polymer, the material weight, the filament structure, and the pore size.

Currently, many alloplastic materials are being used without proper trials and are recommended from manufacturers rather than from data arising from *in vitro* or *in vivo* experiences.

In contrast to medicinal drugs, alloplastic materials are oftentimes implemented into clinical practice with fewer restrictions. Preclinical and clinical trials are not necessarily required as preconditions for clinical use. Assessment tools for meshes prior to their clinical implementation remain reasonable in order to minimize and avoid complications. A surgical mesh must be comparable to other surgical meshes. This remains difficult as there are no standardized tools for comparison, although there are several models for assessing different meshes with regard to biomechanical characteristics.[3,4]

The present study is focussed on the adherence performance of several currently used meshes and aims to show an assessment tool for comparison of this biocompatibility feature.

MATERIALS AND METHODS

Meshes/Patients

We randomly identified alloplastic materials currently applied as implants for different surgical indications covering hernia repair, pelvic organ prolapse (POP), and stress urinary incontinence (SUI). A total of **7** different meshes were investigated in this study. The meshes and the respective biomechanical/material characteristics are listed in Table I. The alloplastic materials were prepared in 2 x 2 cm fragments for further investigations.

Additionally, we harvested tissue probes of muscle, fascia, and renal vein from 10 patients undergoing right-side nephrectomy. All patients had to give informed consent. The tissues and cells were processed equally in all patients. Each mesh was tested with tissue and cells of each patient for comparison purposes.

Tissue Preparation and Mesh Incubation

In an initial cell culture approach investigating the cells of the different tissues we could not identify adherence on the mesh microscopically. In contrast, the cells grew on the bottom of the cell culture device. When performing a tissue culture, we could observe tissue adherence on the meshes as on the bottom of the cell culture device. As cells did not grow on the respective mesh matrices we decided to use tissue culture for the following investigations. In addition, we considered tissue culture more appropriate because of the reduced artificial modification processes due to shorter culture processing. We proceeded as follows: We extracted tissue probes originating from muscle, fascia, and renal veins at a length of 0.5 cm to 1.0 cm each from 10 different patients. Probes were incubated with Liforlab® (Lifeblood Medical, Inc, Freehold, NJ) at room temperature. After crushing, we incubated the tissue with PBS, and after 2 additional washing procedures, incubation with DMEM/F12 plus 10% Serum and 1% Glutamin, +1% Pen/Strep was done. Tissue probes were transferred to the incubator. After successfully expanding and growing (80% to 90% adherent growing) tissue pellets, the different alloplastic materials were added. Thus, the prepared and expanded tissue probes consisting of myoblast, endothelial cells, and fibroblasts presenting relevant tissues of the pelvic floor were used *in vitro* in order to create a model for investigating the integrity of the different mesh types. Immunocytochemistry with specific cell markers was performed to verify the presence of the tissue cells. The detection of myoblasts was realized by α-sarcomeric actin and desmin as markers of myogene differentiation. Fibroblasts were stained with antibodies targeting vimentin, whereas antibodies against CD34 were used for the verification of endothelial cells. We reproduced every single approach 10 times with tissue probes from the 10 different patients.

Morphological Study

Adherence and cell count (where possible) were assessed microscopically using immunohistochemistry after co-incubation of the cells with different types of alloplastic meshes. Test duration was 6 weeks. Meshes were investigated with regard to interstructural tissue connections and quantity of mesh-adherent cells. Tissue culture was maintained up to 4 months with frequent changes of medium, and assessment was repeated if possible.

A descriptive/semiquantitive assessment pattern was used in order to describe the adherence of tissue to the investigated mesh materials. The assessment pattern was based on the maximum identifiable quantity of mesh-adherent cells within a tissue cluster per vision field. Adherence performance was ranked after assessing quality and quantity of the tissue clusters/cells into: none, fair, good, excellent.[5]

Table II
Mesh Ranking

Ranking	Mesh Type	Growth-in score
1	Dynamesh®, FEG Textiltechnik	2.2
2	TFT Motifmesh®, ProxyBiomedical	2.0
3	Vitamesh®, ProxyBiomedical	1.6
4	UltraPro Hernia System Medium UHSM®, Ethicon	1.4
5	Mersilene, Johnson & Johnson	1.2
6	Proceed surgical mesh®, Ethicon	1.2
7	TVT Polypropylene	1.0

For assessing the growth-in score after 6 weeks, we evaluated each mesh with tissue of 10 different patients. After semiquantitative determination, we conducted the mean value of the score results for each mesh. (points/10)

Scoring was based on the classification proposed by Melman et al. [5]:

NONE (0 points): no tissue ingrowth
FAIR (1 point): thin bands of fibroblasts and small collagen deposits between mesh filaments
GOOD (2 points): moderately thick bands of fibroblasts and collagen deposits between mesh filaments
EXCELLENT (3 points): nearly all spaces between mesh filaments occupied by fibroblasts, collagen deposits, and capillaries

RESULTS

Macroscopic Results

Overall, macroscopic evaluation after tissue culture did not show differences in the gross appearance of the meshes. Tissue culture was successful in 100% of the probes. There were no signs of infection within the entire cultivation course.

Microscopic Results

Tissue growth was comparable in all approaches within a test duration of 6 weeks.

The testing of the biocompatibility of myoblasts, endothelial cells, and fibroblasts was observed under addition of BioGlue® (CryoLife Inc, Kennesaw, GA) and revealed unchanged tissue adherence to the mesh.

We did not remark on interindividual differences concerning the growth and adherence performance after incubation with the different meshes in the investigated 10 patients.

According to the descriptive/semi-quantitative approach described above we revealed a ranking of the investigated meshes after 6 weeks. The ranking is shown in Table II. Interestingly, after 4 months of tissue culture, adhesion performance was comparable in all meshes. Tissue growth on PVDF is exemplarily shown in Figure 1.

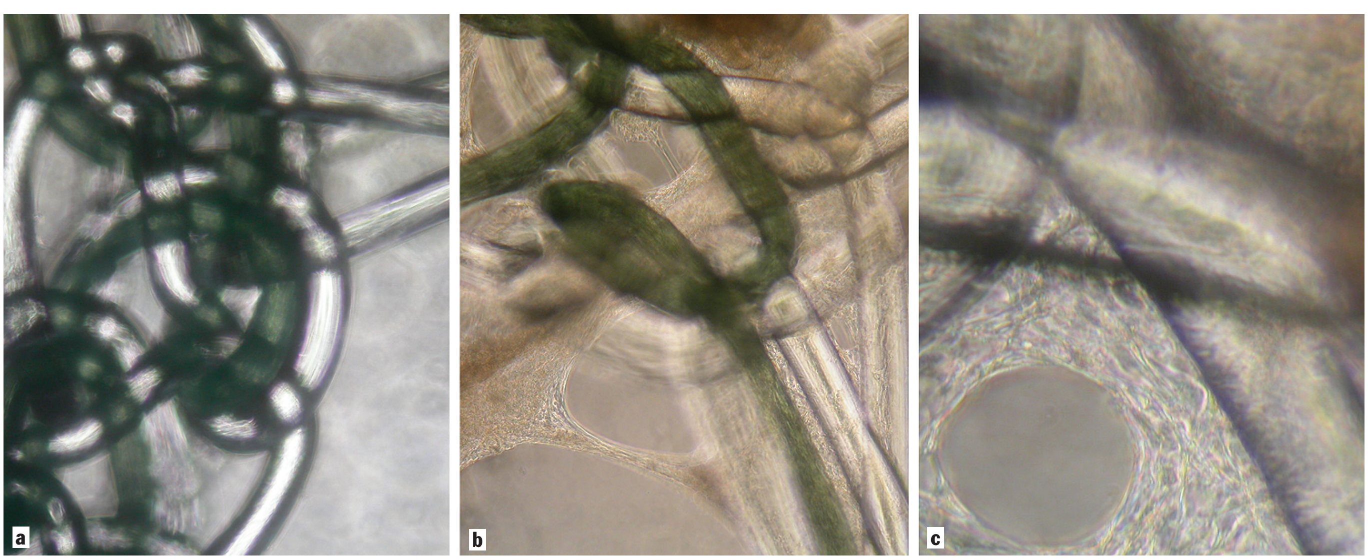

Figure 1. PVDF Tissue adhesion. The picture shows PVDF: A) native prior to tissue culture, B) after 3 weeks tissue culture, and C) after 6 weeks of tissue culture (time point of assessment). In B) and C) spaces between mesh filaments are increasingly occupied by fibroblasts, collagen deposits, and capillaries. As adherence appeared tri-dimensionally pictures can not be shown entirely defined.

DISCUSSION

Mechanical and biocompatibility properties of synthetic materials used to replace or support native tissues play a crucial role in their *in vivo* function. Currently, many alloplastic materials are being used without proper trials and are recommended from manufacturers rather than from data arising from *in vitro* or *in vivo* experiences. An ideal graft material is supposed to be chemically inert, non-toxic, non-allergic, non-inflammatory, resistant to infection, non-carcinogenic, solid, sterilizable, convenient, and affordable.[6]

Amid and co-workers proposed a standardized classification system to distinguish between different types of synthetic meshes, particularly emphasizing physical properties of biomaterials and their predictable impact on possible adverse events (Table III).[7] They classified meshes into 4 different groups mainly focussing on the respective pore size. The authors assumed that the utilization of meshes from the different groups seems to have a prognostic value for different adverse events (e.g., risks of infection, seroma formation, fistula formation, etc.) and therefore may be used as predictors for biocompatibility. They recommended that the classification should have influence on the clinical decision about which alloplastic material to apply in a particular clinical situation. In accordance with those early results it is currently accepted that large porous meshes show the best tissue integration and, owing to the reduced surface area, produce the least foreign body reaction, inflammation, and fibrosis. Small-pore or microporous and foil- or layer-like mesh modifications, however, are associated with a significantly greater foreign body reaction and inflammation frequently related with the phenomenon of bridging, which finally may cause significant contraction or shrinkage of the mesh.

Polypropylene, polyethylene-terephtalate, or polytetrafluoroethylene are currently the most commonly used mesh materials, whereas polypropylene seems to be the most frequently used polymer for the construction of surgical meshes.[8] There seems to be a trend in current mesh development toward the minimization of mesh density and use of macroporous weave patterns of monofilament polypropylene.[9] In a review analyzing the mechanical properties of and the tolerance for synthetic implants for SUI and POP, Cosson et al. identified polypropylene known to offer durability and elasticity as the most promising material for those indications.[10]

In contrast to Cosson and other authors, the aim of this study was to investigate whether different tissues of the pelvic floor show different *in vitro* interaction characteristics with alloplastic materials currently used as meshes in different clinical indications, thus biocompatibility features rather than mechanical characteristics. However, it remains unquestionable that both characteristics are crucial for the performance of a mesh when applied *in vivo*. Most of the meshes investigated in the presented study consist of polypropylene as basic material. We searched for a feasible and reproducible test system allowing us to assess and compare meshes with regard to their *in vitro* growth-in score to different tissues as markers for their biocompatibility.

Biocompatibility assessment of alloplastic materials using appropriate cell cultures *in vitro* is a valid and accepted method that allows us to give information about the toxicity of the investigated material, possible effects on metabolism, and growth of the cells.[11] Although using this method cells can be sensitively characterized and the conditions can be easily standardized, so far, no complex tissue representative for the human body can be investigated. Langer and colleagues investigated the cellular response of human fibroblasts cultured on different polypropylene meshes, in particular with regard to mesh material and structure.[12] They used a method comparable to the one described here implementing scanning electron microscopy. Their major conclusion was that the polymer surface and structure had a paramount influence on the meshes' biocompatibility as they could show fibroblasts preferably growing on lowweight meshes, thin filaments, and mesh nodes. In contrast, heavyweight meshes were shown to induce degenerative cell reactions resulting in reduced biocompatibility.

In contrast to Langer and colleagues we used a tissue culture approach as our initial results with cell culture did not reveal sufficient cell growth. Although the investigation of the adherence of specific cells is useful, we consider the co-incubation of implants with tissue clusters as comparable to *in vivo* processes. We can support the thesis of

Table III
Amid Classification

	1	2	3	4
Characteristics	Completely macroporous mesh, > 75 µm	Totally microporous mesh, < 10µm	Macroporous patch with multifilaments or a microporous component	Submicronic pores, often associated with type 1 materials to prevent adhesion (e.g., peritoneum)
Examples	-Prolene -Marlex -Atrium -Trelex	Gore-Tex surgical membranes	-Mersilene (woven Dacron) -Teflon (PTFE), -Surgipro (woven polypropylene) -MycroMesh (perforated PTFE)	-Silastic, -Celigard, -Dura mater substitute

Classification of biomaterials and their related complications in abdominal wall hernia surgery by Amid. [7]

Langer and colleagues that the microstructures of the meshes have relevant impact on the growth and adherence behavior of cells imitating *in vivo* surroundings. Besides the presence of fibroblasts, we investigated muscle derived and endothelial cells presenting relevant tissues of the pelvic floor. This observation resulted in a ranking of the investigated meshes concerning their affinity to the co-incubated tissues/cells. Our ranking seems to be in accordance with the suggestions of Amid and co-workers.[7] However, material features other than poor size seem to play a role in their *in vitro* performance, explaining the different scores. In addition, we could see and reproduce that the adherence behavior was independent from individual patient features, thus supporting the idea that the biological behavior of a mesh, in contact with host tissue, is mostly conditioned by the structure of the biomaterial and its chemical composition rather than by individual host characteristics and features. Polyvinylidene fluoride (PVDF) is a polymer with improved textile and biological properties that has shown the best adherence performance in our test system. This polymer is currently applied as PVDF-coated polypropylene mesh for intraperitoneal-only mesh repair.[13,14]. The main characteristics of this mesh are its macroporousity, the decreased adhesion rate to the bowel, and the favorable biocompatibility *in vivo* with decreased rates of inflammation and fibrosis.[8] The good performance of PVDF in our test system is therefore not surprising. However, a recent report from Fortelny and co-workers indicates increased complication rates for mesh when retrospectively analyzing 29 patients undergoing intraperitoneal-only mesh repair with PVDF Dynamesh® (FEG Textiltechnik, Aachen, Germany).[15] To date, reported investigations of the cellular reaction on meshes in humans are based on explanted meshes after complicated postoperative courses, thus resulting in negatively preselected alloplastic explants.[16] In an early systematic *in vitro* study comparable to the method presented here, Duchrow and co-workers investigated the influence of heavyweight polypropylene meshes on growth of human cells. They could not attribute a relevant influence of the meshes to the proliferative activity of the cells; however, they observed a significant increase of the apoptosis rate.[17]

The test system presented here is far from being representative of an *in vivo* situation as tissue culture was sterile and no probable physiological *in vivo* reaction such as foreign body reaction or inflammation was imitated. Another criticism may be aimed at the unselective investigation of alloplastic materials. Definitely, meshes for POP, SUI, or hernia repair do not have identical biocompatibility/mechanical requirements. However, assuming the adherence performance of tissue on a mesh as a possible marker for its biocompatibility seems logical independent from the respective clinical use of the implant. The test system may help to select particular alloplastic materials for further investigation, as for instance animal experiments or coating approaches (*in vivo* and *in vitro*), as we reproduce comparable extents of cell adherence on specific meshes independent from the individual patient. Thus, at least *in vitro*, specific patient features do not seem to have influence on the adherence performance and respective biocompatibility of the alloplastic material. Although an exaggerated foreign body reaction/tissue response is assumed to be related to clinical complications, a positive role in mesh incorporation at the implant site may be triggered by bioactive mediators like epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), or transforming growth factor (TGF), and others produced by fibroblasts or smooth muscle cells. Thus, the cultivation and positive adherence of cell clusters consisting of those cell types and the respective assessment and comparison, as shown here, may be helpful for considering a mesh regarding its possible tissue ingrowth and capacity to form connective tissue.

Although with the small number of 4 patients, Falconer and co-workers support the thesis of reactions independent from the individual patient but from the implant when extracting connective tissue previously in contact with alloplastic materials after treatment of SUI in women with TVT.[18]

In vivo behavior of a particular alloplastic material cannot be reliably extrapolated from *in vitro* studies, thus appropriate *in vivo* approaches are required. A possible predictive value of these *in vitro* results with regard to cell and tissue adherence *in vivo* may be a target for further investigations.

We are currently investigating the predictive value of this test system in a sheep model. Modern mesh technology uses the available alloplastic materials as carrier systems for bioactive drugs.[19] Studies in animal models account for the efficiency of these drugs that aim to reduce mesh-related infections or to minimize FBR by influencing inflammation or extracellular matrix remodelling. When coating meshes with antibiotics, promising results could be stated with regard to preventive effects against graft infection without side effects on biocompatibility.[20,21] The test system presented here may be a helpful tool for initial *in vitro* essays prior to investigating mesh coating approaches and their performances in animal studies in order to select optimal meshes and respective modifications.

CONCLUSION

Preclinical assessment and comparison of meshes and alloplastic materials is important to minimize the risk for relevant complications. Biocompatibility is a possible assessment parameter. The test system presented here is a feasible and reproducible method to compare meshes with regard to their biocompatibility. Pore size seems to be a predictor for adherence performance. The test system may be a helpful tool for further investigations, and the predictive value should be assessed in further *in vitro* and *in vivo* investigations. STI

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AUTHORS' DISCLOSURES

The authors have no financial relationships to declare.

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