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Differences in the response of various urogynecology synthetic grafts to infection by *Staphylococcus epidermidis*: an experimental animal study

Razlike u reakciji uroginekoloških sintetskih materijala na infekciju bakterijom *Staphylococcus epidermidis*: studija na eksperimentalnim životinjama

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Abstract

Background/Aim. Polypropylene synthetic meshes are used in urogynecology for the primary treatment of stress urinary incontinence. Infection of the graft could influence the outcome of the surgery as well as the adequate tissue reinforcement. The aim of the study was to compare responses to infection in six different synthetic grafts. **Methods.** The study included six different grafts, with polypropylene as their major component, used for the primary repair of full-thickness abdominal wall defects in male Wistar rats. From a total of 144 Wistar rats, six groups of 24 animals each were created. Each group consisted of 12 animals for noninfected and 12 animals for infected graft testing. In the subgroups for infected graft testing, grafts were inoculated with isolates of *Staphylococcus epidermidis*. After six weeks, the animals were sacrificed, and groups were compared for inflammatory response, collagen quantification, and abdominal wall reinforcement. The inflammatory response was calculated as the total number of inflammatory cells under a magnification of ×200, including polymorphonuclears, foreign body giant cells, and macrophages. Collagen quantification was determined by colorimetric measurement of hydroxyproline for alkaline hydrolysates. Abdominal wall reinforcement was determined as minimal disintegration load on a standardized shredding device. In order to detect bacterial biofilm and characterize collagen fibers, scanning electron microscopy (SEM) of fresh samples was performed. **Results.** Reinforcement of the abdominal wall with a titanium-coated polypropylene graft was most significantly degraded by the infection ($p < 0.001$). The inflammatory response was the most prominent in the infected multifilament polypropylene graft compared to the low-weight polypropylene graft, titanium-coated graft, and multifilament polypropylene graft with polyglactin ($p < 0.01$). In terms of collagen deposition, the greatest differences of all grafts were noted between noninfected and infected low- and high-weight monofilament polypropylene grafts ($p < 0.01$). Using SEM, biofilm formation was detected, and collagen fibers were described as immature. **Conclusion.** The results of this experimental animal study suggest that infection of synthetic urogynecology grafts results in a significant reduction in tissue reinforcement. In addition, the negative effects of the infection are the most pronounced in multifilament and semi-absorbable multifilament grafts.

Key words:
biofilms; infection; rats; surgical mesh; urinary incontinence, stress.

Apstrakt

Uvod/Cilj. Polipropilenski sintetski graftovi se koriste u uroginekologiji za primarni tretman stres urinarne inkontinencije. Infekcija grafta može uticati na ishod operativnog lečenja kao i na odgovarajuću potporu tkiva. Cilj rada bio je da se uporedi odgovor na infekciju kod šest različitih sintetskih graftova. **Metode.** U studiju je uključeno šest različitih graftova, sa polipropilenom kao glavnom komponentom, koji su korišćeni za primarnu reparaciju defekata prednjeg trbušnog zida mužjaka Wistar pacova. Od ukupno 144 Wistar pacova formirano je šest grupa od po 24 životinja. U svakoj grupi bilo je po 12 životinja za testiranje neinficiranih i 12 životinja za testiranje inficiranih graftova. U podgrupama za testiranje inficiranih graftova, graftovi su inokulirani izolatom *Staphylococcus epidermidis*. Posle šest nedelja, eksperimentalne životinje su žrtvovane i unutar grupa je upoređivan stepen inflamacijskog odgovora, količina kolagena i ojačanje abdominalnog zida. Inflamacijski odgovor je kvantifikovan

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izračunavanjem ukupnog broja ćelija zapaljenja pod uvećanjem ×200, uključujući polimorfonukleare, gigantske ćelije stranog tela i makrofage. Kvantifikacija kolagena je određivana kolorimetrijskim merenjem hidroksiprolina za alkalne hidrolizate. Ojačanje abdominalnog zida određivano je kao minimalna dezintegraciona sila na standardizovanom tenzinom meraču. Za detekciju bakterijskog biofilma i karakterizaciju sazrevanja kolagenih vlakana primenjena je skening elektronska mikroskopija (SEM) svežih preparata. **Rezultati.** Ojačanje abdominalnog zida polipropilenskim graftom obloženog titanijumom najznačajnije je degradirano infekcijom ($p < 0,001$). Inflamacijski odgovor bio je najizraženiji kod inficiranog multifilamentnog polipropilenskog grafta u poređenju sa polipropilenskim graftom niske težine, graftom obloženog titanijumom i multifilamentnog polipropilenskog grafta sa poliglaktinom ($p < 0,01$). U pogledu deponovanja kolagena, od svih graftova, najveće razlike su zabeležene između neinficiranih i inficiranih monofilamentnih polipropilenskih graftova niske i visoke težine ($p < 0,01$). Korišćenjem SEM otkriveno je formiranje biofilma, a kolagena vlakna su opisana kao nezrela. **Zaključak.** Rezultati ove studije na eksperimentalnim životinjama sugerišu da infekcija uroginekoloških sintetskih graftova dovodi do značajnog smanjenja potpore tkiva. Takođe, negativni efekti infekcije su najizraženiji kod multifilamentnih i poluresorptivnih multifilamentnih graftova.

Ključne reči:
biofilmovi; zapaljenje; pacovi; hirurška mrežica; inkontinencija, urinarna, stres.

Introduction

Pelvic organ prolapse and stress urinary incontinence (SUI) are common urological pathologies, and surgery is frequently required. The recurrence rate resulting from inadequate tissue support remains a key issue in this area. Polypropylene synthetic meshes are commonly used to treat SUI (tension-free slings) and, in certain instances, pelvic organ prolapse (i.e., sacrocolpopexy and hysteropexy). Although stability and biocompatibility have been substantially proven, there are unresolved concerns and unpredictable consequences in the case of graft infection [1, 2]. The current standard in case of graft infection is to remove the graft completely [3]. On the other hand, when extrusion of the graft occurs, resection of the extruded segment seems to be the most obvious choice [4, 5]. In clinical terms, when resection of the extruded segment is performed, there is an unanswered question of what happens with the intended tissue reinforcement, keeping in mind the inevitable contamination of the residual graft [4]. The steps for preventing unintentional graft inoculation are to give antibiotic prophylaxis. The importance of antibiotic prophylaxis is to secure sterile conditions for graft stabilization and tissue integration [6]. To the best of our knowledge, research on the graft type with the most chance to withstand the infection has not been done. However, cellular changes and fluctuations in tensile strength during graft infection are rarely discussed [6, 7].

The aim of the study was to compare six different grafts in terms of their responses to infection.

Methods

The methodology for this animal experiment was adopted from our previous study, where we successfully analyzed the influence of oxidative stress on abdominal wall (AW) reinforcement [8].

Urogynecology synthetic grafts used in the study

Six graft types were used in the experimental study: two monofilaments Ethicon 76 g/m^2 as high-weight polypropylene (HWPP) and Gynecare Gynemesh® Ethicon 43 g/m^2 as low-weight polypropylene (LWPP); two multifilament grafts Surgipro™ multifilament polypropylene (MPP) Tyco 97 g/m^2 and Vypro mesh Ethicon 25 g/m^2 multifilament polypropylene with polyglactine (MPPG); two coated grafts Sepra meshTM Genzyme® 96 g/m^2 as collagen coated polypropylene (CPP) and Titanium coated polypropyleneTM Gesellschaft für elektrometallurgie® 16 g/m^2 as titanium polypropylene (TPP).

Design of the experimental study

Six groups of 24 animals for each graft group (with 12 animals for noninfected and 12 for infected graft testing) were created from a total of 144 male Wistar rats. Each group was then allocated to use one of the grafts. Experimental animals used in the study were acquired from the Biomedical Research Institute of the Faculty of Medicine of the University of Niš, Serbia. The experimental investigation was approved by the Ethics Committee of the Faculty of Medicine, University of Niš (No. 01-2066-9, from April 1, 2010). Anesthesia for the experimental animals was provided by administering 10% ketamine (Richter Austria) injected subcutaneously. AW defect 20 × 25 mm was made with respect to the peritoneum and repaired with different grafts. When repairing the AW defect, the overlay technique was used with graft dimensions 25 × 30 mm. Nonabsorbable sutures (Surgipro™ II; 4/0) were used for the fixation of the grafts with continuous sutures. In the subgroup of 12 animals, the grafts were inoculated (infected) with isolates of *Staphylococcus (S.) epidermidis* 10^8 colony-forming unit/mL (standardized isolates acquired from the microbiology laboratory of the Faculty of Medicine of the University of Niš) *via* swabs three times in a row for 15 sec on the entire surface of the graft. The subcutis (subcutaneous layer) and skin were sutured with absorbable 3/0 polyglactin suture in all groups and subgroups. Prophylactic antibiotic treatment with gentamycin 60 mg/mL in the dosage of 0.2 mL/day was administered for three days.

Six weeks after AW repair, animals were sacrificed by ketamine overdose. The entire AW was dissected with a graft in the middle and at least 30 mm of neighboring tissue. Explants were dissected into 50 × 10 mm samples with graft in the middle and stored in saline solution for tensiometry. Load-displacement minimal disintegration limits were determined for both infected and noninfected groups.

Mechanical sample testing for minimal disintegration load

As *per* Afonso et al. [9], specimens standardized to 50 × 10 mm were obtained from each experimental animal, and the specimens were tested for minimal disintegration load (MDL). An HBM Spider 8 (HBM, Darmstadt, Germany), a digitalized acquisition system with an HBM catman, was used for the mechanical testing of the MDLs. The samples were tested until they were completely disrupted, at which point the ratio of applied force (given in Newton – N) to material stretching (mm) was determined. Mechanical testing was performed at the Faculty of Mechanical Sciences of the University of Niš.

Histological sample preparation and inflammatory cell quantification

Tissue samples for histology analysis were prepared in a standard manner, and hematoxylin and eosin staining was then performed. Inflammatory cells were quantified as described by Konstantinovic et al. [10]. Two different observers quantified the number of inflammatory cells under x200 magnifications (in matrices) on ten high-power fields in the near proximity of the grafts. The middle value of ten fields for inflammatory cell numbers in each graft group was further included in the calculations. The total number of inflammatory cells, including polymorphonuclears, foreign body cells, and macrophages, was calculated.

Quantification of the collagen deposits

Collagen quantification was performed as described by da Silva et al. [11] from tissue stripped directly from the surface of the grafts. Fresh collagen samples were subjected to alkaline hydrolysis in accordance with the specified procedure to produce a sensitive hydroxyproline assay of hydroxylates. Hydroxyproline for alkaline hydrolysates was measured colorimetrically *via* a spectrophotometer (SP-22, Bio Spectro, Brazil) with 1 cm optical glass cuvettes at a 1/100 dilution. The samples were prepared using a 50% solution of sodium hydroxide (Vetec Brazil). After each sample was hydrolyzed for 40 min, it underwent an identical pH correction procedure *via* a pH meter (model HI3222, Hanna, Instruments, USA).

Electron microscopy of the explanted samples

Explanted samples were analyzed by scanning electron microscopy (SEM) for polypropylene fibers related to inflammatory cells and collagen deposits as well as for bacterial biofilm analysis. The freshly explanted samples were covered with gold *via* the "sputter" method for 10 min and then analyzed *via* SEM.

Statistical analysis

For pairwise analysis, ANOVA Kruskal Wallis variance followed by the Mann-Whitney *U* test was performed. Comparisons of inflammatory cell numbers, collagen amounts, and MDLs were performed for infected vs. noninfected grafts. For paired comparison, corrections were made according to Bonferroni. Values of $p < 0.05$ were considered significant. SPSS 16 Chicago USA statistical package was used in the calculations.

Results

All 144 animals survived the entire six-week study period. During the study period, infections occurred in all groups inoculated with *S. epidermidis.* In the infected MPP graft group, one mesh extrusion was detected and excluded from further studies. In 2 out of 12 animals in the MPP group, pus was detected on the surface of the graft when it was explanted.

The results of the AW reinforcement tests of the noninfected explants are presented in Figure 1. The noninfected group presented mostly comparable MDL results with no statistical differences among tested grafts. The strongest AW reinforcement was measured for the TPP, which reached a 14.2 N MDL. HWPP graft groups presented better tolerance for distention compared to other grafts.

The results of the AW reinforcement tests of the infected explants are presented in Figure 2. Compared with noninfected samples, all infected samples presented significantly weaker AW reinforcement ($p < 0.05$). When infected, the deterioration level of the strongest TPP in the noninfected samples barely reached the 4.1 N limit for the MDL ($p < 0.001$). Infection was the most significant parameter in the semiabsorbable MPPG group, where the weakest degree of AW reinforcement was measured (3.8 N). When the HWPP and the MPP were infected as the heaviest grafts (g/m^3), the MDL was 6.6 N despite their difference in construction. Displacement tolerance was comparable between the HWPP groups in both the infected and noninfected circumstances ($p = 0.23$). All other samples presented slightly lower displacement tolerances when infected ($p = 0.79$).

Inflammatory cell quantification results (noninfected and infected grafts) are presented in Figure 3. Compared with the noninfected grafts, all the infected grafts presented with greater numbers of inflammatory cells. The most significant difference between infected vs. noninfected grafts was in the TPP group ($p < 0.001$) compared to the CPP and LWPP ($p < 0.01$) and the HWPP, MPP, and MPPG groups ($p < 0.5$). Significant differences were also detected among the infected grafts. Compared with the LWPP-, TPP-, and MPPG-infected ($p < 0.01$) and HWPP- and CPP-infected ($p < 0.05$) grafts, the infected MPP groups presented more

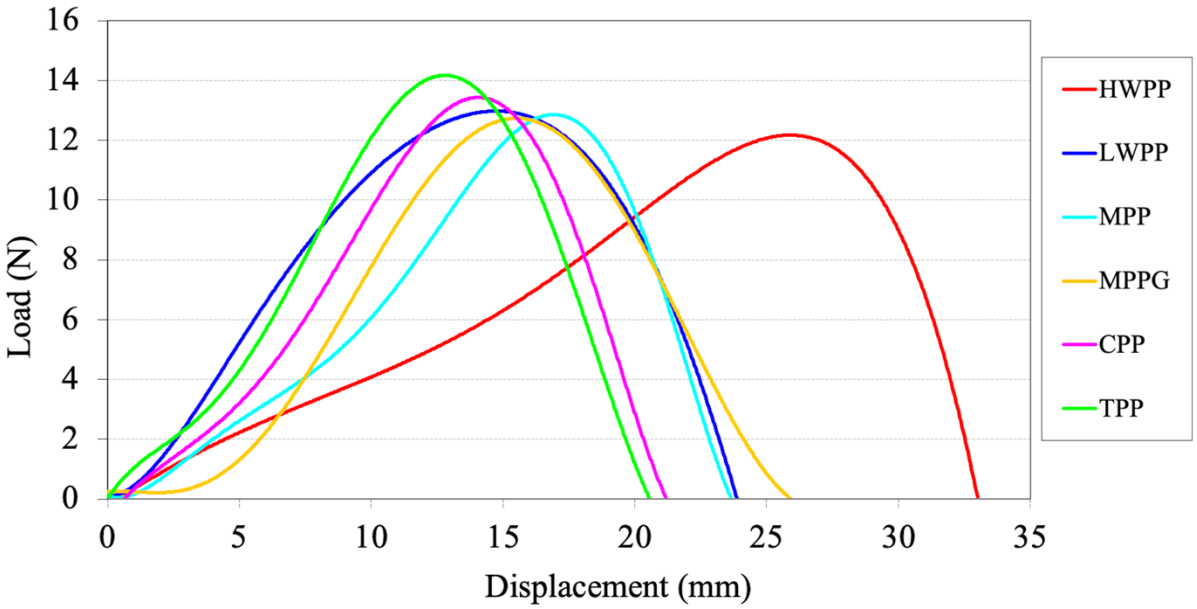

Fig. 1 – Uniaxial tension test results for minimal disintegration load of the abdominal wall explants with noninfected grafts after six weeks. HWPP – high-weight polypropylene; LWPP – low-weight polypropylene; MPP – multifilament polypropylene; MPPG – multifilament polypropylene with polyglactin; CPP – collagen-coated polypropylene; TPP – titanium-coated polypropylene; N – Newton.

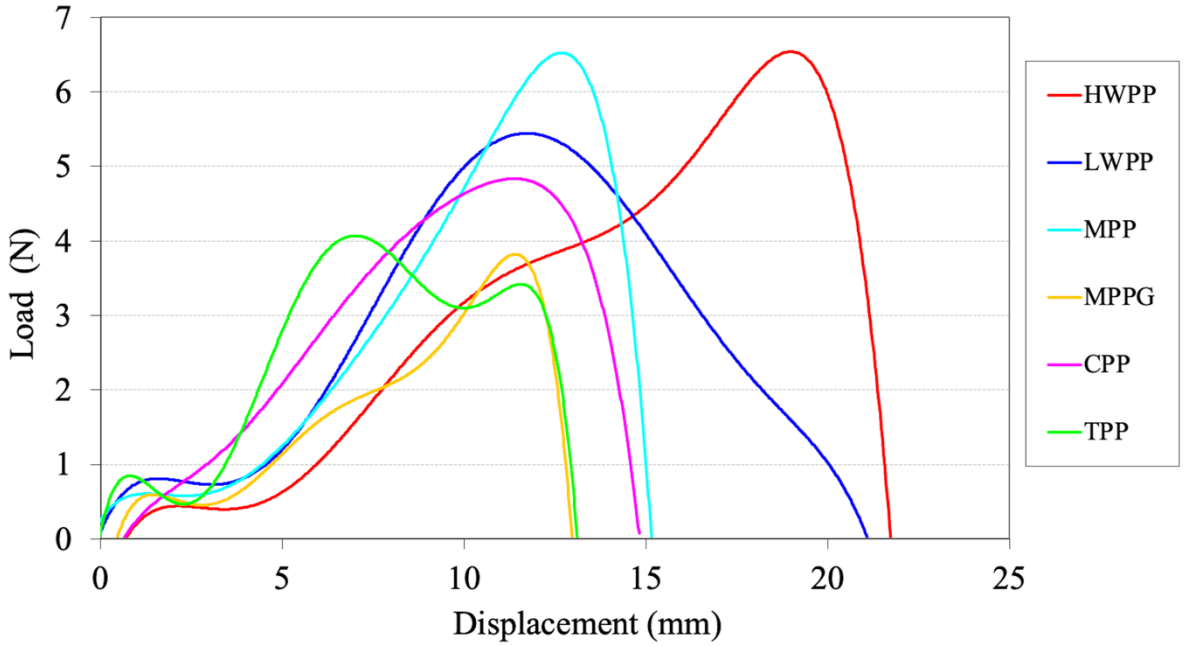

Fig. 2 – Uniaxial tension test results for minimal disintegration load of the abdominal wall explants with infected grafts after six weeks. For abbreviations, see Figure 1.

pronounced inflammatory reactions. Compared with those in the MPPG ($p < 0.05$) and MPP ($p < 0.001$) groups, the number of inflammatory cells in the noninfected groups was lower.

Collagen quantification from samples stripped from the grafts is presented in Figure 4. In all infected samples, collagen deposits presented greater amounts of collagen. The monofilament grafts (HWPP and LWPP) unexpectedly presented the greatest difference in all samples between the infected and noninfected groups ($p < 0.01$). Collagen- and titanium-coated graft collagen deposits between infected and noninfected grafts were slightly more pronounced than those in the multifilament groups ($p < 0.05$). The least significant differences in collagen deposition among the infected and noninfected groups were recorded for the semi-absorbable

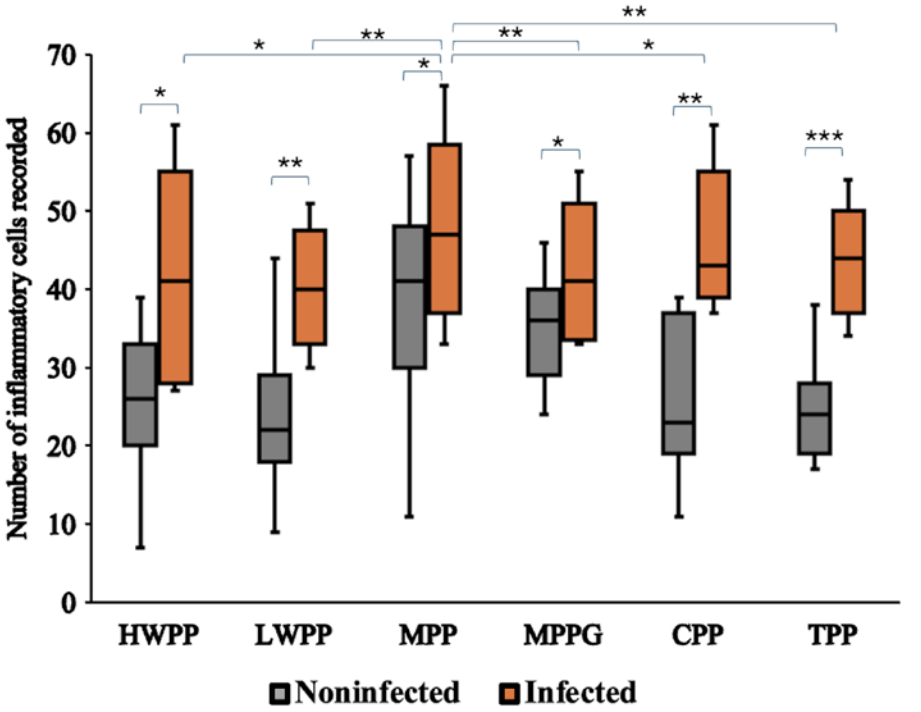

Fig. 3 – Number of inflammatory cells recorded (at magnification ×200) in the near proximity of the grafts (*per* high power field) after six weeks (median/quartile range).
***p* < 0.05; ****p* < 0.01; *****p* < 0.001. For abbreviations, see Figure 1.**

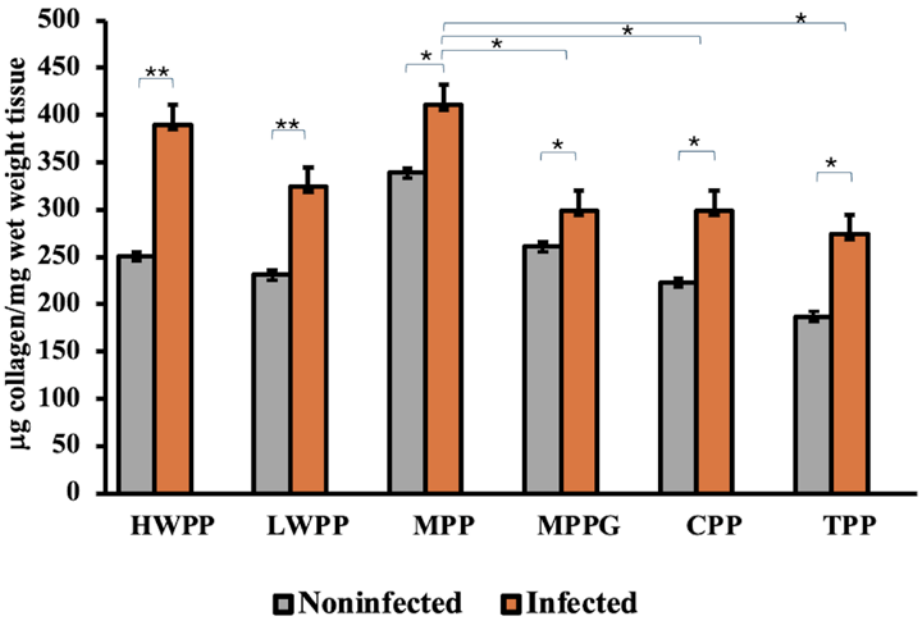

Fig. 4 – Collagen quantification from explanted tissue samples stripped down from the grafts after six weeks (mean + standard error).
***p* < 0.05; ****p* < 0.01. For abbreviations, see Figure 1.**

MPPG in all the samples ($p < 0.05$). When infected grafts are compared, the MPP presented significantly higher collagen deposition compared to the MPPG, CPP, and TPP ($p < 0.05$).

SEM studies of the fresh samples revealed biofilm formation in all the infected groups. Fibroblasts were detected on the surface of the grafts in the noninfected samples, whereas in the infected samples, fibroblasts were detected on the surface of the biofilm. The characterization of collagen fibers differed among the groups. In the noninfected samples, the collagen fibers were characterized as mature, organized, and in contact with the filaments filling the pore spaces of the grafts. In infected samples, collagen fibers were characterized as predominantly immature, in abundance, and not penetrating the interfilamentous spaces (Figure 5). In the infected grafts, inflammatory cells were recorded in abundance on the biofilm covering the fibers.

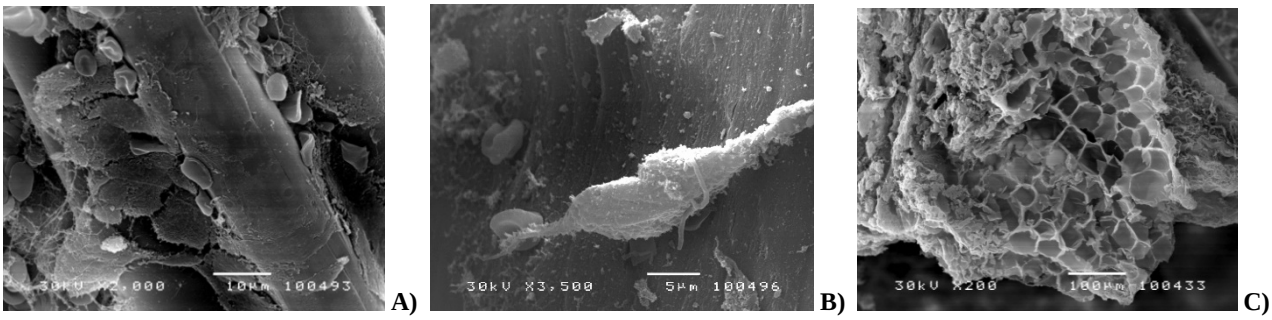

Fig. 5 – Scanning electron microscopy characteristics of the samples: A) biofilm identification; B) fibrocyte detected on the biofilm; C) exposed multifilament graft with no interfilamentous infiltrate.

Discussion

Polypropylene meshes are now commonly used to treat SUI in women. Nevertheless, these meshes are still linked to certain problems, such as mesh shrinkage, mesh migration, and the possibility of infection [12]. The incidence of mesh infection in the human population ranges from 0.3% to 8%. However, the exact incidence is not well established because of the lack of a consistent definition [13].

Our investigation revealed a 100% infection rate when *S. epidermidis* was inoculated according to the described method. We focused our work on *S. epidermidis* because these bacteria are frequently associated with biofilm infections of surgical implants [14, 15]. Several investigations have suggested that infection can be prevented when antibiotic prophylaxis is given [16, 17]. In our study, antibiotic prophylaxis proved not to be successful. One of the reasons could be the time of only three days of administration. In our opinion, the biofilm formation on the graft filaments protected the bacteria from antibiotics and thus enabled the infection to persist. Furthermore, the intentional inoculation, as described with large quantities of bacteria, might be the reason for prophylaxis to be unsuccessful. The presence of bacterial biofilms has been observed in both inguinal and ventral hernia repair, suggesting that they are important causative mechanisms of non-septic failure in most surgical implants investigated to date [13, 15, 18].

The inflammatory response was severe, as anticipated in the infected groups, with noticeable variations observed among the different mesh groups. The TPP and LWPP were the most significantly different between the noninfected and infected groups in all the samples ($p < 0.001$). Based on prior studies, the presence of many inflammatory cells in the MPP- and HWPP-infected graft groups indicates that the strength of the inflammatory reaction may be determined by the sheer quantity of the graft, namely its weight [2]. When infected, the TPP and CPP coatings designed to enhance biocompatibility presented a greater presence of inflammatory cells than the monofilament alone. The presence of a pronounced inflammatory reaction in all infected graft groups indicates a protracted infection, whereas the noninfected graft group had already completed its acute inflammatory reaction. Zheng et al. [19] reported that acute infection reached its highest point between 7 and 14 days and then became insignificant by day 90, which is like our noninfected control groups. The acute inflammatory response is replaced by a persistent reaction that facilitates healing and produces low-intensity granulomas, which subsequently leads to collagen deposition [20]. The persistence of infection and the elevated presence of inflammatory cells in our infected sample group resulted in a longer healing phase that lasted for six weeks. Several studies have suggested that *S. epidermidis* adhesion is greater in multifilament and composite (semi-absorbable) grafts than in monofilament grafts, which supports the findings of our study [21]. This may explain the most significant disparity in inflammatory cell counts between noninfected and infected MPPG grafts in our study. Furthermore, compared with the other samples, the infection had the most significant effect on reducing the strength (MDL) of the MPPG.

Fibroblasts play a significant role in the inflammatory response by producing collagen in response to activation by macrophages [22]. Under typical conditions, collagen is deposited outside of the cells in the matrix and pore spaces, where it covers the mesh fibers [23]. Our investigation revealed that collagen deposits in the infected subgroups covered the pore gaps rather than filled them. Unlike previous studies suggesting that steroid soaking is a means of decreasing collagen deposition [21, 24], our investigation revealed that infection of the graft significantly increased the inflammatory response and promoted collagen deposition. The collagen deposits exhibited a lack of organization and were present in large quantities. Yet, they did not have any effect on the structural support of the tissue, as evidenced by previous research [8].

Using SEM, we successfully identified the fibroblasts. However, variations were observed in the spatial distribution of the fibroblasts. In noninfected grafts, fibroblasts were observed in direct contact with the filaments in all experimental groups. Nevertheless, in the infected graft groups, fibroblasts were discovered specifically on the biofilm that covered the graft or graft bundles, as illustrated in Figure 5. Fresh sample testing, as recommended by Patiniott et al. [15], successfully confirmed the accurate identification of the biofilm. Discrepancies were observed in the maturation of collagen. Infected grafts had a high presence of immature collagen, with collagen fibers visibly not in contact with the graft filaments, indicating excessive scarring. In the noninfected groups, the collagen fibers were predominantly mature, in direct contact with the filaments, and covered the pore spaces. The presence of a bacterial biofilm in infected samples hinders direct contact between collagen fibers and polypropylene filaments,

thus affecting their integration and proper support. The fibers appear to be more encapsulated rather than incorporated into the AW. The work of Klinge and Klosterhalfen [25] defined simple mesh porosity in contrast to effective mesh porosity, with bacterial biofilms being responsible for reducing effective porosity due to mesh constriction.

The results of tensile strength testing of the infected graft groups revealed that increased collagen deposition did not result in enhanced abdominal support, contrary to what other studies have suggested [26]. In fact, all infected samples presented significantly weaker abdominal support and lower tolerance to elongation than the noninfected samples. Our findings indicate that reinforcement in the event of graft infection is insufficient despite the high levels of collagen observed. The SEM images suggest that the collagen fibers are disordered, which may result in inadequate support and excessive scarring. The persistence of a high number of inflammatory cells may contribute to the insufficient bonding of collagen with the graft filaments. The quantity of collagen did not correlate with studies on strengthening the abdominal wall, even in the groups without any infection in the graft.

This study has several limitations. The experimental animal study is performed on Wistar rats to gain insight into the cellular and tensile changes. Although conclusions can be drawn, there may be differences in the human population. Bacterial biofilms are not readily characterized in standard histopathological and SEM techniques due to their challenging composition assessment. The causative organisms require a broader evaluation to identify all bacteria implicated in the biofilm. We used SEM biofilm identification only as an orientation to confirm the presence of biofilm.

Conclusion

The findings of the presented animal study have indicated that infection of the urogynecology synthetic graft leads to a substantial decrease in tissue reinforcement in all grafts. The presence of an infection causes an increase in the inflammatory response, affecting the titanium-coated grafts the most and changing the way collagen is deposited. This results in a situation where, despite the presence of a large amount of collagen, it does not correlate with tissue reinforcement. Our investigation revealed that the overall unfavorable consequences of infection are more evident in multifilament and semi-absorbable multifilament grafts. According to our study results, low-weight polypropylene is the most resilient to infection and, therefore, can be preferred for use. Antibiotic prophylaxis has not been efficient in our study, probably because of the bacterial biofilm formation on the polypropylene fibers.

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