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Original Research

Predictive Value of Tissue-induced Oxidative Stress on Urogynecology Synthetic Graft Reinforcement: An Experimental Animal Study

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Abstract

Background: The success of urogynecology synthetic grafts depends on adequate tissue reinforcement. This experimental animal study aimed to determine the abdominal wall reinforcement achieved by different urogynecology synthetic grafts, including the influence of inflammatory cells, collagen deposits, and tissue-induced oxidative stress. **Methods**: Electron microscopic analysis of six different grafts, all with Polypropylene as their major component, was performed to determine the primary mesh characteristics. Full-thickness abdominal wall defects were repaired using monofilament, multifilament, and coated grafts in male Wistar rats. After six weeks, the animals were sacrificed and the inflammatory response, collagen deposition, and oxidative stress levels were quantified. Using the digital acquisition system (Hottinger Baldwin Messetechnik (HBM) "Catman Easy", Darmstadt, Germany), mechanical testing of the native grafts and of the reinforced abdominal wall was conducted and measured in a controlled environment. Multivariate analysis was performed to determine the predictive value of inflammatory cell numbers, collagen amount, oxidative stress, and native graft strength on the final abdominal wall reinforcement. **Results**: The inflammatory response was significantly more prominent with the multifilament polypropylene compared to the low-weight monofilament polypropylene ($p < 0.05$). Collagen deposits varied between the groups, reaching statistical significance only for multifilament polypropylene vs. titanium-coated polypropylene ($p < 0.05$). The oxidative stress results demonstrated a positive correlation with graft weight, regardless of coating or different graft structures ($p < 0.05$). The number of inflammatory cells and collagen amount did not influence the final abdominal reinforcement, while tissue-induced oxidative stress presented with a negative influence in all groups. **Conclusions**: Tissue-induced oxidative stress negatively affected grafts in this animal experiment. This finding might be useful (at least partially) in predicting the effectiveness of urogynecology synthetic graft tissue reinforcement and also, in promoting this reinforcement.

Keywords: inflammation; mesh; oxidative stress; mechanical strength; collagen quantification

1. Introduction

Synthetic grafts have demonstrated superior durability and long-term success over biomaterials for treatment of stress urinary incontinence [1]. Biocompatibility has been established as the most crucial factor for both short- and long-term success [2,3]. Quantifying the biocompatibility and establishing its statistical relationship with abdominal wall reinforcement can bring further understanding of polypropylene meshes. Graft variables, such as mesh thickness, mesh weight, pore surface, and the oxidative stress levels induced, may also define the quality of a reinforcement [4]. An interesting factor that is emerging as possibly influencing the overall success of such grafts may be the cell oxidative stress induced.

This experimental animal study aims to evaluate, through multivariate analysis, multiple graft and biocompatibility factors to identify their influence on the quality of the reinforcement and on the overall success of the procedure.

2. Materials and Methods

2.1 Electron Microscopy Analysis of the Meshes Included in the Experimental Study

Six different types of polypropylene graft were used in the experiments: high weight polypropylene (HWPP; Prolene mesh, monofilament, Ethicon, UK, 76 g/m^2), low weight polypropylene (LWPP; Gynecare Gynemesh, monofilament, Ethicon, UK, 43 g/m^2), multifilament polypropylene (MPP; Surgipro multifilament, Tyco, BLG, 97 g/m^2), multifilament polypropylene with polyglactin (MPPG; Vypro mesh, Ethicon, UK, 25 g/m^2), collagen-coated polypropylene (CPP; Supra mesh, Genzyme, USA, 96 g/m^2), and titanized polypropylene (TPP; titanized mesh, GFE, DE, 16 g/m^2). These were analyzed using scan electron microscopy (SEM) for pore size, filament thickness, and graft thickness. The native grafts were covered with gold using the "sputter" method for five minutes and then analyzed with SEM using Image J 1.49v software (Java Oracle free software).

2.2 Mechanical Mesh Testing (Dry Meshes) for Minimal Disintegration Load

For each type of polypropylene graft, three specimens, standardized to 40 × 10 mm, were obtained and tested for minimal disintegration load (MDL), as described by Afonso *et al*. [2]. The samples were fixed in clamps modified from the standard shredding device in two places (longitudinally), with a clamp grasping 5 mm of the graft, at each end. For mechanical testing of the MDLs, Spider 8 (Hottinger Baldwin Messetechnik (HBM), Darmstadt, Germany), a digitalized acquisition system with HBM Cat-man Easy software, paired with a standard shredding device, was used, with a crosshead speed of 5 cm/min. Force was applied to the grafts in a vertical direction in a controlled environment that was identical for all samples. The paired system was automated, recording, in total, not less than 1700 measurements (N/mm ratio) in one disruption. The sample testing continued until there was complete disruption of the grafts, and the ratio of applied force (N) to the stretching of the material (mm) was measured. This mechanical testing was performed at the Faculty of Mechanical Sciences, University of Nis.

2.3 Experimental Study Design

A total of 144 male Wister rats, each weighing 200/250 g, were divided into six groups (24 animals in each group), each group being assigned for use with one of the grafts. All experimental procedures involving the animals were conducted in compliance with the European Council Directive (EU directive of 2021; 2010/63/EU) and the Guide for the Care and Use of Laboratory animals (10th edition, National Academy Press). The Ethics Committee for Animal Experimentation of the Faculty of Medicine, University of Nis, approved the experimental study. The animals were anesthetized with 0.3 mL 10% Ketamidor (Richter, Austria) injected subcutaneously, dosed in relation to body mass. Monofilament, multifilament, and coated polypropylene grafts were used for the primary repair of a full thickness abdominal wall defect (20 × 25 mm) in relation to the peritoneum. The graft implants were standardized to 25 × 30 mm, which was 2.5 mm larger than the abdominal defect (overlay technique), and then fixed with Surgipro II (4/0) at four points. This was followed by an additional running suture without tension. The skin and subcutis were closed with a 3/0 polyglactin absorbable suture (VicrilTM, Ethicon, UK). The animals received prophylactic antibiotic therapy (gentamycin 0.2 mL/60 mg/mL) for three days. They were housed at the Biomedical Research Institute of the Faculty of Medicine, University of Nis. After six weeks, the animals were sacrificed by administering an overdose of Ketamidor. During necropsy, the entire abdominal wall was dissected, en block, with the graft in the middle, including the interface and at least 25 mm of neighboring native tissue. The specimens were cut transverse to the long axis of the animal, and standardized to 10 × 50 mm, with the graft in the middle. They were then stored in 0.9% NaCl solution at room temperature for tensiometry, which was carried out within 4 h of the sacrifice. Minimal disintegration loads were determined for all groups, with the same procedure as used for the graft testing.

2.4 Histology Preparation of the Samples and Inflammatory Cell Quantification

Tissue samples were stored in a 10% buffered formalin solution and then were fixed and dehydrated in ethanol solutions of increasing concentration (50%, 70%, 90%, and 100%). Upon dehydration, samples were fixed in paraffin blocks (boiling point: 58 °C) and then sliced into 3–5 μm. The tissue samples were then submerged in a series of solutions for hematoxyline and eosin (H&E) (Fig. 1). Inflammatory cells were quantified as described by Konstantinovic *et al*. [3]. Ten identical high-power fields, randomly selected in the near proximity of the polypropylene filaments (recorded under microscope-×200), were analyzed for each histology specimen. Inflammatory cells were counted in identical fields (matrices) by two independent observers and recorded. The middle value of the inflammatory cell numbers was calculated for the ten fields analyzed for each sample, and this was included in the calculation. All inflammatory cells were analyzed, and their total numbers recorded (foreign body giant cells [FBGCs] + macrophages + polymorphonuclears).

2.5 Collagen Quantification

Precise collagen quantification was performed from tissue stripped directly from the surface of the grafts, as described by da Silva *et al*. [4]. The alkaline hydrolysis of collagen in fresh samples was performed as described to obtain a sensitive hydroxyproline assay of hydroxylates. Colorimetric determination (spectrophotometer SP-22, Bio Spectro, Curitiba, Brazil with 1 cm optical glass cuvettes) was performed for hydroxyproline for alkaline hydrolysates in 1/100 dilution. A 50% w/v stock solution of NaOH (Vetec Brazil, CAT No 101) was used to prepare the samples. All samples underwent 40 minutes of hydrolysis, and PH correction was conducted identically on all samples, using a PH meter (model HI3222, Hanna, Instruments, USA).

2.6 Oxidative Stress Analysis

For the oxidative stress analysis, tissue samples removed from the graft were homogenized and then spun at 1500 rpm for 10 minutes. Protein levels in the tissue homogenates were then quantified using Lowrey's method (1951). Malondialdehyde (MDA) levels, as the final product of lipid peroxidation, were quantified (nmol/mg protein) in a 10% homogenate using the thiobarbituric acid (TBA) method (Okhava, 1979). Sample preparation and analysis were conducted at the Laboratory for Medical Biochemistry at the Faculty of Medicine, University of Nis.

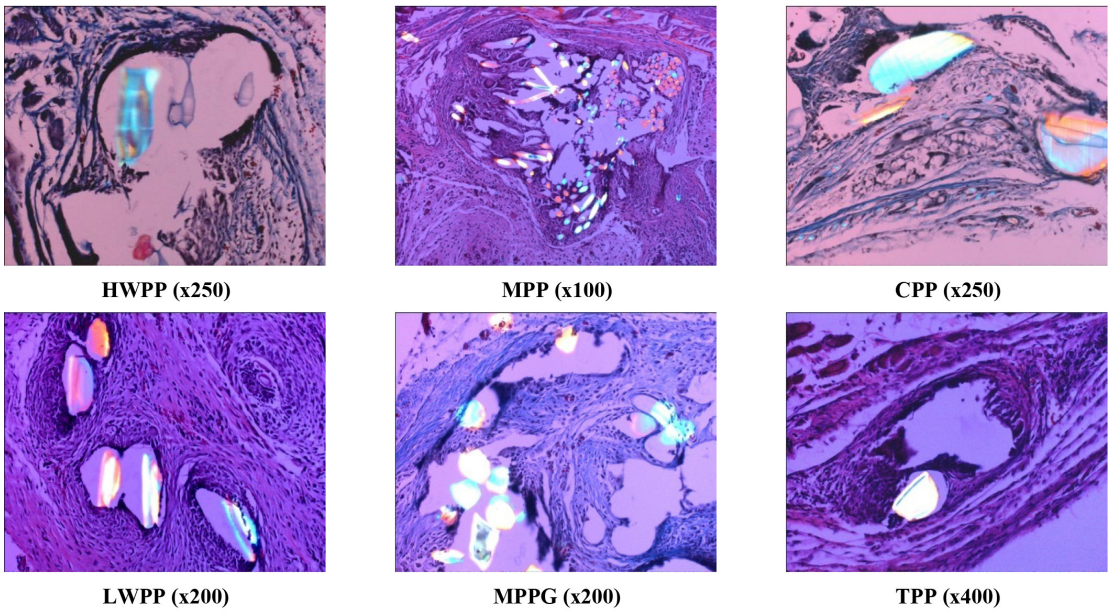

Fig. 1. Polarized microscopy of H&E samples used for inflammatory cell quantification- polypropylene graft position and inflammatory cells in the near proximity of the graft verified in all samples.

2.7 Statistics

A linear correlation test, the Kruskal-Wallis analysis of variance (ANOVA), followed by the Mann-Whitney U-test, was used for the pair analysis. Bonferroni corrections were applied for paired comparison (Statistical package SPSS 11, Chicago, IL, USA was used for all analyses). p values < 0.05 were considered significant. Multivariate analysis was used to determine the influence of filament thickness, pore size, inflammatory cell number, graft strength, collagen deposits, and oxidative stress levels of abdominal wall reinforcements after six weeks.

Table 1. The main mesh characteristics of the tested samples.

Graft type	Pore surface.		Filament thickness.		Graft thickness.	
	mm^2	SD	mm	SD	mm	SD
HWPP	0.570	0.020	0.086	0.009	0.650	0.010
LWPP	0.490	0.010	0.068	0.013	0.430	0.020
MPP	0.190	0.010	0.259	0.002	0.440	0.010
MPPG	1.060	0.080	0.190	0.005	0.340	0.020
CPP	0.080	0.030	0.077	0.003	0.630	0.020
TPP	0.460	0.030	0.048	0.007	0.280	0.010

HWPP, high weighted polypropylene; LWPP, low weight polypropylene; MPP, multifilament polypropylene; MPPG, Multifilament polypropylene with polyglactin; CPP, collagen coated polypropylene; TPP, tetanized polypropylene.

3. Results

Electronic microscopic analysis of the dry meshes indicated significant differences in pore size for the samples tested (Table 1). The most prominent pores were recorded in MPPG, and the least prominent in CPP, MPP, and TPP ($p < 0.001$). LWPP and HWPP also demonstrated significantly smaller pore sizes than MPPG ($p < 0.05$), but they were still considerably larger than those of CPP ($p < 0.05$). Filament thickness varied significantly, with MPP having the thickest filaments overall as compared to HWPP ($p < 0.05$), LWPP ($p < 0.05$), CPP ($p < 0.001$), and TPP ($p < 0.001$). The scan electron microscopy showed that MPPG, as a multifilament, showed comparable filament thickness results to MPP.

The samples presented with significant differences when the native mesh samples were tested for minimal disintegration load (Fig. 2). Almost identical minimal disintegration loads were detected for HWPP and MPP. A comparable graft strength was presented by the CPP samples, while LWPP ($p < 0.05$) and TPP ($p < 0.05$) presented with significantly lower minimal disintegration loads. The minimal disintegration load was lowest in the MPPG group, with significant differences compared to all the other grafts ($p < 0.001$).

The abdominal wall reinforcement testing is presented in Fig. 3. While the TPP was weakest on the native graft testing, it presented as the strongest abdominal wall reinforcement, reaching a 15.8 N minimal disintegration load. A statistically significant difference was reached for TPP vs. HWPP ($p < 0.05$), whereas the other grafts presented with comparable results. Slightly better tolerance for displacement was shown in the HWPP group, which reached 27.6 mm for its disintegration limit.

Oxidative stress levels relative to graft weight are presented in Fig. 4. Overall, the lowest expression of oxidative stress levels was recorded for the TPP group. When the

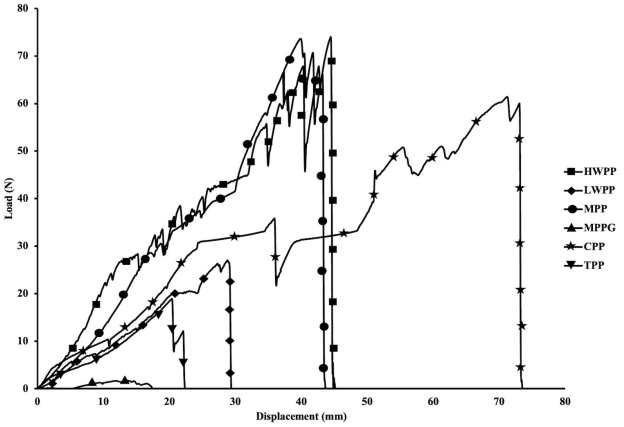

Fig. 2. Experimental results for native (dry) mesh-uniaxial tension test.

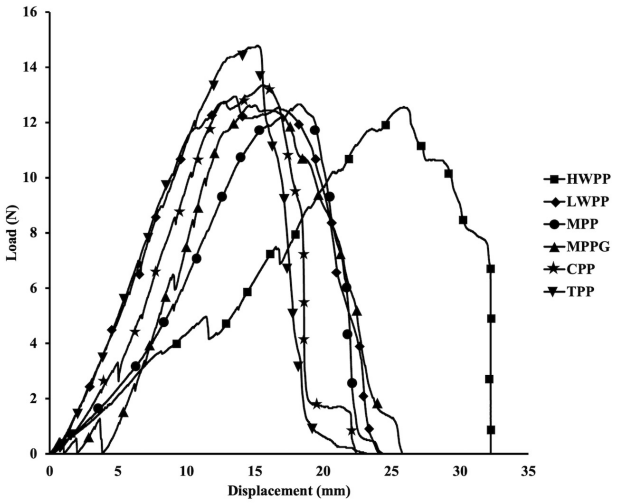

Fig. 3. Uniaxial tension test of abdominal wall explants after six weeks.

MPP and MPPG groups were compared as multifilament groups, there was no statistically significant difference between them ($p = 0.56$). No statistically significant difference was shown in oxidative stress levels when comparing the TPP and LWPP groups ($p = 0.21$) or the TPP and MPPG groups ($p = 0.32$). A significant difference in oxidative stress levels was evident when comparing HWPP to TPP ($p < 0.001$), to MPPG ($p < 0.05$), and to LWPP ($p < 0.05$). Both MPP and CPP induced greater oxidative stress than TPP ($p < 0.001$), MPPG ($p < 0.001$), and LWPP ($p < 0.001$). All grafts showed a positive correlation between graft weight and oxidative stress ($p < 0.05$). In our study, the coating of the grafts with collagen or titanium did little to reduce the oxidative stress. A comparison of the grafts coated with CPP and TPP shows significant differences in oxidative stress ($p < 0.05$), but this is attributed mainly to their difference in graft weight. When similarly weighted grafts were compared to the coated grafts, comparable oxidative stress levels were recorded.

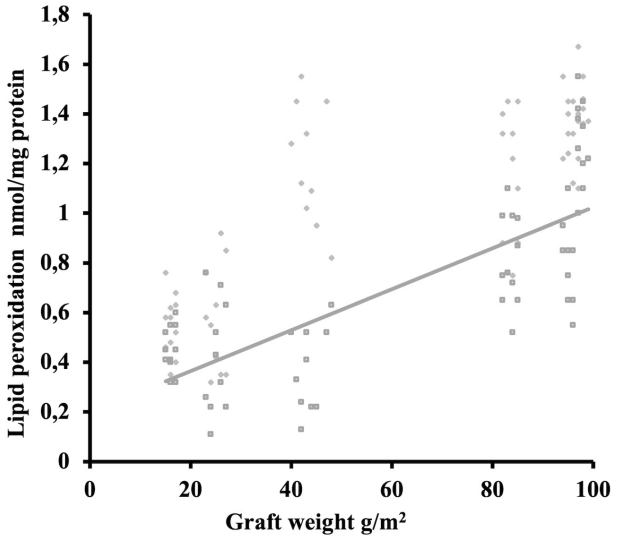

Fig. 4. Induced oxidative stress level results in accordance to graft weight (line presenting Pearson's correlation).

The results of the inflammatory cell quantification are presented in Fig. 5. Significant differences are noticeable among the tested grafts: MPP recorded the most pronounced inflammatory reaction in comparison to HWPP, LWPP, CPP, and TPP ($p < 0.001$), and to MPPG ($p < 0.05$). The lowest number of inflammatory cells were recorded in the LWPP group as compared to MPP ($p < 0.001$) and MPPG ($p < 0.05$). A comparison of non-coated and coated grafts (HWPP and LWPP vs. CPP and TPP), in terms of inflammatory cell induction, showed a marginal preference for coated grafts in relation to biocompatibility. No statistically significant relationships were recorded between graft weight and the number of inflammatory cells.

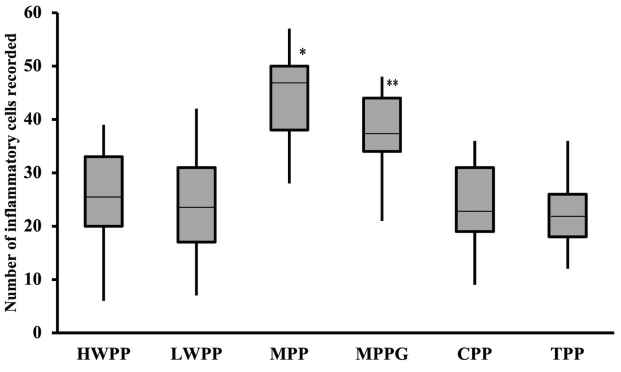

Fig. 5. Number of inflammatory cells recorded per high power field after six weeks (median/quartile range). *statistical significance $p < 0.001$ compared to LWPP. ** statistical significance $p < 0.05$ compared to LWPP.

Table 2. Multivariate analysis–influence of inflammation, collagen deposits, native graft strength, oxidative stress and pore size finding on the mechanical strength of the reinforced abdominal wall (*p* values presented).

Graft type	Inflammatory cells	Collagen deposited	Graft strength	Oxidative stress	Pore size
HWPP	0.9971	0.6012	0.4837	0.0486*	0.1019
LWPP	0.6012	0.5915	0.5951	0.0403*	0.6114
MPP	0.4837	0.0780	0.9745	0.0471*	0.4467
MPPG	0.6486	0.7403	0.5571	0.0072*	0.4044
CPP	0.3858	0.7121	0.6372	0.0229*	0.7921
TPP	0.1019	0.6140	0.4467	0.0044*	0.8962

*statistically significant $p < 0.05$; HWPP, high weighted polypropylene; LWPP, low weight polypropylene; MPP, multifilament polypropylene; MPPG, multifilament polypropylene with polyglactin; CPP, collagen coated polypropylene; TPP, titanized polypropylene.

The collagen quantification of the tissue samples is presented in Fig. 6. There were significant differences among the grafts tested, with the multifilament graphs having pronounced, but largely disorganized, collagen bundles recorded on the SEM, indicating over-scarring (Fig. 7).

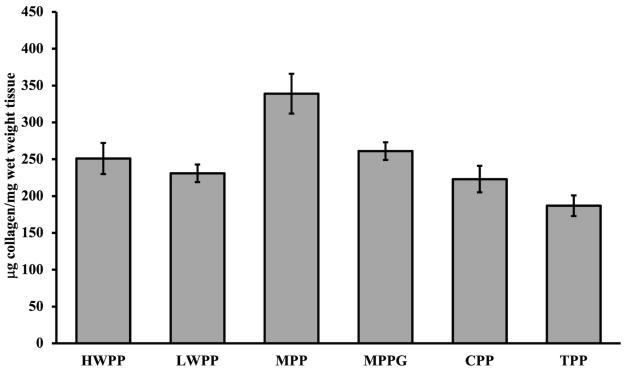

Fig. 6. Collagen quantification of explanted samples after six weeks (mean/standard error).

The amount of collagen detected varied the most between the MPP (standard error (SE) = 27 μg collagen/mg wet weight tissue) and HWPP (SE = 21 μg collagen/mg wet weight tissue) groups, while other groups had relatively close values when the detailed collagen quantification was performed. Statistical significance was reached for TPP vs. MPP ($p < 0.05$), while somewhat higher collagen levels were measured in HWPP, MPPG, LWPP, and CPP, but with no statistically significant differences. Overall, the most consistent results were found in the TPP group (SE = 12 μg collagen/mg wet weight tissue).

A multivariate analysis of graft pore size, graft strength, number of inflammatory cells, collagen amount, and oxidative stress relative to abdominal wall strength after six weeks is presented in Table 2.

The abdominal wall reinforcement was not influenced by the number of inflammatory cells in the groups. Graft-specific variables, such as filament thickness and pore size, also failed to present as statistically significant. The oxidative stress induced by the grafts proved to be significant in all groups ($p < 0.05$). HWPP ($p = 0.0486$) and MPP ($p = 0.471$) barely reached statistical significance, while TPP (0.0044) and MPPG (0.0072), although higher, presented statistical relevance in the $p < 0.05$ range as well. In all cases, oxidative stress level was the single independent factor influencing overall abdominal wall reinforcement strength ($p < 0.05$).

4. Discussion

To the best of our knowledge, direct oxidative stress analysis of tissue stripped from explanted grafts has not been done before. A specific analysis of the oxidative stress levels of the tissue in direct contact with the graft indicates somewhat different results from oxidative stress as measured in blood [5]. Oxidative stress is a well-established measure and is widely used when assessing tissue cellular damage [6]. Since Spiteller reviewed the involvement of lipid peroxidation in various chronic diseases, lipid oxidation end-products have emerged as oxidative stress markers, with Trans-4hydroxy-2nonenal (4-HNE) and MDA among those most investigated [7].

The main reason for testing different grafts was to gain insight into the cellular and sub-cellular differences influenced by graft specificity. An obvious result was the positive correlation between graft weight and oxidative stress level. This result has not been presented until now, and it suggests a restrictive use of polypropylene. Bearing in mind that oxidative stress correlates positively with graft weight, one can assume that the graft weight and graft surface (as the quantity-weight of the implanted graft is increased) will determine the cellular damage induced by the oxidative stress. The mass of the graft itself is the most important independent factor affecting direct oxidative stress as expressed in the tissue in the immediate proximity. The complication rates with high-weight polypropylenes are significant, at least in vaginal surgery [8–10]. An important aspect is that the collagen and titanium coatings, intended to reduce the foreign body reaction, did little to reduce it in our study, as has also been demonstrated in other studies [11,12]. An alternative method for decreasing the local ox-

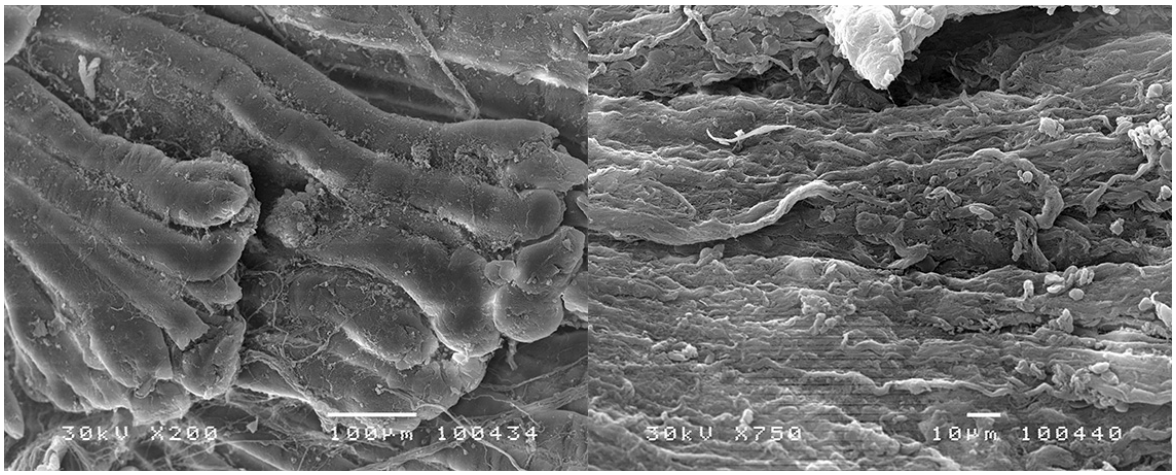

Fig. 7. Scarcely organized collagen fibers of multifilament graft indicating over scaring (left ×200, right ×750, SEM).

idative stress could be a platelet-rich plasma covering of the polypropylene mesh, as suggested in a study by Belebecha *et al*. [13]. A comparison of grafts of similar weight, where one was collagen-coated,did not indicate any mitigation of the cellular oxidative stress of tissue in direct contact with the graft. A semi-absorbable multifilament mesh induced similar oxidative stress levels relative to its weight, despite the evident absorption of some filaments. Junge *et al*. [14] concluded that the absorbable filaments did not influence the biocompatibility, favoring our study results. Some studies have suggested that oxidative stress could be an initial factor in malignant transformation, quite apart from the inflammatory processes [15–17].

Several studies have shown that the mesh construction may be the ultimate factor in tissue ingrowth, final graft stabilization, and tissue reinforcement [18–20]. A revealing study [21], analyzing English and German literature, emphasizes graft structure and construction. Our results suggest that graft weight should be reduced to the limits of sound tissue reinforcement, while being light enough to reduce the inflammatory foreign body reaction to a minimum. The intense inflammatory response recorded with the heavier grafts in our study resulted in greater collagen deposition. These collagen deposits presented as disorganized on the electronic scan microscopy, suggesting over-scarring (Fig. 7). Collagen and collagen organization are essential for abdominal reinforcement, as demonstrated in other studies [22]. Our recent study showed that all grafts provided similar tissue reinforcement, regardless of the graft strength shown in a controlled environment [23], favoring having just the right amount of reinforcement (i.e., reducing the amount of mesh support), as mentioned above. The current study results show least oxidative stress expression with the lightest meshes, regardless of mesh construction or coating. In our opinion, the oxidative stress results indicate the need for a critically determined amount of mesh, or mesh surface, relative to the minimum needed for the reconstruction. This would permit oxidative stress and cell damage to be reduced to a minimum, allowing ingrowth and stabilization without complications. This is in contrast to other studies that have highlighted the graft structure and construction [24,25]. In our research, graft structure did not influence the final abdominal wall reinforcement after six weeks. Aspects of graft damage by oxidative degradation highlight the oxidative stress aspect even more when a detailed chemical analysis is performed. Imel *et al*. [26] demonstrated damage to in vivo polypropylene by oxidative degradation by performing detailed chemical analysis as well as by using the electron microscope. However, the statements “polypropylene is highly susceptible to the oxidative effects of the metabolites produced by phagocytic cells during inflammatory response” and “These byproducts of the inflammatory response may degrade and embrittle the material causing it to become rigid” are open to question. Mesh degradation, reported to cause surface cracking, mesh contraction, loss of mass, decreased melting temperature, embrittlement, and reduced compliance of the polypropylene, is directly influenced by oxidative stress that is induced locally through chemical degradation [25]. In vivo degradation of both hernia and pelvic meshes has been demonstrated in several studies that question the inertness of implanted polypropylene [27–30].

A recent study by Poppas *et al*. [31] reports that a hydrogel coating reduces oxidative stress significantly, but this type of mesh coating is not available in our country. They measured 8-hydroxydeoxyguanosine (8-OHDG), an intracellular oxidative stress marker known to adhere to DNA lesions created by oxidative stress. The lower oxidative stress levels they report differ significantly from our results, but it is necessary to bear in mind the different coating and the oxidative stress markers that were measured.

Limitations of the study

This is an experimental animal study and the results might be different in the human. The follow-up period of six weeks might be considered too short, leaving uncer-

tainty as to whether the results would remain the same after a longer follow-up period. The experimental animal study used abdominal wall defects as a model for testing grafts used in vaginal surgery.

5. Conclusions

In our experimental animal study, tissue-induced oxidative stress levels were negative predictors for urogynecology synthetic graft tissue reinforcement. The mechanical strength of the graft was not relevant either to the process of stabilization or to the quality of the final tissue reinforcement. According to our experimental animal study results, the expression of oxidative stress presented with a positive correlation to graft weight.

Author Contributions

PM—idea, writing of the manuscript, correcting, statistical analysis; II—structure corrections, language editing, statistical corrections; VB—provided help and advice on the analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

All experimental procedures that involved animals were conducted in compliance with the European Council Directive (EU directive of 2021; 2010/63/EU) and Guide for the Care and Use of Laboratory animals (10th edition, National Academy Press) and ARRIVE guidelines 2.0. The Ethics Committee for Animal Experimentation of the Faculty of Medicine, University of Nis approved (No 2477-19) the experimental study.

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Conflict of Interest

The authors declare no conflict of interest.

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