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The long-term behavior of lightweightand heavyweight meshes used to repair abdominal wall defects is determined by the host tissue repair process provoked by the mesh

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Background. *Although heavyweight (HW) or lightweight (LW) polypropylene (PP) meshes are widely used for hernia repair, other alternatives have recently appeared. They have the same large-pore structure yet are composed of polytetrafluoroethylene (PTFE). This study compares the long-term (3 and 6 months) behavior of meshes of different pore size (HW compared with LW) and composition (PP compared with PTFE).*

Methods. *Partial defects were created in the lateral wall of the abdomen in New Zealand White rabbits and then repaired by the use of a HW or LW PP mesh or a new monofilament, large-pore PTFE mesh (Infinit). At 90 and 180 days after implantation, tissue incorporation, gene and protein expression of neocollagens (reverse transcription-polymerase chain reaction/immunofluorescence), macrophage response (immunohistochemistry), and biomechanical strength were determined. Shrinkage was measured at 90 days.*

Results. *All three meshes induced good host tissue ingrowth, yet the macrophage response was significantly greater in the PTFE implants (*$P < .05$*). Collagen 1/3 mRNA levels failed to vary at 90 days yet in the longer term, the LW meshes showed the reduced genetic expression of both collagens (*$P < .05$*) accompanied by increased neocollagen deposition, indicating more efficient mRNA translation. After 90–180 days of implant, tensile strengths and elastic modulus values were similar for all 3 implants (*$P > .05$*).*

Conclusion. *Host collagen deposition is mesh pore size dependent whereas the macrophage response induced is composition dependent with a greater response shown by PTFE. In the long term, macroporous meshes show comparable biomechanical behavior regardless of their pore size or composition. (Surgery 2012;152:886-95.)*

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Despite the appearance of many new prosthetic materials designed to repair abdominal wall defects, polypropylene (PP) continues to be used the most widely. This is because of the good cost/benefits and excellent biocompatibility of PP, along with an improved tolerance to infection compared with other materials.[1] However, because of certain adverse effects produced when it is placed at the peritoneal interface, namely adhesions to the intestinal loops and fistulas,[2,3] PP is not recommended for use in contact with the visceral peritoneum. Notwithstanding, when extraperitoneal placement is called for in hernia repair, this material continues to be used the most widely.[4]

Research and development in prosthetic materials has aimed to improve the wound repair process elicited by prosthetic mesh implant. Thus, rather than being relegated, macroporous meshes have been subjected to modifications to their structure, porosity, and composition. This has led to the construction of new large-pore meshes composed of other polymers such as polytetrafluoroethylene (PTFE)[5] and polyvinylidene fluoride.[6]

One of the main goals of surgery has been to assess the effects of varying the amount of implanted material. To this end, composite meshes have been designed[7,8] with both absorbable and nonabsorbable components. Pore size has also been considered an important factor in new mesh designs, along with other characteristics such as the diameter and spatial distribution of fibers.

These new designs have led to the classification of macroporous meshes[9] as heavy weight (HW), medium weight (MW), or low weight (LW), respectively, according to whether their density values are greater than 80 g/m^2, between 50 and 80 g/m^2, or less than 50 g/m^2. Some authors[10] have even defined an ultralightweight material whose density is less than 35 g/m^2.

Prosthetic mesh density is sometimes independent of pore size, and some designs, despite having a small pore size, are classified as LW because they are constructed from a loosely woven light monofilament conferring them an overall low density in g/m^2.

Despite this classification, in line with the concepts of the German authors,[11] we consider pore size to be the main factor that determines whether a material is HW or LW. Thus, it is generally considered that HW meshes have a small-pore design and LW meshes have large pores.[12]

Given that when a LW mesh is used, less material is implanted in the host, we would expect a reduced foreign body reaction and a repair process that generates less fibrosis in the host tissue, with the consequence of improved tissue compliance.[13] Although individual variation exists in terms of the repair process induced by the implant of a biomaterial,[14] it is clear that the sometimes excessive fibrosis induced by conventional HW materials could be minimized through the use of a LW implant.

In recent work,[15] we observed the excellent short-term collagenization of LW-PP implants. This prompted the design of the present study, in which we sought to determine whether during longer periods (3 and 6 months) the behavior of a LW mesh (tissue incorporation and tensile strength) remains the same regardless of pore size or its composing polymer (PP or PTFE). A further objective was to determine the effect of the implant material on the host tissue response produced in the long term.

MATERIAL AND METHODS

Experimental animals. The experimental animals were 36 male New Zealand White rabbits weighing approximately 2,200 g caged under conditions of constant light and temperature according to European Union animal care guidelines (European Directive 609/86/EEC and European Convention of the Council of Europe ETS123). All procedures were approved by our institutions Review Board.

Prosthetic materials. The biomaterials used were (Fig 1, A–C) as follows:

- Surgipro (Covidien, Mansfield, MA): HW PP (85 g/ m^2); pore size 0.26 ± 0.03 mm^2;
- Optilene elastic (B/Braun, Berlin, Germany): LW PP (48 g/m^2); pore size 7.64 ± 0.32 mm^2; and
- Infinit mesh (Gore and Associates, Flagstaff, AZ): LW nonexpanded PTFE (70 g/m^2); pore size 4.05 ± 0.22 mm^2.

Surgical technique. To minimize pain, all animals were administered 0.05 mg/kg buprenorphine (Buprecare; Divasa Farmavic, Barcelona, Spain) 1 hour before and 3 days after the surgical procedure. Anesthesia was induced with a mixture of ketamine hydrochloride (Ketolar, 70 mg/kg; Parke-Davis, S.A., Spain), diazepam (Valium, 1.5 mg/kg; Roche, Madrid Spain), and chlorpromazine (Largactil, 1.5 mg/kg; Rhone-Poulenc, S.A., Spain), administered intramuscularly.

With the use of a sterile surgical technique, 4 x 4-cm defects were created in the lateral wall of the abdomen comprising the planes of the external and internal oblique muscles, sparing the transversalis muscle, parietal peritoneum, and skin. The defects were then repaired by fixing a mesh of the same size to the edges of the defect with a running 4-0 PP suture interrupted at the 4 corners (Fig 1, *D–F*). The skin was closed by 3-0 PP running suture.

Experimental design. A total of 36 animals were implanted with each of the materials to establish 3 groups of 12 animals each. In each of these groups, 6 animals were euthanized in a CO_2 chamber after 90 days, and the remaining 6 were euthanized at 180 days post-implant.

Shrinkage. Shrinkage of the implanted meshes was determined by image analysis. For this purpose, we designed a set of transparent templates of the same dimensions as the original meshes (4 x 4 cm). At the end of the implant period, the outlines of the meshes were traced on the templates before their removal. The surface area of the templates could them be determined by computerized image analysis with the MIP program incorporated in the image analyzer (MICRON, Barcelona, Spain). Results are expressed as the percentage size reduction suffered by each implant. Shrinkage was assessed at 90 days after implant when the tissue repair process is practically complete.

Morphological analysis. *Light microscopy*. For light microscopy, specimens were collected from the mesh/host tissue interface. The samples were fixed in F13 solution (ethanol 60%, methanol 20%, polyethylene glycol 7%, water 13%), embedded in paraffin, and cut into 5-μm sections. Once cut, the sections were stained with Masson's trichrome (Goldner–Gabe) and examined under the light microscope (Zeiss Axiophot; Carl Zeiss, Oberkochen, Germany).

Gene expression of collagens. *Real-time reverse transcription polymerase chain reaction (RT-PCR)*. Tissue fragments 1 cm^2 in size were obtained from the central mesh zone, and stored at -80°C until use. RNA was extracted by the use of guanidine-phenol-chloroform isothiocyanate procedures with trizol (Invitrogen,

Carlsbad, CA). The RNA was recovered from the aqueous phase and precipitated by adding isopropanol and incubating overnight at -20°C. Complementary DNA was synthesized with 200 ng of the total RNA by RT with oligo dT primers (Amersham, Fairfield, CT) and the M-MLV RT enzyme (Invitrogen). RT reactions were run in the absence of M-MLV to confirm the RNA lacked genomic DNA.

cDNA was amplified using the following primers: collagen one (sense 5′-GAT GCG TTC CAG TTC GAG TA-3′ and antisense 5′-GGT CTT CCG GTG GTC TTG TA-3′); collagen three (sense 5′-TTA TAA ACC AAC CTC TTC CT-3′ and antisense 5′-TAT TAT AGC ACC ATT GAG AC-3′); GAPDH (sense 5′-TCA CCA TCT TCC AGG AGC GA-3′ and antisense 5′-CAC AAT GCC GAA GTG GTC GT-3′).

The RT-PCR mixture contained 5 μL of the inverse transcription product (cDNA) diluted 1:20, 10 μL of iQ SYBR Green Supermix (Bio-Rad, Laboratories, Hercules, CA), and 1 μL (6 μM) of each primer in a final reaction volume of 20 μL. RT-PCR was performed in a StepOnePlus Real-Time PCR System (Applied Biosystemx, Foster City, CA). Samples were subjected to an initial stage of 10 min at 95°C. The conditions for cDNA amplification were: 40 cycles of 95°C for 15 seconds, 60°C (collagens I and III) or 55°C (GAPDH) for 30 seconds, and 72°C for 1 minute. Negative controls containing ultraPureTM DNase, RNase-free distilled water (Invitrogen) were run in each reaction. Products were subjected to 2% agarose gel electrophoresis, stained with SYBR Green II RNA gel stain (Invitrogen), and visualized with ultraviolet light. Gene expression was normalized against the expression recorded for the constitutive gene glyceraldehyde 3-phosphate-dehydrogenase.

Immunofluorescence. To detect the protein expression of collagens I and III, tissue fragments were fixed in F13 solution, embedded in paraffin, and cut into 5 μm-thick sections. Once cut, the sections were deparaffinated, hydrated, equilibrated in phosphate-buffered saline buffer and incubated with the monoclonal antibodies anticollagen I (Sigma Chemical Co., St. Louis, MO) and anti-collagen III (Medicorp, Montreal, Canada). The secondary antibody used was conjugated with rhodamine. An immunofluorescence technique was used to detect the antigen–antibody reaction. Cell nuclei were counterstained with DAPI. Samples were examined under a confocal microscope Leica SP5 (Leica Microsystems, Wetzlar, Germany) to detect fluorescence.

Macrophage response. For immunohistochemistry, a specific monoclonal antibody to rabbit macrophages, RAM 11 (DAKO M-633, USA), was applied to paraffin-embedded sections. The alkaline phosphatase-labeled avidin-biotin method was performed as the following steps: incubation with the primary antibody (1:50 in Tris-buffered saline or TBS) for 30 minutes, incubation with immuno-globulin G and biotin (1:1,000 in TBS) for 45 minutes, and labeling with avidin (1:200 in TBS) for 30 minutes. These steps were conducted at room temperature. Images were developed with the use of a chromogenic substrate containing naphthol phosphate and fast red. Nuclei were counterstained for 5 minutes in acid hematoxylin. RAM-11–labeled macrophages were quantified according to a method described elsewhere.[16]

Biomechanical strength. To determine the biomechanical strength and modulus of elasticity of the meshes after implant, strips of the different biomaterials 1 cm wide and 5 cm long, with an effective gauge length of 3 cm, were analyzed with an

INSTRON 3340 (static load 500 N; Instron Corp.,High Wycombe, UK). The cross-head speed was 5 cmper minute and recording speed 2 cm per minute.

The strips obtained at 90 and 180 days after implantation included the mesh and infiltrated host tissue. All tests were conducted immediately after animal sacrifice.

Statistical analysis. Statistical analysis was performed by use of the Graph Pad Prism 5 package. Shrinkage percentages, collagen one and three mRNA expression, RAM-11–positive cells, biomechanical strength, and modulus of elasticity values were compared among the 3 study groups using the Mann-Whitney U test. The level of statistical significance was set at $P < .05$.

RESULTS

There were no cases of mortality or signs of infection and/or rejection of the implants in the animals operated on. Seroma was detected in 2 of the animals with PTFE implants at 14 days afterimplantation.

Shrinkage. Shrinkage values determined at 90 days after implantation were as follows: Surgipro (13.69 ± 3.52%), Optilene (10.11 ± 3.07%), and Infinit (10.42 ± 1.19%). These values failed to differ significantly ($P < .05$).

Morphological analysis. *Light microscop*y. At 90 days after implantation, the three biomaterials tested showed ingrowth by a disorganized, well-vascularized, loose connective scar tissue. This neoformed tissue occupied all the spaces between the PP (Surgipro and Optilene) and PTFE (Infinit) filaments and was interspersed with areas in which the infiltration of adipose tissue could be observed in all the implant types. After 6 months, there was a significant increase in adipose tissue ingrowth. Most neoformed connective tissue was observed around the prosthetic filaments. The preserved transversalis muscle in the lower zone of the partial defect showed no evident morphological alterations at any of the follow-up times or any of the study groups (data not shown).

Gene expression of collagens. *Real time RT-PCR*. The three mesh types induced similar collagen gene expression patterns reflected by the collagen one and three mRNA levels detected. At 90 days after implantation, the PP biomaterials (Surgipro and Optilene) induced the higher expression of mRNA for collagen three (immature) and one (mature) with significant differences with PTFE (Infinit) emerging at 180 days for collagen three when compared with the PP-HW mesh (Surgipro; $P < .05$; Fig 2, A) and for collagen one, compared with both PP-HW ($P < .01$) and PP-LW ($P < .05$; Fig 2, B). In the PTFE (Infinit) mesh group, the drop produced in collagen one mRNA expression from 90–180 days (Fig 2, B) was significant ($P < .01$).

Immunofluorescence. Both collagen types were immunodetected in the three implant groups at both study times. Collagen fibers ran parallel to the mesh surface in zones far from the filaments or were arranged concentrically to these filaments in areas closer to the implant edges. For Surgipro and Optilene, collagen III protein expression was homogeneously distributed throughout the newly formed tissue around the prosthetic filament at 90 and 180 days after implantation. In contrast, the Infinit mesh induced an intense pattern of collagen III expression confined to localized areas around the filaments.

Labeling for the mature form of collagen (collagen I) was more extensive and intense for the higher porosity implants (Optilene and Infinit) at both time points,

but Optilene showed the greatest staining for this type of collagen. Surgipro showed moderate collagen I staining. In all the study groups, collagen I staining was confined to areas of new tissue formation adjacent to the prosthetic filaments (Fig 3).

Macrophage response. In all the study groups, macrophage cells were detected in the neoformed tissue between the mesh filaments. Most inflammatory cells were found to concentrate around the filaments where, besides macrophages, multinucleated foreign-body giant cells, typical of a wound repair response, could be seen. These cells appeared mostly around the filaments of PTFE (Infinit).

At both time points, macrophage numbers were significantly greater for the PTFE meshes compared to the PP implants ($P < .05$). The macrophage reaction gradually diminished from 90 to 180 days in all 3 groups (Fig 4).

Biomechanics. The tensile strengths, or breaking points, recorded for the different meshes implanted for 90 and 180 days were comparable ($P = .05$; Fig 5, A).

At 90 days, the postimplant elastic modulus was significantly greater for PTFE ($P < .05$) than the PP meshes, although by 180 days, this variable was similar across the 3 groups (Fig 5, B).

DISCUSSION

As standard permanent prosthetic materials, PP and expanded PTFE (ePTFE) have been constantly subjected to modifications to improve both their host tissue incorporation and complications of bowel injury and infection, in an effort to achieve the best functional repair of the abdominal wall possible.

The most recent modifications made to PP meshes have involved minimizing the material implanted in the host without compromising their mechanical resistance. This approach led to the development of composite[8] and large pore meshes.[17]

The modifications made to sheets of ePTFE prosthetics, such as introducing multiperforations[18] or creating a rough surface on one side,[19] have not improved their biomechanical strength. The only strategy that has served to improve tissue incorporation and tensile strength has been the construction of a largely porous ePTFE mesh.[5] Bioassays conducted on this mesh have revealed that rather than the chemical composition of the biomaterial, it is its loosely woven structure that determines its tissue behavior. Accordingly, the behavior of classic microporous-expanded PTFE, which induces little tissue ingrowth and instead becomes encapsulated by host tissue, may be manipulated to simulate that of a largely porous PP mesh.

In the present experimental study, we compared the postimplantation behavior of a conventional PP-HW mesh to that of 2 LW meshes, one composed of PP and the other of nonexpanded PTFE. The first prosthetic materials generated by our group[5] were composed of an expanded PTFE monofilament CV-4. The material examined here is composed of a nonexpanded PTFE monofilament that is knitted to create a large pore size such that it is a MW mesh.

In our study, partial defects were created in the lateral wall of the abdomen to avoid involving the peritoneum in the repair process. When the animals were killed 90 days after implantation, seroma was detected in 2 of the animals who received a PTFE implant (similar to observations after the implant of laminar ePTFE meshes).

This finding seems consistent with our immunohistochemistry results obtained with the anti-RAM-11 macrophage monoclonal antibody. Hence, at each time point, the PTFE implants showed a significantly augmented macrophage reaction over that shown by the PP implants. This behavior would be comparable with that displayed by some absorbable materials in the early postimplant course,[7,20] possibly having clinical implications such as the presence of reactive seroma. For the PP meshes, macrophage counts gradually decreased during the study period as occurred, although at a slower pace, for the PTFE implants. The observed immune response to these implants requires further investigation.

With regard to shrinkage at 90 days, the lack of significant differences observed between the 3 meshes is in line with previous results from our laboratory.[21] After PP mesh placement in dogs, other authors[9] observed significant shrinkage of the implant area close to 30% at 90 days postimplantation. In our study, shrinkage at this time point was closer to 15% and probably attributable to interspecies differences.

We contemplate the phenomenon of prosthetic shrinkage as a physiological factor in the context of the wound repair process.[22] Possible variations among implants could be related to the implant site. Thus, some authors[23] have noted less shrinkage when the implant is placed in a retromuscular compared with a prefascial position.

In terms of host tissue incorporation, the 3 implant types showed good behavior. The PTFE meshes behaved differently than the classic microporous expanded PTFE, which becomes encapsulated by host tissue. Although collagen I (mature) could be observed both at 90 and 180 days in the different mesh groups, the greater porosity meshes (Optilene and Infinit) induced the greater protein expression of mature collagen. This result is in agreement with the findings of Greca et al,[24,25] who observed greater type I collagen deposition after the implant of large-pore prosthetic materials. The greater expression of collagen I protein observed here in the high-porosity meshes was accompanied by reduced mRNA expression for this protein in the long term, indicating the efficient translation of all the mRNA into protein. In contrast, the response to the implant of the low-porosity HW mesh would in the long-term lead to the buildup of mRNA because of the reduced effectiveness of its protein translation.

In previous work[15] in a different defect model with complete excision of the abdominal wall, we noted significantly greater gene expression levels for collagens one and three in meshes with pores larger than 3 mm in the short term (14 days after implantation). This finding could be correlated with colonization of the mesh by the cellular contingency of fibroblasts. A possible explanation could be that these cells undergo stress depending on the pore area that is to be occupied by neoformed tissue. Thus, cells that colonize large pore meshes will need to rapidly synthesize collagen to create a cell substrate. Conversely, if pore size is small, the small amount of space between filaments will require minimal occupation by newly formed tissue.

Similar behavior to this was observed in the present study at this time point of 14 days (data not shown) in that the more porous implants showed greater gene expression for both types of collagen. This finding suggests that in the short term, messenger RNA transcription and translation reach their peak and that hereafter

translation into the proteins diminishes over time.

Our biomechanical results indicated a greater tensile strength for Surgipro at the 2 time points, but differences were not significant compared with the other 2 implants. At 180 days after implantation, the tensile strengths of all three materials had increased, but again no significant differences were observed between the implants. A similar trend towards acquiring similar biomechanical resistance of different implants, including partially absorbable meshes, was observed at 90 days in a previous study.[26] It therefore seems that LW meshes regardless of their chemical composition show a similar response to breakage in the mid- and long term to that shown by HW meshes. This behavior correlates with the optimal collagenization (collagen type I deposition) of LW implants. The deposition of collagen in the repair tissue around the filaments of the LW meshes causes an increase in stiffness that substantially modifies the original properties of the mesh. Thus in long term, the growth of collagen tends to unify the mechanical response shown by LW and HW meshes. The elastic modulus was significantly greater at 90 days ($P < .05$) for the PTFE meshes compared with the other implants, although similar values were attained at 180 days for the 3 implants.

According to the biomechanical data obtained, both the resistance to breakage and elasticity of the different implants was gradually modulated by the host tissue. Thus, besides offering the advantage of a reduced amount of implanted material, the mechanical properties of LW implants seem to be improved, especially in terms of tensile strength, by the newly formed tissue around the prosthetic filaments. In line with this observation, in a recent clinical study of incisional hernia repair,[27] surgical outcomes at three years were similar when small or large pore PP meshes were used. In view of these findings, larger pore meshes would need to be tested to determine how much further the amount of foreign material placed in the host could be reduced without mechanically compromising the implants.

Our study is not without its limitations. In our experience, although the rabbit model has provided excellent results in terms of tissue repair and immune response, its biomechanical behavior is less translatable to human clinical practice.

In conclusion, our findings indicate that the following:

- Compared with PP, the use of PTFE in a macroporous mesh induces an augmented macrophage response;
- In the long term, the collagen mRNA translation induced by a high-porosity mesh is more efficient, resulting in increased collagen deposition in the repair zone; and
- In the long-term postimplantation, the tensile strengths and elastic moduli of both HW and LW materials attain comparable values.

In general terms, it therefore seems that the long-term behavior of LW meshes used to repair an abdominal wall defect, whether composed of PP or PTFE, is conditioned by the host tissue repair process, with a correlation observed between collagen deposition and prosthetic pore size.

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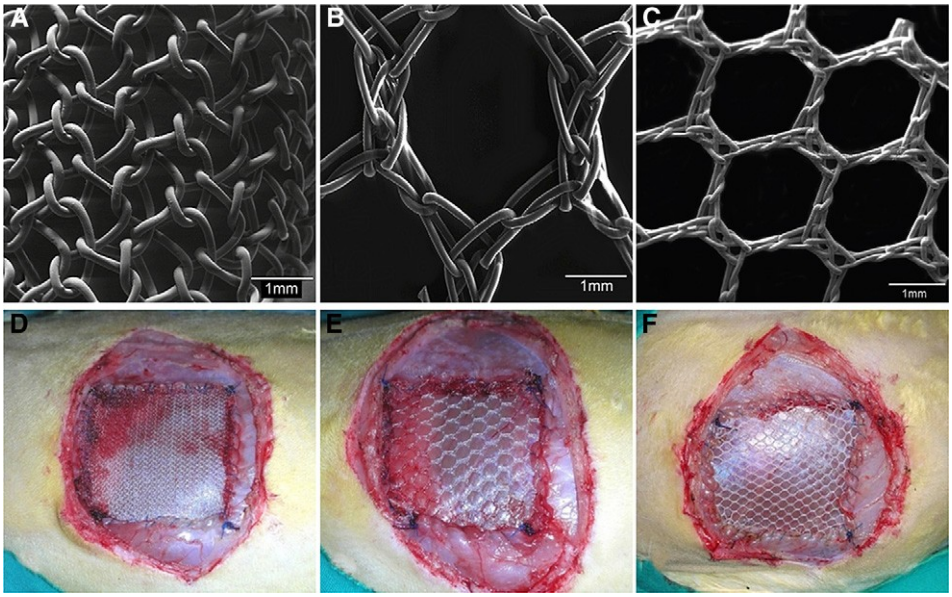

Fig 1. Biomaterials used in this experimental study. SEM images of the pore size detail: (*A*) Surgipro (15x); (*B*) Optilene (15x); (*C*) Infinit mesh (15x). Implanted biomaterials: (*D*) Surgipro; (*E*) Optilene; (*F*) Infinit mesh. (Color version of figure is available online.)

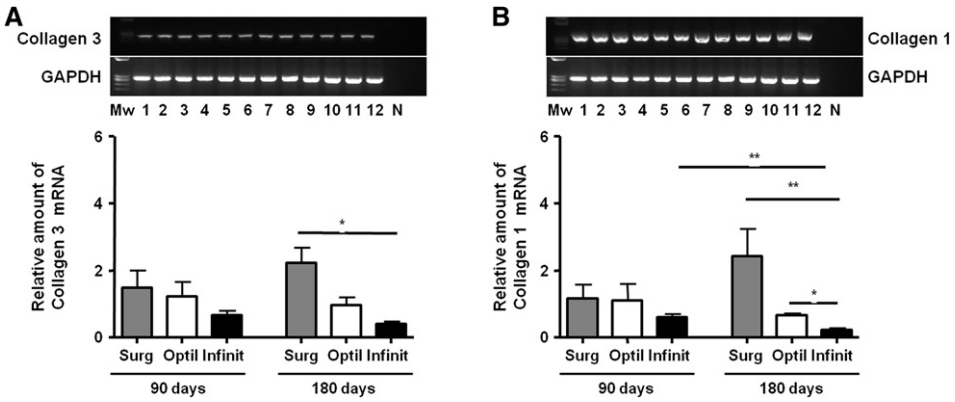

Fig 2. Relative amounts of collagen three (*A*) and one (*B*) mRNA in the implant of Surgipro, Optilene, and Infinit mesh determined by RT-PCR. Upper panels: RT-PCR products of both genes. Lanes: 1/2 Surgipro, 3/4 Optilene, and 5/6 Infinit mesh at 90 days, and 7/8 Surgipro, 9/10 Optilene, and 11/12 Infinit mesh at 180 days. *N*, Negative control; *Mw*, molecular weight markers. Results are the mean ± SEM of three experiments performed in duplicate. Gene expression was normalized to values recorded for the GAPDH gene. **P* < .05; ***P* < .01.

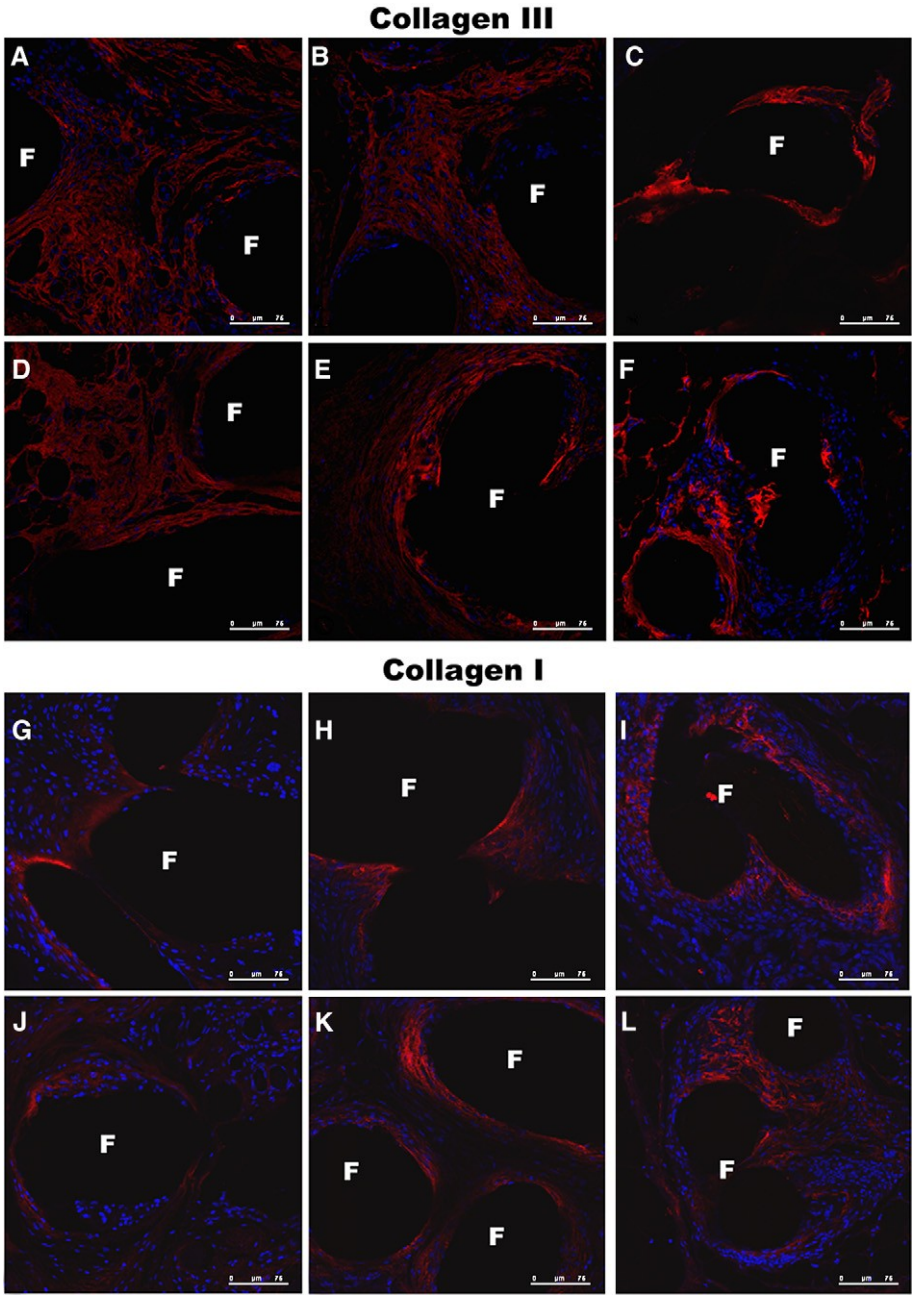

Fig 3. Tissue incorporation and collagen expression around the mesh filaments of the different biomaterials. Collagen appears as red fluorescence observed by laser scanning confocal microscopy. (A–F) Collagen III (immature): (A) Surgipro, 90 days (200x); (B) Optilene, 90 days (200x); (C) Infinit, 90 days (200x); (D) Surgipro, 180 days (200x); (E) Optilene, 180 days (200x); (F) Infinit, 180 days (200x). (G–L) Collagen I (mature): (G) Surgipro, 90 days (200x); (H) Optilene, 90 days (200x); (I) Infinit, 90 days (200x); (J) Surgipro, 180 days (200x); (K) Optilene, 180 days (200x); (L) Infinit, 180 days (200x). F, Prosthetic filaments. (Color version of figure is available online.)

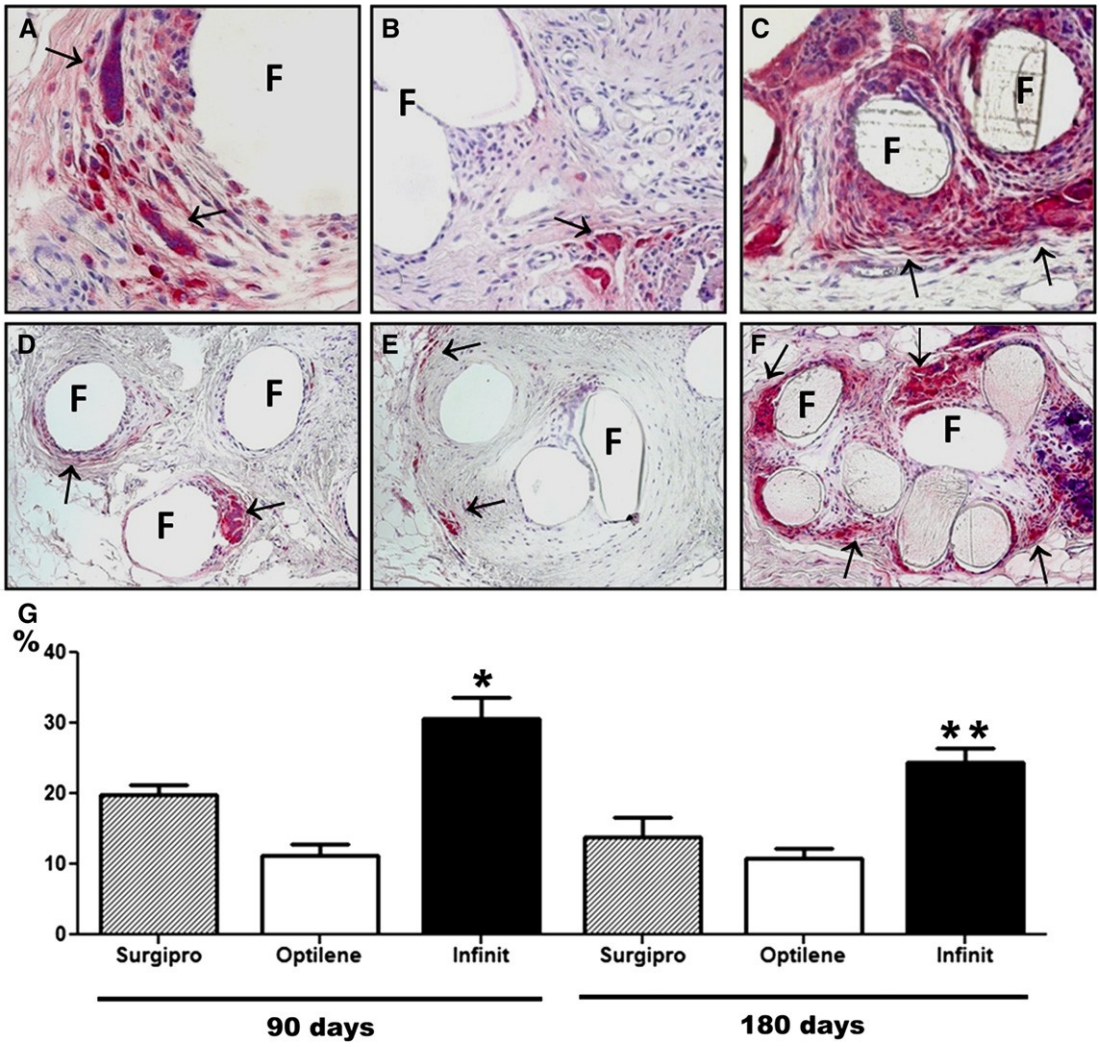

Fig 4. Immunohistochemical labeling of rabbit macrophages (arrows) using the RAM-11 monoclonal antibody. (A) Surgipro, 90 days (640x); (B) Optilene, 90 days (500x); (C) Infinit, 90 days (360x); (D) Surgipro, 180 days (200x); (E) Optilene, 180 days (200x); (F) Infinit, 180 days (200x); (G) mean numbers of RAM-11–positive cells recorded for each study group and follow-up time. Significant differences between Infinit vs Surgipro and Optilene were observed at 90 (*$P < .05$) and 180 days after implantation (**$P < .05$). F, Prosthetic filaments. (Color version of figure is available online.)

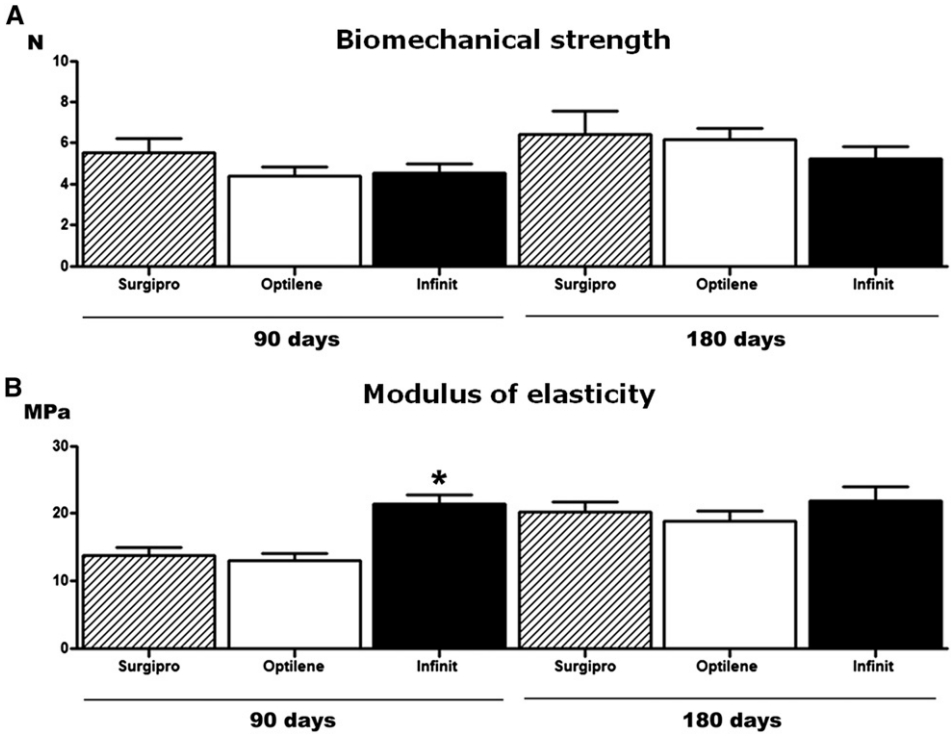

Fig 5. (A) Biomechanical resistance values (Newtons) for each type of prosthesis and study time. No statistically significant differences were observed; (B) modulus of elasticity for each type of prosthesis and study time. Significant differences were observed between Infinit vs Surgipro and Optilene at 90 days after implantation (*P < .05).