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A New Biomaterial for Urinary Catheters

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Abstract

Several studies argue that an ideal biomaterial for urinary catheters is utopian. Based in literature review it seems to be true. However, research advances: the biomaterial itself, new designs, new coatings, associated drugs, etc. Once implanted and interacting with urine, two old problems persist: encrustation and bacterial colonization. In this context, an extracellular product from bacterial synthesis on sugarcane molasses biomaterial has been studied in several experimental and clinical studies. Based on its high biocompatibility, the aim of this study is to evaluate its performance in an *in vivo* model as an endourologic prosthesis implanted in the bladder of Wistar rats. We evaluate physical, chemical and biological phenomena in comparison to an already established biomaterial, polyurethane. Even though it is not a finished product, the sugarcane biopolymer presented similar performance compared to polyurethane in several analyzed parameters and has an important characteristic: low cost.

Keywords

Biomaterial, Urinary Catheters, Encrustation

1. Introduction

Since antiquity there have been urinary catheters usefulness reports. Initially they were made from papyrus or metal and were used for urinary retention relief [1] [2]. Industrialization brought the vulcanized rubber, than they became chemically stable and flexible at different temperatures [3]. In 20th-century various synthetic biomaterials and different applications emerged [4]. Specifically in urology, due to high using frequency and necessity to remain implanted for long term, two urinary catheters have been highlighted: the Foley urethral catheter and the ureteral

stent, and therefore are the most studied [5]. Also, there are two major problems associated with urinary catheters: bacterial colonization (and consequent infection) and encrustation. In North America, more than 100 million urinary devices are implanted each year, bringing immense morbidity and cost [6]. In the United States, approximately two million nosocomial infections occur annually. Forty percent are urinary tract related, and 60% of these are urinary catheters related [7]. A Foley's catheter implanted patient has 100% chance developing bacterial colonization in 30 days term [8]. Despite existence of various biomaterials such as latex (polyisoprene), polyethylene, polyvinylchloride (PVC), polyurethane, silicone, biodegradables ones, and those made from heterologous and autologous tissue, the ideal biomaterial for endourological purpose was not discovered [4] [9] [10]. Which characteristics does it must have? It must be resistant to biofilm formation and bacterial colonization; able to resist encrustation; be biologically inert; have chemical stability when in urine contact; be easy to implant and remove; not prone to migration; allow optimal flow; be sterilizable; durable; radiopaque and low cost [11].

The Sugar Cane Biopolymer (SCB) is a biodegradable biomaterial. It is a polysaccharide obtained by bacterial synthesis from sugarcane molasses [12]. Previous studies indicate that it is biocompatible, has low toxicity and induces tissue remodeling [13] [14]. In clinical applications this biomaterial proves to be versatile and has been applied in different experimental studies [15]-[24]. In this context, the aim of this study was to evaluate a SCB performance when in urine contact comparing with a stablished biomaterial.

2. Materials and Methods

Study Design: Fifty-one male Wistar rats (*Rattus norvegicus albinus*), from Nutrition Department Bioterium were transferred to Experimental Surgery Nucleus, both of the Federal University of Pernambuco. They were 12 - 16 weeks old of age and 260 - 589 grams of weight. They were distributed in five groups:

SCB-3 group (n = 10), operated animals and SCB tubes implanted and followed up for 3 months; DJ-3 group (n = 10), operated animals and double J tubes implanted and followed up for 3 months; SCB-6 group (n = 13), animals operated and implanted with SCB tubes and followed up for 6 months; DJ-6 group(n = 9), animals operated and implanted with double J tubes and followed up for 6 months; and Control Group (9), animals operated without implantation, followed for 6 months.

All animals were kept in cages with wood shavings on the ground, in an environment with temperature and humidity control, day-night cycle artificially established in 12 for 12 hours, free access to drinking water and Labina® ad libitum feed.

Materials: SCB tubes for bladder implantation measured 5 mm in length and 6F in external diameter and were made from SCB films (membranes) made by POLISA Biomaterials for Health®, who ceded the material. For comparison pur-

pose it was used a 6F polyurethane ureteral stent (Stent Ureteral Universa, Handle Cook®) transversely sectioned in 5 mm pieces. The choice of animals for surgery was performed at random. All tubes were sterilized by gamma radiation in the Nuclear Energy Department of Federal University of Pernambuco. Figure 1 illustrates the materials.

Perioperative Procedures: Animals underwent 12 hours fast and were anesthetized under Bioterium protocol that used atropine, xylazine and ketamine. During the surgical procedure receiving supplemental oxygen, the animal was positioned on the surgical table in dorsal decubitus, after abdominal trichotomy was performed antisepsis with povidone-iodine. After apposition of sterile hole drape it was performed a 4 cm length infra-umbilical incision and blunt dissection until peritoneal cavity. The bladder was identified and grasped. A 6 - 7 mm incision was performed at cupula and a tube implanted in vesical lumen. In this point war performed a continuous suture with polyglactin 910 (Vicryl 6-0®). Peritoneal cavity was cleaned and abdominal wall was closed with cat gut 4-0 interrupted suture in two layers (aponeurosis and skin). Animal was taken to individual cages with slightly elevated decubitus, remaining heated under a light source in the first hours. In first week they were evaluated daily and after eighth day, weekly. The evaluation was: consciousness level, motor activity, food and water intake and wound aspect. On euthanasia's day animal was weighted again and received a lethal dose of intraperitoneal anesthetic. It was performed inverted U-laparotomy. Bladder liquid content was aspirated with needle for microbiological analysis than a cystectomy was performed. The bladder was opened longitudinally with introduction of scissors through the urethra. Its macroscopic appearance and content (tubes, calculations, scale, organic material) were checked and the recovered material was put into a sterile, dry tube for further analysis. Figure 2 shows a SCB tube implantation, bladder suture and a SCB tube visualization

Figure 1. SCB tube on the left and polyurethane tube on the right.

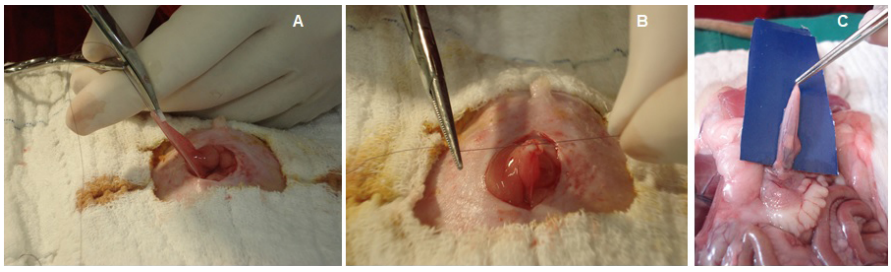

Figure 2. (A) SCB implantation moment in the bladder; (B) Bladder synthesis with Vicryl 6-0; (C) SCB view through bladder wall when euthanasia performed.

through bladder wall on euthanasia's time.

Histological Analysis: Bladders was fixed in 10% formalin on parchment paper to avoid contraction and folds. All material was stained with hematoxylin and eosin. Histopathological evaluation was performed by a single pathologist.

Microbiological Analysis: Urine samples were seeded in MacConkey medium and rich blood agar (Casoy medium with 5% defibrinated sheep's blood) at 35˚C for 18 to 24 hours in aerophilic, and read out after 24 hours.

Chemical Analysis: Encrustation substances and stones underwent qualitative analysis with a urinary stone test often used clinically, and they underwent quantitative analysis by Energy Dispersive X-ray Fluorescence Spectrometer EDX Series EDX-720/800HS.

Analytical Procedures: Each animal was weighted in grams prior to implant surgery and before euthanasia. Macroscopic phenomena consisted of 5 categorical variables: color change, shape change, presence of organic material, encrustation and formation of calculi. These variables were expressed as frequency (proportion) in each group as well the histological categories, if there were changes or not.

Statistical Analysis: Weight in grams of each group and the loss or gain between to the surgery day to euthanasia day were calculated and expressed as mean and standard deviation. Student's t test and Tuckey test for multiple comparisons were used for comparisons between groups. Categorical variables between the groups were compared using Fisher's exact test. It was accepted probabilities with values less than 5%. Epi Info 6.0 software was used to statistical calculations.

Ethical Procedures: This study was submitted and approved by the Animal Ethics and Research Committee of Federal University of Pernambuco, under ID number 23076.013771/2009-25.

3. Results

All animals underwent implantation tube had weight loss, but without statistic differences between groups. Control group had statistically significant weight gain. Table 1 shows these data.

Table 1. Parameters related to weight gain and loss.

Variables	Groups (n)				
	SCB-3 (10)	DJ-3 (10)	SCB-6 (13)	DJ-6 (9)	Control (9)
WID (g) M ± SD	515 ± 40.91	451.2 ± 64.95	424.76 ± 52.97	463.22 ± 42.92	356.0 ± 99.42
WED (g) M ± SD	495.75 ± 33.93	434.5 ± 53.46	413 ± 41.95	450.44 ± 42.13	397.57 ± 104.91
Minimum weight	449	380	350	449	260
Maximum weight	580	589	539	527	511
WED-WID = variation M ± SD	−17 ± 14.2	−16.7 ± 13.7	−10.55 ± 16.3	−12.77 ± 20.0	45.71 ± 9.5
p value	$p < 0.001$ *SCB-3/DJ-3/SCB-6/DJ-6 vs control*				

WID = weight in grams at implant's day; WED = weight in grams at euthanasia's day; SCB = Sugar Cane Biopolymer; DJ = double J; n = sample size; M±SD = mean ± standard deviation; Groups: SCB-3 and SCB-6 = SCB tubes implanted and animals monitored for 3 and 6 months, respectively; DJ-3 and DJ-6 = polyurethane tubes implanted and animals monitored for 3 and 6 months, respectively; Control group = animals operated without implantation monitored for 6 months. Statistically significant if $p < 0.05$.

There were five deaths (9.8%), all occurred in the first 24 h, with two in SCB-3 group, one in SCB-6 and one in control group. All animals underwent necropsy but no important findings. Concerning deaths there is no statistically significant findings (SCB-3 vs DJ-3 p = 0.473; SCB-6 vs DJ-6 p = 1; SCB-3 vs Control p = 0.544; SCB-6 vs Control p = 0.470). On 3 months term some findings were observed: almost all SCB tubes changed its color when compared to DJ tubes (7 of 8 and 0 of 10, respectively = 0.0007). Also, concerning shape changes, the SBC tubes were more likely to this alteration (4 of 9 and 0 of 10, respectively, p = 0.022). When others variable were studied (presence of organic material or calculi, encrustation) there is not differences between groups. On 6 months term, just the shape change variable was different, again in SCB tubes compared with DJ ones (10 of 12 and 0 de 9, respectively, p = 0.0002). The other variables were not observed differences. In control group was not found any organic material, calculi or encrustation. Figures 3-6 illustrate those macroscopic phenomena.

Forty six bladders were resected and processed for histological analysis. Twenty three bladders were classified as normal. When abnormal exhibited two main alterations: Mostly in the epithelial layer (urothelium), all of them considered reaction from injury caused by tubes themselves, stones, and infection; and lamina propria exhibited cells from inflammatory response. In the first ambit there was urothelium thickening, undulations, papillary growth and sometimes more specific architecture such cystic cystitis. In the second, there were found inflammatory cells such as neutrophils, lymphocytes, plasma cells, eosinophils, and mast cells. All benign, no atypia. Comparing groups no statistic differences were found. Figure 7 illustrates common findings in this study.

There were six animals where urine samples microbiological growth (11.76%), with two in the DJ-3 group, three in the SCB-6 group and one in the DJ-6 group.

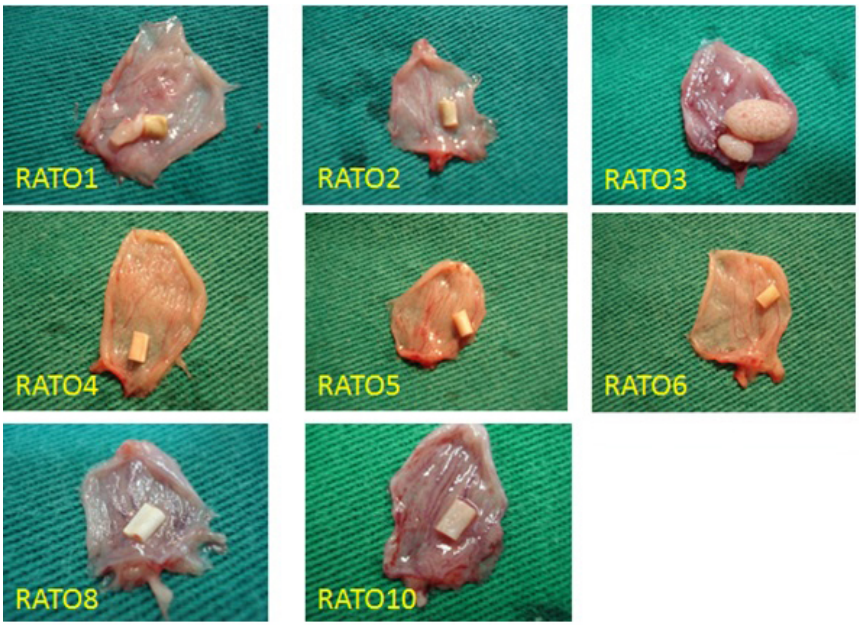

Figure 3. Macroscopic phenomena. SCB group-3 months.

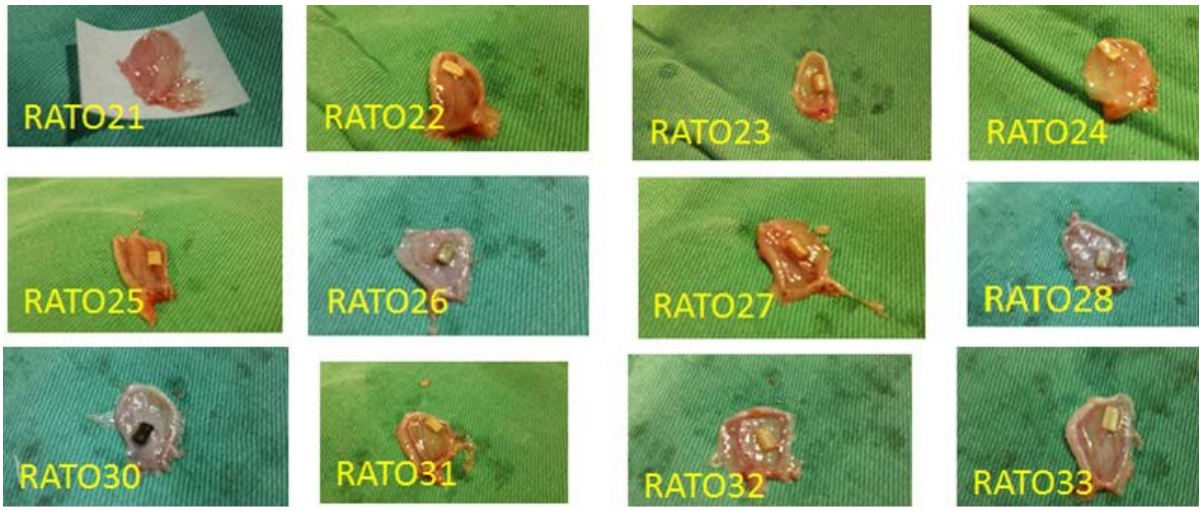

Figure 4. Macroscopic phenomena. SCB group-6 months.

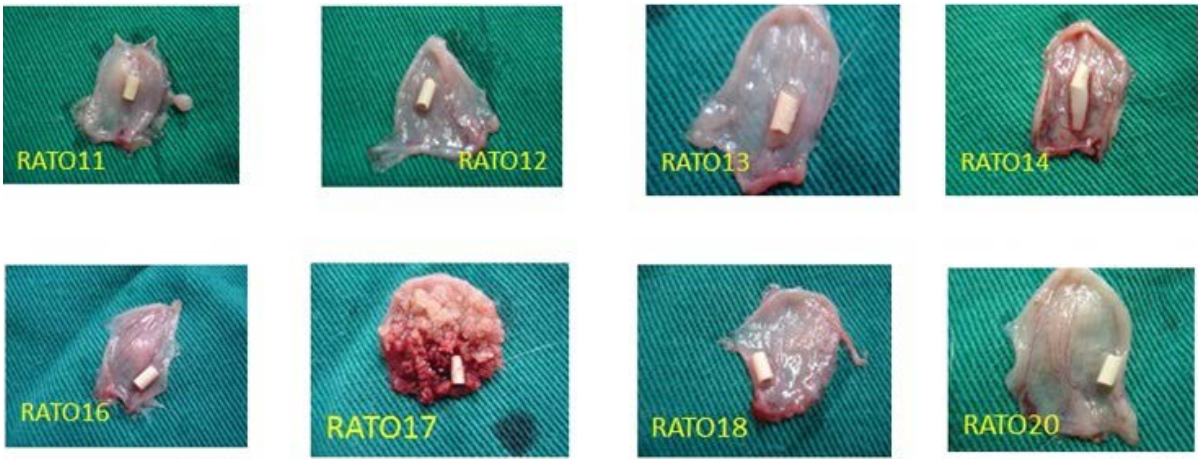

Figure 5. Macroscopic phenomena. DJ group-3 months.

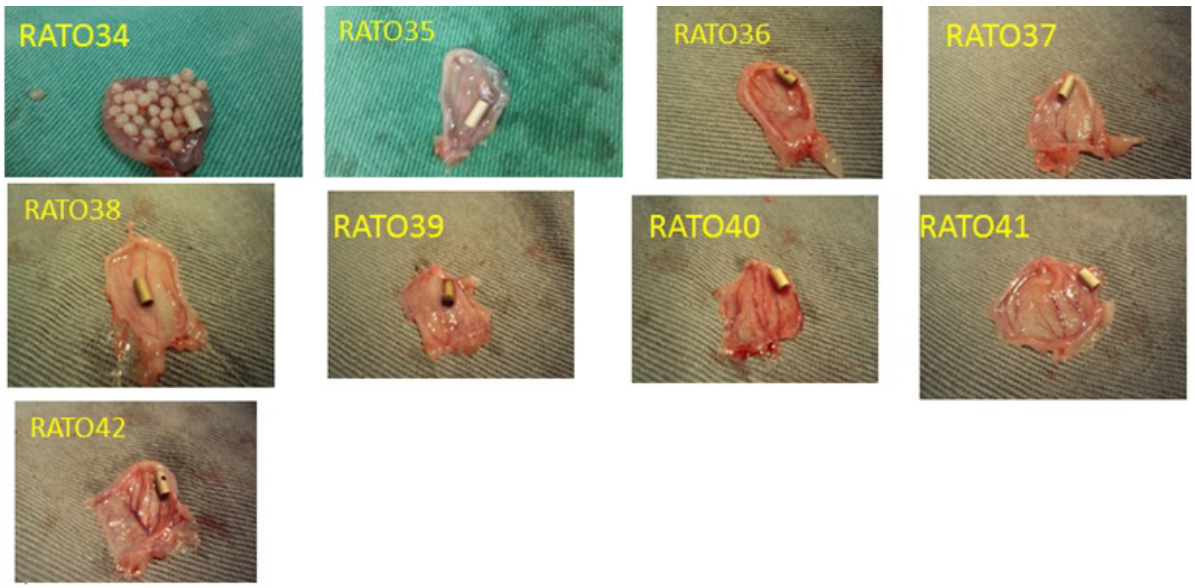

Figure 6. Macroscopic phenomena. DJ group-6 months.

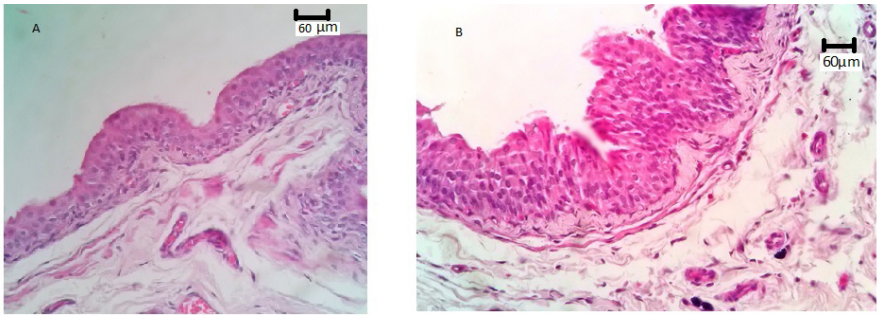

Figure 7. Bladder wall sections: hematoxylin and eosin stain from an optic microscope 400x. (A) Rat 4 showing preserved epithelium and lamina propria; (B) Rat 33 showing increased number of epithelial layers and undulated surface (epithelial hyperplasia).

There is no statistic difference. Isolated microorganisms were: *Staphylococcus epidermidis* and *Staphylococcus aureus*.

The physical-chemical qualitative analysis found three substances: carbonate, phosphate and ammonia in the calculi of the three animals, one from each group below: SCB-3, DJ-3 and DJ-6. Same samples underwent spectrometry revealed: phosphorus, calcium and magnesium. All samples had similar proportions of those elements pointing to higher concentration of struvite stones (magnesium ammonia phosphate) than calcium phosphate.

4. Discussion

Initially, some considerations about the presented methodology. There are several models for assessment encrustation biomaterials for urinary tract application [3] [11] [25] [26]. Basically separated into 2 groups: *in vitro* and *in vivo* models. *In vivo* models several animals have been used such as rats, rabbits, dogs and pigs. These studies precede the application in humans [3]. *In vitro* models are subdivided into those use artificial or human urine and in static or dynamic models (with continuous flow trying to reproduce the urinary tract characteristics). These have advantage of being controlled and of less variation, but do not reproduce the urinary tract's physiology such as peristaltism, bladder filling and emptying, and urothelium interface. *In vivo* models have these advantages reported, but the disadvantages of not controlling urine composition, variations in water intake, feeding, and living being idiosyncrasies. [26] [27]. We chose the *in vivo* model because the Experimental Surgery Nucleus of our University already has know-how in studies like this [15]-[24]. Besides rats are easy to acquire, enable greater samples, great infections resistance, low cost, and genetic homogeneity. Caution should be in mind when extrapolating experimental studies to humans; however, there are many similarities between rats and humans urinary tract structure and physiology, including urine composition and capability of crystallization [28]. Spontaneous lithiasis formation in the lower or upper urinary tract is very rare, but they are widely used as models in calculus formation studies drug induced (e.g. calcium, oxalate) or decreasing protective substances (e.g. citrate, magnesium) [29]. There are also models with implants in the blad-

der of foreign materials (e.g. zinc) or associations of the models [30].

Ford *et al.* and Carvalho Júnior *et al.* used methodology very similar to ours [17] [31]. Ford evaluated performance of several 5mm squares polymers free-floating in bladder lumen for 3 months term. Carvalho Júnior studied the performance of suture thread made from SCB after a transfixing suture in rats bladder for 4 - 8 weeks. Regarding the cross-section of ureteral stents, other studies used same arrangement for encrustation evaluation and comparison [32]. Polyurethane stent was chosen because it is one of the most versatile biomaterials. It has composed numerous biomedical devices such as breast implants, urinary catheters, blood bags, and artificial heart. Durable, elastic, and low cost. It has great interaction with water and blood. As a ureteral stent is the most commonly used polymer in urological practice [9] [10] [33]. About physical phenomena, SCB tubes were made from thin membranes without special coating, its surface is rough, therefore deformities and discolorations were expected. That characteristic may block adequate flow through catheter, but this happens on others biodegradable biomaterials. There is a study where the catheter sustained its patency for only two days [10]. When the tubes were manufactured we used distilled water to mold them, so we already expected that change. One study evaluated macroscopic phenomena and among them the color change as a encrustation predictor and difficulty for the removal as well. This study was hardly criticized for its speculative character under the argument there is no evidence that change color is a good parameter for assessing encrustation and infection [34]. Certainly, there are differences between rats and humans life expectancy, and this aspect has to be observed in experimental studies. Our follow up time was so long. First, we based upon Ford's study [31] that followed animals for 3 months. Also, studies in humans demonstrate increasing complications catheter-related chances beyond 3 months [35]. Second, in the present study, due to the low incidence of encrustation and other phenomena observed in the three months, this time in the following groups was doubled, which gave more robustness to study. There is no study with so long follow up. Probably, this was the reason of SCB biodegradation in one SCB-6 group animal. This fact coincides with Carvalho Júnior's study [17]. Also there was no trace of SCB thread in one animal. There is proportionality between time and stone size. In a rat model for stone formation, rats received zinc implants in the bladders. Rats sacrificed from day 0 to day 7 show inlay progressive stone size 113. A clinical study evaluated time and bacterial colonization on ureteral stents. When evaluated up to 4 weeks, between 4 - 6 weeks, after 6 weeks it found colonization in 2.3%, 2.9%, and 25%, respectively [30].

About bacteriology, we found bacterial growth in few animals equally distributed among groups, despite good sampling. When anesthetized, many animals urinated. *Staphylococcus epidermidis* and *Staphylococcus aureus* were isolated germs, otherwise Ford *et al.* [31] found many colonized animals and in its majority with *Streptococcus faecalis*. Only one animal grown up *Staphylococcus*

epidermidis.

In addition to evaluating the physico-chemical phenomena, our study evaluated the urothelium, an important aspect of the complex called biocompatibility, already pointed out in previous literature as a common lack in studies in this area [36]. All histological changes found in this study may be considered non-specific. Some studies show very similar results as we can see below. Ford *et al.* described the following histological findings in similar study: epithelial hyperplasia, exophytic mucosal growth with deep folds (similar to cystic cystitis found), and areas with inflammatory cells such as lymphocytes, mast cells, and plamocytes [31]. A model to evaluate intersticial cystitis induced rat bladder inflammation. They found epithelial hyperplasia, acute and chronic inflammation, and the presence of mast cells in several groups [37]. Isolato *et al.* evaluated histological findings after rabbit prostatic urethral stenting with two different biomaterials. They found epithelial hyperplasia and polyposis so early as one-month term [38]. Another study evaluated histologically dogs ureters after stenting. Over again, as above reposts they found epithelial hyperplasia, increased lumen, and wall thickening [39]. Not less important, it is malignancy potential. Spontaneous bladder tumors in Wistar rats are very rare. Cases described are usually from older male rats with a mean age of 26 months. Wistar rats live around 36 months. Both urothelial carcinomas and adenocarcinomas are described. Previous studies have suggested epithelial proliferation can induce carcinoma formation [40]. Even under long follow-up, none of ours animals presented atypia.

Chemical analysis confirmed what other studies found: mostly magnesium ammonia phosphate stones (struvite) as well as calcium phosphate (hydroxyapatite). In many studies, struvite is present in all samples collected [31] [40] [41] [42]. Calcium carbonate stone formation is not commonly induced, but it usually appears in spontaneous formation. Some studies found a small fraction of carbonate stones in rats [31] [41] [42].

5. Conclusion

Despite being a prototype and unfinished biomaterial/prosthesis yet, the SCB presented similar performance compared to polyurethane in several analyzed parameters such as biofilm formation, encrustation, and infection., and it holds a relevant attribute: low cost.

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Abbreviations

SCB = sugar cane biopolymer

DJ = double J-stent ureteral