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Comparison of two polymers PDO and PLLA/PCL in application of urological stent for the treatment of male urethral stenosis

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Abstract

PURPOSE: The primary objective of the conducted research was to develop an urological stent design for the treatment of male urethral stenosis. Given the variable loading conditions inside the urethra, the proposed stent should maintain normal tissue kinetics and obstruct the narrowed lumen. The suitable selection for the stent material significantly influences the regeneration and proper remodeling of the urethral tissues.

METHODS: In this work, the mechanical characteristics of some polymer materials were studied, including: polydioxanone (PDO) and poly(L-lactide) (PLLA)/polycaprolactone (PCL) composite. The obtained mechanical properties for static tensile testing of the materials, allowed the determination of such parameters as Young's modulus (E), tensile strength (Rm) and yield strength (Re). Subsequently, the design of a urological stent was developed, for which a numerical analysis was carried out to check the behaviour of the stent during varying loads prevailing in the urethra.

RESULT: The research indicated that PDO has better mechanical properties than the proposed PLLA/PCL composite. The numerical analysis results suggested that the developed stent design can be successfully used in the treatment of male urethral stenosis. The obtained stress and strain distributions in the numerical analysis confirm that the PDO material can be used as a material for an urological stent.

CONCLUSIONS: The biodegradable polymers can be successfully used in urology. Their advantages over solid materials are their physicochemical properties, the ability to manipulate the rate and time of degradation, and the easy availability of materials and manufacturing technology.

KEYWORDS: biodegradable polymer, stenosis, stents, numerical analysis

1. Introduction

The abnormality involving the tissues of the urethra most often results in urethral stenosis. It is defined as a narrowing caused by ischemia and fibrosis of the corpus spongiosum. The condition is more often diagnosed in the male gender [13]. The cause of stenosis can be various, such as mechanical trauma, chronic immune disease, infection or inflammation. Stenosis can include any segment: tissues from the bladder side or on the urethral outlet side. The largest number of diagnosed strictures, about 50%, involve the bulbar urethra, about 30% are strictures within the penile urethra, and the remainder occur in a combination of these two urethral segments. Unfortunately, an increasing number of men have been ignoring symptoms coming from the lower urinary tract for too long and delaying medical visits. A significant number of men show up for consultations only when the spectrum of symptoms significantly impedes normal functioning. Ignoring the first symptoms of abnormal functioning of the genitourinary system, such as frequent urination, a constant feeling of pushing on the bladder, burning and discomfort, unfortunately aggravates the problem, which can eventually lead to kidney failure or bladder stones. The advanced urethral stenosis with a significant reduction in the diameter of the canal, low patency and a significant area covered by fibrosis, makes the treatment process difficult [12], [24], [25], [29]. The treatment and reconstruction of urethral stenosis is still quite a challenge for urological surgery. There is still no indication as to the best method of treatment. Various solutions are used in practice, choosing them appropriately depending on the etiology, location and length of the stricture [5]. Some of the available treatments include urethrotomy, excision of the stricture and end-to-end anastomosis or urethroplasty. The lack of success of these procedures is related, for example, to the lack of access to the transplanted tissues, the advancement of the degree of tissue fibrosis or the patient's general health. Additionally, the European Society of Urology does not recommend the use of these methods when the length of the stenosis involves a tissue segment longer than 2 cm [7]. There is therefore a need to implement new methods, which include stenting. The use of available biodegradable materials, especially polymers such as polydioxanone (PDO), poly(L-lactide) (PLLA) and polycaprolactone PCL in combination with 3D printing technology is a promising starting point for the development and manufacture of urological stents. Above all, the new treatment solution should provide similar structure and function as healthy urethral tissue walls [31]. It is crucial to know the actual conditions in the urethra, which have been more extensively researched and described in previous works [14], [15], [16], [23]. The choice of biomaterial in the form of a polymer for the repair and regeneration of urethral tissues must be a scaffold capable of supporting the processes of biological reconstruction and possessing

the mechanical properties of functional urethral tissues, which would allow the gradual growth of periurethral tissue, without causing a negative response in the form of additional contractures.

Currently, polymers such as the previously mentioned PDO, PLLA and PCL are more often used to produce implantable stent structures. Polydioxanone (PDO) is a semi-crystalline aliphatic polyester produced by p-dioxanone chain-opening polymerization [22]. It has been evaluated that degradable PDO exhibits very low toxicity. It is used in medical and pharmaceutical applications [17], [20]. The PLLA is an aliphatic polymer composed of lactic acid monomers. It is produced from natural products by ring-opening polymerization. It is a biocompatible biomaterial and very well tolerated by the body, as it is a natural product formed in the eccrine sweat glands [2], [9], [27]. Poly(L-lactide) PLLA is an extremely interesting polymer. It has good mechanical properties. The biodegradation time of PLLA may vary and can be manipulated. The time and rate of degradation depend on the adopted manufacturing method. PLLA, due to its good mechanical and structural characteristics, is able to provide implant - tissue integrity while promoting new tissue formation [4]. Polycaprolactone (PCL) is a linear aliphatic biodegradable synthetic polymer that can undergo hydrolytic degradation due to its chemical properties. The monomers formed as a result of degradation are removed naturally. Unfortunately, the total degradation time of PCL is in the range of 2 to 4 years, depending on the molecular weight. Such a long degradation time can promote the formation of inflammation [26], which is why it is most often added to other polymers. In addition, PCL has good mechanical properties, being biocompatible and well tolerated by the body, elasticity and high elongation at break [3], [6], [10], [28].

In the present work, the mechanical properties of two materials PDO and PLLA/PCL were tested to verify their suitability as biodegradable materials used in the construction of urological stents. Based on the properties obtained, a stent design was proposed that meets the basic requirements arising from the function and anatomy of the male urethra. The analysis of the design was carried out using the finite element method - FEM.

2. Materials and Methods

2.1. Materials for experiments

The materials used for the experiments were: Resomer Filament X D1.75 Polydiaxonane from Evonik (Alabama, USA), Resomer® L210S, Poly(L-lactide) (viscosity 3.3–4.3 dL/g) and Polycaprolactone (PCL) (density 1,145g/mL, average Mn 80,000) were

purchased from Merck (Warsaw, Poland). Chloroform (Pol-Aura, Zawroty, Poland) was used as a solvent.

2.2. Preparation of samples for experiments

The research materials were prepared using two methods: 3D printing and solution casting.

The samples of polydioxanone (PDO) were prepared using additive technology - 3D printing (Flashforge Adventurer 3 printer, on the equipment of the Department of Biomedical Engineering, University of Zielona Gora). Printing parameters adopted: nozzle temperature 150 °C, table temperature 90 °C. Printing parameters were adopted according to the manufacturer's recommendations. However, other parameters were determined experimentally in preliminary tests. They were: fill density of 100%, printing speed of 30 mm/s and traverse speed of 30 mm/s. The printing accuracy was in range ± 0.2 mm. The use of such printing conditions made it possible to produce test specimens with a stable and homogeneous structure.

The polymer composite based on poly(L-lactide) PLLA and polycaprolactone (PCL) in this study was prepared in a ratio of 80:20 (the material name adopted in the study was 80PLLA/20PCL). The proper research presented in the paper was preceded by preliminary studies. Based on these and analysis of the results obtained, it was decided that the PLLA/PCL 80:20 polymer ratio used was the best and optimal for the dedicated application. The addition of PCL makes the composite more flexible. PCL can extend the degradation time of the stent, so it was assumed that the time would be sufficient for full regeneration and remodeling of the urethral tissues. The materials were produced by casting from a solvent, which was chloroform. The polymers, after being carefully weighed, were polymerized in chloroform and stirred until completely dissolved on an electromagnetic stirrer. After complete mixing and obtaining a homogeneous structure, the polymer solution was left to evaporate the solvent for a minimum of 12 hours. All procedures were carried out under a laboratory fume hood. After this time, the polymer was finally formed in aluminum mold.

The mechanical test specimens thus manufactured were prepared in accordance with PN-EN ISO 527-1:2020-0 Plastics. Determination of mechanical properties in static tension.

2.3. Mechanical tests

The mechanical tests for the static tensile test were performed on a Zwick Roell EPZ 005 testing machine (Zwick Roell, Ulm, Germany). The test speed was 5 mm/min. Test conditions were 23°C, air humidity 40%. Five repetitions were performed for each type of material tested. The result of the tests performed will be the mechanical characteristics of the

materials determined for the first linear range, including such parameters as longitudinal elastic modulus - Young's modulus (E), tensile strength (R_m) and yield strength (R_e).

2.4. Stent design

Taken into account the variable loading conditions occurring in the male urethral canal, the stent design proposed in this work is not standard, i.e. it is not tubular. The literature indicates that stents with a tubular design very often migrate to distal sections of the urethra, and are misaligned with the highly deformable tissues of the urethra, resulting in severely limited functionality. In order to eliminate these drawbacks, the study adopted the rhombus geometry shown in Figure 1 (A-B). The structure was developed in Ansys Academic R16.2 software in Static Structural in the Geometry module using the Symmetry function.

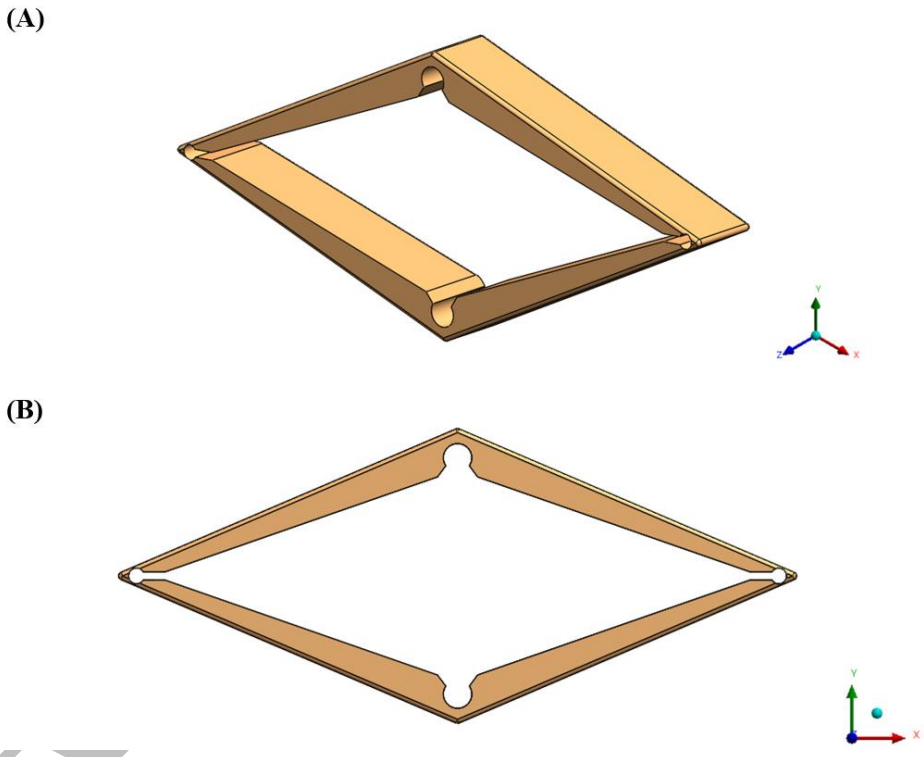

Figure 1. View of the proposed stent design: (A) side view, (B) front view.

The length of the stent is 35 mm, which corresponds to the average length of the prostatic urethra, while the width of the stent is 15 mm. In order to reduce friction between the urethral tissues and the stent, all its outer edges were smoothed. The developed geometry uses chambers (Figure 2) to allow the stent to bend inward when cooperating with the urethral tissues and interacting with forces generated by adjacent structures, which include the circular muscles.

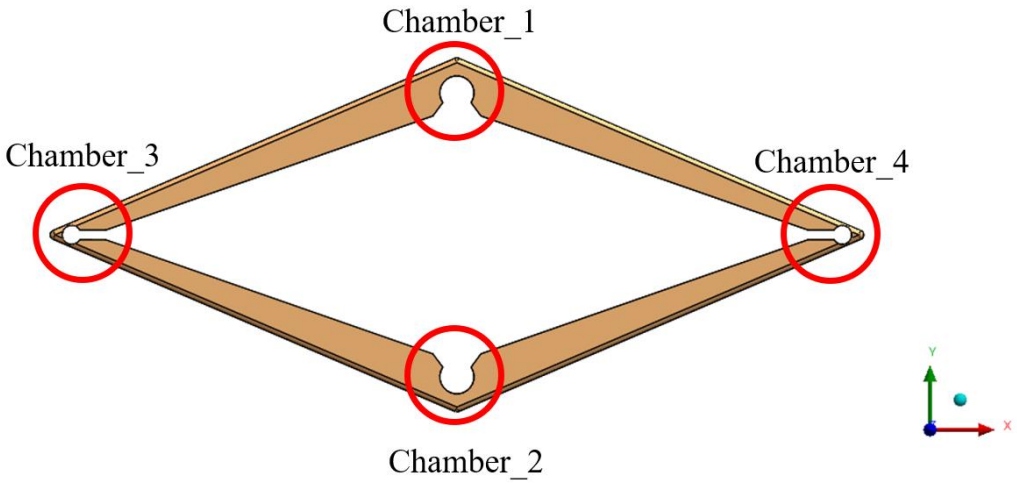

Figure 2. View of the stent with chambers that allow the stent to bend inward.

The diameter of the parallel Chamber_1 and Chamber_2 is 1 mm, while the chambers labeled Chamber_3 and Chamber_4 have a diameter of 0.5 mm. Chamber_1 and Chamber_2 are designed to allow the stent to bend in the direction of its longer diagonal. The Chamber_3 and Chamber_4 chambers support the aforementioned bending and, more importantly, are intended to reduce the stresses generated in the structure. In addition, the introduction of the chambers into the design will facilitate the stent implantation process. Their presence makes it possible to change the size of the stent perpendicular to the direction of urine flow (changing the width from 15 mm to 4 mm). This behaviour of the stent will allow its safe implantation in the pathologically altered section of the urethra. Once placed in the target location, spontaneous expansion of the stent will open the urethral lumen.

2.5. Numerical analysis - finite element method (FEM)

The numerical simulation for the structure began with the generation of a finite element mesh. A mesh composed of SOLID187 elements consisting of more than 43,000 nodes (43968 to be exact) and more than 27,000 tetrahedral elements (27215 to be exact) was used. The loads acting on the stent were defined as boundary conditions in the next step (Figure 3). The structure was restrained at two strategic locations on either side of the stent, parallel to the longer diagonal of the rhombus. The acting load (pressure) was applied to all the outer planes of the stent, which directly interact with the walls of the urethra.

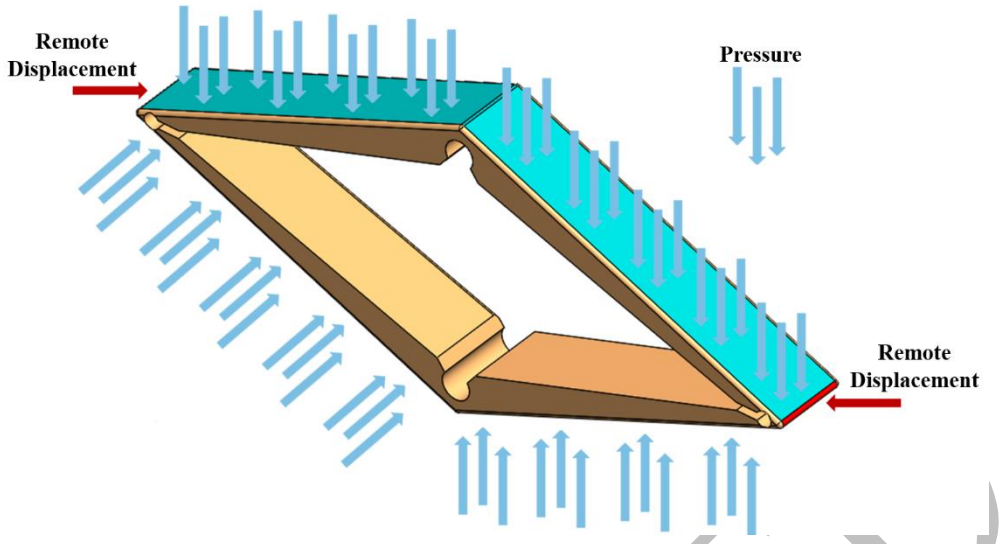

Figure 3. The defined boundary conditions for the proposed stent design.

The values of the applied load were determined and described in detail in earlier studies [23]. Briefly, the values of the prevailing pressure inside the urethra, both at rest (without urine flow) and during micturition (urine flow), were determined in urodynamic studies conducted *in vivo*. The parameters adopted for the calculations are shown in Table 1.

Table 1. Load values for which the behaviour of the stent in the urethral canal was considered.

	Load [kPa]
During the flow of urine	5
Without urine flow (resting)	1.5

The completion of all the steps mentioned and described, made it possible to begin the process of numerical analysis, through which the stresses and elastic and total strains were determined for the developed stent design.

3. Results

The this section presents the results obtained from experimental and simulation investigations.

3.1. Mechanical tests

For static tensile testing in accordance with ISO 527-1:2020-0 Plastics. Determination of mechanical properties in static tension, paddle specimens were produced. Polymer tensile test specimens prepared in the shape of a paddle were made on a scale of 1:4. For specimens

prepared by both PDO and PLLA/PCL materials, the measurement length was 12.5 mm, width 2.5 mm and thickness 1.0 mm, with tolerance less than +/-0,2 mm. These tests made it possible to determine the important parameters of strength characteristics. On the Figure 4, shows exemplary samples mounted in the holders of the testing machine, which was subjected to tension.

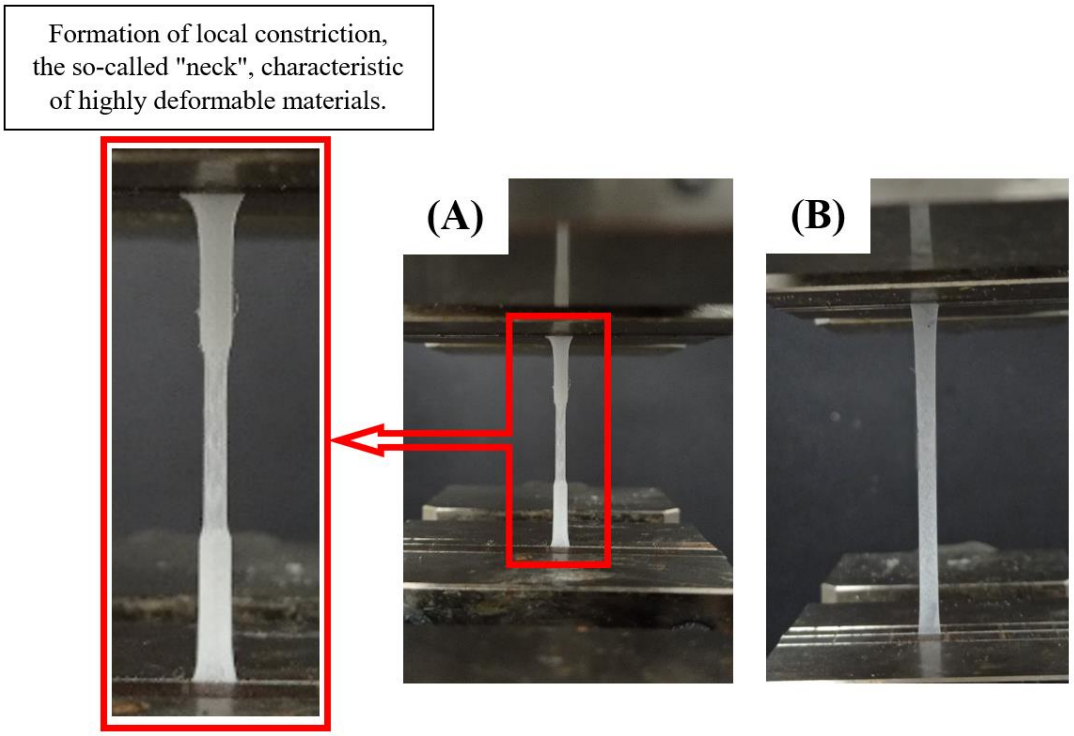

Figure 4. Examples of specimens mounted in the holders of the testing machine: (A). PDO, (B). 80PLLA/20PCL.

Based on the resulting stress-strain curves (Figure 5), the mechanical characteristics for the selected polymers was determined.

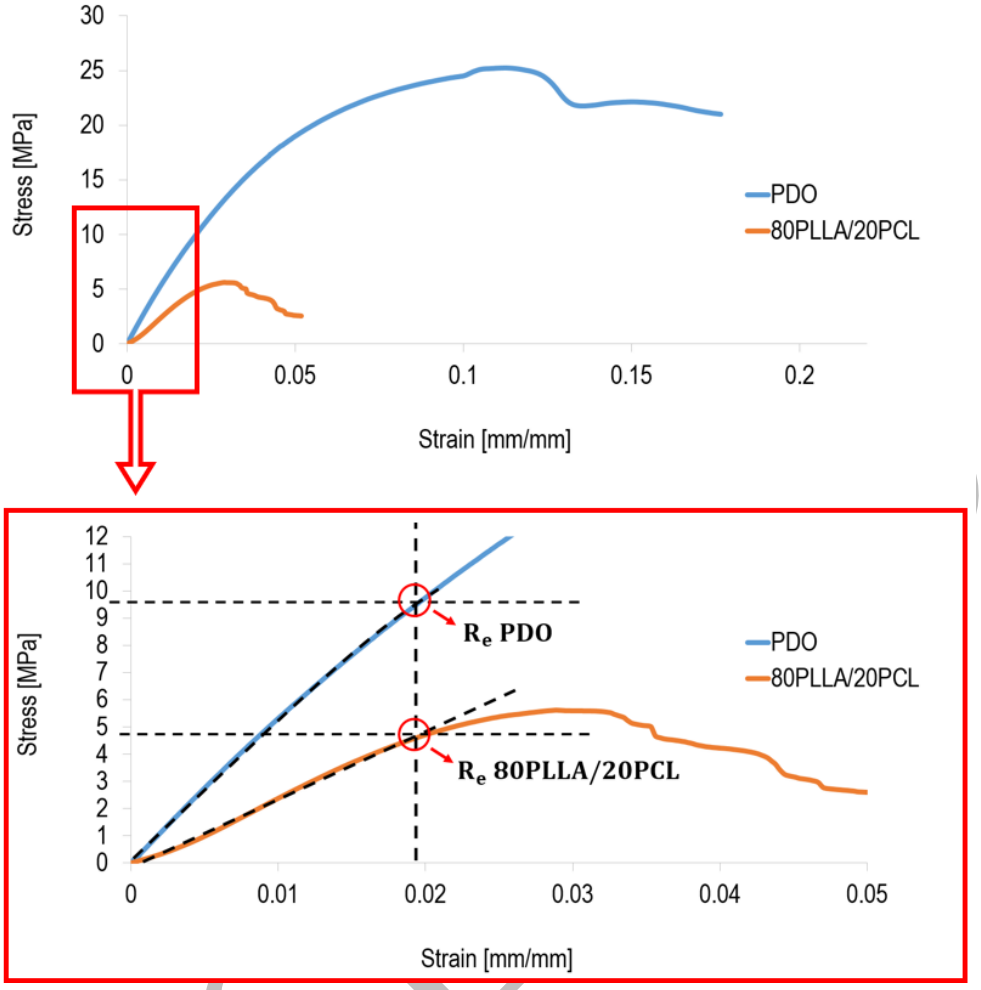

Figure 5. The stress-strain curves for the tested PDO and 80PLLA/20PCL materials.

In Table 2. they averaged results for individual relationship between strain and stress characterised the mechanical properties for the produced polymeric materials. These data are presented in comparison to literature data. For presented experimental result the Young's modulus (E) was determined for the range defined by the Hook law limited to the strain value equal 0.02 mm.

Table 2. The mechanical properties of the tested materials determined by the static tensile test.

	Method of manufacturing	**Young'a modulus (E) [MPa]**	**Tensile strength (R_m) [MPa]**	**Yield strength (R_e) [MPa]**	**Density [g/cm^3]**	**Ref.**
PDO	3D printing	451	43	9.79	1.318	[15]
PDO	Moulding from solution	207	3.68	-	-	[8]

80PLLA/20PCL	Moulding from solution	245	6	4.83	1.19	Own research
80PLLA/20PCL	Moulding from solution	506.9	24.9	12	-	[6]

For the PDO material, the value of Young's modulus (E) is 451 MPa, and for 80PLLA/20PCL it is 245 MPa. The determined tensile strength (R_m) is 43 MPa and 6 MPa, respectively. Due to the numerical analysis planned in the following steps, it was necessary to determine the yield strength (R_e) for the tested materials. In the case of polydioxanone, the yield strength is 9.79 MPa, and for the 80PLLA/20PCL composite it is equal to 4.83 MPa.

3.2. Numerical analysis - finite element method (FEM)

The obtained experimental results for static tensile test for PDO and 80PLLA/20PCL material, provided material data for which numerical analysis was performed. The values and distribution of stress, elastic strain and total strain were analysed for the proposed innovative stent design. The study analysed the behaviour of the stent under non-micturition (no urine flow) and urine flow conditions. Consideration of these conditions and their analysis is important for the performed experiment. The mapped conditions were very close to the real ones prevailing naturally in the urethra. The results of the FEA analysis are shown in Figures 6-7.

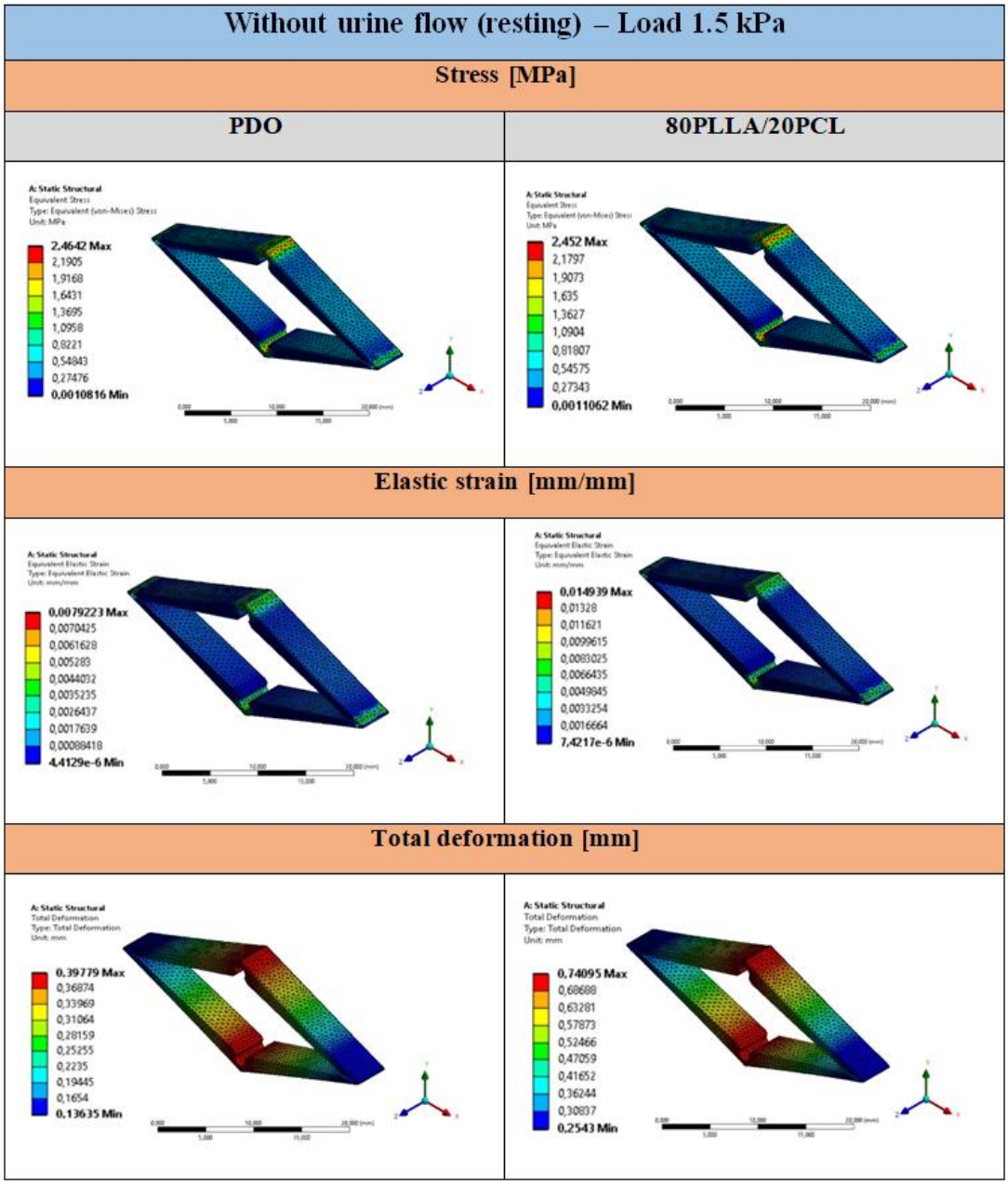

Figure 6. The numerical analysis of stress, elastic and total deformation for the stent design made of PDO or 80PLLA/20PCL material at rest (without urine flow).

In Table 3, the obtained results for the analysed parameters are shown, depending on the defined type of material. Constant conditions, inside the urethra without urine flow of 1.5 kPa don't cause significant changes in the stent structure, such as deflection or deformation.

Table 3. Summary of the results of the numerical analysis performed for the load at rest (without urine flow).

	Maximum Strain [MPa]	**Maximum Elastic Strain [mm/mm]**	**Total Deformation [mm]**	**Yield strength (R_e) [MPa]**

PDO	2.464	0.00792	0.398	10
80PLLA/20PCL	2.452	0.01493	0.741	4

The maximum stresses for both PDO and 80PLLA/20PCL material are similar to each other, at 2.464 MPa and 2.452 MPa, respectively. The elastic strain for the PDO material is 0.00792 mm/mm, while that for 80PLLA/20PCL is 0.01493 mm/mm. The maximum stresses, as well as elastic strains, are mainly localized at the chambers. On the rest of the stent surface, these values are minimal.

In the case of increased pressure inside the urethra caused by urine flow, greater changes in the behaviour of the stent design can be observed (Figure 7). The performance of simulations for this load is extremely important. The obtained analyses and their results will allow verification of the proposed stent design and material selection. The most important thing in these considerations is to check the obtained parameters against the determined mechanical characteristics of selected polymer materials in experimental tests.

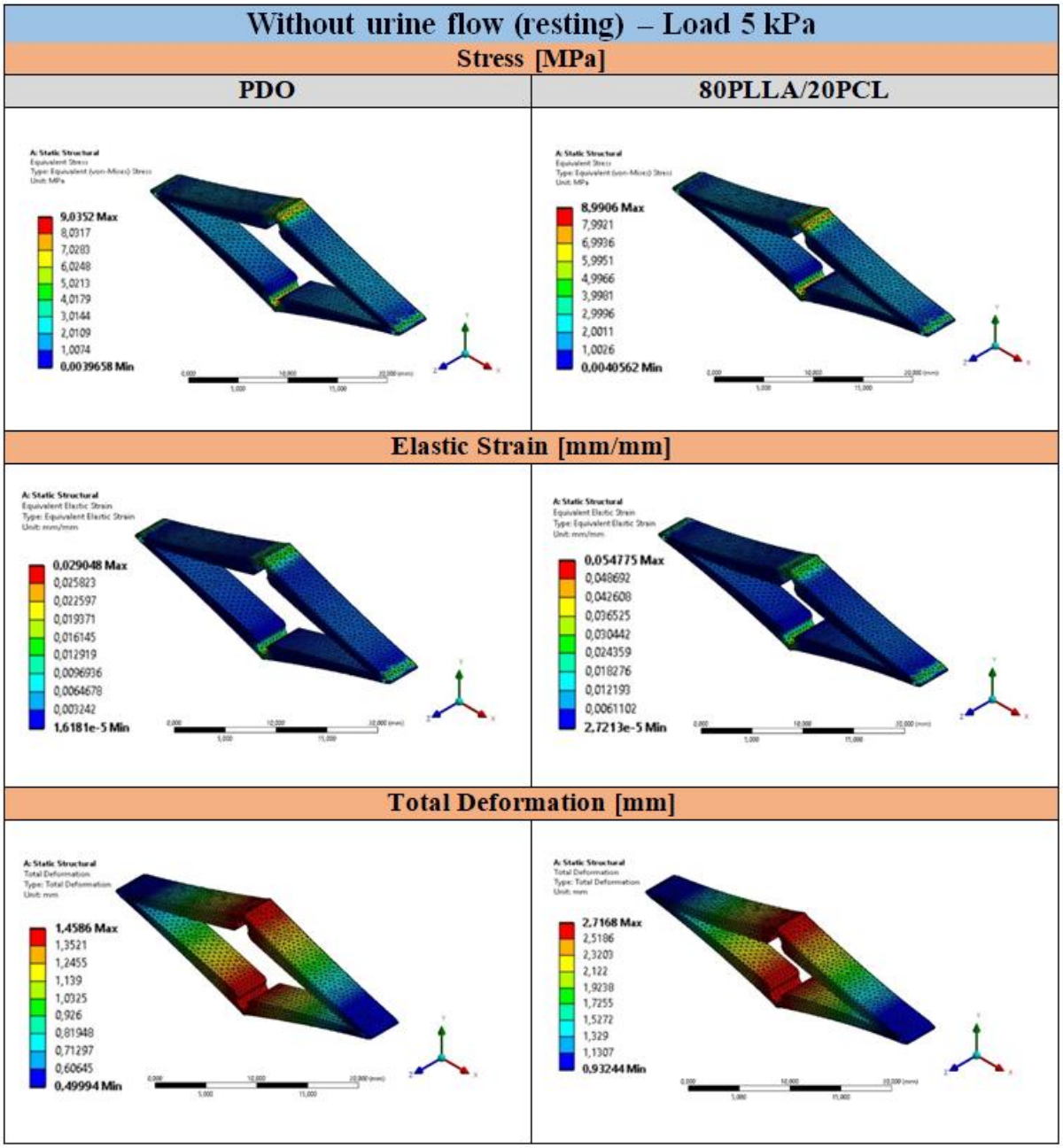

Figure 7. The numerical analysis of stress, elastic and total deformation for a stent design made of PDO or 80PLLA/20PCL material under conditions corresponding to urine flow.

The analysis showed that the force acting on the urethral tissues during micturition significantly affects the deformability of the stent. Taking into account two types of material considered for the stent, based on the results of this analysis, it can be concluded which of them will better cope with the varying loads prevailing inside the urethral canal. Table 4 shows the results obtained.

Table 4. Summary of the results of the numerical analysis performed for the load corresponding to urine flow.

	Maximum Strain [MPa]	Maximum Elastic Strain [mm/mm]	Total Deformation [mm]	Yield strength (R_e) [MPa]
PDO	9.035	0.029	1.459	10
80PLLA/20PCL	8.991	0.055	2.717	4

The experimentally determined yield strength for PDO was not exceeded.

The experimentally determined yield strength for the 80PLLA/20PCL composite was exceeded. The design assumptions were not met.

The PDO material shows a better chance of success in a dedicated application. First of all, for PDO, the yield strength (R_e) determined in experimental tests (10 MPa) was not exceeded in the simulation analysis (9.035 MPa). Unfortunately, for the proposed 80PLLA/20PCL polymer composite, the yield strength (R_e) determined in the experiment (4 MPa) was significantly exceeded in the FEA analysis (8.991 MPa). Unfortunately, this means that this material will not be able to fully fulfilled all constraints and requirements involving with the strength of this construction. In conclusion, a suitable material for the proposed stent design will be polydioxanone (PDO). Both experimental studies and numerical analysis confirmed the effectiveness of the developed solution in treating male urethral stenosis.

4. Discussion

The genitourinary system is one of the most important systems in the body and is responsible for monitoring and controlling electrolyte levels, as well as regulating blood volume, pressure and pH, and in the case of men, is also responsible for reproductive functions [30]. Abnormal functioning of the urethra in men, leads to disruption of the urethral mucosa, which causes extravasation of urine, and subsequently is the cause of chronic inflammation, which is the first stage of the resulting fibrosis, or narrowing of the urethral lumen [2]. The main cause of pathological changes in the urethra is injury to the epithelial and spongy parts. The specific physiological conditions in the urethra and its mechanical properties depend on the structure and thickness of the connective tissue and muscle membrane. The urethral tissues have an anisotropic structure and exhibit nonlinear deformation characteristics. This is due to the presence of collagen and elastin fibers and biological fluids that give it viscoelastic properties. The presence of elastin in tissues gives them elasticity but low strength, while the

presence of collagen gives them stiffness [14]. The biomechanical characteristics of the urethra, and in particular the stress-strain relationship, determine the relationship between the structure and functions of the urethra. The variable pressure in the cross-section of the urethra indicates that these tissues are highly deformable at low pressure (enables proper micturition), but at higher stress values their deformability is lower, which protects the tissues from excessive stretching [2], [19].

The urethral stenosis remains a significant reconstructive challenge especially given the unsatisfactory results of previous solutions and the sizable number of diagnosed recurrences of stenosis. The successful treatment of urethral stenosis is influenced by the length of the of the segment affected by the stenosis and the severity of the lesion. The sooner the stenosis can be diagnosed, the shorter the length of the altered section in the form of fibrosis. This increases the percentage of treatment success and reduces the time required for tissue recovery. Taking into account the severity of the stenosis, it is estimated that the time required for urethral tissue regeneration can range from 30 (diagnosis at the early stage of the condition) to as long as 60-90 days (significant progression of the stenosis).

The disadvantage of standard tubular urological stents is their migration into the distal urethral segments. Therefore, it is necessary to develop a design that can resist the pressure, stress and deformation of the urethra and simultaneously will allow the free flow of urine. One such concept is to move away from existing designs and replace them with a new one that allows the stent to anchor well in the tissues. When developing a new stent geometry, special attention should be paid to the forces stressing the urethral system. The current stresses and strains in the urethra acting on the stent design, affect the durability of the design, so it should have elastic deformation capabilities. In addition, the stent should be manufactured from a material adapted to function under the specific conditions of the urethra.

The author of this article finds it difficult to discuss the obtained results with the literature. Previously used therapies fail to create adequate conditions for the formation of healthy tissue and are ineffective in restoring proper urethral functions. Additionally, there is little information in the literature about the actual conditions in the urethra. The author's previous work with the team [23] allowed for the establishment of criteria for urological stents for the treatment of stenosis.

The based on the experiments performed for PDO and PLLA/PCL materials, it was found that PDO has better mechanical properties for the dedicated application. The main advantage of PDO over other materials is that it is highly deformable. The based on the requirements formulated in this article, it was shown that the proposed stent design will meet

the assumptions of more effective treatment of stenosis. Numerical tests examined the behaviour of the stent in two cases loads: at rest, i.e. without micturition, for which the constant load is 1.5 kPa and for the case during micturition with a load of 5 kPa. The numerical studies are important. They are increasingly used, for example, in the evaluation of stents applicable to the treatment of carotid artery pathology [21].

In summary, the appropriate selection of material for the stent was possible after determining the mechanical properties of the selected polymeric materials. The detailed analysis was carried out, showing which parameters describing the materials have a direct impact on the urethral tissues, and thus on the treatment process.

5. Conclusions

Based on the presented research, the following final conclusions were provided:

- Polydioxanone (PDO) as a biomedical material shows good and promising properties for urology applications.
- The developed custom-shaped stent design is innovative and meets the goals of treating male urethral stenosis more effectively.
- For the proposed stent geometry made of PDO, the numerical simulation proves that PDO could be a potentially suitable stent material.
- The numerical studies verified the behaviour of the stent for two loading cases: at rest, i.e. without micturition, for which the constant load is 0.0015 MPa, and for the case during micturition with a load of 0.005 MPa.
- The deformation results indicate that the proposed stent geometry and material selection are correct. They will allow to keep normal tissue kinetics, which will counteract secondary fibrosis.
- The numerical simulation confirmed the proper cooperation and interaction between the stent and the adjacent urethral wall. This is important because a suitable fit can successfully prevent the stent migrating along the distal urethral segments.
- The realization of future research should include mechanical analysis of the stent with the target geometry and selected material.

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