# *Characterization of biodegradable PCL cog threads for pelvic organ prolapse treatment*

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***Abstract*****—** *Pelvic organ prolapse (POP) is a disease that progressively affects women, creating a growing demand for the development of new techniques and methods to treat this type of disorders. The correction of POP is complex, where the mainstay of treatment for these problems continues to be surgical correction, which is presented, in most cases, as a highly invasive procedure in the pelvic area with several associated risks and a relatively high failure rate. With this, our multidisciplinary team studies the potential of providing to healthcare professionals a novel and beneficial solution to correct pelvic organ prolapse (POP). Our proposal is based on the application and proof of concept of novel minimally invasive technique, using biodegradable PCL (polycaprolactone) cog threads for vaginal tissue reinforcement and prolapse correction. At the moment, the provisional results obtained from the in vitro controlled degradation and mechanical tests carried out on the cog threads demonstrate that they have the desired properties for the formulation of a new technique for prolapse correction. These results are encouraging and suggest the need for additional testing to better understand mechanical and biological properties of the PCL cog threads.*

***Keywords—Pelvic organ prolapse, Cog Thread, Surgical Intervention, Biodegradable PCL.***

## I. Introduction

POP is a pelvic condition that occurs when the muscles, tissues and/or ligaments, with support function in the woman's pelvic area, weaken, losing their normal functions, causing displacement of the uterus and vaginal walls [1]. This common condition influenced by several factors and causes, negatively impacting the woman's quality of life. POP prevalence differs between ethnic groups and the probability of its appearance increases may be related to several factors, since daily habits to diseases [2]. Multiple vaginal deliveries, during childbirth, gone through menopause and after a hysterectomy are the most often factors related to this kind of disorders, and, according to healthcare professionals, the most common repaired areas for POP, in the pelvic zone, are the anterior and posterior compartments.

In the female pelvic area, there is a close anatomical connection between the vaginal wall, bladder and rectum that often contributes to the emergence of these type of dysfunctions in adjacent organs [2]. In fact, the vaginal canal, located in the region between the bladder and the rectum, is the anatomical site most susceptible to changes in structure. As a rule, the anterior and posterior walls of the vagina are affected by the descent of the intrapelvic organs caused by the prolapse [3].

Accordingly on data from High Income Countries (HIC), treatment of genital prolapses, including vaginal prolapse, is mainly surgical, and presents itself as one of the most common gynecological surgical procedures performed with a lifetime risk of 11 to 19% [4]. The estimated prevalence of POP, in the female population, is between 3 to 8 % [4–6]. In countries like Germany, France and England, in 2005, the number of admissions for POP surgeries was close to 102,000 with a substantial cost near 308 million euros, and in the UK is estimated that 20 % of gynecological surgeries, on the waiting list, are for prolapse treatments [7,8]. In United States of America, the values reveal that approximately 300,000 women, per year, undergo surgical procedures to treat these same problems and in Western Australia studies reveal that there is a relatively high probability of a women, during her lifetime, will undergo surgery to treat POP [5,9].

Although there are several solutions this type of problem, sometimes the prolapse is complex, due to the disorder itself, and the patient need different types of treatment and intervention. As a rule, in milder cases, when the severity and symptoms of the prolapse are barely insignificant, non-surgical procedures can be an effective solution to treat these disorders. Lifestyle changes like avoiding heavy lifting, losing weight or exercise the pelvic muscles, like Kegel exercises, may be some of the solutions that can be adopted. In moderate cases, the prolapse can be correct with the use of pessaries. These mechanical devices are designed to support the vagina walls and hold the prolapsed organs back in their anatomically correct position. Pessaries are used by many women who wish to avoid surgical procedures or, in particularly, when the surgery may not be the best solution to adopt due to underlying health conditions of the patient [10]. These treatments mentioned, lifestyle changes, pelvic floor exercises and pessaries, are minimally invasive and are the best options to adopt when the pelvic organ prolapse can be effectively treated. However, in many cases, the POP is detected at a more advanced stage, when the patient starts experiencing the first symptoms, and in such situations surgical correction becomes the most effective solution.

Some of the well-known surgical treatments for POP repair are native tissue repair, vaginal mesh correction, laparoscopic surgery and hysterectomy. These procedures currently have associated risks, including pain, mesh erosion and infection, and their long-term benefits have not been thoroughly evaluated [11,12]. At the same time, procedures using surgical meshes in prolapse correction, highly debated topic over the last years, has significantly decreased due to safety concerns and potential complications associated with its use. Surgical meshes are a medical device implanted in the pelvic area, to repair POP and other types of pelvic dysfunctions, that augment soft tissue or bone where weakness exists. Despite the positive results in POP treatments, FDA (Food and Drug Administration) ordered mesh producers to stop selling this type of device for anterior compartment prolapse (cystocele) treatments, in United States, believing that the benefits do not outweigh the risks of the surgical interventions involved [13,14]. Considering the risks associated to surgical interventions, and the reduction of solutions available for POP treatment, there is a growing demand for the development of novel minimally invasive techniques and materials that are both widely accepted and effective.

With this, our team intends to develop a less invasive technique for POP treatment, using biocompatible materials. As an alternative technique to surgical intervention, injectable biodegradable cog threads could be used for vaginal wall reinforcement and defect correction. Threads will be inserted into the vaginal wall under specific angles, creating in this way mesh-like structure, that matches the physiological compliance of the vaginal wall. The advantage of this technique is that threads could be applied for women with a wider age range - compared to conventional meshes. Also, threads could be applied after vaginal delivery (upon doctor recommendation) with a possibility to have vaginal delivery in the future – something not possible with conventional meshes.

With the goal of making the presented solution into a practical implementation, we are conducting several mechanical and degradation tests, on commercially available PCL cog threads, with the aim to determine their potential use in vaginal wall reinforcement. This paper presents the results of the first tests conducted before 60 days of degradation in different mediums.

## II. MATERIAL AND METHODS

### A. *Materials and characterization techniques*

Commercially available cannula cog threads (Yastrid, Shanghai, China), commonly used for face lifting, made of biodegradable polycaprolactone (PCL) will be characterized and mechanically analyzed. Controlled *in vitro* degradation tests will be carried out in accordance with the ISO 10993 standard 10993 "Biological evaluation of medical devices". To study the processes of dissolution and resorption *in vitro*, Phosphate Buffer Solution (PBS) (Sigma-Aldrich, United States of America) will be used as a model of biological fluid (with pH = 7.4). The biodegradation can occur under a wide range of pH, including acid mediums associated with inflammation. Therefore, Potassium Hydrogen Phthalate (KHP) (Sigma-Aldrich, United States of America) will be used to obtain the acid medium (with pH=4.3). Specimens will be kept at 37°C during 60 and 180 days (as in an animal experimentation). The degradation of the thread will be evaluated via diameter change, mass loss, by differential scanning calorimetry (DSC), via Fourier Transform Infrared Spectroscopy (FTIR) and via Scanning Electron Microscopy (SEM), following tensile and cyclic tests, to analyze the effect of simulated degradation on the mechanical performance of the thread.

The chemical composition of the biodegradable cog threads was analyzed using a Cary 630 FTIR Spectrometer (Agilent Technologies, USA) equipped with a diamond attenuated total reflectance (ATR) accessory. Spectra were acquired over 140 scans with wavelengths ranging from 600 to 4000 $cm^{-1}$, with a resolution of 4 $cm^{-1}$. A background scan was performed before each sample measurement.

The differential scanning calorimetry (DSC) were performed using a thermal analyzer STA 449 F3 Jupiter® (Netzsch, Germany). The samples were hermetically sealed in aluminum crucibles with 3.0 ± 0.5 mg. The measurements were performed in the temperature range from 27 °C to 100 °C at a heating rate of 10 °C $min^{-1}$, with a nitrogen flow rate of 20 mL/min.

SEM analyses were carried out in a JEOL JSM 6301F/ Oxford INCA Energy 350/Gatan Alto 2500 microscope (Tokyo, Japan) at CEMUP (University of Porto, Portugal). Samples were coated with an Au/Pd thin film, by sputtering, using the SPI Module Sputter Coater equipment. This technique was used to analyze the morphology evolution due to degradation.

The protocol is currently on going, and only the results for the degradation tests after 60 days will be presented, as well as the results of the mechanical tests on these cog threads.

### B. *Mechanical and cyclic tests*

Uniaxial tensile tests were performed on biodegradable cog threads after degradation procedure (60 days in PBS and KHP medium) and on cog threads from the control group (without degradation). Cog threads were tested in a tensile testing machine (MultiTest™ 2.5 – dv), with a 500 N load cell, programmed for static load tests at an elongation rate of 10 mm/min, as show in Figure 1. For each test, it was obtained a force vs. displacement curve, from which is possible to evaluate the strength and behavior of the cog thread under tension, after 60 days in *in vitro* degradation. Cyclic tests (fatigue tests) were carried out in the same testing machine with an elongation rate of 10 mm/min with a total of 100 cycles per sample.

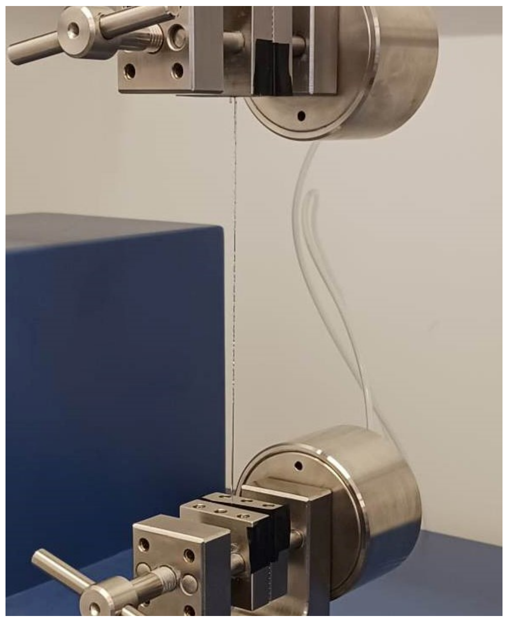

Fig. 1. Uniaxial tensile test performed on cog thread.

## III. Results

### A. *Degradation tests: Fourier Transform Infrared Spectroscopy (FTIR) characterization*

FTIR spectroscopy analysis revealed that cog threads in PBS and KHP medium suffered slight degradations when compared to the values registered in the control cog thread, as show in fig.2. It can be concluded that there is no significant difference in the chemical composition and in molecular structure between the tested cog threads. As a result, the cog threads exhibited a desirable slow degradation rate in the media designed to simulate biological fluid and inflammation. This indicates that the threads are capable of maintaining their structural integrity over an extended period of time, which is a positive outcome.

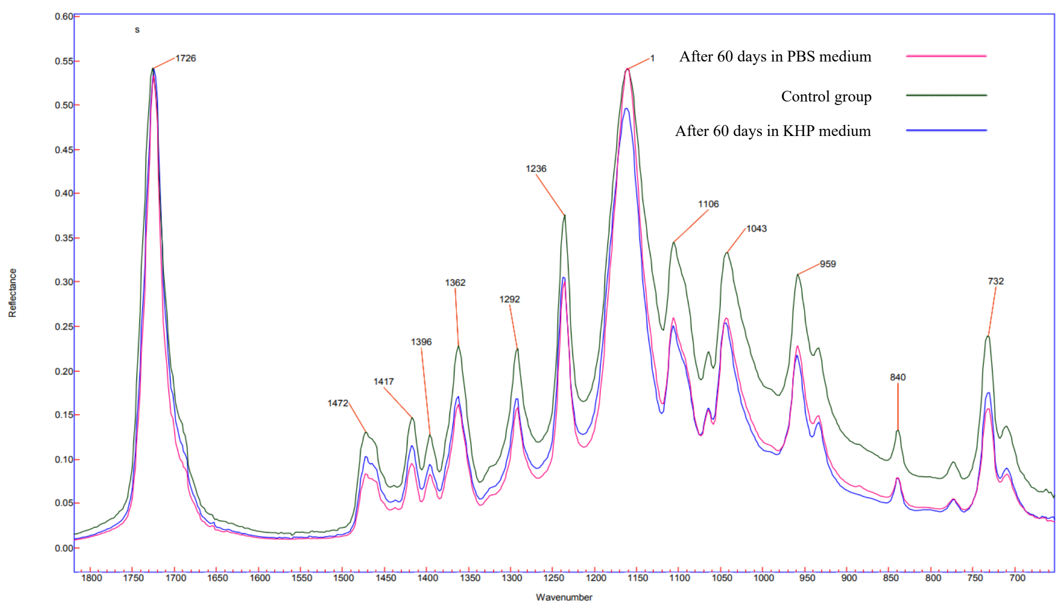


Fig. 2. FTIR spectra of cog threads under 60 days of degradation, *in vitro*, and cog threads not subject to any kind of degradation (control group).

### B. *Degradation tests: Differential Scanning Calorimetry (DSC) characterization*

The DSC thermographs demonstrate that both control cog threads and cog threads in PBS and KHP medium, for 60 days, have similar melting points, as shown in fig.3. The DSC tests yielded results that are very close to the melting point value of PCL, which is around 60.2 ºC, as reported in the literature [15].

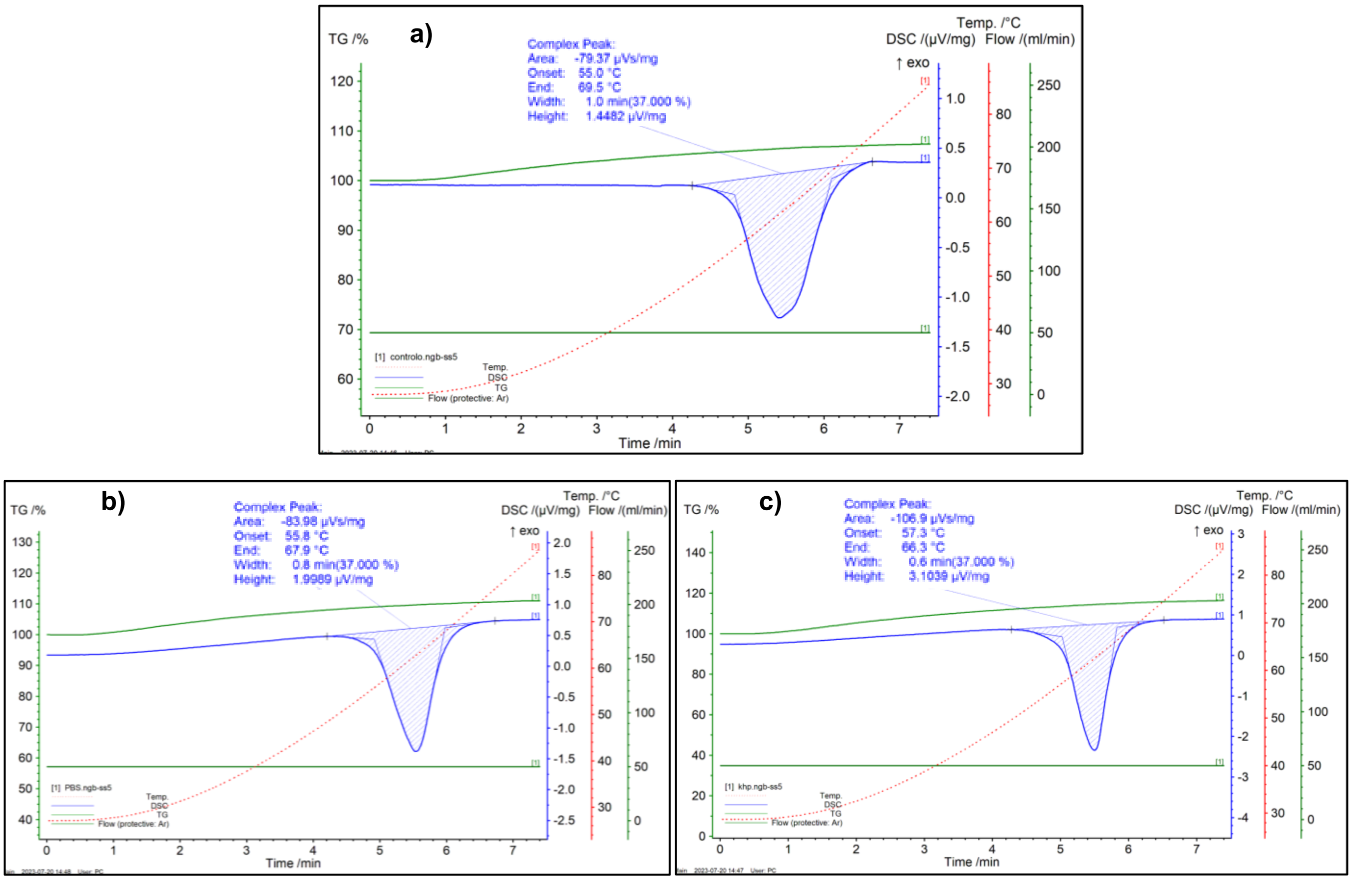


Fig. 3. DSC thermograph of PCL cog threads; **a)** Control group; **b)** Cog threads in PBS medium for 60 days and **c)** Cog threads in KHP medium for 60 days.

### C. *Degradation tests: Scanning Electron Microscopy (SEM) characterization*

The SEM was used to analyse the cog thread surface and diameter values between the control group (without degradation) and cog threads degraded in PBS and KHP medium. As shown in fig.4., SEM evaluations revealed that the surface morphology did not show any differences after the 60 days of degradation, remaining with his original shape. The identical analyses confirm that there were no alterations in the diameter of the tested cog threads. However, it's important to consider that the diameter of the cog thread is not consistent throughout the entire filament.

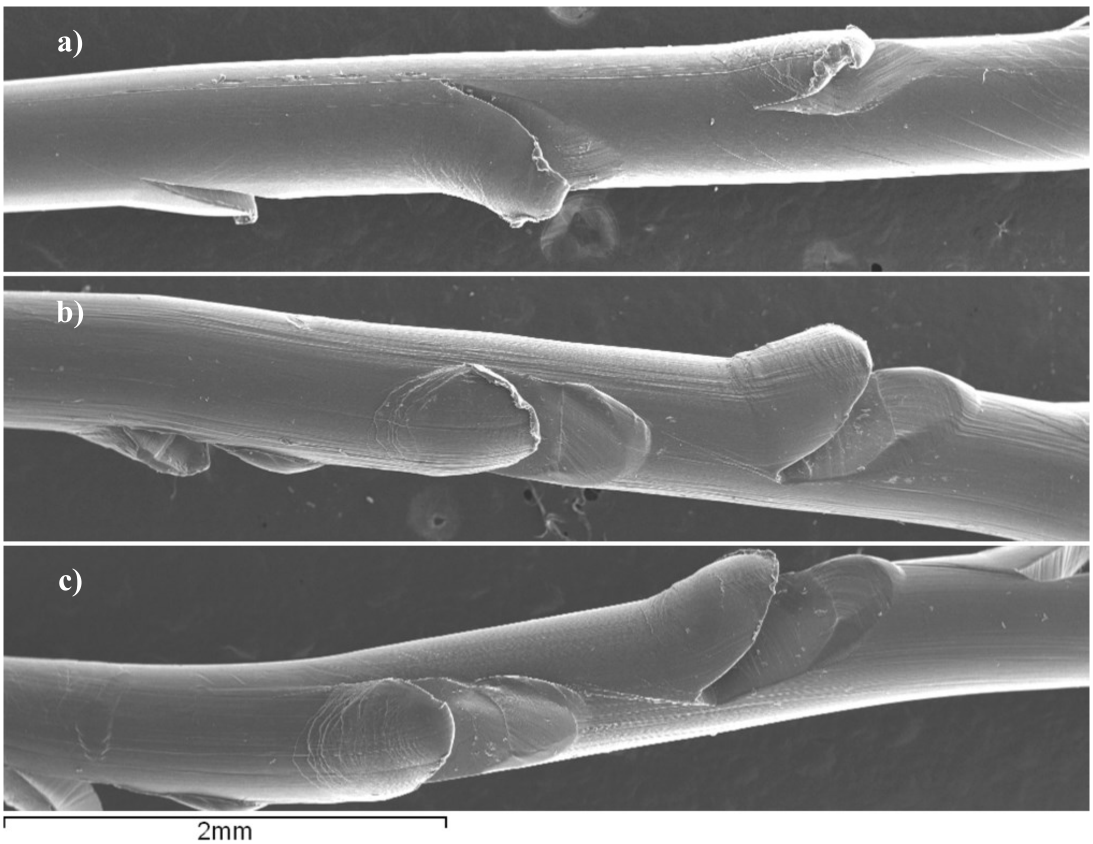


Fig. 4. SEM micrographs of the outer surface of PCL cog threads; a) control group; b) cog threads in PBS medium for 60 days; c) cog threads in KHP medium for 60 days.

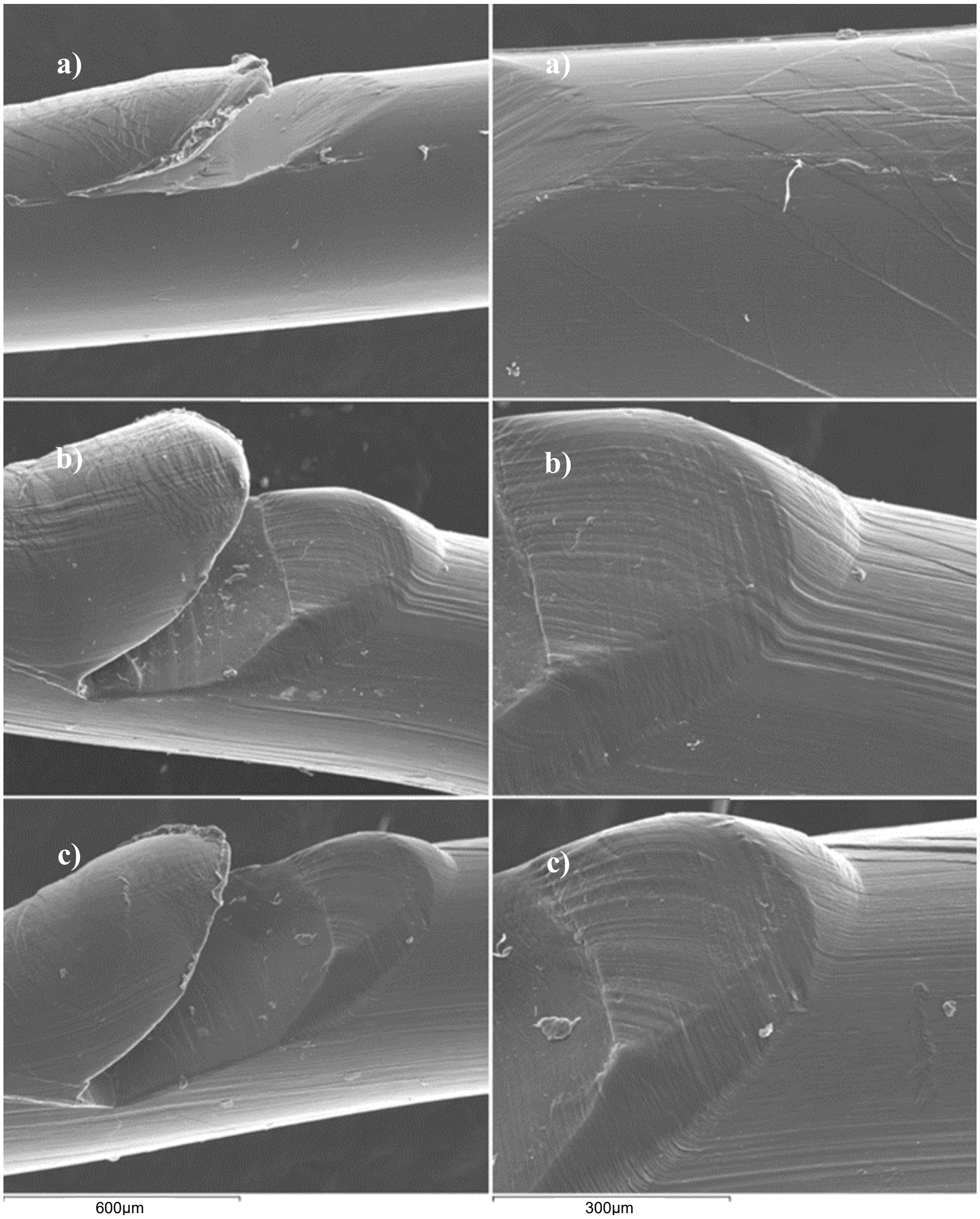


Fig. 5. SEM micrographs of the outer surface of PCL cog threads; a) control group; b) cog threads in PBS medium for 60 days; c) cog threads in KHP medium for 60 days.

*D. Mechanical tests: tensile tests*

The mechanical properties were evaluated at the end of the *in vitro* degradation. The results were compared to mechanical tests conducted, under same conditions, on control cog threads that did not undergo any degradation. Fig. 6 shows the results obtained in the mechanical tests on 4 cog threads (control), Fig. 7 the results of cog threads degraded 60 days in PBS medium and Fig. 8 in KHP medium.

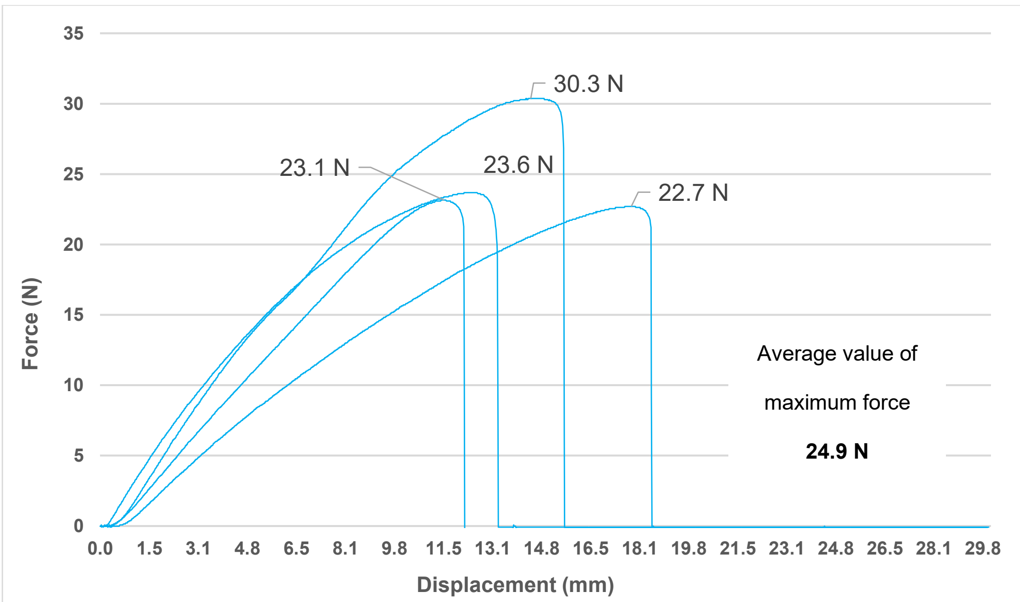


Fig. 6. Mechanical behaviour of PCL cog threads under uniaxial tensile tests.

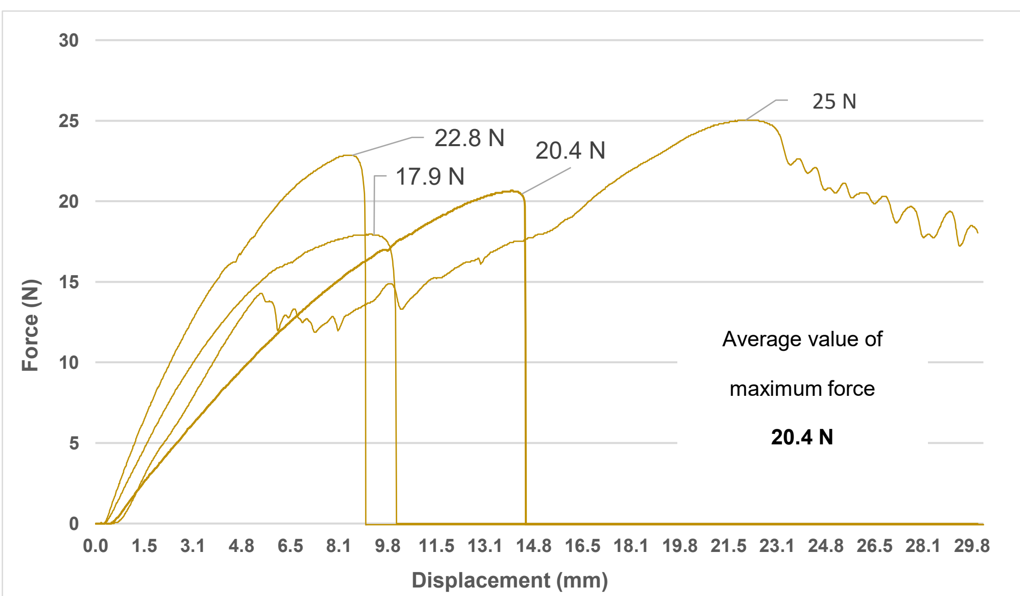


Fig. 7. Mechanical behaviour of PCL cog threads, after 60 days of degradation in PBS medium, under tensile tests.

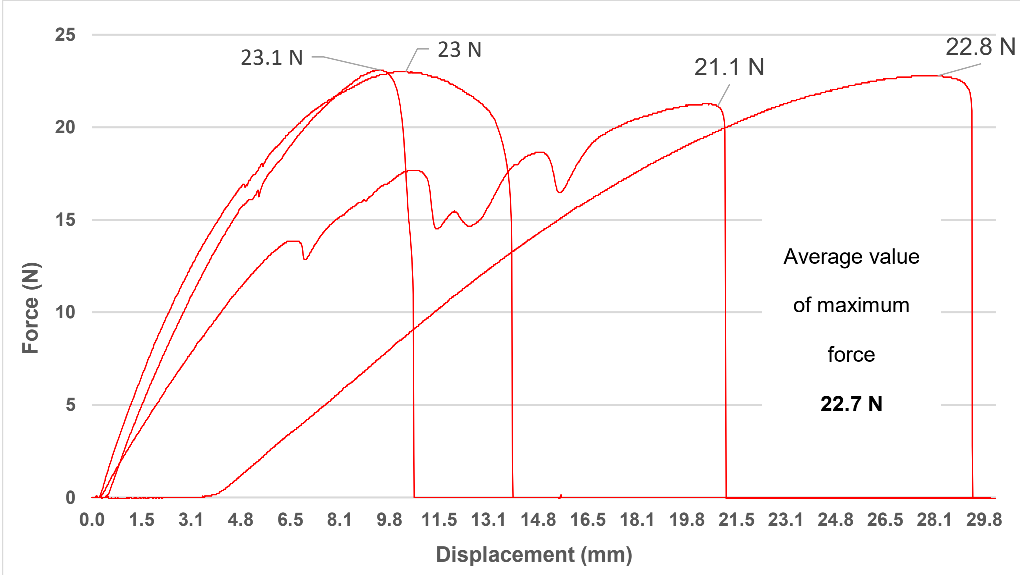


Fig. 8. Mechanical behaviour of PCL cog threads, after 60 days of degradation in KHP medium,under tensile tests.

## *E. Mechanical tests: cyclic tests*

In orders to evaluate the response to repeated loads, similar to the expected loads *in vivo*, cyclic tests were carried out on the cog threads from control group and on the cog threads from the two different mediums tested. Fig. 9 shows the results obtained in the cyclic tests on 3 cog threads (control), Fig. 10 the results of cog threads degraded for 60 days in PBS medium and Fig. 11 in KHP medium. The maximum and minimum values stipulated for the cyclic tests, on cog threads, were calculated taking into account the average values of maximum force obtained in the tension tests of the previous task. For these cyclic tests, the value of the maximum load stipulated is 80% of the rupture force obtained in the tension tests. In this case, the cog threads in the control group, which, on average, break at 23 N of force, the maximum force value for the cyclic test will be 18 N (23 N x 0.80 = 18 N). For cog threads in PBS and KHP medium it will be 17 N and 19 N, respectively. Cyclic tests carried out on cog threads demonstrate that they can withstand the loads to which they are subjected.

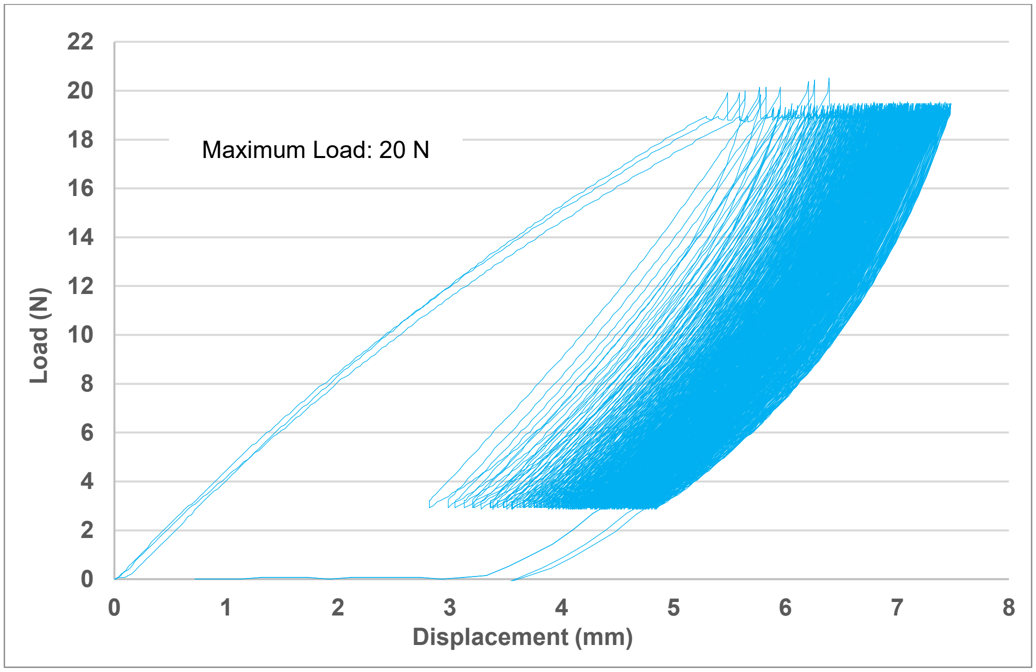


Fig. 9. Mechanical behaviour of PCL cog threads under cyclic tests.

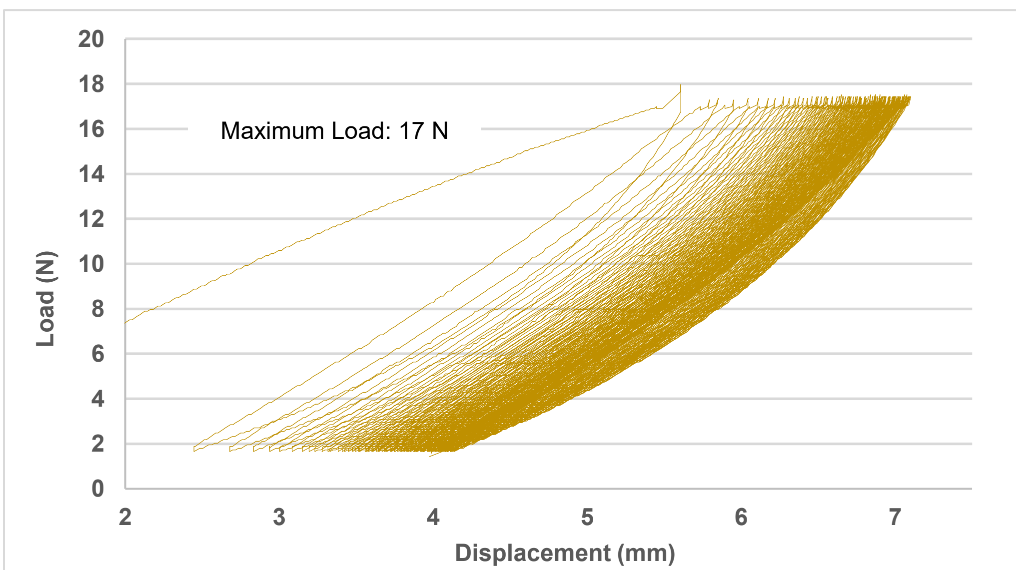


Fig. 10. Mechanical behaviour of PCL cog threads, after 60 days of degradation in PBS medium, under cyclic tests.

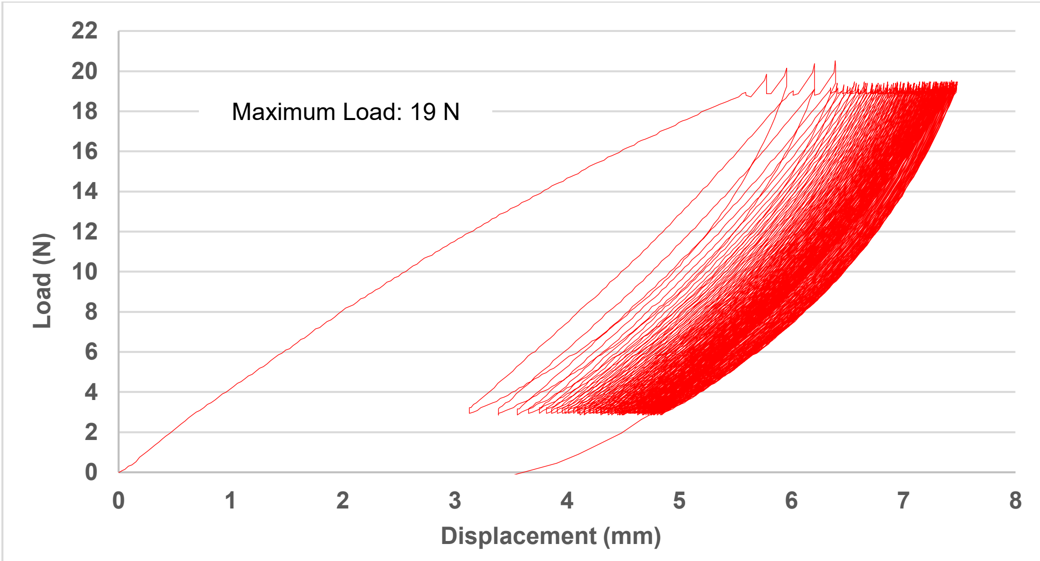


Fig. 11. Mechanical behaviour of PCL cog threads, after 60 days of degradation in KHP medium, under cyclic tests.

# IV. DISCUSSION AND CONCLUSION

Therefore, taking into account the results obtained in the different tests, the cog threads in PBS and KHP medium suffer a slight degradation, which is mechanically verified in the tension tests carried out. For cog threads in PBS medium, there was a maximum average tension of 20.4 N and in KHP medium 22.7 N, numbers slightly lower than those obtained in cog threads from the control group. The remaining tests carried out did not demonstrate major changes in the structure of the material.

In this way, PCL cog threads could be adopted, in the future, for formulating therapies for the correction and treatment of prolapses in women. Still, new tests will be carried out with longer degradation periods.

# ACKNOWLEDGMENTS

The authors gratefully acknowledge funding from project PRECOGFIL-PTDC/EMD-EMD/2229/2020, financed through FCT. This work was supported by FCT, through INEGI, under LAETA, project UIDB/50022/2020 and UIDP/50022/2020. We are also grateful to the FEUP students involved in the project.

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