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Original article

Pentraxin 3, a new biomarker for the diagnosis and management of PJI in primary and revision hip arthroplasty

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Abstract. *Background/Aim of the study:* The periprosthetic or superficial site infections are one of the most catastrophic and difficult to manage complications following total hip arthroplasty. Recently, in addition to well know systemic markers of inflammation, the blood and synovial fluid biomarkers are focused to have a possible role in the infection diagnosis. The long Pentraxin 3 (PTX3) seems to be a sensitive biomarker of acute phase inflammation. The objectives of this prospective and multicentre study were (1) to establish the plasma trend effectiveness of PTX3 in patients undergoing primary hip replacement, and (2) to evaluate the diagnostic accuracy of blood and synovial PTX3 in patients undergoing prosthetic revision of infected hip arthroplasty. *Methods:* Human PTX3 was measured by ELISA in two cohorts of patients, 10 patients undergoing primary hip replacement for osteoarthritis and 9 patients with infected hip arthroplasty. *Results:* The Authors were able to demonstrate that PTX3 is a viable biomarker for acute phase inflammation. *Conclusions:* An increase in PTX3 protein concentration in the synovial fluid of patients undergoing implant revision has a strong diagnostic capacity for periprosthetic joint infection, showing 97% specificity. (www.actabiomedica.it)

Key words: Pentraxin, Hip arthroplasty, THA, Revision hip arthroplasty, PJI, Infection, peri-prosthetic joint infections, Biomarker, Synovial fluid, Prevention

Introduction

Total hip arthroplasty (THA) is one of the most cost-effective and successful surgery performed in orthopaedics (1). One of the most frequent cause of failure is periprosthetic joint infection (PJI), that is a catastrophic complication with an incidence, following primary THA, of 1% to 2% approximately. This is a so important concern that the orthopaedic research focused on PJI increased dramatically in the last years, from 30 articles in 2008 to 364 in 2017 (2). Preoperative identification of risk factors is crucial in prevention of PJI (3), but at the same time early postoperative identification of superficial site infections (SSI) or PJI is also decisive for the management of this complication. The pathogenic mechanism of an early infection (<3 months) is an intraoperative contamination and its presentation consists in pain, oedema and swelling, persistent drainage, warmth, and erythema (tumor, calor, rubor, dolor). For a good management, it is necessary to early diagnose the clinical presentation of a PJI by evidence-based criteria, cultures and

biomarkers (4). In order to make the diagnosis and to prevent the infections, the Musculoskeletal Infection Society (MSIS) had developed a surgical site infection definition that is based on the integration of clinical and laboratory data (5). In addition to systemic markers of inflammation (white blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6), recently research also focused on the possible role of biomarkers contained in the synovial fluid, showing that some cytokines and proteins with antimicrobial function have high concentrations in the synovial joint fluid in case of periprosthetic infection (6). Growing scientific evidence supports the role of long Pentraxin 3 (PTX3) not only as a sensitive biomarker of acute phase inflammation (7), but also of respiratory and urinary system infections (8,9). Furthermore, high levels of PTX3 are correlated with a worse prognosis in septic patients (10). PTX3 is a multifunctional protein ranging from innate immunity, inflammatory process, matrix deposition and female fertility (11). Unlike CRP, PTX3 is expressed at very low levels by the liver and, unlike other long pentraxins, it is not constitutionally expressed by the central nervous system except as a result of inflammatory stimuli. The different tissue expression sites justify its various and particularly heterogeneous roles.

The objectives of this study are two: to establish plasma trend of the humoral biomarker PTX3 and to establish the effectiveness in case of possible early SSI and PJI during the first postoperative 30 days in patients undergoing primary hip arthroplasty; to evaluate the diagnostic accuracy of blood and synovial PTX3 in patients undergoing prosthetic revision of infected THA.

Materials and methods

The present prospective, double-center and consecutive study has been approved by the Internal Review Board of our Institutions and all patients agreed to participate.

PTX3 and primary THA

For the first objective of this study, we enrolled 10 patients undergoing primary THA for osteoarthritis (OA) (3 males and 7 females). The mean age was 65.8 years (range 40-85) with a mean BMI of 27.3 (range 18-35). Inclusion criteria: 40 < age < 85; no surgical procedures in the 90 days prior to admission; 18 < body mass index < 35. Exclusion criteria: chronic inflammatory diseases, previous surgical infections, ongoing infections, intraoperative complications favoring inflammation, cemented prostheses, bilateral prostheses, prosthetic revision operations, invasive surgical procedures in the 90 days prior to inclusion in the study, liver disease, coagulation disorders, previous deep vein thrombosis or embolisms. All patients were monitored with the following parameters: ESR (normal < 3 cm/h), CRP (normal < 5 ng/dl), D-Dimer (normal < 0.8 μg/l) and PTX3, by means of serial blood samples, fixed immediately preoperative (T0) and then at 4-6 hours after surgery (T1) and 3, 5, 15, 30 days (T2, T3, T4, T5) after surgery. Human PTX3 was measured by ELISA (Human Pentraxin 3, HK347, HycultBiotech, Uden - The Netherlands) on EDTA plasma samples according to the manufacturer's instructions. Briefly, freshly blood was collected in EDTA tubes and centrifuged 1500xg, 4° for 15 minutes; the plasma was transferred to a fresh tube, avoiding any contamination with the buffy coat, centrifuged 1500xg, 4° for 15 minutes and stored -80°. In order to perform the analysis, the samples were thawed, diluted 1:4 in supplied dilution buffer and analysed in duplicated as per instructions, along with the supplied standards. The OD was read at 450 nm and PTX3 concentration calculated by the standard curve. From time to time the state of the surgical wound was assessed, noting the main characteristics of the skin, as well as the patient's body temperature. To study the trend of the inflammation indices, and to study the effectiveness of PTX3, these quantitative variables were compared.

PTX3 and revision of infected THA

To achieve the second objective of the study, 9 patients with infected THA were enrolled (4 males and 5 females, mean age 71 years, range 49-90). Among these, 7 patients were affected by chronic PJI, and 2 by acute PJI. In patients undergoing septic revisions, the bacteria isolated with microbiological analysis

included: Staphylococcus Aureus (n=2), Staphylococcus Capitis (n=2), Staphylococcus Lugdunensis (n=1), Staphylococcus Epidermidis (n=1), Enterococcus Faecalis (n=1), Streptococcus group C (n=1). One patient had a culture negative PJI. The diagnosis of PJI was made according to MSIS criteria [5]. Patients with diagnosis of PJI were treated with "debridement, antibiotics and implant retention" (DAIR) (12) (n=1) or two-stage revision (n=5) or one-stage total revision (n=2) or one-stage partial revision (n=1). As control group were enrolled 42 patients undergoing revision of THA for painful prosthesis and in any case without any preoperative parameters attributable to an infection in progress. Among these, 14 patients have been treated with total revision, 22 patients with cup revision, 4 with stem revision, and 4 with two-stage revision. In the last group, the choice to perform a two-stage revision was based on the intraoperative picture suspicious for infection. However, the diagnosis of PJI has not been confirmed by microbiological analysis of intraoperative tissue and synovial samples. For this reason, the patients underwent an early reimplantation. In all patients of both groups, the PTX3 blood test sample was obtained with a peripheral blood sample taken immediately prior to revision surgery. The sample of synovial fluid for the PTX3 assay (at least 1 ml) was taken during the surgery, before performing the arthrotomy in order to limit blood contamination as much as possible. The samples were sent to the laboratory within the same day of collection. All blood and synovial samples for the PTX3 assay were analyzed in the same run in order to minimize measurement bias due to different reagents.

Statistical analysis

Studying primary THA, absolute frequencies and percentages or means and standard deviations were calculated with relative 95% confidence intervals (C.I.) for each categorical or numeric variable.

In the comparison between the revisions of painful or infected prostheses, in the PTX3 threshold value both synovial and hematic, sensitivity, specificity, positive and negative predictive values were calculated using the operating characteristic curve of the receiver (ROC curve) and the Youden Index (J). Each ROC curve was expressed by the area under the curve (AUC) with AUC values greater than 0.9. The Youden index was used to identify the optimal cut-off value for each biomarker. This index is a function of both sensitivity and specificity and allows us to identify where their sum is greater.

Results

Ten patients were collected for the first branch of the study on normal uncomplicated THA. The values of the inflammatory markers are resumed in Figure 1 and Table 1. PTX3 showed a mean peak on day 3 (T3) (4.17 ± 2.24 ng/ml), decrease on T5 (2.51 ± 1.36 ng/ml) and returned to preoperative values on T15 (1.77 ± 0.98 ng/ml). CRP showed a peak on day 3 (T3) (14.21 ± 4.5 mg/dl) and returned under the abnormal values between T5 (5.92 ± 2.40 mg/dl) and T15 (1.06 ± 0.76 mg/dl). ESR peaked at T3 and T5 (6.97 ± 2.63 - 7.02 ± 2.79 cm/h) and returned under the abnormal levels at T30 (2.9± 1.4 cm/h), well higher than the preoperative values (1.13 cm/h). D-dimer increased at T1 (1.08 ± 0.67 μg/l), peaked at T15 (3.26 ± 0.35 μg/l), and persist well upper than normal at T30 (1.46 ± 0.43 μg/l). On this cohort of patients, no fever, skin inflammation, wound dehiscence or swelling nor PJI were observed.

In the second branch of the study, the mean synovial PTX3 level was 27.34 ± 39.32 ng/ml in patients with periprosthetic infection and 2.64 ± 8.97 ng/ml in patients undergoing aseptic revision (P = 0.001). The mean level of PTX3 in blood was 5.96 ± 5.52 ng/ml in patients with periprosthetic infection and 3.55 ± 1.79 ng/ml in patients undergoing aseptic revision (P = 0.05). Synovial PTX3 demonstrated an AUC of 0.96 (Fig. 2) with 44% sensitivity, 97% specificity, 80% positive predictive value, and 88% negative predictive value. Synovial PTX3 reported 1 case of false positivity and 5 cases of false negativity. Blood PTX3 demonstrated an AUC of 0.64 (Fig. 3) with 11% sensitivity, 100% specificity, 100% positive predictive value, and 80% negative predictive value. Blood PTX3 reported no cases of false positivity and 8 cases of false negativity. The identified cut-off value for synovial and blood PTX3 was 3 ng/ml.

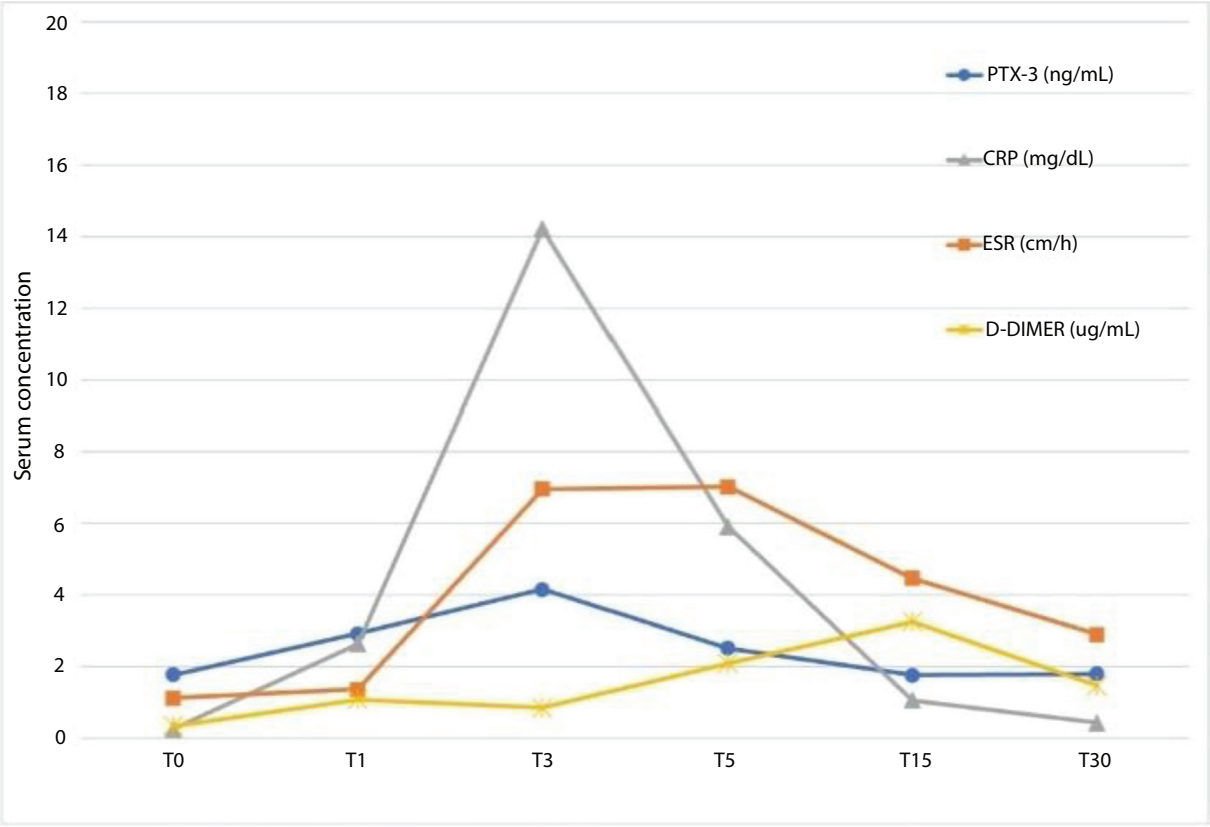

Figure 1. Chart showing the trend of systemic markers of inflammation considered in the first branch of the study. PTX-3 = long Pentraxin 3; CRP= C-reactive protein; ESR = erythrocyte sedimentation rate.

Table 1. Comparison of serum PTX3, ESR, PCR and D-DIMER levels before (T0) and after surgery (T1: 4-6 hours after surgery; T3. third day after surgery; T5. fifth day after surgery; T15. fifteenth day after surgery; T30. thirtieth day after surgery). The data are expressed as mean ± standard deviation.

	T0	T1	T3	T5	T15	T30
PTX-3 (ng/ml)	1,77 ± 1,13	2,93 ± 2,01	4,17 ± 2,64	2,51 ± 1,36	1,77 ± 0,98	1,80 ± 1,08
CRP (mg/dl)	0,25 ± 0,13	2,64 ± 3,12	14,21 ± 4,5	5,92 ± 2,40	1,06 ± 0,71	0,43 ± 0,20
ESR (cm/h)	1,13 ± 0,67	1,37 ± 0,78	6,97 ± 2,63	7,02 ± 2,79	4,47 ± 1,18	2,90 ± 1,40
D-DIMERO (ug/ml)	0,35 ± 0,10	1,08 ± 0,67	0,84 ± 0,31	2,09 ± 0,67	3,26 ± 0,35	1,46 ± 0,43

Discussion

The main finding of this study is that PTX3 is a viable biomarker for acute phase inflammation, proving to be very sensitive to the phlogosis caused in the immediate post-operative period, increasing its blood concentration, while decreasing the values in the physiological follow-up until it becomes negativized. In addition, it has been shown that an increase in PTX3 protein concentration in the synovial fluid of patients undergoing painful THA revision has a strong diagnostic capacity for periprosthetic joint infection.

PTX3, the prototype of long pentraxins, is made up of a C-terminal part of 203 amino acids, like all

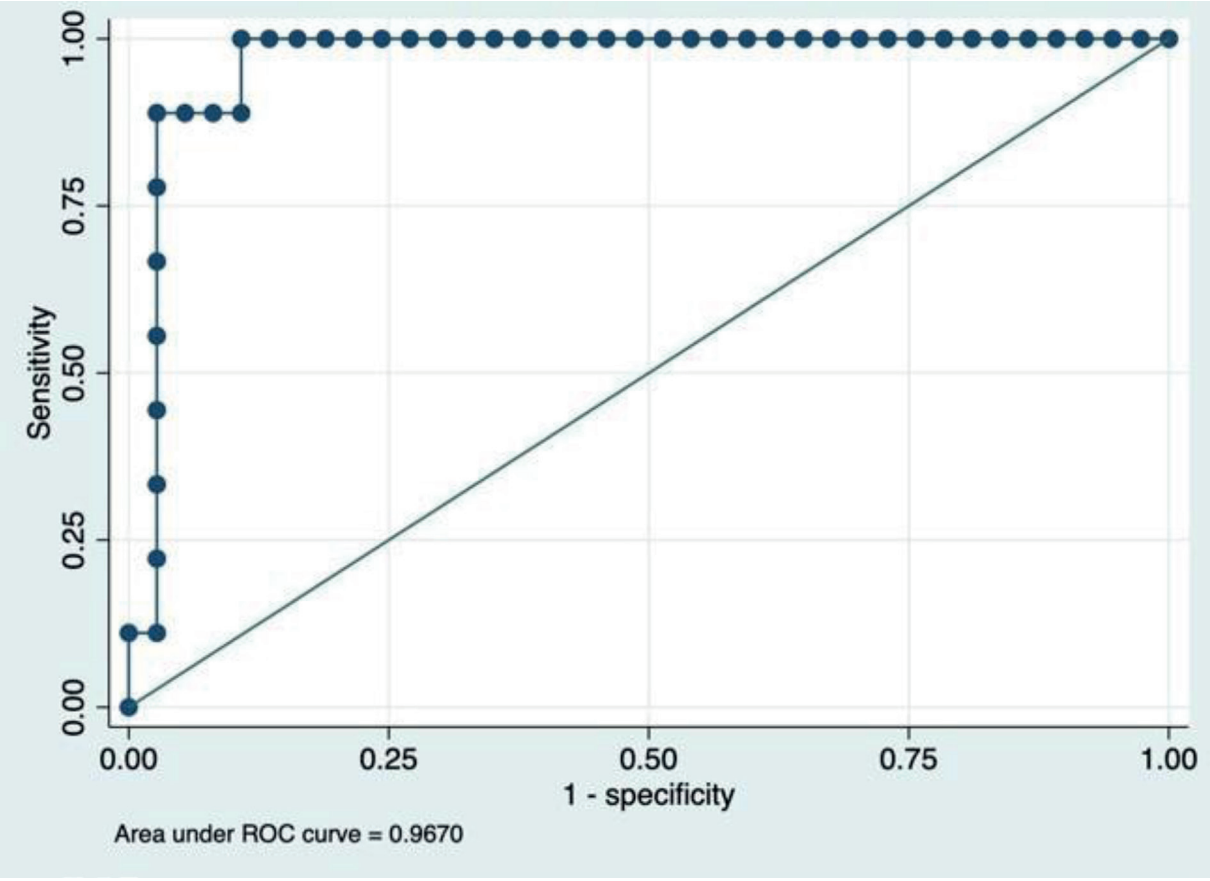

Figure 2. ROC curves of synovial PTX3.

pentraxins, and a particular N-terminal characteristic of 178 amino acids, which makes it a pentraxin belonging to the long pentraxins (13). The gene coding for this protein is located on the long arm of chromosome 3 (3q25). PTX3 is a multimeric glycoprotein of the humoral component of innate immunity. Innate immunity represents the first line of defence against microbes and is activated by molecules with humoral and cell-mediated recognition patterns. During the acute phase response, macrophages, dendritic cells and endothelial cells rapidly synthesize PTX3 which is then released locally at the site of tissue damage or microbial invasion. Furthermore, PTX3 is released locally by polymorphonuclear cells that contain the protein within the intracellular granules. The antimicrobial resistance exerted by PTX3 is expressed through various mechanisms such as opsonization and the promotion of phagocytosis, regulation of complement activity and interaction with antimicrobial proteins (14). PTX3 is able to bind a large variety of microorganisms, including bacteria, viruses and some fungi.

The present study confirmed that the preoperative levels of PTX3 in not infected THA patients are below 2 ng/ml as reported in previous studies (15). In the early postoperative hours (4-6 hours) and the 3rd-day PTX3 rapidly increase in reaction to tissue damage and phlogosis. PTX3 increase more prompt than all the other inflammatory biomarkers (ESR, CRP, D-Dimer) in the first hours after surgery. Abnormal levels, above the baseline, after 5-15 days have to be considered suspicious of infection or inflammation. PTX3 blood trend was very similar to CRP in the immediate post-operative period (3-5-15 days) in primary THA, as reported by Huang et al. (16) in knee arthroplasty for CRP, with a higher sensitivity than ESR and D-Dimer. ESR and D-Dimer have a slower postoperative

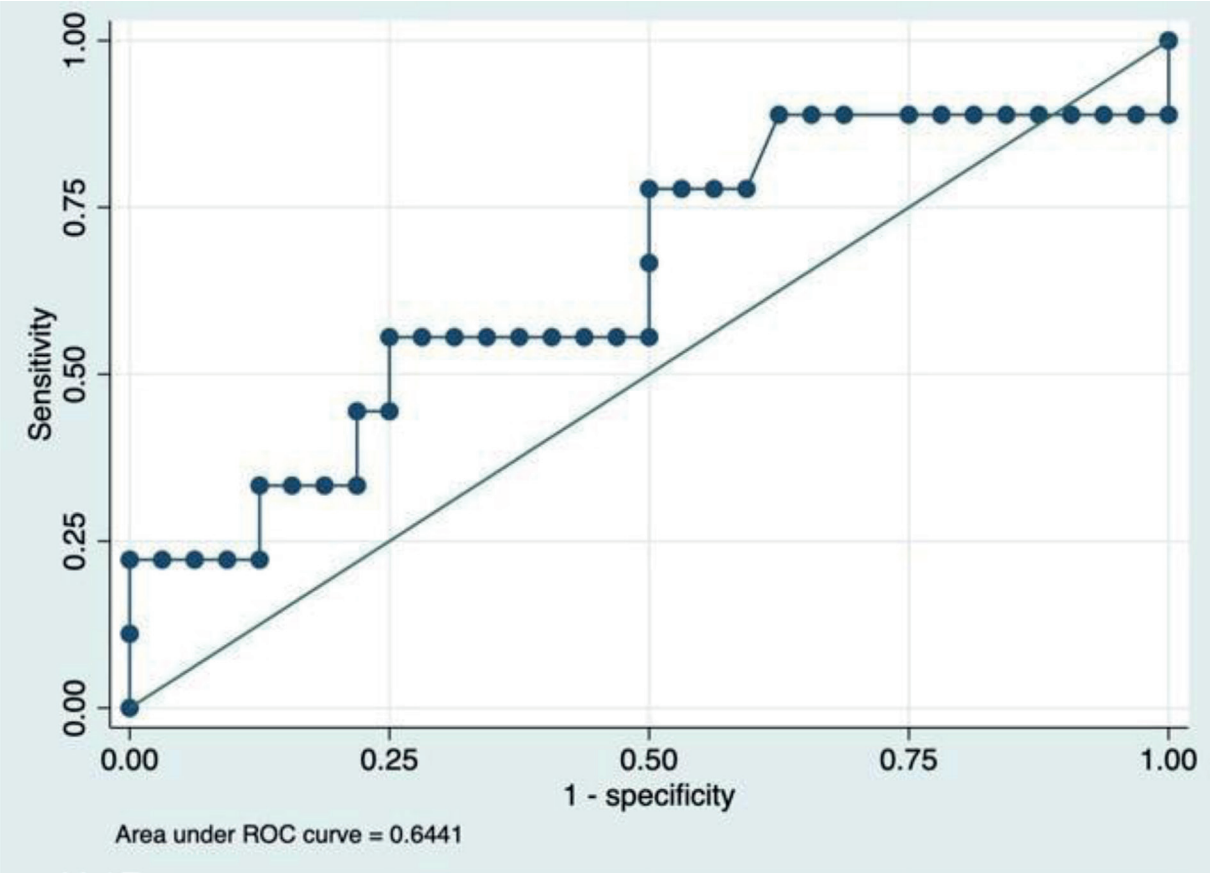

Figure 3. ROC curves of blood PTX3.

increase and peak and a later decrease and so are lesser effective to detect early phlogosis/infection compared to PTX3 and CRP. Similar results on CRP and ESR were previously described in the past by many authors (2, 17, 18). Synovial PTX3 concentration in prosthetic revision surgery demonstrated 97% specificity. Therefore, compared to other synovial markers such as, leukocyte esterase, interleukin-6 and CRP, it has a higher specificity, but a lower sensitivity. In consideration of the specificity value, the PTX3 synovial test would allow to confirm the diagnosis of periprosthetic joint infection in the event of a positive test. On the contrary, the negativity of the test does not allow to rule out the diagnosis of infection, for this reason the association with other more sensitive tests could be useful. In the 5 patients undergoing two-stage revision, no additional levels of synovial and blood PTX3 were performed after removal and reimplantation of the spacer. For this reason, it is not possible to assess whether this protein could be useful for verify the eradication of the infection and identify the correct timing for reimplantation. In the recent years, various biomarkers in blood and/or synovial fluid have been evaluated with the aim of developing new tests to make the process of diagnosing PJI and SSI more effective. In particular, Deirmengian et al. (6) demonstrated that human alpha-defensin 1-3, neutrophilic elastase type 2, bactericidal/permeabilizing protein, neutrophilic gelatinase-associated lipocalin and lactoferrin are able to correctly predict the diagnosis of PJI according to MSIS criteria with sensitivity and specificity up to 100%. The alpha-defensin has had a considerable diffusion in recent years due to the possible overcoming of the ELISA laboratory method to measure the protein in the synovial fluid, thanks to an immunochromatography method that can be performed directly in the operating room. However,

a recent meta-analysis of the literature has shown that the diagnostic capabilities of the two methods are not overlapping, highlighting a superiority of the ELISA method (19). In this study all analyses were performed with the ELISA method, known to have a sensitivity and specificity of 97% (19). Of course, the ELISA method has higher costs: a single kit can cost 10 euros. In any case, if this examination will be performed routinely, then even if with a higher initial investment, it would certainly be possible to amortize the costs of managing a PJI. A rapid diagnosis, in fact, also guarantees rapid treatment, being able to opt for DAIR (12), or antibiotic pearls and implant retention" (DAPRI) (20), which have lower costs, guaranteeing a success of more than 80% and with less invasive procedures for the patients (12,20). In-fact the the early diagnosis of PJI have a financial and clinical impact: one-stage and two-stage revision arthroplasty, due to the prolonged hospitalization, antibiotic therapy, and associated morbidity (22, 23), require fourfold higher costs than DAIR and the retention of the implant (21), PJI prevention is still the key in the current literature (3, 24), but surely a proper and timely diagnosis is crucial to achieve treatment success and subsequently reduce the aforementioned issues (25).

The main limitation of this study is the low number of cases examined and the lack of a comparative analysis with other biomarkers of infection like leukocyte esterase, alpha-defensin or procalcitonin.

Nevertheless, for what is known, this is one of the first studies reporting the baseline values and the postoperative trend (0-30 days) of the biomarker PTX3 in non-infected primary THA and to report the effectiveness of synovial PTX3 in THA PJI diagnosis.

Conclusions

In the present study we investigated the PTX3 blood levels in uncomplicated THA and the PTX3 synovial levels in infected THA. Data collected from this study demonstrated that blood PTX3 levels increase rapidly after surgery in not-infected THA, and decrease to normal levels after 5-15 days, similarly to CRP. In THA revisions synovial PTX3 is an effective indicator of PJI. More extensive studies analyzing a larger cohort of patients undergoing primary, revision and infected hip arthroplasty are required to validate the promising results of this study. Extensive use of PTX 3 in the diagnosis of PJI may decrease the costs.

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Ethical Statements: this Study was approved by: Internal Review Board of University of L'Aquila approved the present study (protocol number 55/2021-2022). And Ethical Commette of Humanitas Research Hospital approved the present study (protocol number 165/17). This study was conducted under the principles of the Declaration oh Helsinki.

Informed Consent Statement: Patients enrolled expressed written informed consent.

Conflicts of Interest: Authors have no conflicts to declare. Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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