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Humeral tissue remodeling in contact with pyrocarbon interposition implant

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Abstract

The interactions between pyrocarbon (PyC) interposition implants and human humeral cancellous bone leads to the formation of a new interpositional tissue made a dense layer of cortical bone and a cartilage-like tissue. A sample of the tissue in contact with the PyC interposition implant was harvested on the humeral bone side from 6 patients undergoing a re-operation for implant removal due to staged surgery or clinical failure related to pain. The samples were then prepared for histology to evaluate the tissue morphology and immunohistology to assess for the presence of collagen I and collagen II within the matrix. For all the cases, a layer of dense cortical bone and a layer of soft tissue was observed between the PyC interpositional implant and the humeral cancellous bone. The nature of the interpositional soft tissue was different between the cases. While the hypothesis that a new tissue was modelled at PyC - humeral cancellous bone interface was confirmed, the nature of the soft interpositional tissue evolved from a fibrocellular to a cartilage-like tissue depending on the cases. The hypotheses for the different nature of the soft interpositional tissue observed between the different cases was based on humeral bone mechanobiological remodeling. The influence of the degree of attachment between the soft and bony interpositional-tissues and on the PISA geometry on the soft interpositional tissue nature are discussed. Further

investigations on the role of humeral bone and on the PISA biomechanics should be performed to better understand this tissue remodeling.

Keywords: Pyrocarbon interposition shoulder arthroplasty, tissue remodeling, mechanobiology, bone-implant interactions

1 Introduction

Basically, there are two types of anatomical shoulder replacements: total shoulder arthroplasty (TSA) or hemi-arthroplasty (HA). While TSA leads to good outcomes when considering short terms clinical results. High rates of the glenoid component failure have been reported at mid and long term follow up in young patients under 60 years [1,2]. On the other hand, 75 % of patients undergoing HA procedure are experiencing shoulder pain due to the glenoid wear in a 17-years follow-up clinical study [3]. Consequently, TSA and HA may not be relevant procedures for younger patients with—glenohumeral osteoarthritis and other innovative solutions are currently explored.

In that context, some current research works are focused on the use of interposition implants. Historically, soft tissues (tendons or ligaments) have been first used as interposition arthroplasties to reconstruct destroyed articulations like the elbow [4]. More recently, spherical Pyrocarbon (PyC) implants have been proposed in hand and wrist reconstructive surgery and now in shoulder surgery reconstruction [5]. Promising results are explained through PyC capacity to induce little damage to bone and cartilage [6,7]. HA using PyC resurfacing implant are also applied [8]. Still, abnormal implant fractures after a HA using a PyC resurfacing implant have been explained by the too low mechanical properties of the PyC to allow for the implant impaction [9,10]. This warrants PyC interposition shoulder arthroplasty (PISA), using spherical PyC implant, to be considered as a relevant healing strategy [11]. Pyrocarbon interposition implant is interesting, due to its spherical shape, its elastic modulus close to cortical bone's apparent modulus [12,13], and its capacity not to adhere to the native bone. Together, these properties have promoted the formation and remodeling of an interpositional-tissue, or interpositional tissue, at the interface between the PyC implant and humeral bone for the 6 cases investigated. To the authors, this is the first time such a tissue is observed at the interface between human bone and a spherical implant. Still, investigating tissues remodeling in contact with PyC is determinant to understand PISA clinical outcomes. While the reaction of sclerotic bone (like the one of the glenoid surface) is partially known, the reaction of pure cancellous bone in contact with a spherical PyC implant is totally unknown.

The purpose of the present study was to perform histologic analysis of the membrane of humeral bone tissue in contact with pyrocarbon interposition implants. The tissue was

harvested in six shoulders of patients re-operated for implant removal in the context of staged surgery (in case of previous infection) or in case of clinical failure related to shoulder pain. We hypothesized that the cancellous bone would resist to loads of the PISA by forming a layer of cortical bone and that some cartilage-like tissue would be found directly in contact with the PISA.

2 Materials and methods

2.1 Cohort

The cohort of the present study consists in 6 patients (Table 1), a revision surgery after a PyC interposition implant arthroplasty was performed between 2013 and 2021 in 4 French different medical centers (Clinique Mermoz, Lyon; Clinique du parc, Lyon; Clinique Monticelli-Vélodrome, Marseille; Hôpital Pasteur 2, Nice). The patients needed surgery revision for different reason, summarized in **Erreur ! Source du renvoi introuvable.** The functional reason signifies that the patient had diminished mobility or suffered from pain. On the other end, 2 patients from the cohort had undergone a PISA as surgical treatment to treat shoulder infection, the PyC implant being used as temporary spacer [14]. For those patients, the revision surgery occurred while no functional issue was claimed.



Figure 1: Case 2 right shoulder radiography before revision surgery.

The pyrocarbon interposition implant has been placed using standards procedures [6,15]. An important point is that the humeral head has been removed, and a cavity has been drilled in the humeral bone to lodge the spherical pyrocarbon implant (Figure 1). Spherical reaming of the proximal humerus is needed to implant the PISA; the reamer must have the same diameter than the definitive implant for perfect congruence between the humeral cavity and the implant. On this radiographic image, one can notice the dense and circular line of cortical bone and the clear space between the humeral bone and the spherical PyC implant, which corresponds to the new formed tissue. Such qualitative morphology was observed for all the clinical cases.

2.2 Interpositional-tissue dissection

During the revision surgery, the surgeons have observed that a new tissue had been synthesized at the interface between pyrocarbon implants and humeral bone (Figure 2). The appearance and handling of this interpositional-tissue was not the same between the different patients. The neo tissue formed in the humeral cavity of case 1 was easily harvested. Macroscopically, this interpositional-tissue appears as a meniscus-like tissue between the bone and the implant, with some attachment sites to the synovial membrane. The

interpositional-tissue was removed from cases 2 and 3 by the surgeon without damaging it. For these cases, the interpositional-tissue could be easily removed from the humeral cavity (Figure 2). By contrast, the tissue in cases 4 and 5 was thin (less than 1 mm) was hardly removed from the humeral bone. In that manner, the samples have been largely damaged during the harvest operation. The interpositional-tissue formed in clinical case 6 was firmly bonded to bone. It has hence been asked to the surgeon to remove a core sample of both the bonded tissue and bone for further analyses. It should be noticed that the interpositional-tissue was never bonded to the pyrocarbon implant surface. In table 1, the Walch classification is associated with the glenoid erosion state in the case of glenohumeral osteoarthritis [16]. This thus provide information on the geometry of the glenoid cavity. The tissue samples were recovered with the patients and the surgeons' consent.

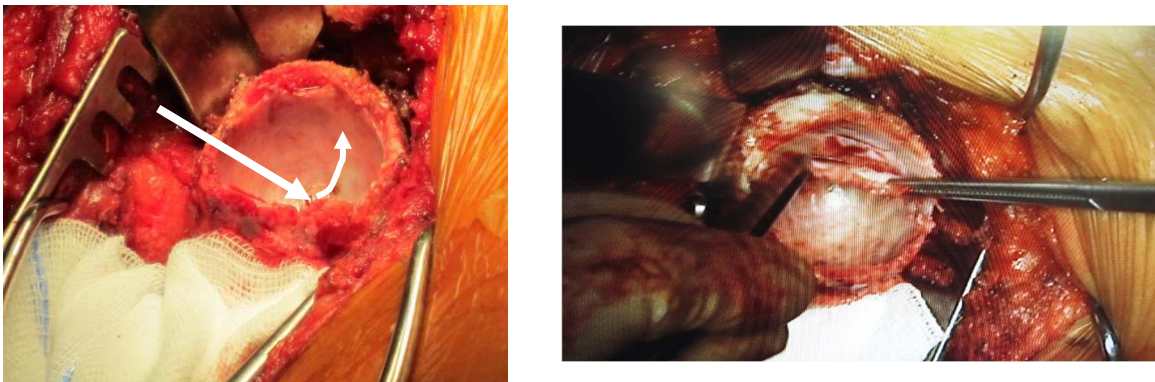


Figure 2 Left: photograph of the interpositional-tissue on the humeral cavity of clinical case 3 before its removal. Right: photograph showing that to remove this interpositional-tissue, the surgeon has to pull it out from the bone, while it has been classified as being only slightly bonded to humeral bone. The interpositional-tissue membrane has been harvested at the center of then cavity, shown by the straight arrow, and toward the border of the cavity, as shown by the curved arrow.

Table 1 Summary of the cohort clinical data

Cases	Sexe	Age (years)	Surgeon*	Implanted time (Months)	Implant diameter (mm)	Walch classification of glenoid morphology before PISA	Indication for PISA	Reason for revision
1	♂	74	PB	6	44	NA	Sepsis on RSA	Temporary spacer
2	♂	78	AG	6	36	NA	Sepsis due to previous surgery	Temporary spacer
3	♀	52	JG	25	32	C	Osteoarthritis due to a brachial plexus paralysis	Small diameter and glenoid dysplasia induced a humeral translation
4	♂	-	JG	31	42	B1	To avoid the placement of a glenoid implant	Pain due to a conflict between calcar and glenoid
5	♀	60	AG	60	34	A1	Post-traumatic osteoarthritis	Pain due to a conflict between calcar and glenoid
6	♂	60	RG	5	46	NA	RSA loosening with suspected infection	Temporary spacer

* : PB : P.Boileau, AG : A.Godenèche, HG : H.Garret, RG : R.Gravier. NA = Non Applicable

1 **2.3 Interpositional-tissue analyses**

2 Once harvested, the samples were placed in a sterile container and sent back to Lyon.
3 Samples were fixed in ROTI®Histofix 4 %, 4 % formaldehyde, ready-to-use, phosphate
4 buffered, pH 7 for 24h before being decalcified for 7h (PEURDO, Eurobio, France). The
5 samples were then dehydrated using successive bath of ethanol, acetone, and xylene, and
6 embedded in paraffin. The samples were embedded so as bone and implant sides of the
7 interpositional-tissue can be easily identified.

8 Different sections of 5 µm were then cut from the embedded samples. After removing the
9 paraffin, Hematoxylin, Eosin, Safran (HES) staining was applied on different sections. HES
10 stains cells nuclei in purple, cells cytoplasm in pink, and extracellular matrix (ECM) in yellow.

11 In addition, immunohistochemical stainings have been applied on 5 µm sections for cases 1,
12 2, and 5. After removing the paraffin, each section has been immersed in 0.5 % hyaluronidase
13 buffered in PBS-BSA 3% for 1h at room temperature, in order to expose the antigenic sites.
14 Sections were then incubated with rabbit anti-human type I collagen (Coll I) antibody diluted at
15 1/1000 (Novotec, 20111), rabbit anti-human type II collagen (Coll II) antibody diluted at 1/500
16 (Novotec, 20211) overnight at 4 °C buffered in PBS-BSA 3%. Sections are then incubated with
17 goat anti-rabbit secondary anti-body coupled with peroxidase (Dako, Envision Lapin, réf.
18 K4002). A further reaction with diaminobenzidine (Dako, K3468) reveals the antigenic –
19 antibody complexes through a brown color. Negative controls were prepared using a solution
20 of PBS-BSA 3% instead of the primary antibodies.

21 The sample preparation and analysis from case 6 were performed by the Ciqle platform (Lyon,
22 France). Samples preparations and analyses from the other cases were performed by Novotec
23 (Lyon, France).

24 **3 Results**

25 All the cases showed radiographical evidence for the formation of a dense cortical layer and a
26 soft layer formed between humeral cancellous bone and the PyC implant (Figure 1). In the
27 framework of the current study, we will mainly focus on the soft interpositional-tissue near the
28 center of the joint, where the loading occurs.

29 **3.1 Case 1**

30 The interpositional-tissue modeled at the bone-implant interface of clinical case 1 formed a
31 dense membrane, from 3 mm to 1 mm in width in the cavity border and cavity center sides,
32 respectively. The thin dense fibrocellular layer is clearly observed (→). Vascular canals (*)
33 were observed, mostly on the bone side (Figure 3).

34 The HES staining showed that this interpositional-tissue was highly cellularized. The cell
35 population was dominated by fibroblastic-type cells (Figure 4).

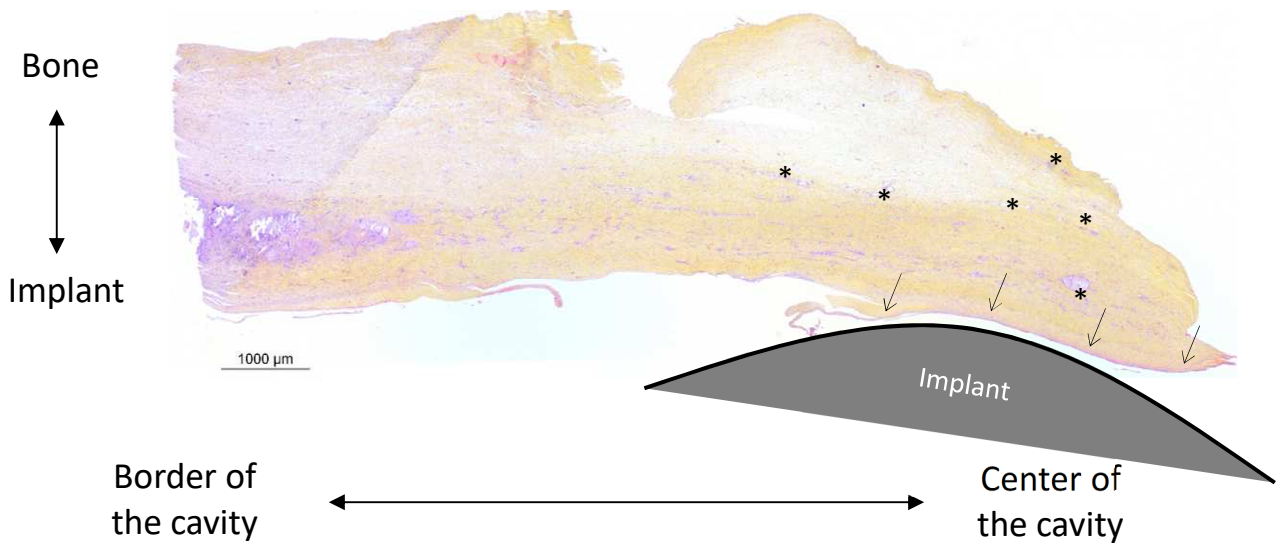


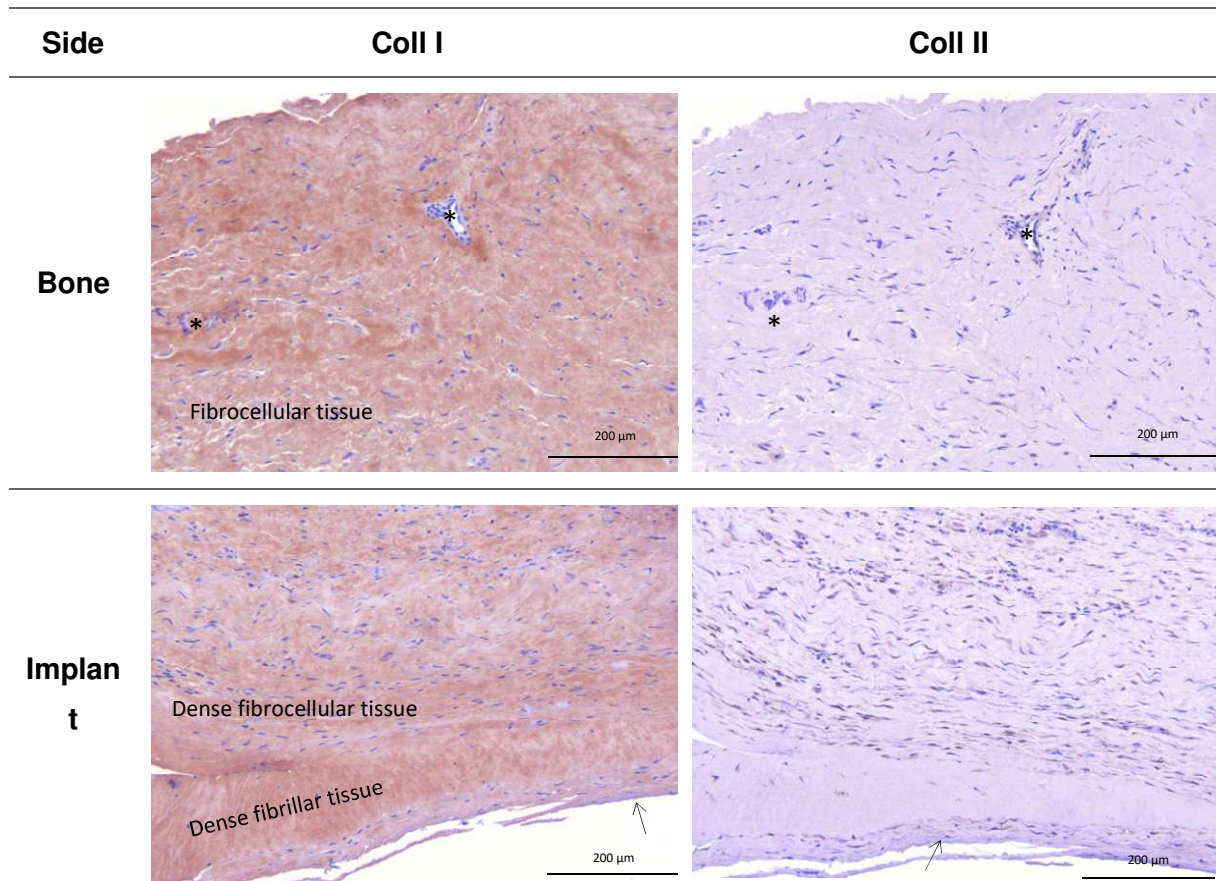
Figure 3 Overall view of the interpositional-tissue synthesized at case 1 bone-implant interface (HES staining).
* identifies the vascular canals. → identifies the dense layer. The implant illustration is not to scale.

36 The immunostaining has revealed a homogeneous presence of Coll I, whereas Coll II were
37 heterogeneously dispersed within the ECM. The interpositional-tissue is formed of both dense
38 fibrillar and fibrocellular matrices made of Coll I. Vascular canals are observed on the bone
39 side (Figure 4).

40

41

42



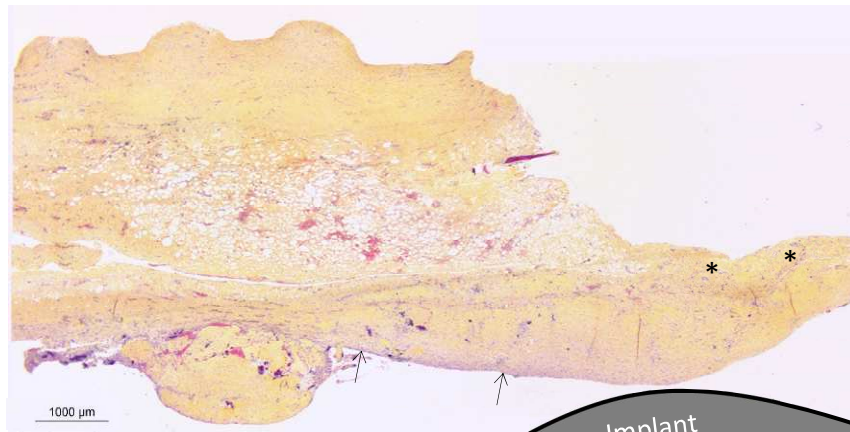
43 *Figure 4 Coll I and Coll II immunostainings of interpositional-tissue from clinical case 1 at the bone (top) and*
 44 *implant (bottom) sides. * identifies the vascular canals. → identifies the external thin dense layer.*

45 **3.2 Case 2 and case 3**

46 For case 2 and 3, the interpositional-tissue was a dense membrane, 1 mm or less in width
 47 toward the cavity center. The thin dense layer (→) at the implant side is less dense in cells that
 48 in the previous case. Highly vascularized (*) areas toward the bone are observed. In the
 49 interpositional-tissue formed at the bone implant interface of case 3, a large amount of adipose
 50 tissue is observed toward the cavity border (Figure 5).

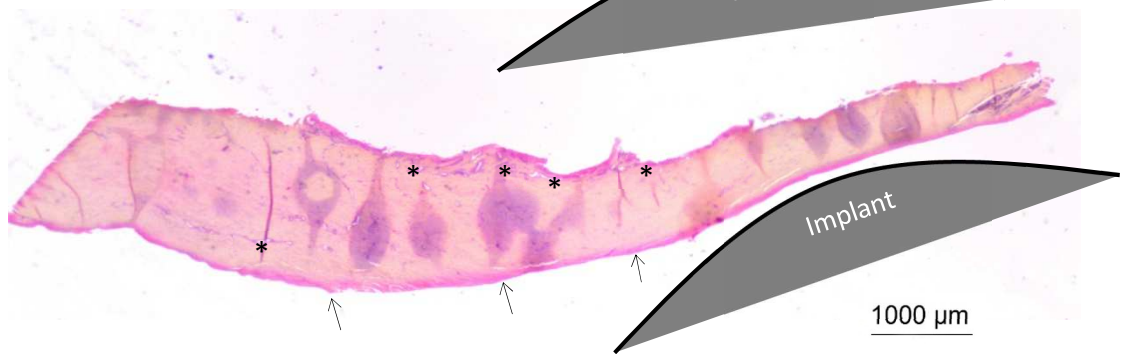
Case 2

Bone
↑
↓
Implant

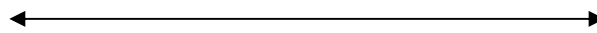


Case 3

Bone
↑
↓
Implant



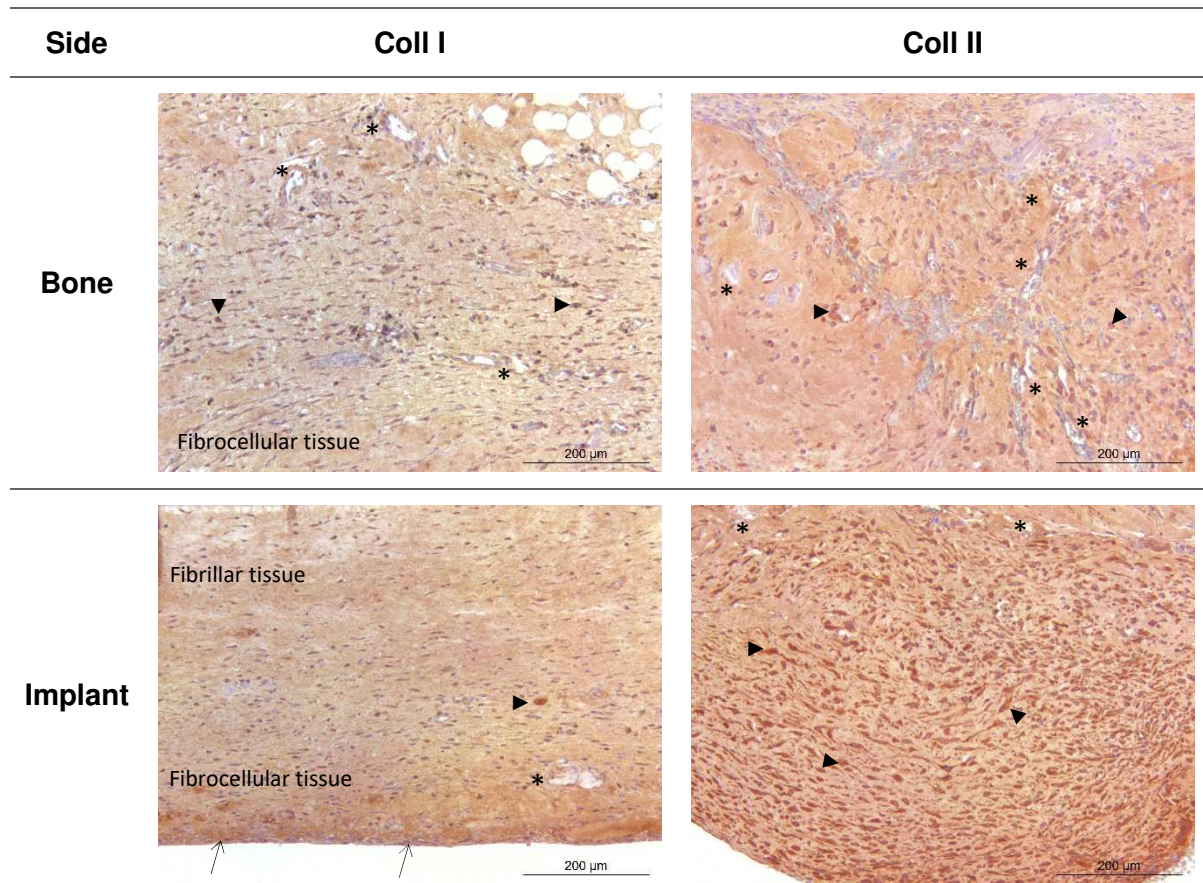
Border of
the cavity



Center of
the cavity

51 *Figure 5: Overall view of the interpositional-tissue synthesized at case 2 (top) and 3 (bottom) bone-implant*
 52 *interface (HES staining). * identifies the vascular canals. → identifies the dense layer. The implant illustrations are*
 53 *not to scale.*

54 Coll I immunostaining showed that the interpositional-tissue is formed of a heterogeneous
 55 matrix, with both fibrillar and fibrocellular tissues. The cells population is mainly fibroblastic. In
 56 contrast with the previous case, Coll II is expressed near the bone surface. Immunostainings
 57 showed Coll I and Coll II markers both in the ECM and intracellularly by the chondroblast-like
 58 cells (►). Intracellular Coll II is more intensively present than intracellular Coll I. Intracellular
 59 Coll II is more present in the implant side compared to the bone side.

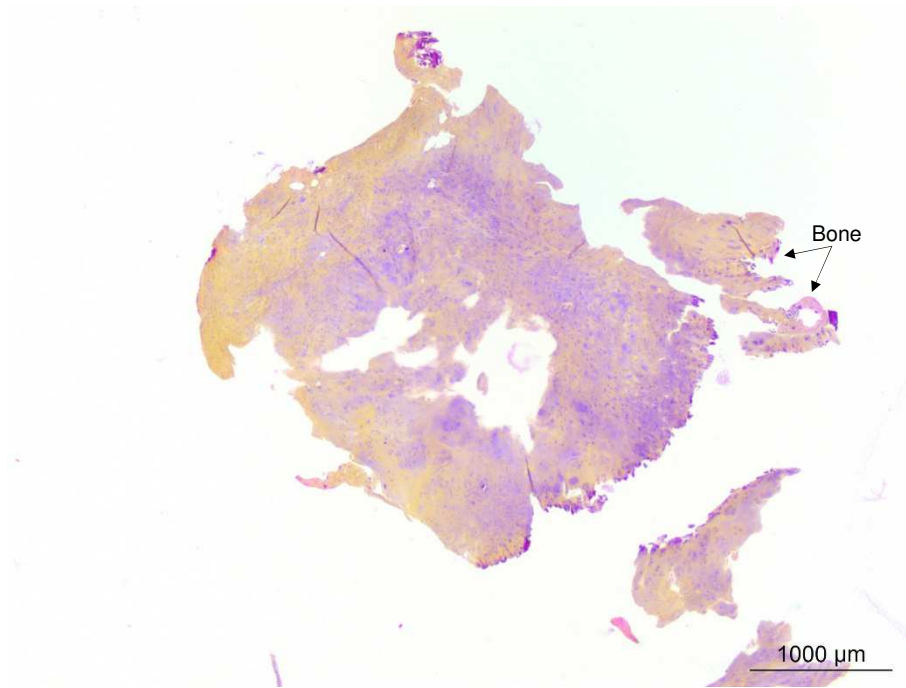


60 *Figure 6 Coll I and Coll II immunostainings of interpositional-tissue from clinical case 3 at the bone (top) and*
61 *implant (bottom) sides. * identifies the vascular canals. → identifies the external thin dense layer. ▴ identifies the*
62 *intracellular Col I and Coll II.*

63 **3.3 Case 4 and case 5**

64 These two samples had to be scratch out from the humeral cavity by the surgeon. This resulted
65 in damaged samples that have been folded during the preparation process. In that case, the
66 bone / implant sides, or the cavity border / cavity center sides were difficult to define. Still,
67 some bone pieces can be observed. It is worth noticing the presence chondrocyte-like cells
68 (O) rounded cells located in lacunae within the ECM, (Figure 7).

Case 4

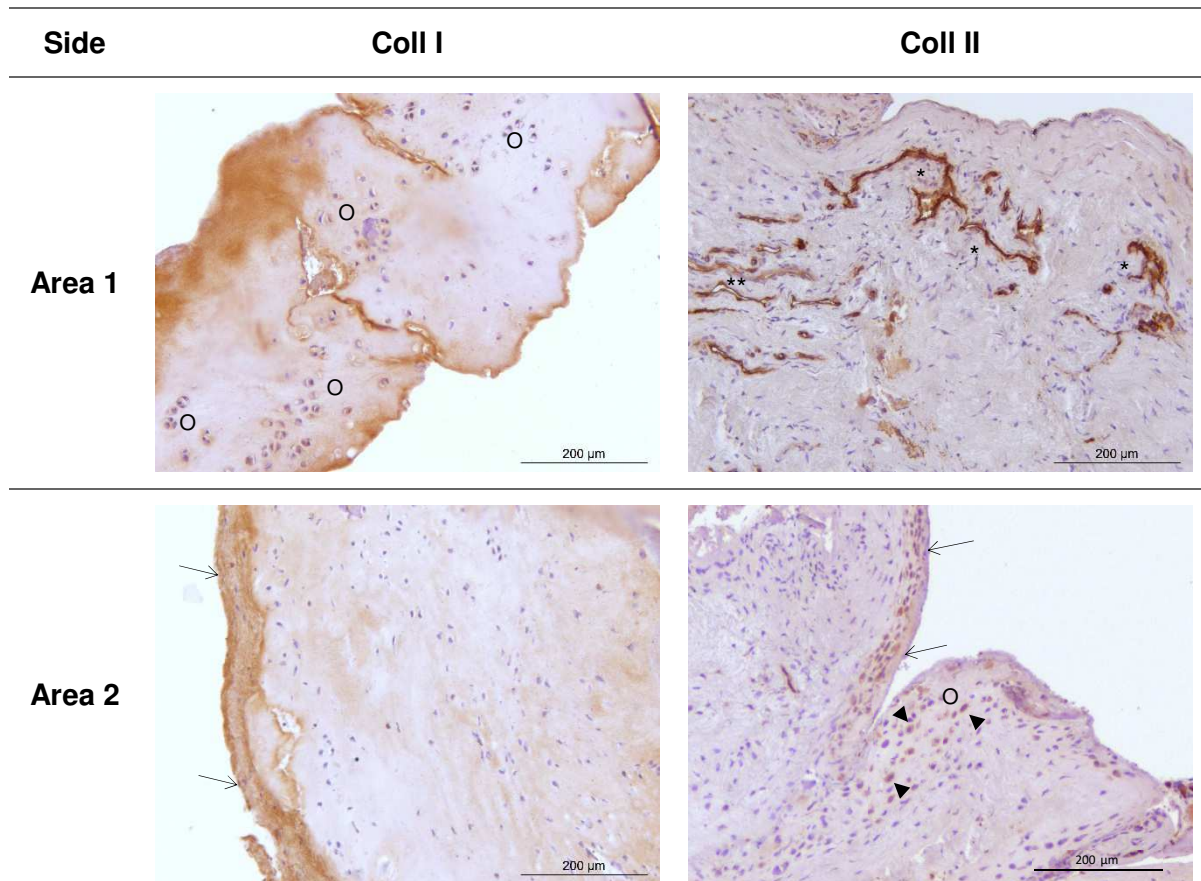


Case 5



69 *Figure 7 Overall view of the interpositional-tissue synthesized at case 4 (top) and 5 (bottom) bone-implant*
70 *interface (HES staining). O identifies chondroblast cell populations. It has to be noticed that the scales between*
71 *case 4 (top) and case 5 (bottom) are different. For these cases, the samples were too much damages during the*
72 *preparation process and the implant and bones sides could not be identified.*

73 Coll I and Coll II immunostainings show a thin layer of dense tissue that looks like the external
74 dense layer observed at the implant side for the previous cases (→). Coll I immunostaining
75 appeared less intense than for the previous cases. Still, some areas of dense Coll I are
76 observed. Coll II is present intracellularly within rounded chondroblast-like cells (▶). A large
77 population of chondrocyte-like cells is observed. Fibroblast-like cells are also observed. Coll II
78 is observed around vascular canals (**) (Figure 8).



79 *Figure 8 Coll I and Coll II immunostainings of interpositional-tissue from clinical case 5 in different areas (area do*
80 *not corroborate between Coll I Coll II immunostainings). * identifies the vascular canals. → identifies a thin dense*
81 *layer that looks like the thin dense external layer. ▶ identifies the intracellular Coll II. For these cases, the*
82 *samples were too much damages during the preparation process and the implant and bones sides could not been*
83 *identified.*

84 **3.4 Case 6**

85 The interpositional-tissue of case 6 was firmly bonded to the humeral bone, making it
86 impossible for the surgeon to harvest it without damaging it. The surgeon was then asked to
87 harvest a core of both bone and interpositional-tissue. The dense bone on the upper side can
88 clearly be observed and identify. Close to the interface with the soft interpositional-tissue, some
89 small porosities (50 – 100 µm in diameter) that widen as we go further from this interface. This
90 reminds the cortical layer and trabecular bone present in joint subchondral bones. The sample
91 showed a dense interpositional-tissue, forming a 2 mm width membrane. The core extraction
92 technique used by the surgeon allowed to observe the firm bonds between the humeral bone
93 and the interpositional-tissue. The vascular canals are clearly observed on the bone side
94 whereas no canal (*) is observed on the implant side. The cell population showed by the HES
95 staining is mainly chondroblast-like. Close to this interface, some cells alignments were
96 observed ([]). Some cells clusters by two (●●) or more (●●●) were also observed, reminding
97 cartilage isogenous groups [17]. Clusters of several cells were organized in circle and found
98 close to the implant interface. Fibers from the interpositional-tissue appear to be inserted within

99 the more mineralized tissue (┐). Some amorphous cartilaginous matrix is also observed,
 100 reminding of articular cartilage. A tidemark I is present between an amorphous matrix and a
 101 bony matrix. Finally, a density gradient is observed from the interpositional-tissue toward the
 102 bone.

103

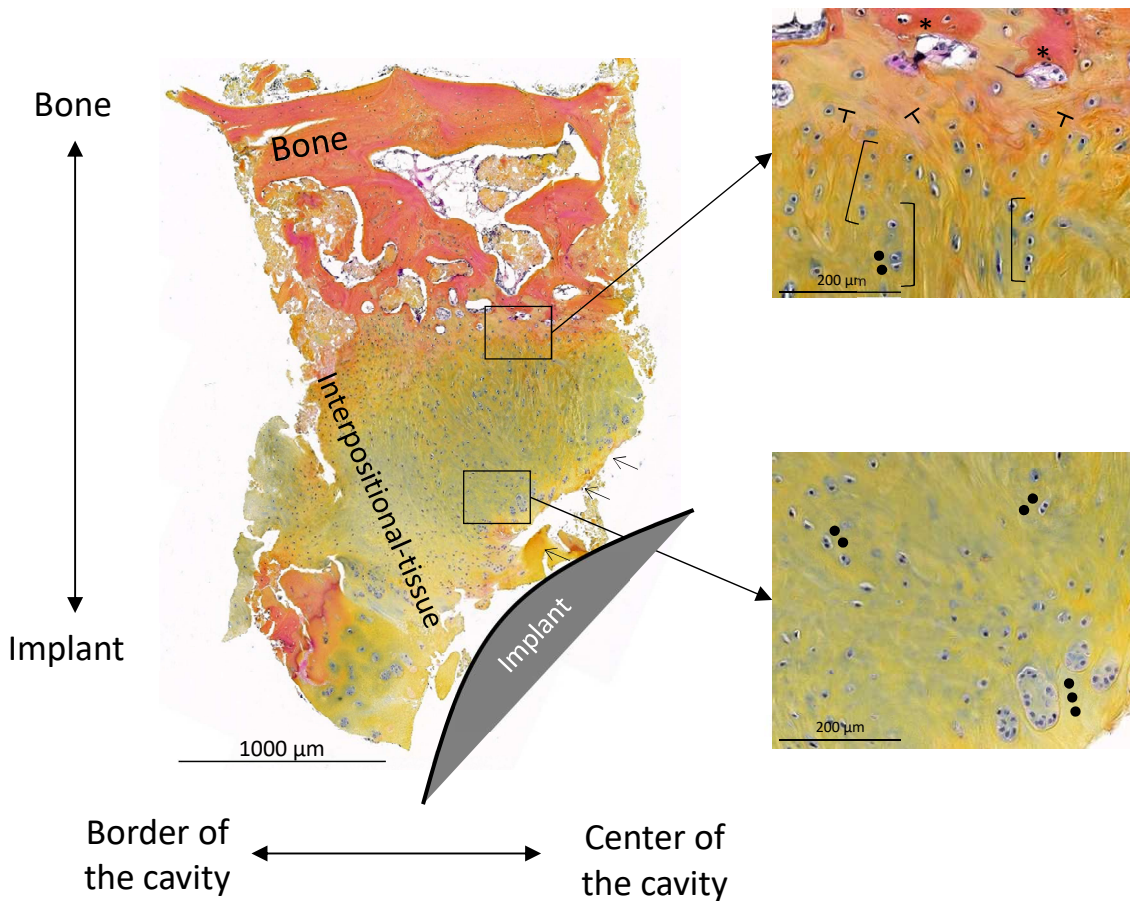


Figure 9 Overall view of the interpositional-tissue synthesized at case 6 bone-implant interface (HES staining).*
 * identifies the vascular canals. ┐ identifies cells alignment close to the bone surface. ●● and ●●● identify the
 isogenic groups of 2 or more cells, respectively. ┐ identifies the interpositional-tissue fiber insertion sites in
 bone. TM: Tidemark. → identifies the external thin dense layer. The implant illustration is not to scale.

104 Coll II immunostaining was much more expressed than Coll I at both bone and implant sides
 105 of the interpositional-tissue. There was a defined interface between bone and the
 106 interpositional-tissue at which Coll II was no more expressed. Still, some Coll II was observed
 107 within the bone away from this interface. Coll II was also observed around the vascular canals.
 108 Close to the implant side, Coll II immunostaining showed an amorphous ECM (Figure 10).

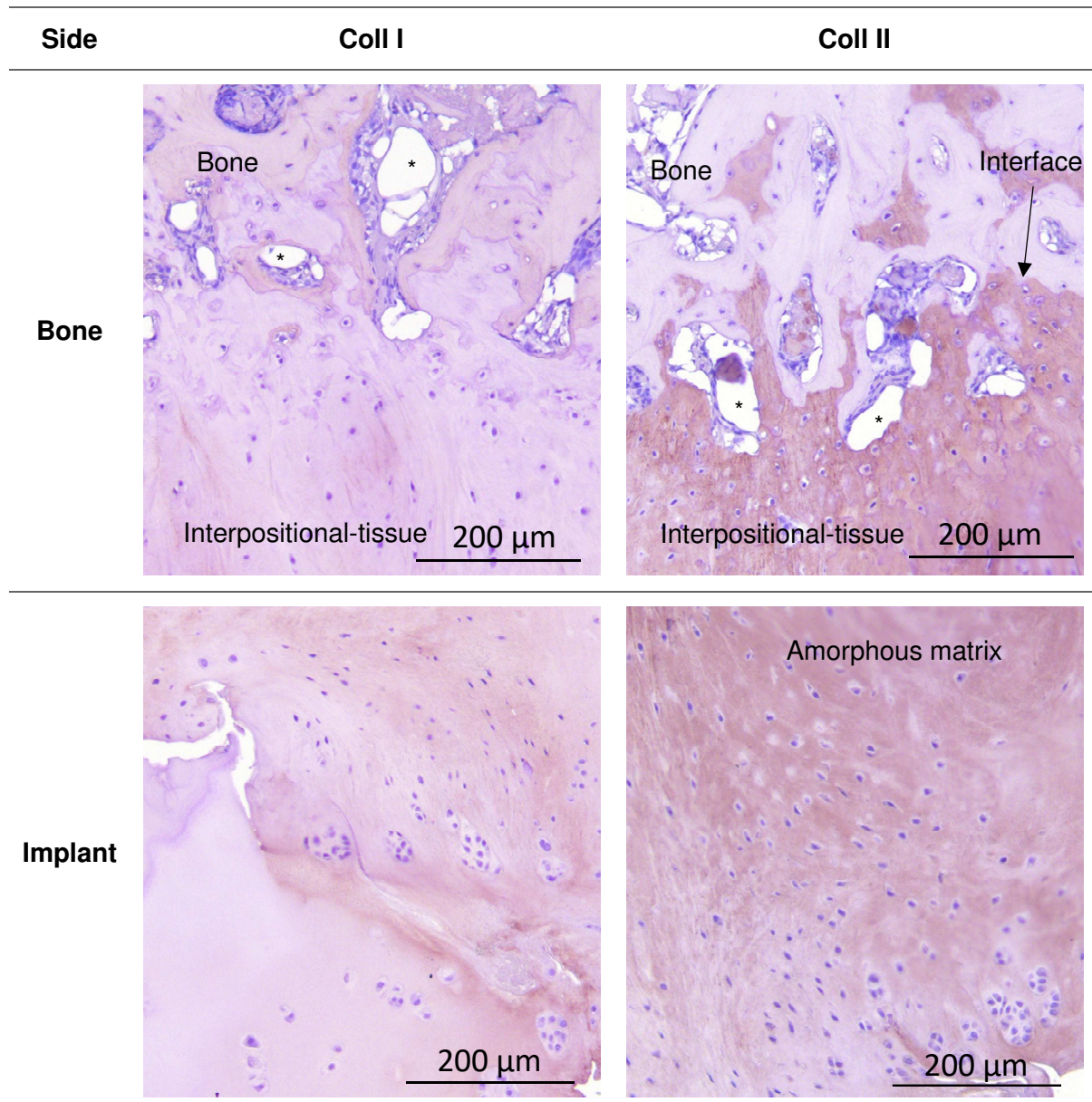


Figure 10 Coll I and Coll II immunostainings of interpositional-tissue from clinical case 6 at the bone (top) and implant (bottom) sides. * identifies the vascular canals.

109
110

111 4 Discussion

112 The results of the present study confirm our hypothesis: for some cases, a layer of cortical
113 bone and some cartilage-like tissue can be observed at the interface between the cancellous
114 bone of the proximal humerus and a spherical pyrocarbon interposition implant.

115 The nature of this interpositional-tissue differs between the different cases. In the results
116 section, these 6 cases were organized in order to follow the evolution of the interpositional-
117 tissue: from a non-cartilaginous (case 1) to the better cartilaginous tissue (case 6). With only
118 six cases with different clinical data, the reason for these differences cannot be defined
119 accurately. Still, some parameters known has being part in tissue modeling can be highlighted.

120 A parameter involved in the course of this interpositional-tissue remodeling can rely on the
121 biomechanical conditions of the humeral bone - PyC implant system. The congruency between
122 the implant and the humeral bone has a determinant influence on the load transmission
123 between the PyC spherical implant and the bone. Such congruency depends on the implant
124 diameter, the reaming of the humeral cavity and the glenoid cavity morphology based on their
125 Walch classification. Additionally, it was interesting to notice that different binding degree
126 between the interpositional-tissue membrane and the underlying bone was qualitatively
127 observed. As an example, in case 1, the membrane of tissue was easily removed from the
128 bone whereas a core was harvested from case 6. Such parameter is also involved in the
129 distribution of the mechanical stresses transmitted to the underlying humeral bone. The degree
130 of binding between bone and the interpositional-tissue influences mechanical loads
131 transmission from the implant toward the humeral bone. While loose bonds allow from slight
132 movements of the interpositional-tissue against humeral bone surface, firm bonds prevent from
133 any relative movement. Load transmission between the interpositional-tissue and the
134 underlying bone is thus better in the case of firm bonds.

135 Tissue differentiation at the bone implant interface highly depends on the mechanical loads
136 transmitted to the cells lying in between the bone and the implant[18]. According to
137 Prendergast et al., the nature of tissue differentiation at the bone implant interface depends on
138 the strain experienced by the ECM, and the fluid velocity surrounding the cells [18]. In that
139 context, PyC interposition implants have interesting properties compared to the general class
140 of articular implants: they are not anchored within bone diaphysis, and they do not adhere to
141 bone tissue. This results in a unique mechanical environment at the interface between humeral
142 bone and the implant. During the patients' movement, the implant is able to glide on the
143 humeral bone surface in a way that looks like humeral head movements within the glenoid[19].
144 The non-adhesive nature of PyC involves a continuous movement between the bone and the
145 implant that prevent from bone formation between them. Instead, due to the shear strain
146 induced by the implant movement, whether a fibrous or cartilaginous tissue will be synthesized
147 [18]. Furthermore, the contact pressure distribution and the sliding speed between the implant
148 and the native tissue are also known to influence the joint behavior by tuning the lubrication
149 mode [20]. Still, the clinical data obtained in the framework of the current study do not allow to
150 estimate such biomechanical parameters. Further investigation using 3D geometrical data
151 might be of great interest to better understand the implanted joint biomechanics.

152 The load transmission from the PyC implant toward bone is of great importance, as it is
153 believed that bone underlying the cartilage plays a major role in cartilage integrity [21]. Firm
154 bonds hence may promote the mineralization of the interpositional-tissue and bone growth
155 through a strain-guided mineralization mechanism [22], while loose bonds may promote the

156 development of a fibrous tissue [18]. This is in accordance with what has been observed in the
157 current study, with the development of a real cartilage-like bone with the higher bone binding
158 degree on case 6.

159 In this regard, investigating the distribution of contact points and pressured between the
160 implant and the bone cavity might be of tremendous importance to understand the
161 interpositional-tissue remodeling. Similarly, studying how and why such bonds between the
162 interpositional-tissue and bone appear may help understanding this interpositional-tissue
163 formation and appears as necessary to further control a suitable remodeling. Interestingly, the
164 behavior of bone insertion sites is intensively investigated in the fields of tendon and ligament
165 regeneration, where entheses play a major role [23]. Interestingly, the interpositional-tissue
166 bone interface shown in Figure 9 presents similar features as cartilaginous entheses, with a
167 gradient of tissue mineralization and fibers insertion sites [24], and cells alignment close to the
168 bone interface [25]. In addition, the increasing content of Coll II in case 6 with a high bonding
169 degree with bone is a marker of hyaline cartilage formation [26,27]. The presence and
170 colocalization of both Coll I and Coll II suggest that this interpositional-tissue looks like articular
171 cartilage, with characteristics of both fibro- and hyaline cartilage.

172 It is important to notice that such hypothesis might be considered for best cases, where the
173 interpositional-tissue formed is adapted to optimal loads transmission. Still, as observed within
174 the current study, this interpositional-tissue can evolve into a fibrocellular tissue that may not
175 be suitable and may lead to disfunctions. Such fibrosis, highlighted by the presence of fibrillar
176 matrix and a fibroblast-like cells population, may be associated with an inflammation of the
177 synovial membrane [28,29]. Due to an abnormal function of the joint, the synoviocytes found
178 in the synovial membrane may react by producing inflammatory factors that finally result in the
179 formation of a fibrous tissue. Thus, the evolution of the properties of this interpositional-tissue
180 lies in a close competition between fibrosis from synovial inflammation and
181 mechanotransduction to the underlying humeral bone. Additionally, the degree of osteoporosis
182 of the proximal humerus, the age and gender of the patients, the initial diagnosis (Primary OA,
183 or fracture sequelae or infection...) are parameters that might be involved in the quality of the
184 formation of the interpositional-tissue. In that context, it might be of great interests to closely
185 investigate the structure and properties of the new formed interpositional cortical bone, down
186 to the lacunocanalicular scale. The implant properties of the implant and the nature of the
187 implant – bone interactions are known to influence osteocytes activity at the bone – implant
188 interface [30,31].

189 The present study is limited to 6 clinical cases only, with microscopic analyses differing
190 between the different cases due to practical issues. Nevertheless, to the authors, this is the

191 first time such interpositional-tissue formation at the humeral bone implant interface is
192 observed and analyzed. This study thus represents a real confirmation that further
193 investigations on this new interpositional-tissue have to be led. Currently, several PISA
194 procedures have shown interesting results, up to 5 years mid-terms results on young patients
195 (50 ± 12 years) [32]. By accurately analyzing the relationships between the PISA geometry
196 and the nature of the interpositional-tissue nature, more personalized treatments could be
197 developed, thus preventing from the PISA failure by reducing the number of bad diagnoses.
198 Understanding what geometry is the most suitable for the patient is an additional step to
199 accurately monitored the success of the PISA. In that context, numerical modelling appears as
200 a relevant tool to define a geometry allowing for a suitable contact pressure distribution [33].
201 In addition, mechanobiological analyses could be performed to understand the chondrogenic
202 power of PyC surface considering different geometries and different mechanical loadings [34–
203 36].

204 **5 Conclusion**

205 In summary, cortical bone and cartilage-like tissues have been observed between the
206 cancellous bone of the humerus and PISA. These observations witness the capacities of PISA
207 to form and maintain an interpositional-tissue at the bone-implant interface. The properties of
208 the interpositional-tissue probably depend on the duration of implantation, the initial diagnosis,
209 and probably on the biomechanical conditions of the humeral bone – PyC implant - glenoid
210 system.

211 **6 Conflict of interests**

212 A.Godnèche and J.Garret are participating to an receives fees for a post marker clinical follow
213 up study initiated by Tornier SAS on this product. P.Boileau is consultant for and receives
214 royalties from Tornier SAS. Their immediate family, and any research foundation with which
215 they are affiliated have not received any financial payments or other benefits from any
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