Case Report

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Use of 3D-printed polycaprolactone + hyaluronic acid-based scaffold in orthopedic practice: report of two cases

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3D-printed (3DP) polycaprolactone (PCL)-based scaffolds have gained popularity in the past decade. Despite the wide utility of autografts for bone regeneration in orthopedics practice, 3DP PCL scaffolds may replace this general application. Here we present a 42-year-old patient who had glenohumeral arthritis due to rheumatoid arthritis accompanied by a Walch 3 glenoid defect, and a 19-year-old patient with neglected Galeazzi fracture–dislocation accompanied by a radius non-union. In both patients, a 3DP PCL + hyaluronic acid-based scaffold was used for bone regeneration purposes. The preliminary results showed that the 3DP PCL + hyaluronic acid scaffold provided bone regeneration and may be a promising alternative to autografting for bone regeneration in orthopedic practice.

Plain language summary: A 3D-printed (3DP) polycaprolactone (PCL) scaffold is a material that can be used instead of bone grafts to support new bone formation. This is a report of two patients who underwent new bone formation with the use of a 3DP PCL + hyaluronic acid scaffold. We found that the 3DP PCL + hyaluronic acid scaffold provided a suitable environment for bone formation in a glenoid bone defect undergoing reverse total shoulder arthroplasty and in radius non-union. These findings suggest that the 3DP PCL + hyaluronic acid scaffold may be an alternative to autografts in orthopedic practice.

Tweetable abstract: 3DP PCL + hyaluronic acid scaffold provided good outcomes in two patients requiring bone regeneration, and may be an alternative to autografts in orthopedic practice.

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Keywords: bone defect • bone graft • Galeazzi fracture • glenoid lateralization • nonunion • reverse total shoulder arthroplasty

3D-printing technology has gained exponential growth since the first patent issued by Charles Hull in 1984 [1]. 3D printing has provided various applications in widespread fields, including dental, medical and automotive industries, due to its versatility and ability to produce complex-shaped materials in a relatively easy manner [2]. Nevertheless, the medical field has grown much more slowly than other industries because of its expected high standards [3].

As the technology of advanced imaging modalities has improved, it has allowed a convenient field to translate these high-quality images for 3D printing to be used in orthopedics. Consequently, one of the earliest adaptations of 3DP in the orthopedics field was the development of patient-specific instruments which allowed precise surgical planning, thereby improving surgical outcomes and ease of use for trainees [4]. Bioprinting with 3D printing has evolved particularly in the last decade due to the advancements in tissue engineering. Many 3D-printed

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(3DP) scaffolds have been introduced to treat multiple orthopedic pathologies, such as bone regeneration and osteochondral defects.

Scaffold production is a growing field in tissue engineering [5,6]. One of the most important properties of an ideal scaffold is its pore size, which needs to allow diffusion of nutrients, migration and attachment of the cells, and promote vascularization [7]. 3D-printing technology basically gives the advantage of organizing the complex microarchitecture of the scaffolds [2]. Material selection is another crucial factor in fabricating a scaffold. Biomaterials determine the mechanical properties of the scaffolds as they need to support the biological medium during the regeneration process [8]. Also, biomaterials need to have similar biomechanical features to native tissue to reduce stress shielding [9]. Various synthetic biomaterials are available in market for use in tissue engineering [10]. In the past two decades, 3D-printing technology has accelerated tissue engineering studies exploring the ideal scaffold for regeneration of musculoskeletal tissues.

Polycaprolactone (PCL) is one of the commonly used biomaterials in tissue engineering studies. PCL is a US FDA-approved, biodegradable, linear polyester material [11]. PCL has good biocompatibility, a slow degradation rate and reduced acidic breakdown end products in addition to its good load-bearing capability. It has a melting temperature of 55–60°C that makes it one of the most preferred polymers for the fabrication of 3DP scaffolds [12]. PCL exhibits good biomechanical features, including high flexibility and elevated elongation capability, in addition to its slow degradation rate which allows bone tissue to remodel after regeneration [13]. These properties make PCL a good candidate for bone and osteochondral regeneration. However, PCL is hydrophobic and does not have osteogenic potential to induce bone healing [14]. For that reason, PCL is generally augmented with varying inorganic substances, metals or collagen to improve the biological properties of the 3DP scaffold.

In orthopedic practice, autografting is the gold standard for bone regeneration [15]. Autografts are used for lateralizing of the glenoid components during reverse total shoulder arthroplasty (RTSA) in patients with glenoid bone defects [16]. Although autografts seem to be successful in this procedure [17], some patients with poor bone stock may require biomaterials for filling the defect size and allowing bone regeneration. In these patients, patient-specific 3DP scaffolds would be a problem-solving alternative for the absence of autografts. In addition, autografting is commonly used for non-union treatment [18]. However, evolving technology and tissue engineering may provide insight into this common practice [19].

Although current literature is expanding, with *in vitro* and *in vivo* studies utilizing 3DP PCL scaffolds in orthopedics, few studies exist investigating the outcomes in humans [20,21]. In this report we aimed to present our cases requiring bone regeneration that underwent treatment with a 3DP PCL + hyaluronic acid scaffold. Moreover, we aim to discuss the current applications of 3DP PCL scaffolds in the field of bone regeneration.

Case presentations

Case 1

A 42-year-old female patient was admitted to our shoulder clinic with ongoing left shoulder pain and restricted range of motion (ROM). The patient's past medical history included rheumatoid arthritis. On the physical examination, the patient had restricted ROM (70 degrees of active forward flexion, 80 degrees of active abduction and 10 degrees of active internal and external rotation) and movement was painful. Neurovascular examination was within normal limits. On radiographs, she had Hamada grade 4B arthritis on the left glenohumeral joint (Figure 1). A shoulder CT scan demonstrated a type B3 bony defect according to modified Walch classification in the central part of the glenoid (Figure 2). We decided to perform RTSA and augment the bony defect with a 3DP PCL + hyaluronic acid matrix (Bloocell®, Sakarya, Turkey).

Bloocell is a CE-marked commercially available product that is 3D-printed within good manufacturing practice-certified production facilities with fusion deposition modeling, extrusion-based 3D printing. Detailed information can be found on the product website (www.bloocell.com). Ethylene oxide was used for sterilization of the products before implantation.

The patient was operated under general anesthesia using a deltopectoral approach in the beach chair position. Humeral head was exposed and cut appropriately, then retractors were placed to expose the glenoid, and the extent of the bony defect in the central part of the glenoid was assessed (Figure 3). Following reaming of the glenoid, the 3DP PCL + hyaluronic acid scaffold (Bloocell), 20 mm in diameter and 10 mm long (Figure 4A), was combined with the glenoid component (Next Shoulder Solutions®, Ivedik, Turkey) (Figure 4B) and then inserted. Then the intramedullary canal of the humerus was prepared and a cementless humeral stem (size 8; Next Shoulder Solutions) was implanted. Trial glenosphere and trial metaphyseal component were then placed to

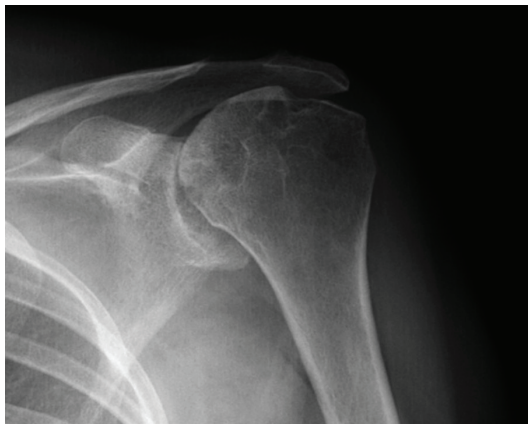

Figure 1. Antero-posterior radiograph of a 42-year-old patient showing Hamada 4B left glenohumeral osteoarthritis.

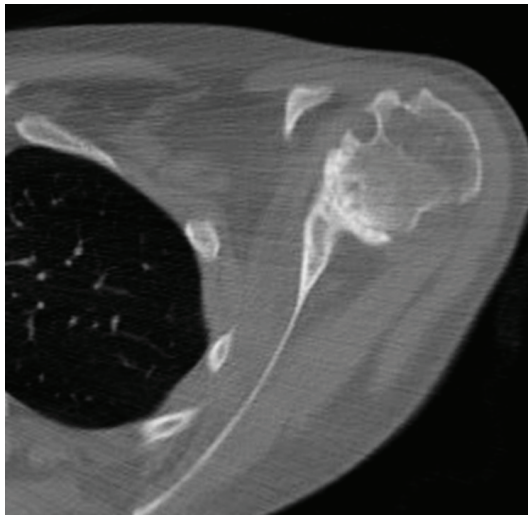

Figure 2. Computed tomography (axial view) of the left shoulder showing type 3 glenoid defect according to modified Walch classification.

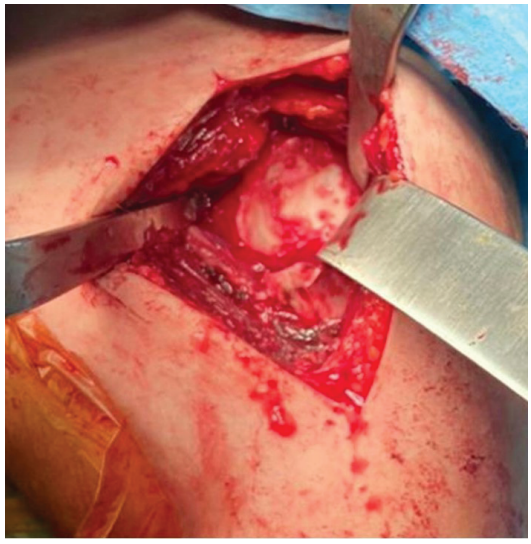

Figure 3. Intraoperative appearance of glenoid confirming central glenoid defect.

determine whether reduction of the components was possible and whether the components were stable. Once the definitive implants were placed, the ROM of the final construct was tested to verify stability of the shoulder, and the wound was closed in layers. Immediate postoperative radiographs revealed good implantation of the components (Figure 5). The patient was placed in an arm sling for 6 weeks. Then physical therapy was initiated and continued

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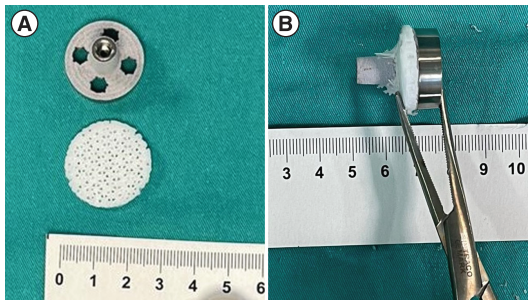

Figure 4. Clinical appearance of 3D-printed polycaprolactone + hyaluronic acid scaffold. (A) Glenoid component and patient-specific 3D-printed polycaprolactone + hyaluronic acid scaffold. **(B)** Combined appearance of scaffold with glenoid component.

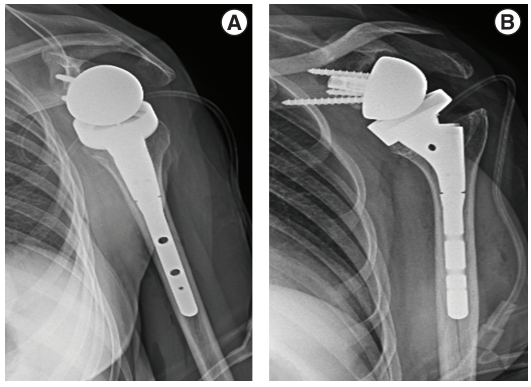

Figure 5. Shoulder radiographs immediately after surgery. (A) Lateral radiograph. **(B)** Anteroposterior radiograph.

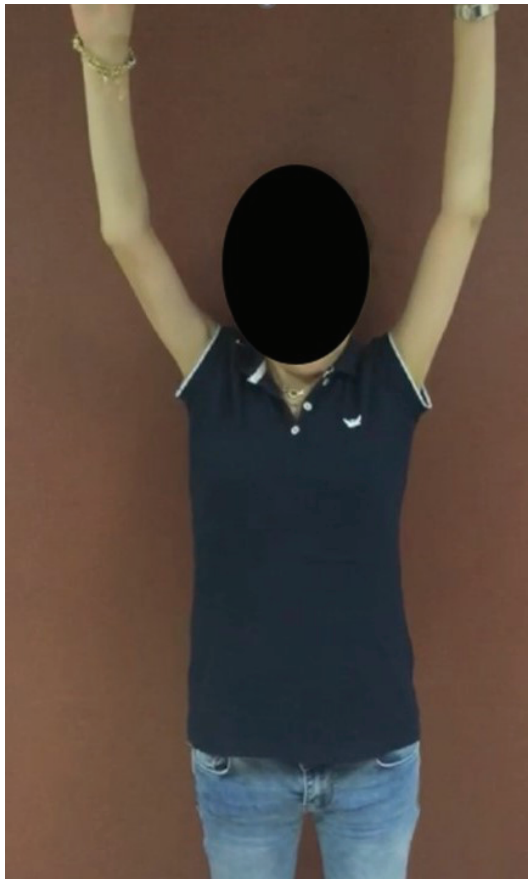

Figure 6. Patient's range of motion at 9-month follow-up.

for 6 weeks. At the final follow-up at 9 months, the patient had full, painless ROM (Figure 6). There was no

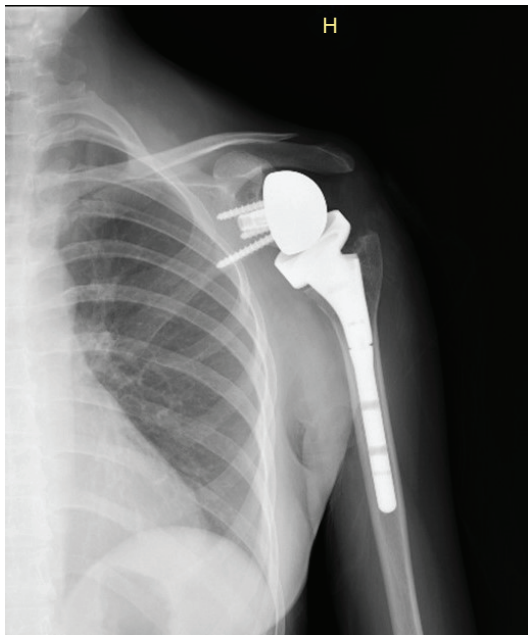

Figure 7. There was no scaffold lysis or implant loosening on radiographs at 9-month follow-up.

loosening of the implants at the final follow-up (Figure 7).

Case 2

A 19-year-old male patient was admitted due to pain in the left forearm and painful wrist movements. The patient noted that he had a forearm injury 1 year previously, for which he was treated with a long arm cast and did not seek any further treatment. On physical examination, the patient's left wrist movements were restricted (20 degrees of extension, 20 degrees of flexion, 5 degrees of ulnar and radial deviation, 5 degrees of pronation and 5 degrees of supination). Neurovascular examination was within normal limits. The distal ulna was prominent at the dorso-ulnar side of the wrist. Radiographic examination revealed a neglected Galeazzi fracture–dislocation accompanied by a radius non-union (Figure 8). We decided to perform open reduction and internal fixation (ORIF) to the radius and to augment the non-union side with a PCL + hyaluronic acid scaffold, and an ulnar shortening osteotomy.

The patient was operated under general anesthesia using the Henry approach for exposure of the radius. After exploration of the non-union side, fibrotic tissue was debrided until healthy bone was exposed. Then a distal ulnar shortening osteotomy was performed for the reduction of the distal radioulnar joint and achievement of compression at the radius fracture site. The non-union side was reduced and enveloped with the 3DP PCL + hyaluronic acid scaffold (Bloocell) (Figures 9 & 10). ORIF was performed with plates and screws on both radius and ulna (Figure 11). Then the layers were closed and the patient was placed in a short arm splint. In the second week, the splint was removed and physical therapy was initiated. At the final follow-up at 6 months, the patient was pain-free on the non-union side (Figure 12). Wrist ROM (40 degrees of extension, 40 degrees of flexion, 15 degrees of ulnar and radial deviation, 30 degrees of pronation and 30 degrees of supination) was improved compared with preoperative examination.

Discussion

Patient-specific 3D-printing technology allows the use of precisely sized materials in orthopedic practice [4]. In our case with a glenoid defect undergoing RTSA, bone regeneration was required for lateralizing the glenoid component. In the current literature, bone autografts harvested from the humeral head are generally used for this purpose [17]. However, our patient was diagnosed with rheumatoid arthritis and her bone stock was quite poor. Therefore we decided to perform an additional bone generation procedure with a 3DP PCL + hyaluronic acid scaffold, and we obtained a good functional outcome. Although autografting is the mainstay of non-union treatment [18], scaffolds may provide insight into bone regeneration and reduce the donor site morbidity of autografts [19]. Our second case with radius non-union obtained good bone healing with the use of a 3DP PCL + hyaluronic acid scaffold envelope on the fracture side.

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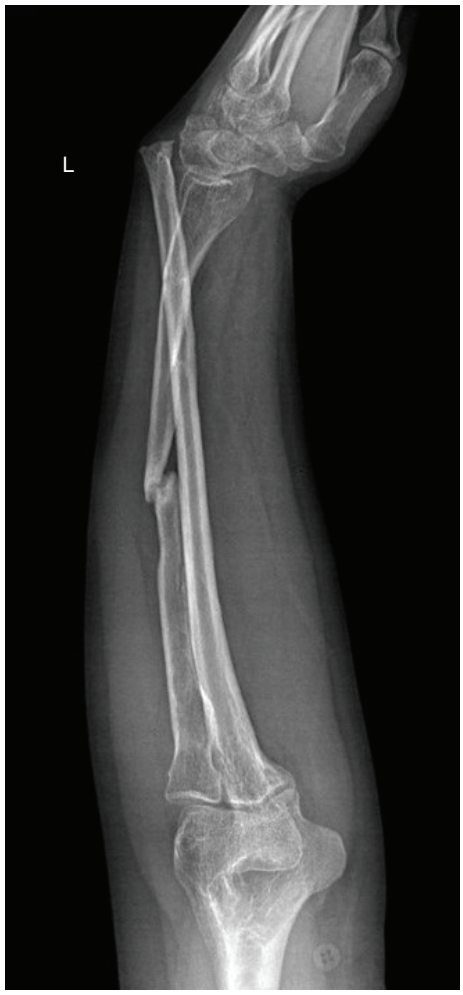

Figure 8. Radiograph of a 19-year-old patient with neglected Galeazzi fracture–dislocation and radius non-union.

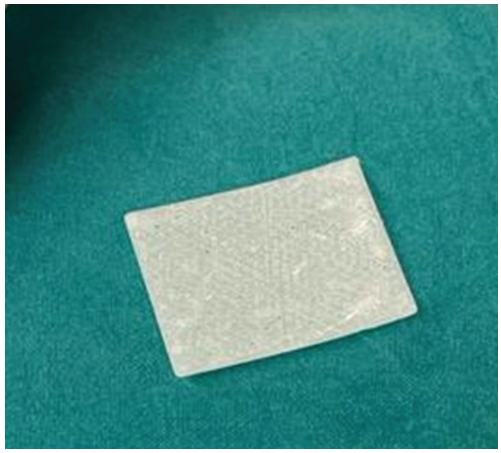

Figure 9. Appearance of the 3D-printed polycaprolactone + hyaluronic acid scaffold before application to the fracture side.

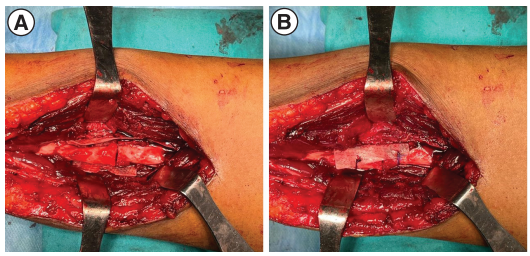

Figure 10. (A) Application of the 3D-printed polycaprolactone + hyaluronic acid scaffold to the fracture and (B) the fracture enveloped with the scaffold.

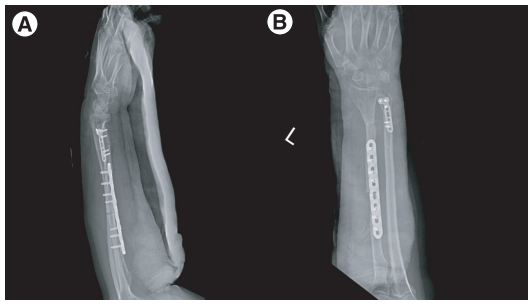

Figure 11. Lateral and anteroposterior radiographs of the patient after fixation with plates and screws.

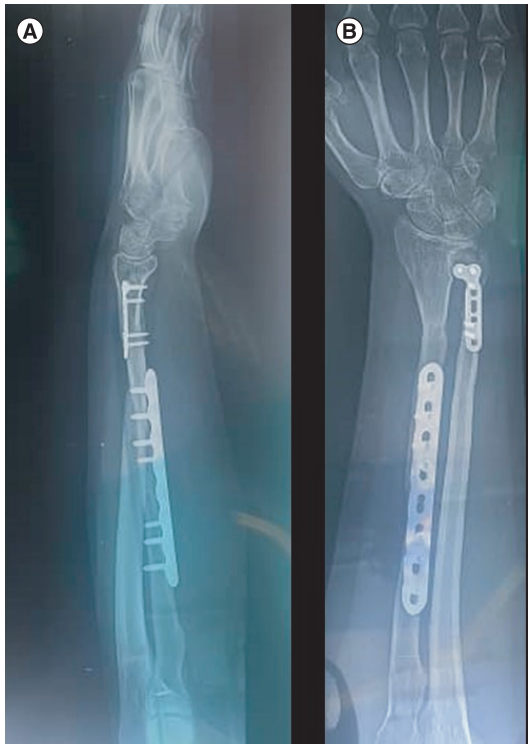

Figure 12. Radiographs showing fracture healing at 6 months. (A) Lateral radiograph. **(B)** Anteroposterior radiograph.

Native and synthetic scaffolds have been studied in bone regeneration. Each scaffold material has its own advantages and disadvantages. Synthetic scaffolds have been criticized for not being precisely identical to native scaffolds in terms of their structural and biochemical properties; on the other hand, the fabrication process of the synthetic scaffolds brings the advantage of greater control of the material characteristics such as shape, bioactivity and porosity [22]. In this regard, PCL has been extensively studied as a promising polymer in the literature for bone regeneration. PCL has been thought a favorable biomaterial for bone regeneration especially due to its similar breakdown rate to native bone tissue, allowing new bone formation [23]. Also, PCL is a suitable polymer for 3D printing, which is an accelerating factor for its use in tissue engineering studies.

3DP PCL-based scaffolds are generally used in three main ways: the 3DP PCL scaffold is combined with bioactive inorganic particles including metals, oxides and other polymers to overcome pure PCL's low hydrophilia and bioactivity [14]; the 3DP PCL scaffolds are loaded with cells to augment their bioactivity [24]; and the 3DP PCL-based scaffolds are used as a carrier for bioactive proteins to increase the local concentration of the desired substances [25].

Pure PCL scaffolds are inherently non-osteoinductive; therefore, numerous forms of calcium phosphate including hydroxyapatite (HA), tricalcium phosphate (TCP) and decellularized bone matrix (DBM) have been incorporated into 3DP PCL scaffolds [26]. HA is a biocompatible and bioactive material that is commonly used as a bone substitute. HA is also used in combination with 3DP PCL scaffolds. Rodrigez *et al.* studied the influence of HA on 3DP PCL scaffolds and concluded that the integration of HA in the 3DP structure of the PCL scaffold improved its

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thermal and biomechanical properties [27]. Park *et al.* compared the biological properties of a pure 3DP PCL scaffold and its combination with HA and stated that the PCL/HA scaffold had a better degree of cell proliferation and differentiation capability [28]. Most recent studies have added a third component, a bioactive protein, to improve the biological properties of PCL/HA scaffolds. Lui *et al.* used VEGF in conjunction with a PCL/HA scaffold and indicated that the PCL/HA/VEGF scaffold initiated better blood vessel formation and was able to enhance bone regeneration better than PCL/HA scaffold [29].

The B-phase form of TCP (B-TCP) has chemically similar apatite to that of native bone tissue; thus B-TCP has been investigated in multiple studies in conjunction with 3DP PCL scaffolds for bone regeneration [24]. Thuaksuban *et al.* demonstrated that the addition of biphasic calcium phosphate accelerated the early differentiation of osteoblasts in the constructs [30]. Chen *et al.* evaluated a PCL/B-TCP scaffold in a rabbit bone-defect model and showed that the PCL/B-TCP scaffold had comparable osteoconduction properties and was associated with equivalent newly formed bone area in the histological analysis compared with a commercially available B-TCP scaffold [31].

Current literature indicates that ceramics made of calcium alginate, aluminum oxide and magnesium phosphate can improve 3DP PCL scaffolds' mechanical properties, degradation time and biocompatibility [23,32]. Although multiple studies exist giving the results of a single 3DP PCL scaffold, only few studies compare the different forms of 3DP PCL scaffolds combined with different materials. Nyberg *et al.* compared four 3DP PCL scaffolds including HA, TCP, Bio-Oss and DBM, respectively, and showed that collagen-1 expression and osteocalcin expression were greater in the PCL/Bio-Oss and PCL/DBM groups. They concluded that PCL/Bio-Oss and PCL/DBM could be more beneficial than PCL/HA or PCL/TCP [33].

Cell loading to 3DP PCL scaffolds has been reported to be a reasonable strategy for bone regeneration. Numerous cells from varying origins have been utilized in this manner, including primary osteoblasts, mesenchymal stem cells from bone marrow and adipose tissue, and dental pulp. Enhancement of PCL scaffolds provided promising outcomes in these studies [34–37]. However, it has been suggested that the effect of seeding cells into scaffolds can be improved with the arrangement of better extracellular matrix within the scaffolds. For this purpose, several types of hydrogels such as hyaluronic acid, agarose and alginate have been proposed to enrich the biological medium for cells on 3DP PCL scaffolds [38]. These hydrogels provide better cellular interaction and biocompatibility under the umbrella of adequately stiff 3DP PCL scaffolds [39]. Hamlet *et al.* combined hyaluronic acid hydrogels, osteoblasts and BMP7 with a 3DP PCL scaffold in a rat model, and concluded that the PCL + hyaluronic acid hydrogel yielded a good environment for bone regeneration [40]. Hyaluronic acid has a similar water content to human tissue, and good biocompatibility, thereby providing a good medium for cell signaling [41]. In our case, given the absence of scaffold lysis in the last follow-up of the RTSA case and good bone healing in the non-union case, we may argue that the 3DP PCL + hyaluronic acid scaffold provided a good environment for bone regeneration.

3DP scaffolds can be used as a carrier for a specific substance to increase its local effects, thereby improving the biological activity of the scaffolds. In addition, the 3DP microarchitecture of the PCL scaffolds can be organized according to the desired release rate of the substances [42]. Several growth factors and cytokines, including bone morphogenic proteins, TGF, PDGF, VEGF and IL-6, have been proven to mediate the important cornerstones of the bone regeneration process [43]. Huri *et al.* studied a 3DP PCL scaffold enriched with BMP7 and BMP2 in a rabbit iliac crest critical-sized bone defect model. Their study showed that the 3DP PCL scaffold with sequential bone morphogenic protein release pattern provided better bone regeneration [25]. Wagner *et al.* showed that VEGF-containing 3DP PCL scaffolds yielded superior vascular proliferation compared with the control group [44]. Li *et al.* implanted traditional and freeze-dried platelet-rich plasma (PRP) on 3DP PCL scaffolds. Their results showed that freeze-dried PRP significantly improved bone formation compared with a pure PCL scaffold and the PCL + traditional PRP group [45].

Despite growing *in vitro* and *in vivo* knowledge regarding 3DP PCL scaffolds, their clinical translation is still scant. Kobbe *et al.* treated a 29-year-old male with a large femoral bony defect due to the sequelae of open fractures using a patient-specific 3DP PCL + TCP scaffold combined with an autologous bone graft and BMP2. After 12 months of implantation, the patient had solid fusion and interconnection of scaffold to the bone [46]. Recently, Castrisos *et al.* reported a series of four patients with critical-sized bone defects treated with a 3DP PCL + TCP scaffold augmented with free corticoperiosteal flaps. Their series included two tibial bone defects secondary to osteomyelitis and Ewing sarcoma, one calvarium defect due to sequelae of infected cranioplasty, and one mandible defect because of hemifacial microsomia. At medium-term follow-up, all four patients had functional volumes of regenerated bone [20]. Laubach *et al.* reported the largest series including post-traumatic lower-extremity long-bone defects treated with patient-specific 3DP PCL scaffolds and autologous bone grafts. The authors produced 3DP

PCL + TCP scaffolds using computed tomography images of the corresponding defects. Three of the patients showed bony ingrowth into the scaffold 8–9 months after the surgery; the remaining patient achieved bone regeneration and was able to give full weight 23 months after surgery [21]. Our cases demonstrated the successful application of the 3DP PCL + hyaluronic acid scaffold for filling the glenoid defect during RTSA and bone regeneration in non-union.

The current study is not without limitations. There was no control group to compare the outcomes of the 3DP PCL + hyaluronic acid scaffold. The long-term follow-up is lacking, despite promising early outcomes. However, the current study has several strengths and novelty. We were able to show that the 3DP PCL + hyaluronic acid scaffold has promising capacity in terms of bone tissue regeneration in humans. We believe this clinical translation will be encouraging for future studies.

Conclusion

In conclusion, the 3DP PCL + hyaluronic acid scaffold had a good outcome in a young patient suffering from rheumatoid arthritis and with severe glenoid bone loss who underwent RTSA, and in a patient with radius non-union treated with debridement of the non-union and ORIF. The 3DP PCL + hyaluronic acid scaffold may be a promising alternative to autografting for bone regeneration in orthopedic practice.

Executive summary

- Polycaprolactone (PCL) is one of the commonly used biomaterials in bone regeneration.
- Clinical translation of 3D-printed PCL scaffolds is currently limited.
- Although autografts are the gold-standard options for bone regeneration, newly produced 3D-printed scaffolds can substitute the use of autografts and reduce donor site morbidities.
- Bone regeneration with a 3D-printed PCL + hyaluronic acid scaffold showed encouraging clinical outcomes in a patient with severe glenoid bone loss who underwent reverse total shoulder arthroplasty and in a patient with radius non-union treated with debridement of the non-union and open reduction and internal fixation.

Author contributions

All the authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work; to drafting the work or revising it critically for important intellectual content; giving final approval of the version to be published; and agreeing to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have followed the principles outlined in the Declaration of Helsinki for all human investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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