Foot and Ankle Surgery 28 (2022) 1293–1299

Contents lists available at ScienceDirect

Foot and Ankle Surgery

journal homepage: www.journals.elsevier.com/foot-and-ankle-surgery

Fiber-reinforced fixation implant for proximal interphalangeal joint arthrodesis shows advanced implant bio-integration at 2-year follow-up

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ARTICLE INFO

Article history:
Received 29 March 2022
Received in revised form 16 June 2022
Accepted 21 June 2022

Keywords:
Arthrodesis
Fusion
Continuous mineral fibers
Hammertoe
Degradation
Bio-integration
Magnetic Resonance Imaging (MRI)

ABSTRACT

Background: A bio-integrative fiber-reinforced implant (OSSIOfiber® Hammertoe Fixation Implant, OSSIO Ltd., Caesarea, Israel) for proximal interphalangeal joint (PIPJ) correction-arthrodesis showed partial bio-integration at 1-year follow-up (1FU) in a previous study. The study was prolonged to assess the bio-integration at 2-year-follow-up (2FU).
Methods: Twenty-four patients with proximal interphalangeal joint (PIPJ) correction-arthrodesis using the fiber-reinforced implant and analysed at 1FU, completed 2FU. Follow-up included clinical examination, patient reported outcomes, radiographs, MRI and bio-integration scoring. Results were compared between the 1FU and 2FU (paired t-test).
Results: Radiographs confirmed fusion in 96 % (n = 23) at 2FU (1FU, 92 % (n = 22)). Implant was no longer visible in 21 % (n = 5), partially visible in 33 % (n = 8), and fully visible in 46 % (n = 11)(1FU, fully visible 100 % (n = 24)). The border between implant and surrounding bone was scored not visible in 88 % (n = 21) and partially visible in 12 % (n = 3) (1FU, border partially visible 100 % (n = 24)). There were no cyst formation or fluid accumulation findings 1FU/2FU. Mild bone edema was detected in 4 % (n = 1) (1FU, 29 % (n = 7)). None of the edema findings were considered as adverse implant related. The mean bio-integration score was 9.71 ± 0.69 at 2FU (1FU, 7.71 ± 0.46). The parameters of border between implant and bone and bone edema further improved at the 2FU compared to the 1FU, total bio-integration score was also higher at 2FU than 1FU (each $p < 0.05$).
Conclusions: This study demonstrates 96 % PIPJ fusion rate and increased bio-integration from 1FU to 2FU, reaching advanced bio-integration of the fiber-reinforced implant at 2FU.

1. Introduction

When considering an ideal orthopaedic fixation implant, such implant should fulfil its intended use, while undergoing an elimination process without causing adverse tissue reaction. For this reason, integration, or better bio-integration with the surrounding tissue, without adverse inflammatory reaction, is an important goal for the ongoing development and wider acceptance of non-permanent orthopaedic devices [1].

A bio-integrative fiber-reinforced material technology has been shown in animal models to maintain strength during bone healing while undergoing a controlled and gradual degradation, with reduced adverse inflammatory response [2,3]. Previous clinical publication for the fiber-reinforced implant used for proximal interphalangeal joint (PIPJ) correction-arthrodesis (OSSIOfiber® Hammertoe Fixation Implant, OSSIO Ltd., Caesarea, Israel) demonstrated favourable PIPJ fusion rates and clinical outcomes at 6-months [4]. A longer follow-up of 1 year (1FU) was the first to assess the bio-integration of an implant for osteosynthesis, using a newly developed scoring system [1]. The bio-integration scoring was devel-

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https://doi.org/10.1016/j.fas.2022.06.013

Table 1
Study inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Subject successfully enrolled in original 26 weeks follow-up study (i.e. treated with OSSIOfiber™ Hammertoe Fixation Implant)	Subject is unable to attend the scheduled follow up visits
Subject completed all required visits under protocol for original 26 weeks follow-up study	Women who are pregnant or who intend to become pregnant during the course of the study.
Subject did not require any revision surgery of the treated toe	Any condition which in the view of the principle investigator makes it unsafe for the subject to participate in this study.
Subject has given voluntary, written informed consent.	
Subject is able to understand the clinical investigation and is able and willing to perform all study follow-up visits and procedures.	

oped based on MRI, as it allows for better evaluation of soft tissue response [1].

Side effects such as inflammation, cyst formation or fluid accumulation were not observed at 1FU [1]. The present study includes 2-year follow-up (2FU), based on material degradation profile as shown in animal models [2,3].

The main purpose of this 2FU was to collect clinical, radiological and bio-integration parameters for comparing with 1FU. The hypothesis was that bio-integration parameters and score will show increased bio-integration at 2FU compared to 1FU.

2. Material and methods

2.1. Study design [1]

This multicentre, prospective, single-arm, open-label study was conducted at an orthopaedic hospital in Slovenia and two foot and ankle surgery centres in Spain between December 2019 and June 2021. Patients aged 18–75 years who required PIPJ arthrodesis and participated in the previous study assessing the safety and performance of the bio-integrative implant for correction of hammertoe deformity and were able to provide written, informed consent were eligible for inclusion in this follow-up study [1]. Further inclusion and exclusion criteria are shown in Table 1 [1]. Recruitment was set at a minimum of 75 % from original study cohort of 25 patients [1]. This study adhered to the Declaration of Helsinki and was approved by the national ethics committee for each institution [1].

During the screening visit, the patient demographic data, medical history, medication information and clinical assessment of the operated foot were recorded [1]. Foot and toe assessment as well as pain score (0–10) [1]. Radiographs were taken and evaluated and computed tomography (CT) scans were ordered at the surgeon's discretion [1].

2.2. Implant [1]

The bio-integrative hammertoe fixation implant (OSSIO*fiber*® Hammertoe Fixation Implant, OSSIO Ltd., Caesarea, Israel) is comprised of continuous, reinforcing mineral fibers (SiO_2, Na_2O, CaO, MgO, B_2O_3, and P_2O_5; approximately 50 %w/w), which have been shown both *in vitro* and *in vivo* to support bone growth and regeneration and are bound together with PLDLA polymer resin (approximately 50 % w/w) [1,3]. Controlled and gradual bio-integration into the surrounding bone without adverse inflammatory response, has been previously shown [1,2]. The implant used in this study has a hexagonal cross-section with a nominal dimension of 2.9 mm diameter and 19 mm length (Fig. 1a) [1]. The ribbed design allows for implant fixation in the phalangeal canal of the toe. The internal structure of the implant consists of layers of oriented continuous fibers (Fig. 1b) that should provide mechanical strength through the bone healing process [1].

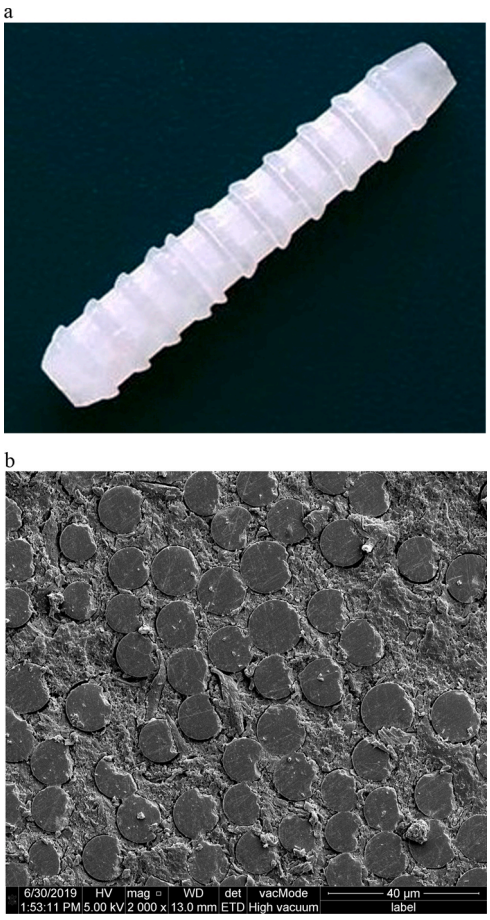

Fig. 1. a. shows the 2.9 mm bio-integrative, fiber-reinforced hammertoe fixation implant (OSSIO*fiber*® Hammertoe Fixation Implant, OSSIO Ltd., Caesarea, Israel) used in this study. b. shows an electron microscope cross-section scan demonstrating continuous mineral fibers surrounded by polymeric material.

2.3. Surgical procedures [1]

Two foot and ankle surgeons performed all surgeries at three different sites. Each surgery took place within 30 days of enrolment or pre-screening radiographs (Fig. 2a and b). On the day of the surgery, patient eligibility was confirmed, medications information was recorded, and a foot and toe assessment were performed. For the surgery, local and/or regional anaesthesia was administered.

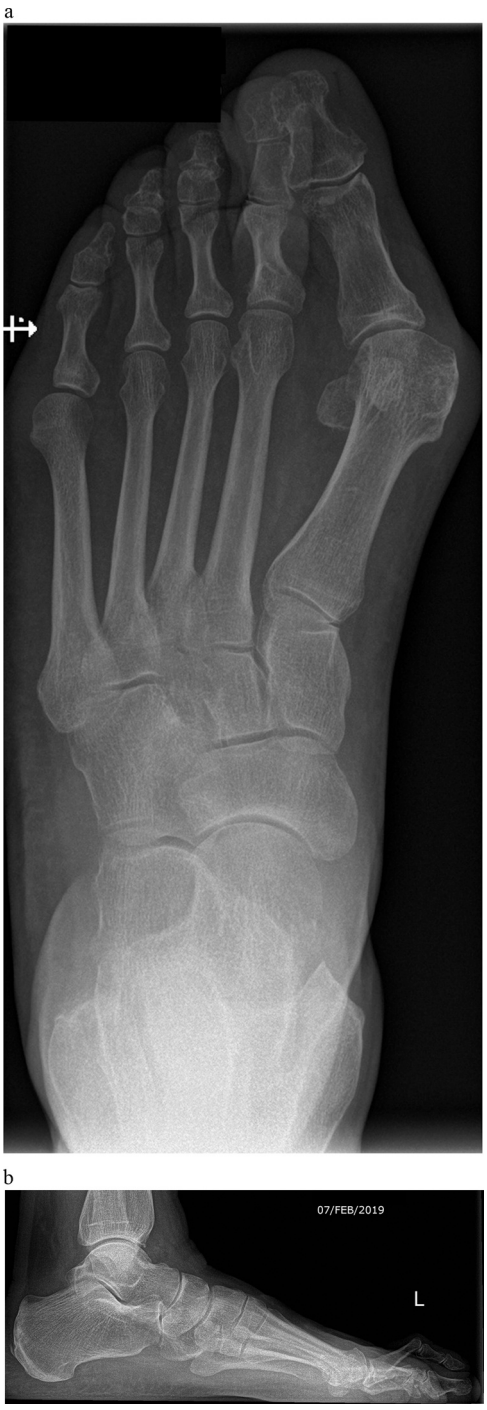

Fig. 2. Study case, initial assessment [1]. A 64-year-old female with forefoot deformity including Hallux valgus and hammertoe at the 2nd ray without relevant overlength of the metatarsal at the left foot. a. shows the dorsoplantar preoperative radiograph with full weight bearing. b. shows the lateral preoperative radiograph with partial weight bearing following the local standard showing the plantarflexed subluxation of the 2nd PIPJ.

Following the site standard of care, some patients received prophylactic antibiotic. During the surgery, fluoroscopy imaging was used. A straight longitudinal midline approach over the PIPJ was used. Resection of both joint surfaces followed. The proximal phalanx diaphyseal canal and the middle phalanx diaphyseal canal were drilled with 2.9 mm diameter to the appropriate depth (Fig. 3a). Using the implant holder, the proximal end of the fiber-reinforced hammertoe fixation implant was introduced into the proximal phalanx, parallel to the long axis of the drill hole to prevent bending (Fig. 3b-c). The middle phalanx was manually reduced over the distal end of the implant while applying slow, steady pressure until bone-to-bone contact was reached (Fig. 3d). After confirming that the implant was properly fitted and fixated to the bone, the surgeon completed the procedure using routine soft tissue closure.

2.4. Aftertreatment [1]

Dorsoplantar, lateral and lateral oblique radiographs were taken immediately following the procedure. All patients were fitted with a protective shoe for six weeks. Patients were advised to elevate the foot for the early postoperative days. At one week postoperative, patients returned to clinic for a dressing change and wound evaluation.

2.5. Follow-up

The 2FU was performed analogue to the previous 1FU except for patient satisfaction and function level questionnaires which were not repeated [1]. Clinical examination, radiographs (Fig. 4a), pain score, and MRI assessments (Figs. 4b-c and 5a-c, minimum resolution 1.2 mm, Table 2) were included [1]. A MRI based bio-integration score has been developed, and adequate intra-observer reliability has been proven during the 1FU-study (Table 3) [1]. MRI was reviewed and analysed by a certified, independent reviewer [1]. Adverse events (AE) were registered.

2.6. Bio-integration score [1]

We were not aware of a scoring system for implant degradation or bio-integration; therefore, we created a system for the previous study (Table 3) [1]. Optimal bio-integration was considered as a non-visible border between implant and bone, and lack of fluid, implant-related bone edema or cyst formation [1]. This finding results in a maximum bio-integration score of 10 points [1]. In contrast, clearly visible border between bone and implant, with evidence of cyst formation, implant-related bone edema and fluid result in a minimum bio-integration score of 0 points [1].

2.7. Statistics

Excel Version 1809 (Microsoft, Redmont, WA, USA) was used for the statistical comparison of 1FU/2FU (paired t-test, heteroscedatic).

3. Results

3.1. Patients

From a potential cohort of 25 patients, 24 were screened and enrolled in the longer term 2FU, including 23 female (96 %) and 1 male (4 %) [1]. The one excluded was hospitalized due to breast cancer recurrence at the time she was approached regarding the study, and she was not available to continue the screening process. The mean age of the cohort was 64.9 ± 7.3 (range, 50–75) years.

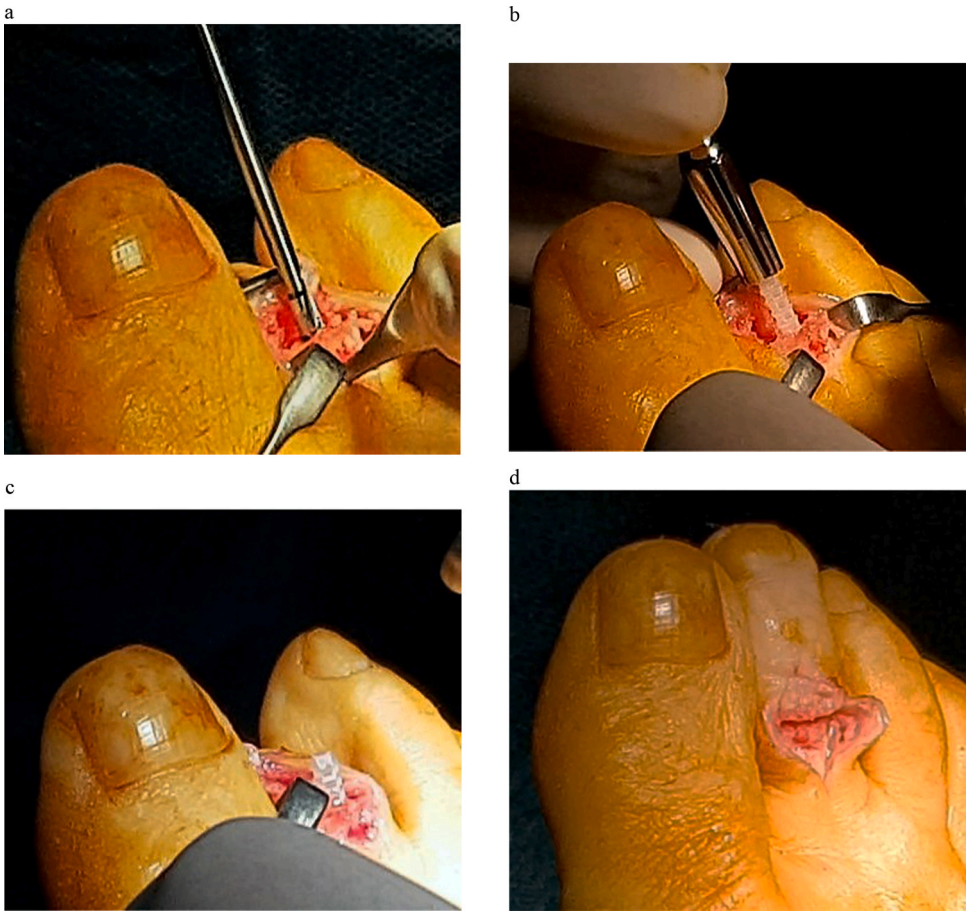

Fig. 3. Intraoperative situs. A 2.9 mm diameter, marked drill to create tunnel in the proximal phalanx (a). Implant insertion with inserter retrograde into proximal phalanx (b). Implant distal side visible following insertion into the proximal phalanx (c). After mounting the middle phalanx onto implant gradual pressure is applied until bone to bone contact is achieved (d).

3.2. Procedures

The hammertoe deformity affected the second toe in 23 patients (96 %), and the third toe in one patient (4 %). Nineteen patients (76 %) underwent concomitant procedures for first ray deformities, including corrective osteotomies and first metatarsophalangeal joint fusion.

3.3. Follow-up

All 24 patients completed 2FU. Radiographs confirmed fusion in 96 % (n = 23) at 2FU (1FU, 92 % (n = 22), p = 0.16). While at the 1FU visit implant was visible on MRI for all patients (n = 24), at the 2FU implant was no longer visible for 21 % (n = 5), partially visible for 33 % (n = 8), and fully visible for 46 % (n = 11) of patients. Table 4 shows the results of the MRI bio-integration assessment and scoring. The border between implant and surrounding bone was scored not visible in 88 % (n = 21) and partially visible in 12 % (n = 3)(1FU, partially visible 100 % (n = 24)). There were no cyst formation or fluid accumulation findings at 1FU/2FU. Mild bone edema was detected in 4 % (n = 1)((1FU, 29 % (n = 7)). None of the edema findings were considered as adverse implant related. The mean bio-integration score was 9.71 ± 0.69 at 2FU (1FU, 7.71 ± 0.46). Implant to bone border, bone edema and total bio-integration scores improved at the 2FU compared to 1FU (each $p < 0.05$). Pain scores further improved to 0.04 ± 0.20 at 2FU (pre-operative screening, 5.3 ± 2.5, 1FU, 0.29 ± 1.08; p = 0.12). No implant or procedure related AEs were registered.

4. Discussion

Many implants are classified as “resorbable”, “absorbable” or "degradable", even Magnesium-alloys and Polyvinyl implants [1,4–9]. There are many benefits for non-permanent implants in orthopaedic surgery, however tissue adverse reaction to the degradation by-products remains a challenge. There is an unmet need for a fixation implant that will maintain mechanical strength while undergoing a process of quiescent degradation, i.e., a controlled, paced bio-integration process in sync with the healing bone that avoids an adverse inflammatory response [1,4–9]. This is the first study showing advanced bio-integration of an implant for osteosynthesis at 2FU [1] The advanced bio-integration occurred in combination with 96 % fusion rate and without implant or procedure

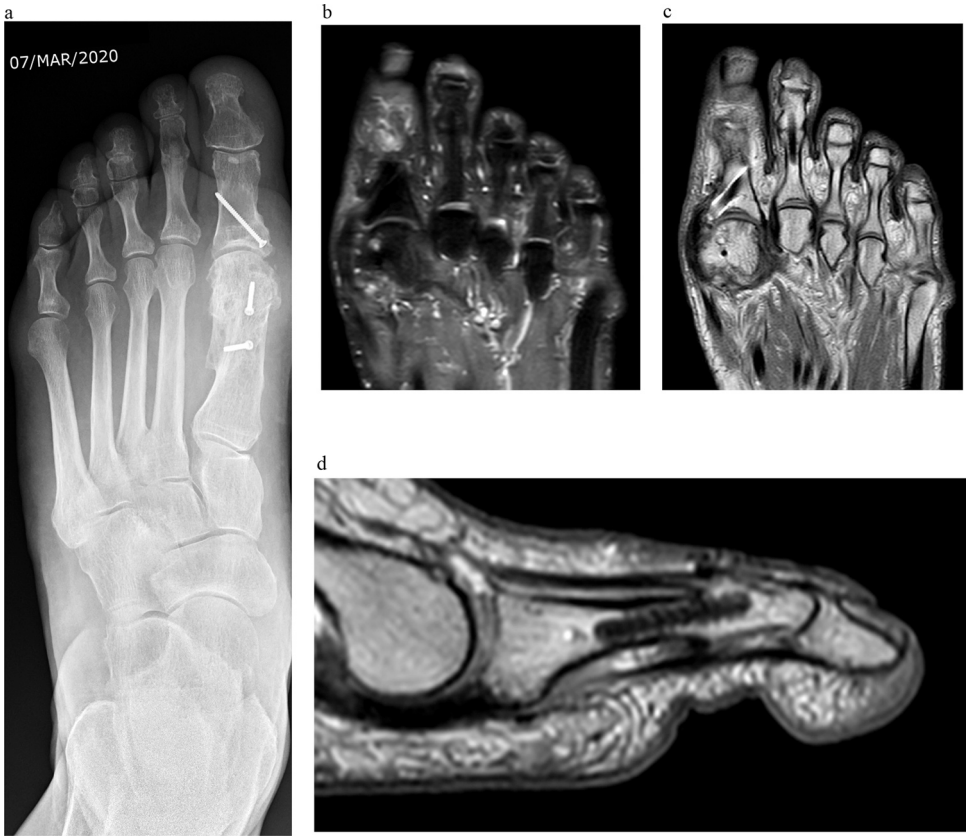

Fig. 4. Same study case as Fig. 2. 1-year follow-up [1]. a. shows a dorsoplantar radiograph with full weight bearing at 1-year follow-up confirming complete fusion of the 2nd PIPJ. b. is a coronal inversion recovery MRI image without edema or cystic change. c. is a coronal proton density image demonstrating no edema or cystic change and a partially visible border between implant and bone. d. shows a parasagittal proton density image with blurred margins about the implant in the process of bio-integration. The bio-integration score calculates as follows, Border between implant and bone, partially visible, 2 points; bone edema, none, 2 points; cyst formation, no, 2 points; fluid accumulation, no, 2 points; total score, 8 points.

related AEs, correlating well with results previously demonstrated for these implants in animal models [2,3].

Different options for the assessment of bio-integration were discussed including CT and MRI [1]. The potential advantage of MRI over CT lies in better detection of tissue inflammation parameters whereas CT was considered for its higher resolution abilities [1]. Based on a special scanning protocol, we could achieve a resolution/slice thickness of 1.2 mm which we considered as adequate and lessens the potential risk of missing important data (Figs. 4b-d, 5a-c).

The bio-integration assessment and score were developed for 1FU (Table 3) [1]. Optimal bio-integration was considered as a non-visible border between implant and bone, and lack of fluid, implant-related bone edema or cyst formation [1]. This finding would result in a maximum bio-integration score of 10 points [1]. In contrast, clearly visible border between bone and implant, with evidence of cyst formation, implant-related bone edema and fluid results in a minimum bio-integration score of 0 points [1]. The average bio-integration score in our study was 9.71 ± 0.69 corresponding to advanced bio-integration by definition. The score massively increased in 2FU compared to 1FU (7.71 ± 0.46). We consider this a very favourable result. We cannot compare this with the literature since to our knowledge there is no published comparable data. Although the implant was still visible in 79 % (1FU, 100 %), the border between implant and surrounding bone was not visible in 88 % and only partially visible in the remaining 12 % (1FU, partially visible 100 %). These findings show the significant progress of implant bio-integration between 1FU and 2FU. There were no cyst formation or fluid accumulation findings at 1FU/2FU. These parameters of cyst formation and fluid accumulation, did not differ between the time-points, thus did not affect the bio-integration score results. However, both have been commonly described in the literature as possible side effects of degradation response and therefore remain an important part of the bio-integration score [1,4–9]. One potential disadvantage of any intramedullary implant would be difficult implant removal in case of infection. Partial bio-integration would potentially make it more difficult to remove the remaining implant. However, the bio-integrative implants can be drilled through and removed in case of a suspected infection. This study was looking into fusion rates, bio-integration scores, and adverse events. We did not observe infection in this 2FU study but in the case a need to remove an implant occurs, this could be easier than removing a permanent highly osteoconductive implant such as titanium alloy, especially with additional coating.

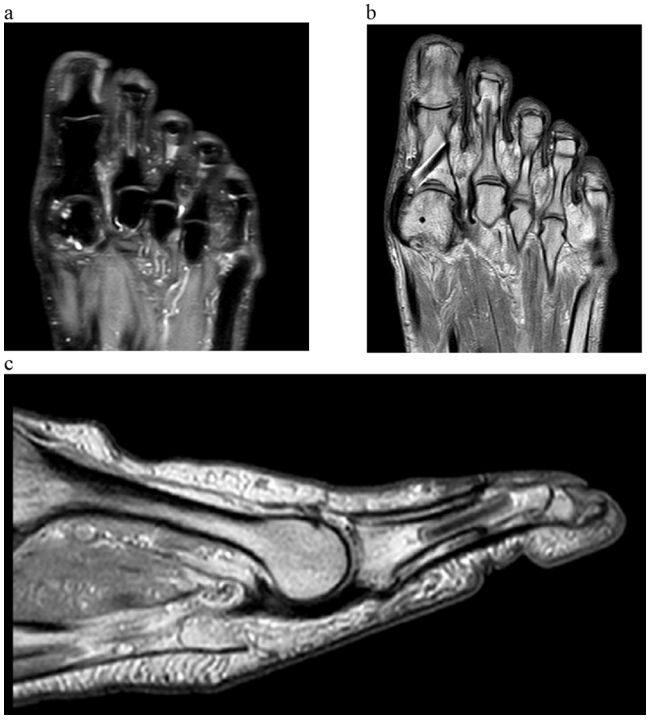

Fig. 5. Same study case as Figs. 2 and 3. 2-year follow-up. a. shows a coronal inversion recovery image demonstrating marked blurring of the margins of the implant with a thin shell of hyperintensity felt to represent the bio-integration response. b. shows coronal PD -with a markedly defined and blurred border between implant and bone. c. shows a parasagittal reformation proton density with blurred margins about the implant in the process of bio-integration. The bio-integration score calculates as follows, Border between implant and bone, not visible, 4 points; bone edema, none, 2 points; cyst formation, no, 2 points; fluid accumulation, no, 2 points; total score, 10 points.

Table 3
Bio-integration Score (BIS).

Parameter	Points
Border between implant and bone	
Not visible	4
Partially visible	2
Clearly visible	0
Bone edema	
None	2
Mild	1
Moderate/massive	0
Cyst formation	
No	2
Yes	0
Fluid accumulation	
No	2
Yes	0

In total Minimum 0 = no bio-integration, maximum 10 = complete bio-integration.

Table 4
Bio-integration score results at 1-/2-year follow-up.

Parameter	Points		
	mean ± std		paired
	1 year follow-up	2 year follow-up	t-test, p
Border between implant and bone (0–4)	2.0 ± 0	3.8 ± 0.7	< 0.001
Bone edema (0–2)	1.71 ± 0.46	2.0 ± 0.2	0.005
Cyst formation (0–2)	2.0 ± 0	2.0 ± 0	(1)
Fluid accumulation (0–2)	2.0 ± 0	2.0 ± 0	(1)
Total score (0–10)	7.71 ± 0.46	9.71 ± 0.69	< 0.001

std, standard deviation.

4.1. Shortcomings of the study

Shortcomings of this study are low case number, missing control group, and the relatively short follow-up time. The case number was calculated with a focus on safety and implant performance. A missing control group is a methodological shortcoming as in many other studies that we cannot invalidate. A follow-up time of 2 years meets international scientific standards for clinical studies with a minimum of 2-year follow-up. The results demonstrate that advanced bio-integration has occurred by two years of implantation (9.71 bio-integration score of a maximum of 10). Another potential limitation is the assessment method of bio-integration with a new

Table 2
MRI protocol.

Coil	8ch. foot/ankle coil / 16ch flex coil
Position	–
Landmark	–
Series I	Axial FSE TR 3400 /TE 4000msec; BW 31 kHz; ETL 7–9; NEX 2; FOV 10 cm; SL 3–3.5 mm; matrix 512 × 320
Series II	Coronal STIR TR 4000 /TE 17msec; TI 150(1.5T) 190(3T); BW 31 kHz; ETL 7–9; NEX 2; FOV 16 cm; SL 3 mm; matrix 256 × 192
Series III	Sagittal thin Oblique FSE angled to the operated toe metatarsal shaft TR 4000/TE 34msec; BW 31.2 kHz; ETL 7–10; NEX 2; FOV 15 cm; SL 1.2 mm; matrix 512 × 384
Series IV	Sagittal Oblique FSE 2nd through 5th MT shafts TR 4000/TE 34msec; BW 31.2 kHz; ETL 7–10; NEX 2; FOV 15 cm; SL 2–2.5 mm; matrix 512 × 320–384
Series V	Coronal FSE TR 4000/TE 34msec; BW 31.2 kHz; ETL 7–10; NEX 2; FOV 12 cm; SL 1.2–2 mm; matrix 512 × 320–352
Series VI	Sagittal STIR TR 4000 /TE 17msec; TI 150(1.5T) 190(3T); BW 31 kHz; ETL 7–9; NEX 2; FOV 15 cm; SL 25–2.8 mm; matrix 256 × 192

BW – bandwidth.
ETL – echo train length.
SL– slice thickness.
NEX – number of excitations.

scoring system as introduced before [1]. As far as we know, no other system for assessment/scoring exists. Also, in some cases the prescribed MRI protocol was not fully adhered to, nonetheless the images submitted for review were deemed diagnostic.

5. Conclusions

This study demonstrates 96 % PIPJ fusion rate, an increase bio-integration score results in comparison with the 1FU and advanced bio-integration of the fiber-reinforced implant at 2FU.

The implants gradual elimination was not associated with any adverse tissue reaction. These results of better bio-integration with the surrounding tissue suggest that fiber-reinforced implants are an important step forward in advancing the beneficial clinical use of non-permanent orthopaedic devices.

Declaration of Competing Interest

I declare the following potential conflicts of interest. Luke D. Cichinelli, Martinus Richter and Stuart Miller are consultants of Ossio. Martinus Richter is consultant of Curvebeam, Geistlich, Intercus, and Implants International, proprietor of R-Innovation, and shareholder of Curvebeam.

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