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Clinical Outcome After Anterior Lumbar Interbody Fusion With a New Osteoinductive Bone Substitute Material

A Randomized Clinical Pilot Study

Marcus Rickert, MD, Christoph Fleege, MD,* Ioannis Papachristos, MD,* Marcus R. Makowski, MD,† Michael Rauschmann, MD,* and Mohammad Arabmotlagh, MD**

Study Design: Pilot, single-center, single-blinded, parallel-group, randomized clinical study.

Objective: The aim of this study was to pilot a randomized clinical study to evaluate whether instrumented anterior lumbar interbody fusion (ALIF) with a new nanocrystalline hydroxyapatite embedded in a silica gel matrix (NH-SiO_2) leads to superior radiologic and clinical outcomes at 12-month follow-up compared with instrumented ALIF with homologous bone.

Summary of Background Data: ALIF completed with interbody cages is an established technique for performing arthrodesis of the lumbar spine. There is ongoing discussion about which cage-filling material is most appropriate. This is the first study to assess the efficacy of NH-SiO_2 in ALIF surgery.

Materials and Methods: This randomized, clinical, pilot trial included 2 groups of 20 patients with monosegmental or multisegmental degenerative disease of the lumbar spine who were suitable to undergo monosegmental or bisegmental ALIF fusion at the level L4/L5 and L5/S1 with a carbon fiber reinforced polymer ALIF cage filled with either NH-SiO_2 or homogenous bone. Primary outcome was postoperative disability as measured by the Oswestry Disability Index (ODI). Secondary outcomes were postoperative radiographic outcomes, pain, and quality of life. Patients were followed 12 months postoperatively.

Results: Mean ($\pm$SD) 12-month ODI was 24 ± 17 in the NH-SiO_2 group and 27 ± 19 in the homologous bone group ($P = 0.582$). Postoperative radiography, functional outcomes, and quality-of-life indices did not differ significantly between groups at any of the regularly scheduled follow-up visits.

Conclusions: This clinical study showed similar functional, radiologic, and clinical outcomes 12 months postoperatively for instrumented ALIF procedures with the use of NH-SiO_2 or homologous bone as cage filling. In the absence of any relevant differences in outcome, we postulate that the pivotal clinical study should be designed as an equivalence trial.

Key Words: spine, ALIF, fusion, hydroxyapatite, randomized clinical trial, outcomes

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Anterior lumbar interbody fusion (ALIF) performed with interbody cages restores physiological disk height and stabilizes spinal segments.[1,2] Secondary fixation is obtained by through-the-implant growth of bone, which is obtained by filling the central cavity with cancellous bone, sterilized allograft bone, or other osteoconductive and osteoinductive material.[3,4] NanoBone Putty (Artoss GmbH, Rostock, Germany) is a soft, malleable paste made of nanocrystalline hydroxyapatite embedded in a silica gel matrix (NH-SiO_2). This synthetic hydroxyapatite (HA) scaffold is manufactured in a sol-gel process.[5] Its chemical composition and crystalline structure is similar to the body's own HA. The porous silica gel matrix gives the material a high specific surface area, enhances the material's solubility, and facilitates the adhesion of autologous molecules and rapid vascularization. Preclinical studies have shown that NH-SiO_2 has osteoinductive and bioresorbable properties, and is highly biocompatible. In addition, it shows a high angiogenic response, and induces fast bone regeneration.[6–9] Good early clinical results were obtained with NH-SiO_2 as bone graft material in tibiae of sheep.[7] In-vivo, it has also been successfully used to fill dentoalveolar defects.[10–12] However, to the authors' knowledge, there are no published results from clinical studies that have used NH-SiO_2 in spinal surgery.

The aim of the present study was to conduct a trial of NH-SiO_2 embedded in a porous silica gel matrix in patients undergoing lumbar ALIF with a carbon fiber reinforced polymer cage, in order to guide future research. The primary outcome of the present study was the Oswestry Disability Index (ODI) at 1-year follow-up. Secondary outcomes were postoperative fusion rates, back

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From the *Orthopaedic University Hospital Friedrichsheim gGmbH, Frankfurt am Main; and †Department of Radiology and Neuroradiology, Charité-University, Berlin, Germany.

The authors declare no conflict of interest.

Reprints: Marcus Rickert, MD, Orthopaedic University Hospital Friedrichsheim gGmbH, Marienburgstrasse 2, 60528 Frankfurt am Main, Germany (e-mail: marcusrickert@gmx.de).

and leg pain, and quality of life as measured by the EuroQoL 5D (EQ-5D). All patients were monitored until 12-month follow-up.

MATERIALS AND METHODS

A randomized, clinical, pilot study was conducted, in which 40 patients scheduled to undergo surgery of the lumbar spine between July 2012 and October 2013 gave informed consent. Ethics committee approval was obtained before study initiation. Eligible for the study were mature patients with monosegmental or multisegmental degenerative disease of the lumbar spine suitable to undergo monosegmental or bisegmental spondylodesis at the level L4/L5 and L5/S1 with a carbon fiber reinforced polymer ALIF cage (ALIF CFRP I/F Cage, DePuy Synthes Inc., Warsaw, IN) filled with either NH-SiO_2 (NanoBone Putty) (Fig. 1) or homologous bone (HB) (Tutoplast Tutogen spongiosa chips, Tutogen Medical GmbH, Neunkirchen am Brand, Germany). Study inclusion criteria included: chronic low back pain, radiculopathy, and spinal claudication symptoms caused by degenerative changes in the lumbar spine that were resistant to conservative pain therapy and/or physiotherapy. The diagnosis was verified by imaging by conventional radiography and magnetic resonance imaging (MRI), unless contraindicated, in which case computed tomography (CT) and conventional radiographs were used.

Exclusion criteria included relevant previous surgeries in the abdominal region with scarring and adhesions, as well as previous fusion surgery in the lumbar spine. Also excluded were patients with systematic infection, infection at the surgical site, patients with osteoporosis to an extend that spinal instrumentation would be contraindicated, patients with body mass index $>35\,kg/m^2$ and patients with significant comorbidities, defined as American Society of Anesthesiologists Classification 4 or 5. Finally, patients unwilling to complying with preoperative and postoperative visit requirements or unwilling to provide informed consent were not included. Previous microdiscectomies and decompressions did not represent exclusion criteria.

FIGURE 1. Carbon fiber reinforced polymer cage filled with nanocrystalline hydroxyapatite is shown. full color online

Immediately after providing informed consent, patients were randomized to allocate them to ALIF cage filled with either NH-SiO_2 or HB as filling material. A block randomization schedule was used. Random numbers were generated via the use of the website http://www.randomization.com. Patients were blinded to the treatment group allocation.

Surgical Procedure

Surgical access was obtained through a subumbilical, standard midline approach followed by a left-sided incision of the anterior lamina of the rectus sheath. This was followed by blunt preparation retroperitoneally at the appropriate intervertebral disk space or index segment level. The iliac vessels were mobilized and protected by a retractor. For the levels L4/L5, a ligature of the ascending lumbar and iliolumbar veins was performed. After coagulation of the median sacral artery and vein, the intervertebral disk space was opened for the thorough removal of disk material from the intervertebral disk space. The respective, corresponding endplates were debrided. After selecting a suitable cage with appropriate size, height, and lordosis, the definitive implantation was performed. Patients with symptomatic radiculopathy were treated with supplemental posterior decompression with an additive dorsal screw/rod system in a single session. Patients without radiculopathy received ventral plate augmentation.

As deemed appropriate by the surgeon, the procedure was either performed as ALIF with anterior plating or as anteroposterior lumbar fusion (APLF), consisting of ALIF supplemented with a posterior screw-rod system. In the treatment group, NH-SiO_2 was directly injected from the delivery syringe into the cage. In the control group, the ALIF cage windows were filled with HB only.

Clinical evaluation using the Oswestry Disability Index (ODI),[13] health-related quality of life (EQ-5d)[14] alongside the Visual Analogue Scale[15] with a scale graduation of 0 to 10 for back pain and leg pain, was carried out preoperatively and at 3, 6, and 12 months postoperatively.

After 3 months, a radiologic follow-up was performed with a thin-layer CT-scan (1 mm cuts) to assess fusion. The presence of fusion was assessed using Bridwell's criteria[16] with Grade 1 defined as fusion with remodeling and trabeculae present. Grade 2 was an intact graft with incomplete remodeling and no lucency present. Grade 3 was defined as an intact graft with potential lucency at the cranial or caudal end, and grade 4 was an absent fusion with collapse/resorption of the graft. Bridwell grade 1 and grade 2 were classified as solid fusion.[16]

In case of fusion, patients were gradually cleared for bending and twisting movements, as well as for heavy lifting. In case of delayed fusion, patients were followed-up over time, with additional CTs at 6 months. In case of symptomatic nonunions, patients are scheduled for revision surgery.

Conventional radiography in 2 planes was taken at the 6-month and 12-month follow-up intervals. Additional functional radiography of the lumbar spine was taken

12 months postoperatively. For functional radiography, a difference of >5 degrees in segmental lordosis in flexion/extension and translation of >3 mm was considered to be a sign of instability and, therefore, as an indirect sign of nonunion.[17,18] All radiographic assessments were performed by an independent, blinded radiologist.

Statistics

On the basis of a study by Parker et al,[19] the minimal clinically relevant difference for the Oswestry Disability Index was set at 11. SD was set at 11.3.[19] To detect a clinically relevant difference between the two treatment groups, using a 2-sided *t* test with a significance level of 5% and a power of 80%, a total of 34 patients is required (17 per group).

Assuming a drop-out rate of approximately 10% until final follow-up, 40 patients must be included in the study.

Normally distributed, continuous data are presented as mean SD. Student *t* test was used for between-group comparisons. Non-normally distributed, continuous data are presented as medians [interquartile range (IQR)] and were analyzed with the Mann-Whitney *U* test. Categorical variables are presented as frequencies and percentages, and were analyzed with a Fisher's exact or a χ^2 test.

Significance level was 5% using 2-tailed testing. Stata12.1 (Stata Corp, College Station, TX) was used for all analyses.

RESULTS

The 2 patient groups were comparable in terms of sex, age, weight, and operated segments (Table 1). In the NH-SiO_2 group, the main indication for surgery was degenerative disk disease in 15 cases, and failed back surgery syndrome in 3 cases. There was 1 case each of degenerative spondylolisthesis and spondylarthrosis. In the HB group, the main indication for surgery was degenerative disk disease in 12 cases, and failed back surgery syndrome in 8 cases.

Four patients (1 from the NH-SiO_2 group and 3 from the HB group) did not attend the final follow-up because of concomitant diseases, which were unrelated to the study procedure (Fig. 2). All 4 patients who did not attend this follow-up had shown a solid fusion (Bridwell grade 1) at 3- and 6-month follow-up. Their fusion status at the 12-month follow-up was assumed to have been unchanged.

No intraoperative complications were recorded in either group. Cardiovascular or pulmonary complications were not recorded in the study. In 2 patients in the NH-SiO_2 group, decompression surgery of the neuroforamen was necessary in the first and seventh postoperative week, respectively. In the NH-SiO_2 group, 1 additional patient experienced a pedicle fracture 4 weeks postoperatively, which required operative revision and extension of fusion. Finally, in 1 patient in the NH-SiO_2 group, a revision and repositioning of the metalwork was performed 2 weeks postoperatively because of the cut-out of screws.

TABLE 1. Baseline Characteristics of the Study Population

Variable	NH-SiO_2 (n = 20)	HB (n = 20)
Age (y)*	60.6 ± 12.5	66.1 ± 9.6
BMI (kg/m^2)*	26.4 ± 4.6	26.5 ± 4.9
Female/male	14:6	16:4
ASA classification*	2.0 ± 0.6	2.3 ± 0.7
Single-level cage	15	15
Two-level cage	5	5
Levels with cage insertion		
L4/L5	7	8
L5/S1	18	17
ALIF	5	5
APLF	15	15
EQ-5D*	0.43 ± 0.21	0.48 ± 0.22
EQ-5D VAS*	46 ± 21	50 ± 26
ODI*	51 ± 14 (13–80)	50 ± 23 (31–71)
VAS Back†	7.5 (6–8)	7 (5–8)
VAS Leg†	7 (4–8)	7 (3–8)

*Presented as mean ± SD. For the primary outcome additionally the range is provided.

†Presented as median (interquartile range).

ALIF indicates anterior lumbar interbody fusion; APLF, anteroposterior lumbar fusion; ASA, American Society of Anesthesiologists; BMI, body mass index; EQ-5D, Euro-QoL-5D; HB, homologous bone; NH-SiO_2, nanocrystalline hydroxyapatite embedded in a silica gel matrix; ODI, Oswestry disability index; VAS, visual analogue scale.

In the HB group, there was 1 case of wound healing disorder, which healed uneventfully after wound revision and antibiotic use. The implants were left in situ. Lastly, for 1 patient in the HB group, an anterior-posterior revision with cage revision and implantation of an additional screw-rod system was required 3 months postoperatively because of nonunion. The radiographic findings of this patient at the 3-month follow-up were carried forward to the 6- and 12-month follow-up visits in order to avoid informative censoring.

All clinical outcomes improved markedly postoperatively. At 12 months, the mean difference between the groups was 4 ± 9 points. A *t* test yielded a *P*-value of 0.582 (Table 2). Postoperative functional outcomes and quality-of-life indices did not differ significantly between groups at any of the regularly scheduled follow-up visits (Table 2).

No statistically significant radiographic differences were discerned at any time postoperatively (Table 3). The computerized tomography (CT) analysis conducted at the 3-month follow-up demonstrated high fusion rates (Figs. 3, 4). At the 3-month follow-up, Bridwell grade I was seen in 40% of the patients in both groups ($P = 1.00$), whereas complete fusion (Bridwell grade 1 or 2) was seen in 92% in the NH-SiO_2 group and 80.0% in the HB group ($P = 0.417$). Complete fusion rates at 12 months were 96.0% and 88.0%, respectively ($P = 0.609$). Pseudoarthrosis was established by functional radiographs taken at the 12-month visit in 1 segment in the NH-SiO_2 group and in 3 segments (3 patients) in the HB group ($P = 0.609$).

The aforementioned revision surgery concerned the patient with Bridwell grade 4. The clinical presentation of patients with Bridwell grade 3 was moderate, and a revision surgery was not required.

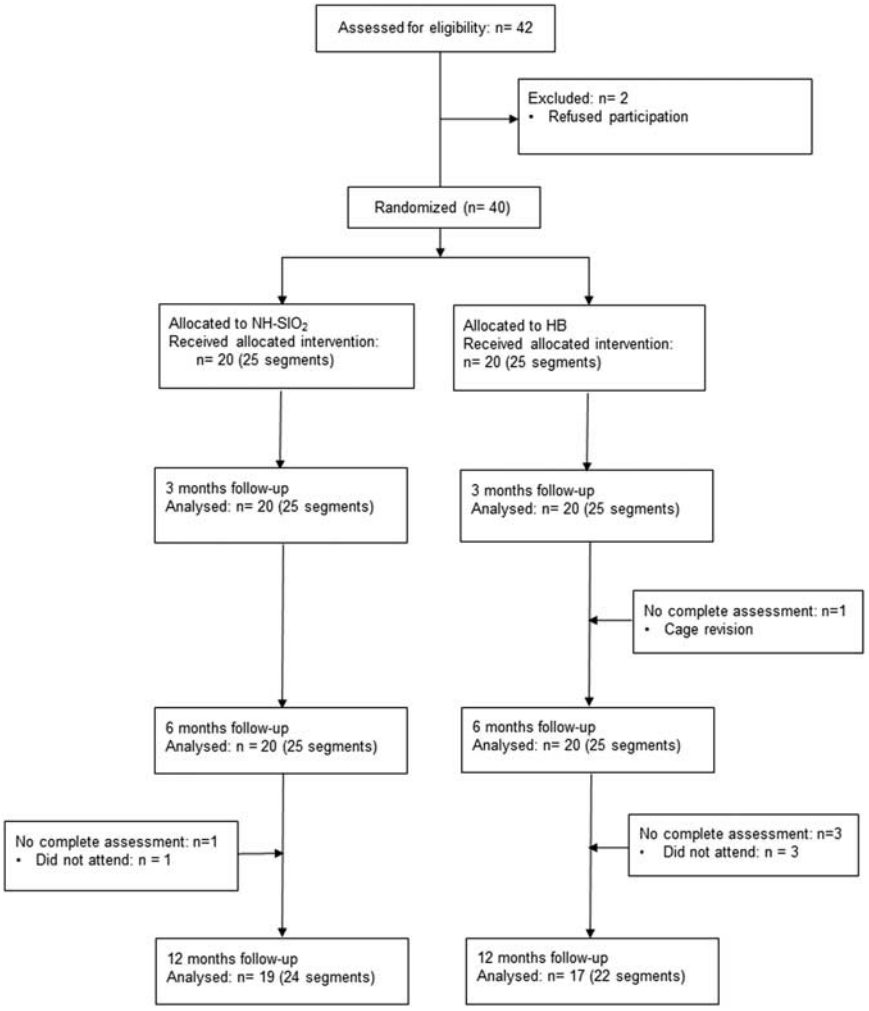

FIGURE 2. Consort study flow diagram is shown. NH-SiO_2 indicates nanocrystalline hydroxyapatite embedded in a silica gel matrix; HB, homologous bone.

DISCUSSION

There is an ongoing debate about which cage-filling material is most appropriate. Autologous iliac bone graft (AIBG) is commonly used as filling material. It demonstrates reliably high fusion rates, and does not carry the risk of disease transmission or immunological response.[20] However, the use of AIBG causes donor-site related morbidity in a large proportion of patients, including pain, wound infection, hematomas, and nerve injuries of the lateral femoral cutaneous nerve.[21] Several materials have been proposed as a substitute for AIBG in spinal interbody surgery. The main benefit of allograft bone is that

TABLE 2. Study Outcomes

	3 mo			6 mo			12 mo		
Outcome	**NH-SiO_2**	**HB**	***P***	**NH-SiO_2**	**HB**	***P***	**NH-SiO_2**	**HB**	***P***
EQ-5D*	0.69 ± 0.20	0.71 ± 0.22	0.868	0.72 ± 0.17	0.76 ± 0.18	0.495	0.77 ± 0.19	0.74 ± 0.23	0.700
EQ-5D VAS*	64 ± 19	67 ± 20	0.615	68 ± 20	66 ± 20	0.827	72 ± 18	65 ± 24	0.336
ODI*	35 ± 18 (0–58)	38 ± 18 (7–76)	0.583	29 ± 16 (2–53)	31 ± 19 (0–67)	0.647	24 ± 17 (0–56)	27 ± 19 (0–51)	0.582
VAS Back†	3 (1-5)	4 (2–5)	0.660	3 (1–5)	3 (2–5)	0.519	2 (1–4)	3 (2–5)	0.110
VAS Leg†	2 (0–4)	3 (0–5)	0.289	2 (1–3)	2 (1–4)	0.819	2 (1–4)	1 (0–4)	0.656

*Presented as mean ± SD. For the primary outcome additionally the range is provided.
†Presented as median (interquartile range).
Presented as median (interquartile range).
EQ-5D indicates Euro-QoL-5D; HB, homologous bone; NH-SiO_2, nanocrystalline hydroxyapatite embedded in a silica gel matrix; ODI, Oswestry disability index; VAS, visual analogue scale.

TABLE 3. Fusion Rates (Bridwell Grading)

	3 mo		6 mo		12 mo	
Bridwell Grade	**NH-SiO_2**	**HB**	**NH-SiO_2**	**HB**	**NH-SiO_2**	**HB**
Grade 1	10 (40)	10 (40)	12 (48)	12 (48)	13 (52)	14 (56)
Grade 2	13 (52)	10 (40)	12 (48)	10 (40)	11 (44)	8 (32)
Grade 3	2 (8)	4 (16)	1 (4)	2 (8)	1 (4)	2 (8)
Grade 4	0	1 (4)	0 (0)	1 (4)	0 (0)	1 (4)
P	0.621		0.826		0.660	

Presented as n (%).

HB indicates homologous bone; NH-SiO_2, nanocrystalline hydroxyapatite embedded in a silica gel matrix.

there are no risks of donor-site morbidity. However, allograft has significant drawbacks. Since allograft bone does not contain viable tissue, it is not as effective as autograft.[22,23] In addition, there is a small risk of disease transmission.[22,23] Inorganic implants, such as synthetic calcium-phosphate-based bone substitutes, are increasingly used as an alternative to AIBG.[23,24] The advantage of these synthetic materials is that they offer easy cage filling. The principal inorganic bone matrix component of calcium-phosphate-based bone substitute is HA. Synthetic HA has demonstrated a high level of biocompatibility, supporting osteoconduction. After implantation, the material is slowly replaced by native tissue. The material has been used clinically since the 1980s in orthopedic, craniofacial, and dental medicine.[7] There are currently no reported experimental or clinical data with the use of NH-SiO_2 in the field of spinal surgery. To our knowledge, this is the first clinical study to evaluate pertinent clinical outcome measures using NH-SiO_2 as filling material for lumbar cages. The main finding of this pilot study was that high fusion rates can be obtained with both filling materials. Overall, satisfactory high fusion rates were found in both groups, albeit the fusion rate was somewhat higher in the NH-SiO_2 group (96%) than in the HB group (88%). However, the difference between the 2 study groups was statistically not significant.

Similar high fusion rates as found in our study have also been reported by other groups. Using standard radiography, Anderson et al[25] found 95% fusion at 12-month follow-up for ALIF procedures with HB and recombinant human bone morphogenetic protein (rhBMP2). Behrbalk et al[26] found 91% fusion at 6-month follow-up on standard radiographs after stand-alone ALIF with interposition of a PEEK cage with rhBMP2. McCarthy and colleagues compared fusion rates of stand-alone spondylodesis with ALIF cages and combined ALIF with dorsal instrumentation. They used autologous bone as cage-filling material in both groups. At 12 months, CT analysis found fusion rates of 65% and 100%, respectively.[27] El Masry et al[28] reported a fusion rate of 97% in 47 patients at 12 months postoperatively after ALIF using an autogenous iliac bone graft in combination with posterior pedicle fixation dorsal instrumentation. Finally, Sarwat et al[29] reported outcomes of 43 patients who received ALIF with the use of allograft bone and dorsal instrumentation. Radiographically, they found a fusion rate of 100% at the monosegmental interventions and 93% at the bilateral and trisegmental interventions at 12-month follow-up.[29] However, because of inter-observational variation in fusion criteria, the validity of this between-study comparison is limited.[30]

In the current study, fusion determined at the 3-month assessment was predictive of fusion outcome at 12 months. However, the absence of fusion only moderately predicted instability and revision for instability. We, therefore, believe CT assessment as early as 3 months postoperatively is justified.

A follow-up with CT after 3 months corresponds to the standard practice of our clinic, and we aim to return patients as early as possible to their normal activities. The fusion rate in the NH-SiO2 group 12 months postoperatively is similar to the fusion rates of other studies.

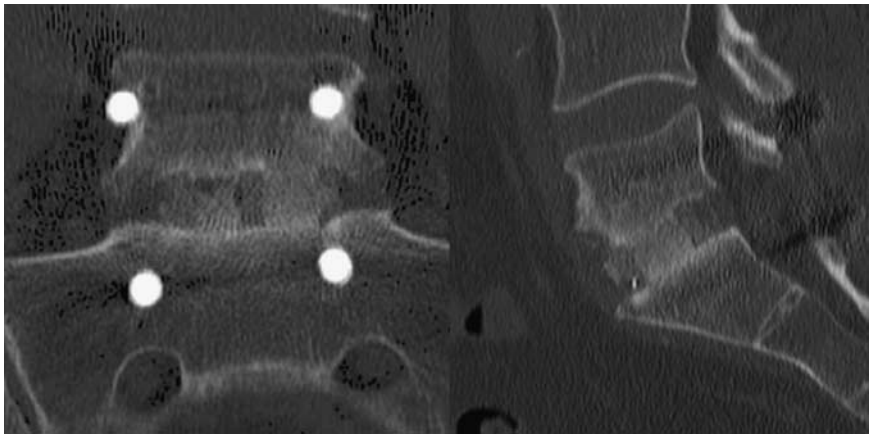

FIGURE 3. Patient in the NH-SiO_2 group was classified as Bridwell 1 at 3-month follow-up. No signs of loosening of metalwork, adequate bony bridging between the endplates, and no vacuum sign. NH-SiO_2 indicates nanocrystalline hydroxyapatite embedded in a silica gel matrix.

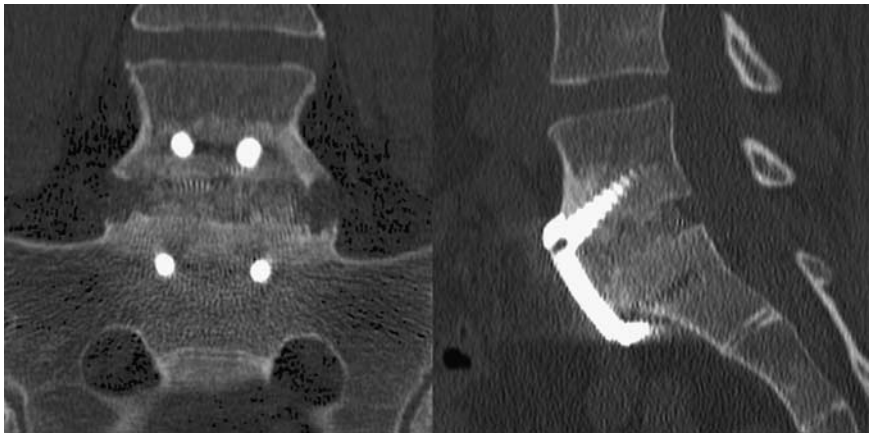

FIGURE 4. Patient in the homologous bone group was classified as Bridwell 1 at the 3-month follow-up. No signs of loosening of metalwork, adequate bony bridging between the endplates, and no vacuum sign were observed.

This pilot study has a relatively small sample size. On the basis of the power analysis, there were sufficient patients to compare ODI between the 2 groups. The difference between the 2 group at 12 months was neither statistically significant ($P > 0.05$), nor was it clinically relevant (ie, the difference was smaller than 11 points on the ODI). For the primary outcome, we therefore deem to the study to be adequately powered, and, hence, we postulate that future studies should be designed as equivalence trials.

However, particularly for the secondary outcomes, the results continue to be subject to type II error. The findings of the current randomized trial should therefore not be taken as a definitive test of the intervention hypothesis. A larger randomized study, which is currently being planned, is warranted to allow more robust statistical conclusions to be drawn. In the absence of any relevant differences in the outcome, we postulate that such a study should be designed as an equivalence trial.

This study has several limitations. Follow-up time was limited. Secondly, fusion rates were determined by CT at the only the 3-month follow-up (because of radiation-exposure concerns), thus limiting our ability to compare these outcomes against fusion rates at 12 months. Thirdly, 4 patients were lost to follow-up. However, each of these patients had shown a complete fusion (Bridwell grade 1 or grade 2) at the 3-month follow-up. Attrition was therefore unlikely to be related to the intervention. Finally, we did not compare outcomes against autologous bone graft with bone morphogenetic proteins (BMPs) in this study. Iliac crest harvest is considered to be the "gold standard" by many.[31] Although similar clinical outcomes and similar fusion rates as found in our study can be expected for autologous bone autograft,[31] the incidence of post-operative donor site complications following iliac crest harvesting is significant,[31] which, in our view, makes this option less attractive. Furthermore, BMPs are not used in primary fusion cases in our department because of potential adverse and unknown long-term effects as well as additional costs.[32] Consequently, since we chose to compare NH-SiO_2 material with HB, the study may be of limited relevance to surgeons using autologous bone graft material or BMPs to facilitate fusion. The strength of our study includes the methodology of the randomized, clinical trial, which was achieved without protocol violations or crossover of patients.

In conclusion, this clinical study showed similar radiologic, functional, and clinical outcomes for instrumented ALIF procedures with use of NH-SiO_2 or with HB as cage filling, and fusion rates were not significantly different. The findings from this pilot study will be helpful to guide future randomized clinical trials.

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