Original article

Efficacy and safety of the magnesium-hydroxyapatite bone graft substitute in postero-lateral spinal fusion: observational, spontaneous clinical study

B. ZANOTTI*, A. NATALONI**, V. CANELLA**, F. MUGGIOLU*

* *Neurosurgery Unit, Neuroscience Department, "C. Poma" Hospital, Mantua, Italy*
** *Finceramica S.p.A., Faenza (Ravenna), Italy*

SUMMARY: ***Aims.*** *Iliac Crest Bone Graft (ICBG) is considered the "gold standard" option for achieving fusion in spinal surgical procedures, thanks to its known osteoinductive and osteoconductive properties. However, complications related to harvesting and donor site morbidity have been largely reported in literature, favouring the development of a wide range of alternative products to be used as bone graft extenders or substitutes. Ceramic-based biomaterials are since years employed as bone graft substitutes to replace autograft, due to their similarity with the mineral component of human bone. Recently, new generation of hydroxyapatite biomaterials have been developed with superior properties to promote a faster remodelling and new formation of human bone, and a rapid cell-mediated material resorption. We report here the results of a prospective study aiming to evaluate the degree of fusion obtained by the use of a magnesium-doped hydroxyapatite product to achieve postero-lateral fusion in degenerative spine diseases. Second aim of the study was to evaluate of the safety profile of the bone graft in spinal arthrodesis procedures.*

Materials and methods. *A prospective, spontaneous, observational, post-marketing clinical study was conducted. Twenty subjects were included in the study and underwent surgery for postero-lateral fusion with the use of the magnesium-doped hydroxyapatite bone graft.*

Results. *At 12 months follow-up, more than 70% of fusion was reached. A statistically significant improvement was observed for clinical parameters related to the improvement of life quality following spinal fusion.*

Conclusions. *The magnesium-doped hydroxyapatite bone graft substitute SintLife represents a good alternative to autologous bone graft. The device can be safely used alone performing in a similar manner as the "gold standard" autologous bone.*

KEY WORDS: *spinal fusion, hydroxyapatite bone graft, magnesium-hydroxyapatite.*

INTRODUCTION

Lumbar spinal fusion (i.e. arthrodesis) is one of the most used surgical procedures for the treatment of deformities, trauma and degenerative diseases with instability of the spine[1,2]. A successful fusion (intended as radiographically detectable neo-formation of trabecular bone, in particular at the interface with the receiving bone surface) depends on the characteristics and properties of the bone graft used, as well as on the surgical technique employed. The biological process leading to new bone formation is

Corrispondence: Valentina Canella, Clinical Department, Fin-Ceramica Faenza S.p.A., via Ravegnana 186, SP 302, 48018 Faenza (RA), Italy, ph. +39-0546 607355, e-mail: valentina.canella@finceramica.it
Progress in Neurosciences 2021; 6 (1-4): 27-35. *ISSN: 2240-5127.*

LIST OF ACRONYMS AND ABBREVIATIONS: **β-TCP** = Beta-TriCalcium Phosphate; **BMPs** = Bone Morphogenetic Proteins; **CaP** = Calcium Phosphate; **CE-marked** = Conformitè Europëenne (European conformity)-marked; **CT** = Computed Tomography; **DBM** = Demineralized Bone Matrix; **HA** = HydroxyApatite; **hMSCs** = human Mesenchymal Stem Cells; **ICBG** = Iliac Crest Bone Graft; **Mg** = Magnesium; **ODI** = Oswestry Disability Index; **ROI** = Region of Interest; **VAS** = Visual Analog Scale.

characterized by three critical elements: the osteogenic potential, the presence of osteoinductive factors and the osteoconductive properties of the bone graft used, either if it is autologous bone from the own patient or a synthetic bone graft substitute.

The ideal bone substitute shows all three of these properties, associated with excellent compatibility and biological safety[3,4].

In this perspective, autologous bone graft from the iliac crest is considered the "gold standard" because of these properties[5-9]. Nevertheless, autologous bone harvesting has shown limitations and significant drawbacks, including superficial infection, wound complications, sensory abnormalities, persistent pain, hematomas, as well as need for reoperation, scarring, graft site fracture[8-11].

To overcome these limitations, different alternatives have been developed, clinically tested and currently available on the market, including allograft[4,12], bone morphogenetic protein, DBM[13-15], BMPs[16,17], hMSCs and bioceramics[14].

Although extensively studied, clinical data available for all these materials are often heterogeneous in quality, type of study, evaluations performed and conclusions reached[11,13,15,18].

Bioactive ceramics (i.e. tricalcium phosphate, calcium phosphate, calcium sulphate, hydroxyapatite and collagen)[19] are synthetic products which have been developed as osteoconductive scaffolds with chemico-physical properties very similar to the mineral component of human bone[18,20-22]. These biomaterials are able to stimulate cell proliferation and differentiation, bone tissue regeneration/remodelling while undergoing in the meantime slow resorption. Among all, HA is the most similar, for chemico-physical composition and stoichiometric formula (Ca/P ratio = 1.67), to the mineralized phase of human bone. To further improve their features, new generation HA-based biomaterials have been developed with superior properties, strongly influenced by the nature of components, the composition and the morphology. Calcium ions, phosphate ions, and hydroxyl groups can be replaced by other ions, and studies in animal models have demonstrated that HA-substituted ions enable the crystal cell structure of ceramic derivatives to become unstable and more biologically active, thereby promoting rapid cell-mediated material resorption, new bone formation and remodelling[23].

Magnesium is certainly one of the most important bivalent ion associated with biological apatite: it is one of the most abundant minerals in the human body and approximately 50% of Mg^{2+} is naturally present in the composition of bone tissue.

Mg^{2+} enables the HA crystal cell structure to become unstable and more biologically active, promoting rapid cell-mediated material resorption, new bone formation and remodelling by cross-talking with progenitor cells at the molecular level. In vitro experiments have revealed an active interaction between Mg-HA biomaterials and hMSCs, with an improvement of metabolic cell activity[24,25]; preclinical studies in large animal models[26,27] have demonstrated good osteo-integration and the deposition of new bone tissue.

In this context, an Mg-HA bone graft substitute has been employed to achieve fusion in a cohort of patients undergoing postero-lateral fusion for degenerative lumbar spine diseases.

Aim of the present prospective, observational study was to evaluate the performance (in terms of fusion and improvement of life quality) and safety of the Mg-HA bone graft substitute (*SintLife, Finceramica, Faenza, S.p.A., Italy*) in procedures of spinal stabilization.

□ MATERIALS AND METHODS

■ **Clinical study design.** A prospective, spontaneous, observational, post-marketing clinical study was conducted at our Centre from March 2020, after approval of the local Ethic Committee, to December 2021. Consecutive patients who had indications for single or multi-level posterolateral spinal fusion due to degenerative lumbar spine diseases were screened to be enrolled in the study. For all the patients included (according to inclusion/exclusion criteria), informed consent was required.

The enrolment period was from March 2020 to December 2021, and patients were followed up from the pre- pre-operative visit to 12 months post-

operative, with intermediate post-operative visit just after surgery and at 6 months. Specific inclusion criteria were as follows: skeletally mature subjects, at least 18 years of age at the time of surgery, affected by symptomatic spinal diseases, due to degenerative or oncological conditions or trauma, and requiring interbody postero-lateral fusion at C2-T1 tract with stabilization systems and bone graft; patients for which autologous bone was not sufficient to allow arthrodesis and requiring the use of a bone graft substitute; patients participating in the study who provided informed signed consent. Patients' exclusion criteria were applied in case of local or systemic infections, inflammatory or autoimmune disease, hypercalcemia, coagulation/metabolic disorders, insulin-dependent diabetes, previously known allergy to calcium phosphate salts, drugs or magnesium, active neoplasia. The sample size population was estimated in 20 subjects to be included. However, due to the concomitant development of the COVID-19 pandemic in 2020 (which resulted in a slowdown of surgical activities in our Centre) a delay in patient enrollment has been observed. For this reason, in order to respect the timelines of the study, on September 2021 we decided to retrospectively enroll the remaining number of patients that were missing to reach the sample size population estimated. This was done by screening all the subjects that underwent postero-lateral fusion with the device under analysis from March 19, 2020 (day of study initiation) backwards, and responding to the inclusion and exclusion criteria settle in the study.

■ **Follow-up plan.** A schematic view of the visits planned during the study is reported in Table 1. According to the chemico-physical properties of the Mg-HA bone graft SintLife, which is reported by the Manufacturer to be resorbed in a period of about 6-18 months, follow-up was set up at 12 months.

■ **Surgical procedure.** Conventional posterior approach for lumbar spinal fusion was performed. After the positioning of pedicle screws, decompression of the cauda and nerve roots was achieved with a hemilaminectomy and foraminotomy. SintLife was put on the hemi-laminae and transvers process on the contralateral side of the hemilaminectomy. During surgery, SINTlife was mixed with antibiotics (rifampicin in powder, 60 mg) in order to reduce the any risk of early infection.

■ **Biomaterial.** SintLife is an implantable, non-active, CE-marked medical device that acts as a bone graft substitute. The device is made of biomimetic HA enriched with magnesium ions (Mg^{2+}) in a similar amount as in human bones. The device interacts with bone tissue-forming cells to promote bone regeneration. Its biomimetic chemical composition, structured geometry, and surface properties allow new bone formation: the presence of Mg^{2+} ions, introduced into the HA crystalline cell in the same position and percentage found in the mineral phase of human bone, makes the device unstable and biologically active, thus favoring interaction with key proteins involved in osteogenesis and bone remodeling. The device is therefore quickly resorbed by osteoprogenitor cells in a physiologically adequate period of time (6-18 months), while sustaining new bone formation by osteoprogenitor cells.

■ **Radiographic and clinical outcomes measure.** Radiographs were taken pre-operatively, immediately following surgery and at 1-year follow-up, and were reviewed by an independent radiologist. Fusion was defined as a continuous trabecular bone bridge in the entire fusion area with no radiolucency between the graft bone and the vertebral bone through diagnostic imaging (TC scan). We used the classification of Brantigan and Steffee[28], as defined in Table 2.

Study visits flow chart	Pre-op.	Immediate post-op. surgery	6 months FU	12 months FU
Assessment of patients eligibility (Inclusion/exclusion criteria)	X			
Informed consent signature	X			
Patients anamnesis	X			
Surgical report		X		
ODI and VAS scores recording	X		X	X
CT acquisition	X	X		X
Adverse events recording		X	X	X

Table 1. Flow chart visits. *Legend:* CT = Computed Tomography; FU = follow-up; ODI = Oswestry Disability Index; post-op. = post-operative; pre-op. = pre-operative; VAS = Visual Analog Scale.

Classification	Description
A. Obvious radiographic pseudoarthrosis	Pseudoarthrosis, collapse of construct, loss of disc height, vertebral slip, broken screw, displacement of the cage, resorption of bone graft
B. Probable pseudoarthrosis	Significant resorption of bone graft, major lucency or gap visible in the fusion area > 2 mm
C. Radiographic status uncertain	A small lucency or gap may be visible with at least half of the graft area showing no lucency between the graft bone and the vertebral bone
D. Probable radiographic fusion	Bone bridges the entire fusion area with at least the density originally achieved at surgery. There should be no lucency between the graft bone and the vertebral bone
E. Radiographic fusion	The bone in the fusion area is more dense and more mature than originally achieved at surgery; there is no interface between the donor bone and the vertebral bone: a sclerotic line between the graft bone and the vertebral bone indicates solid fusion. Other indicators of solid fusion is fusion at facet joints and anterior progression of the graft in the disc

Table 2. Brantigan and Steefe classification of spinal fusion.

The following clinical parameters were evaluated: the VAS for patient's pain intensity and the ODI for the quantification of patient's disability for low back pain, which were assessed pre-operatively, at 6 and 12 months post-operative.

■ **Safety assessment.** The safety of SintLife was assessed by the rate of adverse events and complications recorded during the whole study period.

■ **Statistical analysis.** The sample size was defined according to the real clinical practice of the clinical site developing the study, and estimated in 20 subjects to be included and enrolled. Considering the heterogeneity of the patient population included in the study, no specific statistical analyses have been carried out. Descriptive statistical analysis has been provided for clinical scores (VAS, ODI).

Results are presented as number, mean ± standard deviation and percentage, as appropriate. Changes from baseline to follow-up scores were analysed using the t-student test. The level of statistical significance was set at $p < 0.05$. The SAS software 9.201 was used. Assessment of fusion and the incidence and type of any adverse event recorded has been reported.

□ RESULTS

The study was approved by the local Ethic Committee and informed signed consent was obtained from each patient. Twenty patients were included in the study, of which 13 male (75%) and seven female (35%. Mean age at the time of surgery was 64.7-year-old (range 36-85). Eighty-five percent of subjects were treated for lumbar stenosis, 10% for pathologies following trauma and 5% for infective diseases. Forty-five percent of subjects underwent one level of fusion, 40% had 2 levels and 15% four or more fusion levels. The bone graft substitute SintLife was used alone to allow fusion. The followings were identified as possible risk factors: hypertension (recorded in 30% of cases), diabetes (25% of cases), previous known allergies (5%). Out of the total number of 20, 10% of patients were contemporarily affected by more than one risk factor. The full-set population analysed was of 20 subjects. The full-set of "completers" (i.e. subjects completing all the post-operative visits) was of 15 patients.

Bony fusion was evaluated by an independent radiologist on TC images at 12 months follow-up, for the full-set of "completers" (N = 15). A successful fusion was considered where Brantingan score of 5, 4 and 3 was reached. Accordingly, 11 subjects (73.4%) reached a successful fusion (Table 3). The results were confirmed by quantification of the structural homogeneity of the bone graft area (ROI) (data not shown). The VAS score at baseline in the full-set group was 7.2 ± 1.3, 2.1 ± 1.15 at 6 months follow-up and 0.5 ± 0.5 at 12 months follow-up, with statistically significant differences between pre-baseline and 6 months ($p < 0.01$) and between baseline and 12 moths post-operative ($p = 0.001$) (Table 4 and Figure 1).

The ODI score in the full-set group was 25.1 ± 6.6 at baseline, 8 ± 4.55 at 6 months follow-up and 1.9 ± 1.8 at 12 months follow-up, with statistically significant

Brantingan score	Number of patients reaching fusion according to the Brantingan score	%
5	2	13.3
4	6	40
3	3	20
2	4	26.7
1	0	0

Table 3. Number of patients reaching fusion.

differences between pre-baseline and 6 months ($p < 0.001$) and between baseline and 12 moths post-operative ($p < 0.001$) (Table 5 and Figure 2).
The same analysis was performed for the full-set "completers", which is of 15 subjects. ROI values for ODI and VAS were equivalent to the full-set population. At 6 and 12 months follow-up, the trend was confirmed for both VAS and ODI scores.
Clinical scores (ODI, VAS) were calculated for subgroup populations (i.e. < 65 years old versus ≥ 65 year old) No statistically significant differences were recorded (data not shown).

■ **Safety Analysis.** One minor adverse event was recorded (i.e. superficial inflammation). The event was evaluated by the Surgeon as partially related SintLife. The event was treated with anti-inflammatory therapy and no surgical revision was required.

□ DISCUSSION

There are varieties of bone graft substitutes that are available for use in spine fusion surgery. In general, these types of bone graft are a synthetic and, recently, most of them are naturally-occurring products. During years, the interest in developing and refining bone graft substitute options for use in lumbar spinal fusion surgery procedures has improved, aimed at eliminating the need to harvest the patient's own bone, thus potentially reducing the risk and pain associated with the procedure and resulting in higher fusion rates.
Among the synthetic options, the family of ceramic biomaterials represents and interesting alternative, due to their chemico-physical features. Ceramic-based bone graft substitutes (CaP, β-TCP, HA) can vary according to the different compositions, manu-

Visual analogue scale	N.	Mean	SD	Median	Min.	Max.	P
Pre-operative	20	7.2	1.27	7.5	5	9	
6 months	20	2.1	1.15	2	0	4	< 0.001
12 months	15	0.5	0.52	1	0	1	0.001

Table 4. Visual analog scale. *Legend:* Max = Maximum; Min = Minimum; N. = Number; SD = Standard Deviation.

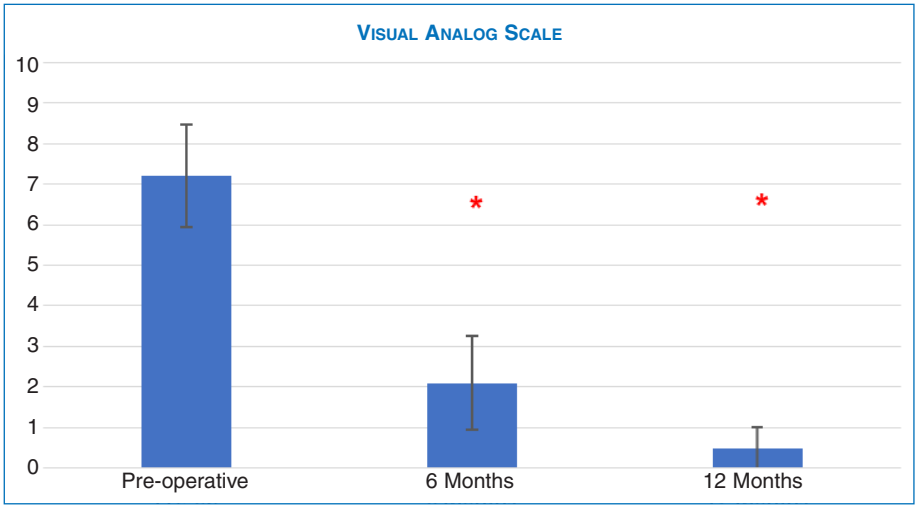

Figure 1. Plot of Visual Analog Scale scores evaluated pre-operatively, at 6 and 12-months follow-up. The *red asterix* highlights a significant difference between post-operative and pre-operative values.

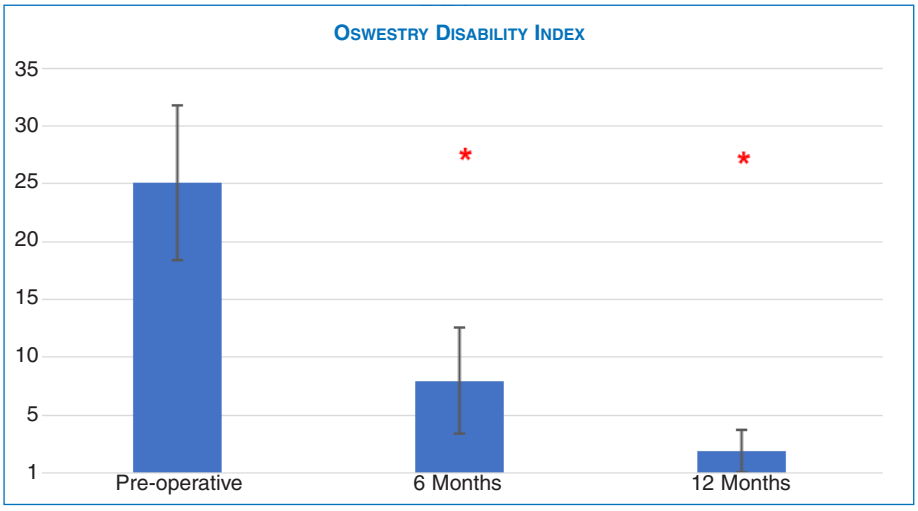

Figure 2. Oswestry Disability Index scores evaluated pre-operatively, at 6 and 12 months follow-up. The *red asterix* highlights a significant difference between post-operative and pre-operative values.

facturing, porosity and structure, but they all mainly have a composition which mimics the mineral phase of bone. Ceramics are osteoconductive and osteointegrative, but not osteogenic nor osteoinductive. They can have pores with different sizes, which are critical for osteoprogenitor cells migration and differentiation in functional osteoblasts.

Hydroxyapatite, a naturally occurring mineral form of calcium apatite with the formula $Ca_5(PO_4)_3(OH)$, has a stoichiometric formula (Ca/P ratio = 1.67) and a chemico-physical composition which is very similar to the mineral phase of human bone. The porous structure of HA, with its macropore network and the micropores interconnection, induces rapid vascular and mesenchymal invasion, providing a specific cell flow and the optimal environment for cells to attach, proliferate, and finally differentiate into functional osteoblasts. HA shows high biomimetic properties, osteoconductive potential and excellent biocompatibility, is biodegradable and pose virtually no risk of infection or donor site morbidity[12].

In the last decades, research into synthetic material composites as bone graft substitutes has increased due to the ability to manipulate composite properties, and "new generation" biomaterials have been developed, to the aim of "mimicking" the osteoregenerative processes typically found in the human bone mineral turn-over. Magnesium is certainly one of the most important bivalent ions associated with biological apatite, being one of the most abundant minerals in human bones. Mg^{2+} enables the HA crystal cell structure to become unstable and more biologically active, promoting rapid cell-mediated material resorption, new bone formation and remodelling by cross-talking with progenitor cells at the molecular level[29,30].

For this reason, in our Institute we have approached to a HA-based bone graft substitute enriched in Magnesiun named SintLife. The device has been used safely in a number of clinical cases and has become a commonly used bone graft substitute in procedures of spinal arthrodesis.

Previous pre-clinical experiments tested the performance and safety of the device. In vitro tests revealed an active interaction between SintLife and hMSCs, with an improvement of cell metabolic activities and bone remodelling[24,25]. An *in vivo* study on sheep treated for posterolateral fusion with SintLife or autologous bone showed the deposition of new bone tissue provided by SintLife, without quali-

Oswestry disability index	N.	Mean	SD	Median	Min.	Max.	P
Pre-operative	20	25.1	6.66	25	15	37	
6 months	20	8.0	4.55	7	0	17	< 0.001
12 months	15	1.9	1.79	3	0	4	< 0.001

Table 5. Oswestry disability index. *Legend:* N. = Number; Max = Maximum; Min = Minimum; SD = Standard Deviation.

tative and quantitative differences with respect to new bone formed with autologous bone graft[31]. Other preclinical studies[26,27] demonstrated good osteointegration and deposition of new bone tissue by the use of SintLife.

In the present observational, prospective clinical study, we investigated the use of Sintlife used alone in procedures of postero-lateral fusion, showing 73.4% of successful fusion reached, which is in line with previous findings , reporting a fusion rate of 70-90% obtained by the use of hydroxyapatite-based bone grafts used alone, as compared to autograft[32]. Although only few studies to date have evaluated successful fusion of HA-based bone grafts used alone, data from this prospective study confirm the efficacy of the Mg-HA bone graft SintLife in arthrodesis procedures. The success of fusion was also confirmed by an improvement of those values (i.e. ODI and VAS) which are used in the clinical practice to measure patients' disability, pain and quality of life before and after spinal stabilization by arthrodesis. No statistically significant differences were reported when considering the age (adults versus elderly patients) at the time of surgery, highlighting a satisfactory reaction to the surgical treatment.

The safe profile of SintLife is confirmed by the lack of adverse events related to the product, as also previously demonstrated in a Post-Marketing Surveillance analysis[33] involving the device and confirmed in the present study. Only one minor event (i.e. a local infection treated with antibiotic therapy) has been recorded during the study, possibly related to the patient's clinical conditions, which may affect the post-operative course. Available literature reports about cases of inflammatory reactions following bone grafts substitutes use for spinal fusion[34-36]. These events are always related to previous patients' clinical inflammatory conditions.

Nonetheless, hypersensitivity to some components of the device have always to be taken into account, and are usually reported in the Manufacturer Instruction For Use.

Limitations of the study are mainly related to the low number of subjects enrolled and then completing all the follow-up visits: possible causes can be found in the concomitant worldwide pandemic COVID-19, which drastically reduced clinical activities during the period of the study conduction. By the other side, patients satisfied by the improvement of their quality of life following spinal fusion tend to avoid subsequent visits.

Being understood that future searches are needed to further investigate the use of SintLife in procedures of spinal fusion on larger populations, the biomaterial has shown good performance in terms of fusion achievement and improvement of clinical scores. The satisfying biocompatibility as well as the safe profile confirm the use of the device in spinal fusion procedures.

CONCLUSIONS

In conclusion, the Mg-doped HA bone graft substitue SintLife represents a good alternative to autologous bone graft. The device can be safely used alone performing in a similar manner as the "gold standard" autologous bone.

REFERENCES

1. Rajaee SS, Bae HW, Kanim LE, Delamarter RB. Spinal fusion in the United States: analysis of trends from 1998 to 2008. Spine 2012; 37 (1): 67-76.
2. Yoshihara H, Yoneoka D. National trends in the surgical treatment for lumbar degenerative disc disease: United States, 2000 to 2009. Spine J 2015; 15 (2): 265-271.
3. Ludwig SC, Kowalski JM, Boden SD. Osteoinductive bone graft substitutes. Eur Spine J 2000; 9 (Suppl 1): S119-125.
4. Park JJ, Hershman SH, Kim YH. Updates in the use of bone grafts in the lumbar spine. Bull Hosp Jt Dis 2013; 71 (1): 39-48.
5. Ahlmann E, Patzakis M, Roidis N, Shepherd L, Holtom P. Comparison of anterior and posterior iliac crest bone grafts in terms of harvest-site morbidity and functional outcomes. J Bone Joint Surg Am 2002; 84 (5): 716-720.
6. Arrington ED, Smith WJ, Chambers HG, Bucknell AL, Davino NA. Complications of iliac crest bone graft harvesting. Clin Orthop Relat Res 1996; 329: 300-309.
7. Banwart JC, Asher MA, Hassanein RS. Iliac crest bone graft harvest donor site morbidity. A statistical evaluation. Spine 1995; 20 (9): 1055-1060.
8. Dimar JR 2nd, Glassman SD, Burkus JK, Pryor PW, Hardacker JW, Carreon LY. Two-year fusion and clinical outcomes in 224 patients treated with a single-level instrumented posterolateral fusion with iliac crest bone graft. Spine J 2009; 9 (11): 880-885.
9. Kim DH, Rhim R, Li L, Martha J, Swaim BH, Banco RJ, Jenis LG, Tromanhauser SG. Prospective study of iliac crest bone graft harvest site pain and morbidity. Spine J 2009; 9 (11): 886-892.
10. Gruskay JA, Basques BA, Bohl DD, Webb ML, Grauer

JN. Short-term adverse events, length of stay, and readmission after iliac crest bone graft for spinal fusion. Spine 2014; 39 (20): 1718-1724.

11. Miyazaki M, Tsumura H, Wang JC, Alanay A. An update on bone substitutes for spinal fusion. Eur Spine J 2009; 18 (6): 783-799.
12. Gupta A, Kukkar N, Sharif K, Main BJ, Albers CE, El-Amin Iii SF. Bone graft substitutes for spine fusion: a brief review. World J Orthop 2015; 6 (6): 449-456.
13. Abdullah KG, Steinmetz MP, Benzel EC, Mroz TE. The state of lumbar fusion extenders. Spine 2011; 36 (20): E1328-1334.
14. Fischer CR, Cassilly R, Cantor W, Edusei E, Hammouri Q, Errico T. A systematic review of comparative studies on bone graft alternatives for common spine fusion procedures. Eur Spine J 2013; 22 (6): 1423-1435.
15. Hsu WK, Nickoli MS, Wang JC, Lieberman JR, An HS, Yoon ST, Youssef JA, Brodke DS, McCullough CM. Improving the clinical evidence of bone graft substitute technology in lumbar spine surgery. Global Spine J 2012; 2 (4): 239-248.
16. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J 2011; 11 (6): 471-491.
17. Kannan A, Dodwad SN, Hsu WK. Biologics in spine arthrodesis. J Spinal Disord Tech 2015; 28 (5): 163-170.
18. Alsaleh KA, Tougas CA, Roffey DM, Wai EK. Osteoconductive bone graft extenders in posterolateral thoracolumbar spinal fusion: a systematic review. Spine 2012; 37 (16): E993-1000.
19. Nickoli MS, Hsu WK. Ceramic-based bone grafts as a bone grafts extender for lumbar spine arthrodesis: a systematic review. Global Spine J 2014; 4 (3): 211-216.
20. Gao C, Deng Y, Feng P, Mao Z, Li P, Yang B, Deng J, Cao Y, Shuai C, Peng S. Current progress in bioactive ceramic scaffolds for bone repair and regeneration. Int J Mol Sci 2014; 15 (3): 4714-4732.
21. Kaiser MG, Groff MW, Watters WC 3rd, Ghogawala Z, Mummaneni PV, Dailey AT, Choudhri TF, Eck JC, Sharan A, Wang JC, Dhall SS, Resnick DK. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes as an adjunct for lumbar fusion. J Neurosurg Spine 2014; 21 (1): 106-132.
22. Korovessis P, Koureas G, Zacharatos S, Papazisis Z, Lambiris E. Correlative radiological, self-assessment and clinical analysis of evolution in instrumented dorsal and lateral fusion for degenerative lumbar spine disease. Autograft versus coralline hydroxyapatite. Eur Spine J 2005; 14 (7): 630-638.
23. Nandi SK, Roy S, Mukherjee P, Kundu B, De DK, Basu D. Orthopaedic applications of bone graft and graft substitutes: a review. Indian J Med Res 2010; 132: 15-30.
24. Barbanti Brodano G, Mazzoni E, Tognon M, Griffoni C, Manfrini M. Human mesenchymal stem cells and biomaterials interaction: a promising synergy to improve spine fusion. Eur Spine J 2012; 21 (Suppl. 1): S3-9.
25. Manfrini M, Di Bona C, Canella A, Lucarelli E, Pellati A, D'Agostino A, Barbanti-Bròdano G, Tognon M. Mesenchymal stem cells from patients to assay bone graft substitutes. J Cell Physiol 2013; 228 (6): 1229-1237.
26. Sartori M, Giavaresi G, Tschon M, Martini L, Dolcini L, Fiorini M, Pressato D, Fini M. Long-term in vivo experimental investigations on magnesium doped hydroxyapatite bone substitutes. J Mater Sci Mater Med 2014; 25 (6): 1495-1504.
27. Pola E, Nasto LA, Tampieri A, Lattanzi W, Di Giacomo G, Colangelo D, Ciriello V, Pagano E, Spinelli S, Robbins PD, Logroscino G. Bioplasty for vertebral fractures: preliminary results of a pre-clinical study on goats using autologous modified skin fibroblasts. Int J Immunopathol Pharmacol 2011; 24 (1 Suppl. 2): 139-142.
28. Brantigan JW, Steffee AD. A carbon fiber implant to aid interbody lumbar fusion. Two-year clinical results in the first 26 patients. Spine 1993; 18 (14): 2106-2107.
29. Kurien T, Pearson RG, Scammell BE. Bone graft substitutes currently available in orthopaedic practice: the evidence for their use. Bone Joint J 2013; 95-B (5): 583-597.
30. Landi E, Logroscino G, Proietti L, Tampieri A, Sandri M, Sprio S. Biomimetic Mg-substituted hydroxyapatite: from synthesis to in vivo behaviour. J Mater Sci Mater Med 2008; 19 (1): 239-247.
31. Bròdano GB, Giavaresi G, Lolli F, Salamanna F, Parrilli A, Martini L, Griffoni C, Greggi T, Arcangeli E, Pressato D, Boriani S, Fini M. Hydroxyapatite-based biomaterials versus autologous bone graft in spinal fusion: an in vivo animal study. Spine 2014; 39 (11): E661-E668.
32. Buser Z, Brodke DS, Youssef JA, Meisel HJ, Myhre SL, Hashimoto R, Park JB, Tim Yoon S, Wang JC. Synthetic bone graft versus autograft or allograft for spinal fusion: a systematic review. J Neurosurg Spine 2016; 25 (4): 509-516.
33. Barbanti Brodano G, Griffoni C, Zanotti B, Gasbarrini A, Bandiera S, Ghermandi R, Boriani S. A post-market surveillance analysis of the safety of hydroxyapatite-derived products as bone graft extenders or substitutes for spine fusion. Eur Rev Med Pharmacol Sci 2015; 19 (19): 3548-3555.
34. Feng JT, Yang XG, Wang F, He X, Hu YC. Efficacy and safety of bone substitutes in lumbar spinal fusion: a systematic review and network meta-analysis of randomized controlled trials. Eur Spine J 2020; 29 (6): 1261-1276.
35. Mokawem M, Katzouraki G, Harman CL, Lee R. Lumbar interbody fusion rates with 3D-printed lamellar titanium cages using a silicate-substituted calcium phosphate bone graft. J Clin Neurosci 2019; 68: 134-139.
36. Bolger C, Jones D, Czop S. Evaluation of an increased strut porosity silicate-substituted calcium phosphate,

SiCaP EP, as a synthetic bone graft substitute in spinal fusion surgery: a prospective, open-label study. Eur Spine J 2019; 28 (7): 1733-1742.

Conflict of Interest Statement: *The Authors declare they have no financial or other conflict of interests in relation to this research and its publication.*