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A post-market surveillance analysis of the safety of hydroxyapatite-derived products as bone graft extenders or substitutes for spine fusion

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Abstract. – OBJECTIVE: Iliac crest bone graft (ICBG) is considered the gold standard for spine surgical procedures to achieve a successful fusion, because of its known osteoinductive and osteoconductive properties. Considering its autogenous origin, the use of ICBG has not been associated to an increase of intraoperative or postoperative complications directly related to the surgery. However, complications related to the harvesting procedure and to the donor site morbidity have been largely reported in the literature, favoring the development of a wide range of alternative products to be used as bone graft extenders or substitutes for spine fusion.

The family of ceramic-based bone grafts has been widely used and studied during the last years for spine surgical procedures in order to reduce the need for iliac crest bone grafting and the consequent morbidity associated to the harvesting procedures.

PATIENTS AND METHODS: We report here the results of a post-market surveillance analysis performed on four independent cohorts of patients (115 patients) to evaluate the safety of three different formulations of hydroxyapatite-derived products used as bone graft extenders/substitutes for lumbar arthrodesis.

RESULTS: No intraoperative or post-operative complications related to the use of hydroxyapatite-derived products were detected, during medium and long follow up period (minimum 12 months-maximum 5 years).

CONCLUSIONS: This post-market surveillance analysis evidenced the safety of ceramic products as bone graft extenders or substitutes for spine fusion. Moreover, the evidence of the safety of hydroxyapatite-derived products allows to perform clinical studies aimed at evaluating the fusion rates and the clinical outcomes of these materials as bone graft extenders/substitutes, in order to support their use as an alternative to ICBG for spine fusion.

Key Words:
Hydroxyapatite, Bone graft extenders or substitutes, Spine fusion, Surveillance analysis.

Introduction

During the past few decades spinal fusion procedures has significantly increased to treat a wide range of spinal disorders of degenerative, traumatic and oncological origin[1,2]. Autologous bone graft from iliac crest (ICBG) has been classically used to provide spinal fusion and immediate structural support. Harvesting of autologous bone graft has limitations and significant morbidity, including superficial infection, wound complications, sensory abnormalities, persistent pain, hematomas, need for reoperation, scarring, graft site fracture, with reported rates between 10% and 39%. Donor site pain can be considered the major complication associated to ICGB harvesting, even if reported numbers significantly vary. Acute pain has been reported in 2.8% to 27.9% of patients[3-5] and chronic pain in 2.4% to 60% of patients[6,7].

Despite these complications, iliac crest autograft still remains the "gold standard" for spine surgery because of its osteoconductive and osteoinductive properties, allowing excellent fusion rates[7-12].

Autologous laminectomy bone is often used as bone graft instead of iliac crest autograft and also has excellent fusion rates as it contains three critical elements for osteogenesis: bone trabeculae providing an osteoconductive scaffold, bone morphogenetic protein (BMP) having an osteoinductive potential and osteoblasts as a source of osteogenic cells[13,14].

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Moreover, a wide range of products has been proposed in recent years to enhance or substitute autologous bone graft for spine fusion, including allograft, bone morphogenetic protein, demineralized bone matrix (DBM), platelet gel, mesenchymal stem cells (MSCs) and ceramics.

These products are the focus of ongoing research investigating the safety and efficacy of their use in the setting of spinal fusion[15,16]. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) has become controversial within the spine community due to its high cost, widespread off-label use, surgical risks, a wide range of adverse effects, disagreement regarding clinical indications[17,18].

Demineralized bone matrix (DBM) is an allograft-based osteoinductive and osteoconductive agent used to elicit spinal fusion. Spinal fusion studies in the rat model have shown that different DBM formulations demonstrate marked variability in osteoinductive potential, correlated to differences in growth factors concentration, while it may potentially serve as a bone graft extender, because of its osteoconductive properties, when used in combination with autograft[19,20].

Mesenchymal stem cells (MSCs) are pluripotent cells that exhibit self-renewal, plasticity and multilineage potential. In the proper biological environment these cells can differentiate into primary osteoblasts with the capacity for bone formation and subsequent bone fusion. The use of MSCs as a bone graft extender/substitute in clinical trials is growing, in order to prepare cell-based treatments for patients in the near future[21-23].

Bioactive ceramics are synthetic products which have received great attention in the past decades due to their success in stimulating cell proliferation, differentiation and bone tissue regeneration. As these products can actively interact with cells and tissues in the human body, forming chemical bonds, they are considered the most promising materials for bone tissue engineering and in particular, for bone grafting in spine surgery to reduce the need for ICBG. Ceramics vary widely based on differences in composition, manufacturing, porosity and structure. Some bioactive materials such as hydroxyapatite, tricalcium phosphate, bioactive glass and calcium silicate have been largely investigated because of their ability to form direct bonds with the existing bone after implantation in bone defects. They have different binding, biodegradability and mechanical properties[24,25].

Hydroxyapatite (HA) is a major component of natural bone. It can combine with tissues by chemical bonds to form new bone tissue when implanted[26]. Tricalcium phosphate (TCP) has good bioactivity, biodegradability, biocompatibility and it can enhance stem cells proliferation and bone formation[27]. Bioactive glass (BG) promote gene expression and production of osteocalcin. Calcium silicate (CS) has excellent bioactivity and ability to bond with living bone and soft tissue.

Ceramics provide an osteoconductive matrix but they generally lack osteoinductive potential. Thus, successful arthrodesis rates can increase when bioceramics are used with a source of cells such as local autograft or bone marrow aspirates. Ceramics have several advantages with respect to other bone graft substitutes[24]:

- They do not induce a host inflammatory response;
- They are able to be sterilized minimizing the risk for disease transmission, without loss of structural integrity;
- They can be adapted to different surgical environments by various shapes;
- Their cost is less than that of other bone graft substitutes such as growth factors.

Among the synthetic bioceramic bone graft substitutes currently in use, at least three can be used successfully in spinal surgery. The first bone substitute is a porous hydroxyapatite (HA) bone substitute in chips form with high porosity, between 80 and 90%, and a trabecular structure very similar to that of the natural bone, which maximize the possibilities of osteointegration and bone regeneration. Despite the high porosity, this material is able to withstand compression loads similarly to the spongy bone[28].

The second bone substitute is composed by nanocrystals of Mg-substituted HA in putty, paste and granule form. In these formulations, the Mg ions are placed in the crystalline HA cell in the same position and percentage found in the mineral phase of the human bone. It has been demonstrated that the presence of Mg ions modifies the crystalline HA structure, making it unstable and biologically active. Thus, the Mg-HA material is able to interact with the cells that form bone to elicit new bone deposition and it is remodelled and resorbed in a physiological manner, through the action of osteoclasts, in an adequate amount of time (6-18 months). Consider-

ing its chemical and structural properties, Mg-HA bioceramic bone substitute promotes physiological, rapid and effective bone regeneration[28].

The third type of bone substitute is a composite material formed by Mg-substituted HA nucleated on equine collagen fibres (type I). This product is completely biomimetic, because its chemical and structural characteristics make it completely similar to the human bone, and it is also biodegradable. Its architecture promotes cell attachment and proliferation[28].

We recently reported the results of a pre-clinical study performed using Mg-substituted HA to induce spinal fusion in an animal model[29].

During the last years some authors reported the results of clinical trials concerning the use of hydroxyapatite products, compared with autograft, for spinal surgery and evaluated the outcome measures, in terms of pain, disability, quality of life, complications and radiographical parameters to assess fusion status[30-33]. However, these trials presented methodological limitations and only demonstrated the feasibility of utilizing ceramic products as graft extenders or substitutes for spinal surgery[34].

The safety of using hydroxyapatite products in the patients should be the first point analyzed in order to consider these materials as graft extenders or substitutes. Recently, a comparison of outcomes and safety of using HA granules as a substitute for autograft in cervical cages for anterior spine fusion has been published by Mashhadinezhad et al[35]. Moreover, a post-marketing surveillance analysis has been reported for three different hydroxyapatite-derived products used as bone graft substitutes for cranioplasty[36-38]. We report here the results of a Post-Marketing Surveillance Analysis performed using the same three different hydroxyapatite formulations (HA in chips form with high porosity, Mg-substituted HA in putty, paste and granule form, Mg-substituted HA nucleated on equine collagen fibres type I) for posterolateral lumbar arthrodesis procedures, collecting data concerning adverse intra-operative and post-operative events.

Patients and Methods

We present here a post-marketing surveillance report performed according to medical device vigilance regulations (MEDDEV 2.12-1 rev.6, European Commission, DG Enterprise). This report has been drawn up analyzing four independent cohorts of 115 patients (47 male, 40.9%; 68 female, 59.1%) surgically treated in four different Italian Hospitals for spine diseases of degenerative origin and traumatic origin. The average age was 57.6 years (range 25-86).

To induce spinal fusion three different HA synthetic bone substitutes (Finceramica, Faenza, Italy) were used: HA chips with high porosity, Mg-substituted HA in putty, paste and granule form and Mg-substituted HA nucleated on equine collagen fibres type I.

Patients were examined for the occurrence of peri-operative and post-operative complications, requiring the patient's hospitalization, at medium or long follow up periods (minimum 12 months-maximum 5 years) and only complications possibly related to the bone substitutes were reported to the manufacturer, following the guidelines of post-marketing surveillance.

Statistical Analysis

Differences between groups were tested with Chi square test. This analysis was performed using SPSS 14.0 for Windows, version 14.0.1 (SPPS Inc., Chicago, IL, USA).

The data, collected by four principal investigators, one for each Centre, were finally analyzed by one independent neurosurgeon, who drafted the final report for the post-market surveillance analysis of bone graft substitutes. $p < 0.05$ was considered statistically significant.

Results

We observed that in the cohorts examined 85.4% of patients were surgically treated for spine diseases of degenerative origin and 14.6% of patients were treated for spine diseases of traumatic origin (Figure 1).

Most of the patients were treated by posterolateral lumbar and lumbosacral arthrodesis (89.6%); 49.6% of patients underwent posterior decompression of the nervous structures (Figure 2). In most of the cases 1 or 2 levels were treated (59.1% of patients) and only 9.6% of patients were treated on 3 or more levels.

HA synthetic bone substitutes were used to induce spinal fusion, as shown in Figure 3 and 4:

– HA in chips form with high porosity was used in 37 patients (alone or combined with autologous bone in 20 cases or with another bone substitute in 1 case);

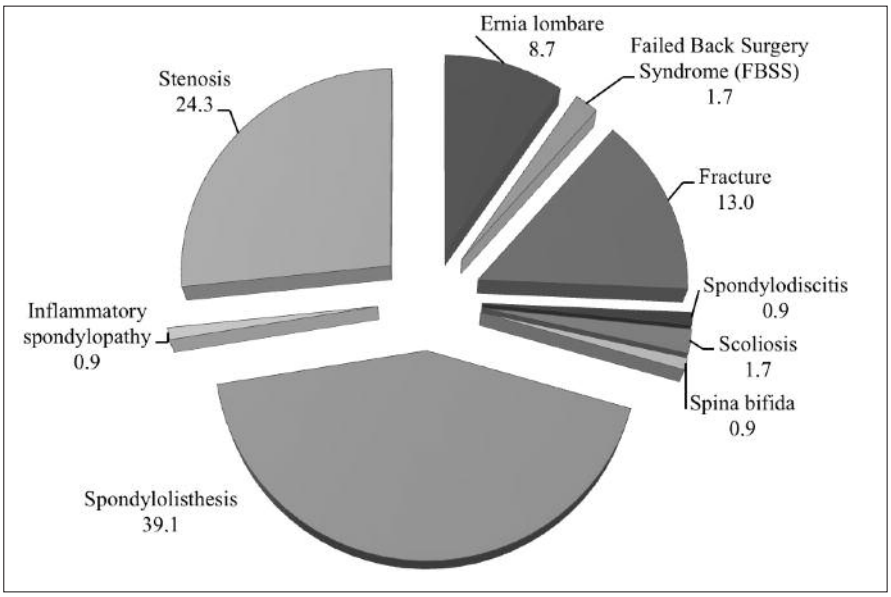

Figure 1. Distribution of degenerative and traumatic pathologies of the lumbar spine surgically treated using HA-derived products as bone graft extenders.

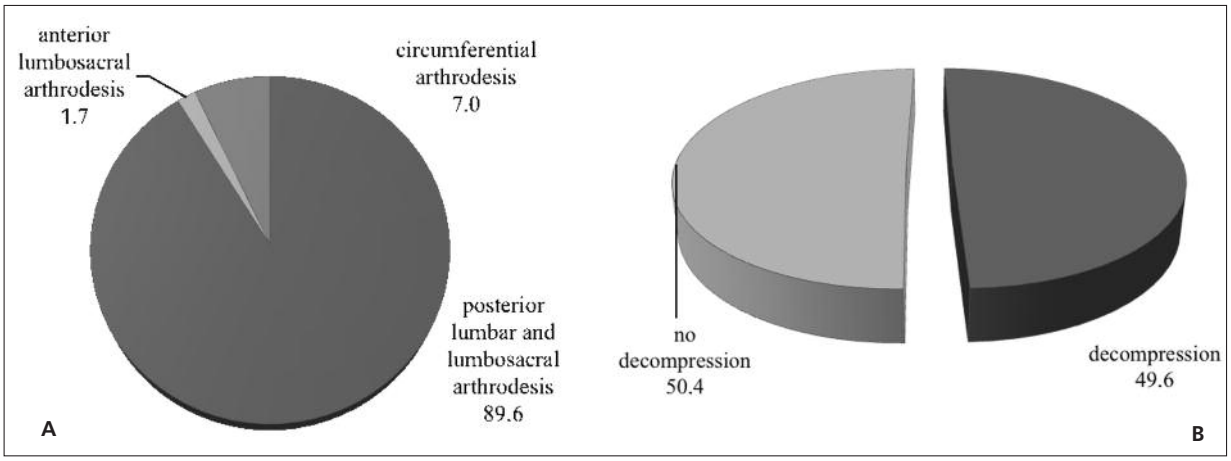

Figure 2. Distribution of the surgical treatments performed in the cohort of patients analyzed for the study. ***A,*** Surgical approaches used for the spinal stabilization. ***B,*** Presence or absence of surgical decompression

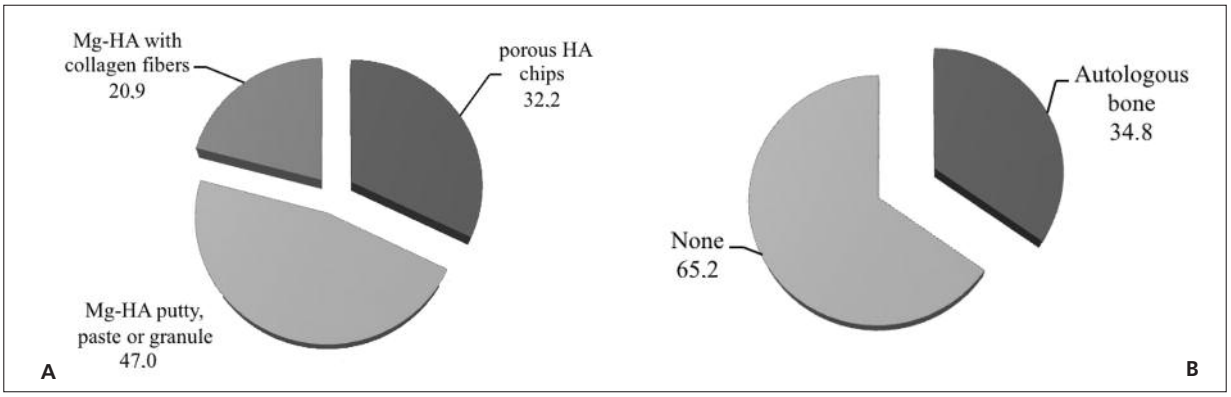

Figure 3. ***A,*** HA-derived products used as bone graft extenders/substitutes for spinal fusion treatments. ***B,*** Use of autologous bone graft in association with ceramic bone graft extenders/substitutes.

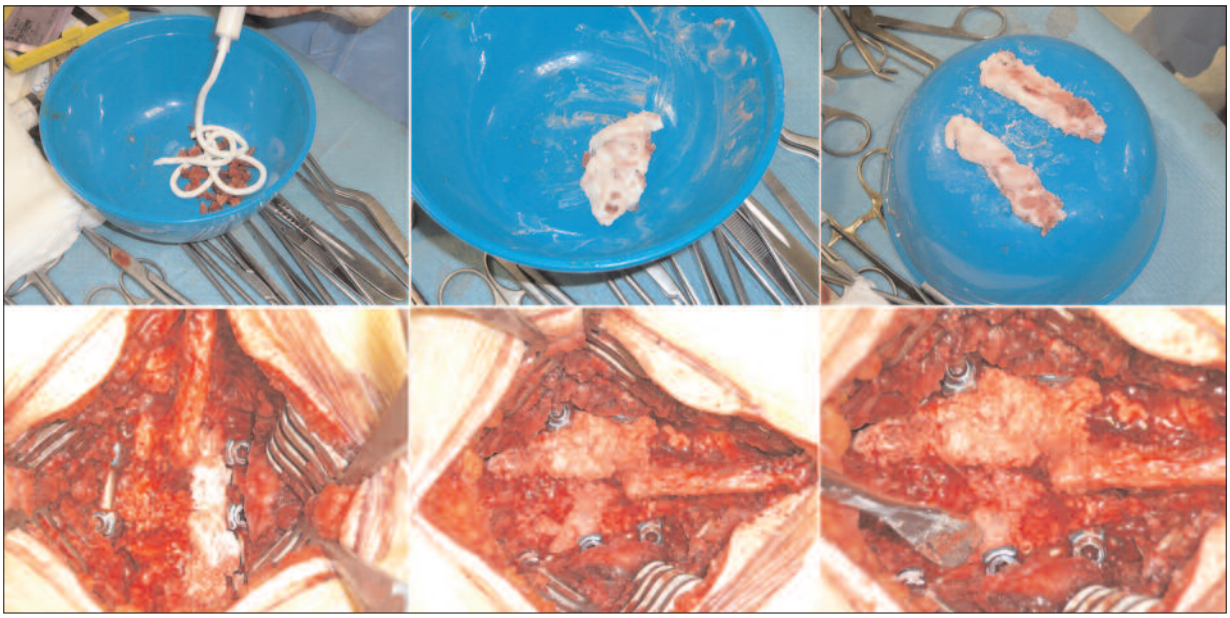

Figure 4. Intraoperative images showing the use of Mg-HA product in association with autologous bone for posterior L3-L5 stabilization.

– Mg-substituted HA in putty, paste and granule form was used in 54 patients (alone or combined with autologous bone in 5 cases or with another bone substitute in 2 cases);
– Mg-substituted HA nucleated on equine collagen fibres type I was used in 24 patients (alone or combined with autologous bone in 15 cases).

Concerning Post-market surveillance analysis, we observed the absence of adverse events related to the use of ceramic bone graft substitutes in the cohorts of patients examined.

Rates of hospital readmission or return to the operating room were not increased in the cohort of patients treated with HA bone graft substitutes. We detected 5 cases of readmission or early return to the operating room in the cohort of 115 patients treated with ceramic bone graft substitutes (4.3%). This rate can be compared to a mean rate of 5% cases of readmission or early return to the operating room registered in our series of patients treated with autologous bone for spinal fusion. The difference between the two data is not statistical significant according to the chi-square test ($p = 0.06$).

There was not an increase in the post-operative infection rate. We detected 3 cases of post-operative infection in the cohort of 115 patients treated with ceramic bone graft substitutes (2.6%). This rate can be compared to a mean rate of 3.3% cases of post-operative infection registered in our series of patients treated with autologous bone for spinal fusion. The difference between the two data is not statistical significant according to the chi-square test ($p = 0.11$).

Finally, no cases of morbidity or mortality where detected in the study cohort of 115 patients treated with HA bone graft substitutes for spinal fusion.

Data concerning the clinical outcomes and the radiographical fusion will be evaluated separately, in order to compare the clinical performance of bone graft substitutes to that of the autologous bone used as gold standard for spinal fusion procedures.

Discussion

Ceramic-based bone grafts represent one member of the heterogeneous family of spinal biologics. They harbor osteoconductive properties, but they need for an osteoinductive stimulus that poses limitations to their use. They offer several advantages compared with other bone graft extenders, such as inertness, ease of sterilization, flexibility of the shape and safety profile. Thus, ceramics are extensively studied as bone graft extenders in order to be used as alternative to the iliac crest bone graft for spinal fusion.

We collected during the past years and reported here data regarding a Post-market surveillance analysis performed on four different cohorts of patients who underwent surgical stabilization for degenerative and traumatic spine diseases using HA-derived products as bone graft substitutes. We did not observe any peri-operative and post-operative complications related to the use of HA materials.

Iliac crest bone graft is still considered the gold standard for the spinal fusion necessary after surgical treatment of spinal disorders, because of its osteoconductive and osteoinductive properties allowing excellent fusion rate and because of its safety related to the autogenous origin.

No significant effect of ICGB on the outcome of spinal fusion in the treatment of degenerative spondylolisthesis was detected in a subgroup analysis of the Spine Patient Outcomes Research Trial (SPORT). Only operative time was higher for the ICGB group, while no significant differences were detected concerning clinical scores, blood loss, hospital stay and postoperative complications, including wound infection, wound hematoma, and need for additional surgical procedures[39].

A recent study[40] used a large American database cohort of patients undergoing spinal fusion between the years of 2010 and 2012 (13,927 patients) to analyse 5.9% of cases where ICBG was used.

No severe adverse events (SAE) were found to be associated with the ICBG group. However, increased postoperative blood transfusion, extended operative time and increased length of hospital stay (LOS) were identified as short-term outcomes associated with ICBG on multivariate analysis.

The need for transfusion is due to increased blood loss, caused by added soft-tissue dissection, additional incisional site and extended operative time associated with bone graft harvest.

Extended LOS was significantly associated with ICBG use by multivariate analysis, although it is questionable whether the effect size (+ 0.2 days) is clinically significant.

Rates of readmission were not significantly different between the groups on bivariate or multivariate analyses. There was not an increase in infection rate in the ICBG group (at 30-day post-operative follow up). There was also not an increase in return to the operating room. Finally, ICBG use was not associated with additional risk of mortality in the cohort of study[40].

Even if the absence of adverse events directly associated with the use of ICBG supports its safety as autologous bone graft for spine fusion procedures, the increase of morbidity related to the graft harvest has to be taken into account and favors the use of alternative products as bone graft extenders/substitutes.

We demonstrate here the safety of HA-derived products as bone graft extenders/substitutes. Clinical studies supporting their efficacy in terms of fusion rate and favorable clinical outcomes are necessary to consider ceramic-based products as bone graft extenders with competitive performances for spine surgery.

A recent review[24] analyzes a total of 30 studies examining over 1300 patients who underwent lumbar spine arthrodesis with a ceramic as bone graft extender in association with local autograft or other adjuncts. On the whole these works demonstrate a fusion rate of 86.4%, which is comparable to the reported rates from ICBG in the same anatomic location. Only three level I studies analyzed the use of ceramic products for lumbar arthrodesis in comparison with ICBG, suggesting their efficacy for spine fusion, if combined with local autograft[30-32].

Conclusions

We propose to evaluate and report soon the data concerning spine fusion at follow up in the same cohorts of 115 patients studied for this Post-market surveillance analysis, in connection with the use of bioceramic products. The results of Post-marketing clinical studies concerning fusion rates in spine surgical procedures performed with hydroxyapatite-derived products will support their use as bone graft extenders/substitutes to achieve successful lumbar arthrodesis, which is the ultimate goal in the surgical treatment of degenerative, traumatic and oncological spine diseases.

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Conflict of Interest

Dr. Bruno Zanotti has a consulting contract with Finceramica, Faenza, Italy. No other conflict of interest is declared by the Authors.

References

1) Yoshihara H, Yoneoka D. National trends in the surgical treatment for lumbar degenerative disc disease: United States, 2000 to 2009. Spine J 2015; 15: 265-271.
2) Rajaee SS, Bae HW, Kanim LE, Delamarter RB. Spinal fusion in the United States: analysis of rends from 1998 to 2008. Spine (Phila Pa 1976) 2012; 37: 67-76.
3) Hu SS. Iliac crest bone graft: are the complications over-rated? Spine J 2011; 11: 538-539.
4) Howard JM, Glassman SD, Carreon LY. Posterior iliac crest pain after posterolateral fusion with or without iliac crest graft harvest. Spine J 2011; 11: 534-537.
5) Myeroff C, Archdeacon M. Autogenous bone graft: donor sites and techniques. J Bone Joint Surg Am 2011; 93: 2227-236.
6) Goulet JA, Senunas LE, DeSilva GL Greenfield ML. Autogenous iliac crest bone graft. Complications and functional assessment. Clin Orthop Relat Res 1997; 76-81.
7) 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: 880-885.
8) Dimar JR, Glassman SD. The art of bone grafting. Curr Opin Orthop 2007; 18: 8.
9) 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: 716-720.
10) 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.
11) Banwart JC, Asher MA, Hassanein RS. Iliac crest bone graft harvest donor site morbidity. A statistical evaluation. Spine (Phila Pa 1976) 1995; 20:1055-1060.
12) 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: 886-892.
13) Eder C, Chavanne A, Meissner J, Bretschneider W, Tuschel A, Becker P, Ogon M. Autografts for spinal fusion: osteogenic potential of laminectomy bone chips and bone shavings collected via high speed drill. Eur Spine J 201; 20: 1791-1795.
14) Kho VK, Chen WC. Posterolateral fusion using laminectomy bone chips in the treatment of lumbar spondylolisthesis. Int Orthop 2008; 32: 115-119.
15) 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: 1423-1435.
16) Kannan A, Dodwad SN, Hsu WK. Biologics in spine arthrodesis. J Spinal Disord Tech 2015; 28: 163-170.
17) 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: 471-491.
18) Fu R, Selph S, McDonagh M, Peterson K, Tiwari A, Chou R, Helfand M. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. Ann Intern Med 2013; 158: 890-902.
19) Lee KJ, Roper JG, Wang JC. Demineralized bone matrix and spinal arthrodesis. Spine J 2005; 5: 217S-223S.
20) Tilkeridis K, Touzopoulos P, Ververidis A, Christodoulou S, Kazakos K, Drosos GI. Use of demineralized bone matrix in spinal fusion. World J Orthop 2014; 5: 30-37.
21) Agacayak S, Gulsun B, Ucan MC, Karaoz E, Nergiz Y. Effects of mesenchymal stem cells in critical size bone defect. Eur Rev Med Pharmacol Sci 2012; 16: 679-686.
22) Roseti L, Serra M, Canella F, Munno C, Tosi A, Zuntini M, Pandolfi M, Sangiorgi L, Biso P, Pittalis MC, Bini C, Pelotti S, Gasbarrini A, Boriani L, Bassi A, Grigolo B. In vitro gene and chromosome characterization of expanded bone marrow mesenchymal stem cells for musculo-skeletal applications. Eur Rev Med Pharmacol Sci 2014; 18: 3702-3711.
23) Oehme D, Goldschlager T, Rosenfeld JV, Ghosh P, Jenkin G. The role of stem cell therapies in degenerative lumbar spine disease: a review. Neurosurg Rev 2015; 38: 429-445.
24) 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: 211-216.
25) 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: 4714-4732.
26) Zhou H, Lee J. Nanoscale hydroxyapatite particles for bone tissue engineering. Acta Biomater. 2011; 7: 2769-2781.
27) Liu B, Lun DX. Current application of β-tricalcium phosphate composites in orthopaedics. Orthop Surg 2012; 4: 139-144.
28) Barbanera A, Longo GP, Vitali M, Sprio S, Tampieri A. Potential applications of synthetic bioceramic bone graft substitues in spinal surgery. Progr Neurosci 2012; 1: 97-104.
29) 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 vs. autologous bone graft in spinal fusion: an in vivo animal study. Spine (Phila Pa 1976) 2014 Apr 8. [Epub ahead of print]

30) 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: 630-638.

31) Kanayama M, Hashimoto T, Shigenobu K, Yamane S, Bauer TW, Togawa D. A prospective randomized study of posterolateral lumbar fusion using osteogenic protein-1 (OP-1) versus local autograft with ceramic bone substitute: emphasis of surgical exploration and histologic assessment. Spine (Phila Pa 1976) 2006; 31: 1067-1074.

32) Dai LY, Jiang LS. Single-level instrumented posterolateral fusion of lumbar spine with beta-tricalcium phosphate versus autograft: a prospective, randomized study with 3-year follow-up. Spine (Phila Pa 1976) 2008; 33: 1299-1304.

33) Lee JH, Hwang CJ, Song BW, Koo KH, Chang BS, Lee CK. A prospective consecutive study of instrumented posterolateral lumbar fusion using synthetic hydroxyapatite (Bongros-HA) as a bone graft extender. J Biomed Mater Res A 2009; 90: 804-810.

34) 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: 106-132.

35) Mashhadinezhad H, Samini F, Zare R. Comparison of outcomes and safety of using hydroxyapatite granules as a substitute for autograft in cervical cages for anterior cervical discectomy and interbody fusion. Arch Bone Jt Surg 2014; 2: 37-42.

36) Staffa G, Barbanera A, Faiola A, Fricia M, Limoni P, Mottaran R, Zanotti B, Stefini R. Custom made bioceramic implants in complex and large cranial reconstruction: a two-year follow-up. J Craniomaxillofac Surg 2012; 40: e65-70.

37) Stefini R, Esposito G, Zanotti B, Iaccarino C, Fontanella MM, Servadei F. Use of "custom made" porous hydroxyapatite implants for cranioplasty: postoperative analysis of complications in 1549 patients. Surg Neurol Int 2013; 4: 12.

38) Stefini R, Zanotti B, Nataloni A, Martinetti R, Scafuto M, Colasurdo M, Tampieri A. The efficacy of custom-made porous hydroxyapatite prostheses for cranioplasty: evaluation of postmarketing data on 2697 patients. J Appl Biomater Funct Mater 2014 Dec 19; 13: 0. doi: 10.5301/jabfm.5000211. [Epub ahead of print].

39) Radcliff K, Hwang R, Hilibrand A, Smith HE, Gruskay J, Lurie JD, Zhao W, Albert T, Weinstein J. The effect of iliac crest autograft on the outcome of fusion in the setting of degenerative spondylolisthesis: a subgroup analysis of the Spine Patient Outcomes Research Trial (SPORT). J Bone Joint Surg Am 2012; 94: 1685-1692.

40) 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 (Phila Pa 1976) 2014; 39: 1718-1724.