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Assessment of the injection behavior of commercially available bone BSMs for Subchondroplasty® procedures

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ABSTRACT

Background: Bone substitute materials (BSMs) have been commercially available for over 30 years and have been used extensively in orthopedic procedures. Some BSMs are described as "injectable." With rising focus on minimally invasive surgical procedures, the range of applications in which these materials are injectable is of clinical interest. Specifically, their performance in closed, pressurized environments in the trabecular bone with microdamage or abnormal bone remodeling have not been well characterized. This issue arises often in the presence of bone marrow lesions of the subchondral bone in early onset osteoarthritis. The objective was to evaluate the in vitro injectability of several common commercially available BSMs. It was hypothesized that some materials self-described as "injectable" would fail to function in a small microarchitecture in comparison to the large void areas.
Methods: Mechanical testing was performed and force data was collected. Each sample was additionally radiographed and then imaged under micro-computed tomography (CT).
Results: Most of the BSM materials failed to be successfully injected into a simulated trabecular model. Simplex™, AccuFill® and StrucSure™ materials were the only ones that were injected successfully. Many of the materials underwent phase separation at higher pressures and were not able to be deployed from the injection syringe. In addition, a clinically relevant difference was seen between the manners in which the materials interdigitated into the existing structure.
Conclusion: The AccuFill® was the only material able to inject in a closed model and demonstrate adequate implantation of BSM into the simulated trabecular bone.
Clinical Relevance: Injectability of BSMs is clinically relevant as the interest in minimally invasive surgical procedures is rising rapidly.

1. Introduction

Orthopedic surgery often requires bone substitute materials (BSMs) for filling bony defects, prosthesis fixation, and fracture fixation. There are many categories of materials that are characterized as BSMs for surgical usage varying in composition, strength, and application. In general, BSMs have been designed to fill open voids or gaps in a macro-environment under little to no pressure. Many materials are described as moldable and can be manually placed. The most widely used classic bone cement is poly(methyl methacrylate) (PMMA) and most widely used BSMs are calcium phosphate (CaP) based. PMMA is indicated for the fixation of prostheses, fixation of fractures, and void filling for reinforcement of living bone during orthopedic procedures [1–3]. PMMA is known for its strength and permanence, but unpopular for its handling properties and the peripheral damage to the living bone during the exothermic setting reaction [4,5]. The use of PMMA in primary surgical interventions also poses complications for future secondary surgeries. Calcium phosphates (CaPs) have come into favor for their ability to form a bioactive apatitic compound similar to bone mineral. They also have improved handling properties that result in a paste-like material which can be injected or molded into non-weight-bearing defects. Calcium phosphate BSMs can crystallize at body temperature without any adverse effect in the host area [6,7].

In general, BSMs differ from classic bone cements not only in their composition but also in their intended method of action. They are designed to be osteoconductive and resorbable [8]. For example, CaPs can be partially resorbed by osteoclastic elements, releasing in the process calcium and phosphate ions, which are promoters of bone apposition [9]. This quality makes calcium phosphate an osteoconductive

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ceramic by nature with a good biocompatibility specific for bone [10]. How the BSM behaves during the healing process depends both on the properties of the BSM as well as the size and location of the bone defect. These properties result from the combination of the powder and liquid form of the bioactive and biodegradable bioceramics, forming a paste that can be molded to fit the affected area. When hard, this mixture yields a non-stoichiometric calcium-deficient hydroxyapatite or brushite [11].

Bone marrow lesions (BMLs) are identified on magnetic resonance imaging (MRI) rather than on radiographs, and are sometimes called bone marrow edema (BME) due to their edema-like appearance on imaging. Histologic analysis of BMLs has shown micro-trabecular damage characteristic of a stress or insufficiency fracture. In this situation, there are micro-fractures within the architecture of the trabecular bone. The surgical placement of materials into such a closed fracture requires the ability to inject into a highly pressurized environment with the innate increased risk of damage to surrounding tissue [6]. The ideal surgical technique utilizes a minimal entry point to preserve the cortical bone integrity while being able to deliver enough BSM to treat the defect without allowing any leakage outside the affected area.

First described in 2007, the Subchondroplasty® (Zimmer Knee Creations, West Chester, PA) is a technique of injecting flowable CaP BSM into the space between the trabeculae of cancellous bone in the subchondral region of the knee joint [6] (Fig. 1). This procedure is deemed appropriate when a BML is observed using a T2 MRI [12], and is a possible treatment to alleviate the pain for patients who did not exhibit severe radiographic cartilage changes requiring a total knee replacement.

Bone cements such as PMMA are readily manipulated to change their viscosity and flowability at the expense of their setup time, whereby less viscous materials take longer to cure. In contrast, the biphasic nature of CaP BSM materials requires a specific mixture such that their viscosity is not easily manipulated for the application. Understanding the BSM injection behavior and accurately predicting the BSM placement and volume within the trabecular space could offer significant clinical guidance. As there is no standardized model for the subchondral bone of the knee, we propose utilizing standardized polyurethane block material that has been shown to behave similar to the trabecular bone of the knee to examine the BSM injection behavior. We hypothesize that many BSMs are only injectable in large microarchitectures and would fail to function in a small microarchitecture environment.

2. Materials & methods

2.1. Preparation of the blocks

Commercially available 12.5 closed-cell polyurethane foam sheets (Pacific Research Laboratories, Vashon Island, Washington) were acquired and cut into 7.62 centimeters blocks. This foam material was chosen because it has been shown to possess similar mechanical properties as the cancellous bone in the distal femur and the proximal tibia [13,14]. A three-millimeter diameter drill hole was prepared into each block to accommodate an 11-gauge cannula to a depth of 3.81 centimeters (center of the block). The empty (dry) foam was individually weighed and recorded.

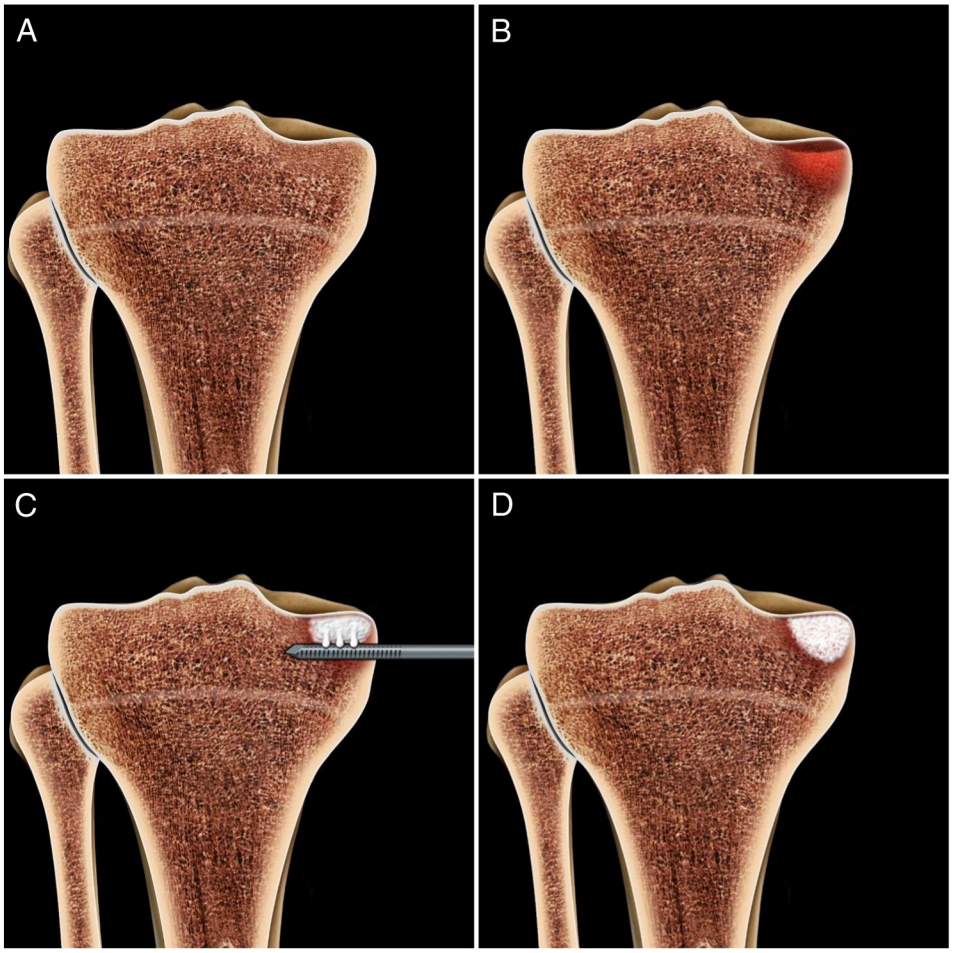

Fig. 1. Subchondroplasty®. A) Healthy tibial plateau. B) BML in tibial plateau. C) BSM injection into the affected area. D) BSM filled BML in tibial plateau.

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Table 1
Evaluated bone substitute materials and their manufacturer's described properties.

Product name	Manufacturer	Composition	Max. compr. force	Setup time	Working time
AccuFill®	Zimmer, Inc.	Nanocrystalline $CaPO_4$ (CaP)	10 MPa	10 min	15 min
Beta-BSM™	Zimmer, Inc.	Nanocrystalline CaP	30 MPa	3–5 min	2 min
Cerament™	Biomet, Inc.	HA and $CaSO_4$ (CaS)	0.000025 Mpa	9 min	4 min
HydroSet™	Stryker®	$H_4Ca_2O_6P$, TTCP, and $Na_3C_6H_5O_7$	15 MPa	24 h	4.5 min
Norian™ SRS	DePuy Synthes®	CaP with Na	55 MPa	3–6 min	2 min
Pro-Dense®	Wright Medical, Inc.	CaS and CaP	40 MPa	2 h	3–5 min
StrucSure™ CP	Smith & Nephew plc	Nanocrystalline CaP	24 MPa	24 h	2 min
Simplex™ P	Stryker®	PMMA	7.3 MPa	8.5 min	2–4 min

2.2. Preparation of the BSMs

Eight commercially available BSMs were acquired along with the respective mixing instrumentation (Table 1). Each of the eight BSMs was prepared according to the manufacturers' Instructions for Use (IFU) (Fig. 2), to include the use of any recommended machinery or instrumentation.

2.3. Measurement of dry, cured weight

In order to analyze the post-weight measurements after mechanical testing, separate samples of each of the BSMs were prepared. After mixing, one cubic centimeter of each material was placed in a weighing container. The material was weighed as a wet paste, hardened (pre-lyophilized), and cured (post-lyophilized). The percentage of water lost from the initial mixed state was calculated (Table 2).

2.4. Mechanical testing

A standard 11-gauge injection cannula, 2.39 mm ID, 3.05 mm OD (Ranfac, Avon, MA) was inserted into the pre-drill channel to the 3.81 centimeters depth in the foam block. The cannula and foam construct were placed in a saline bath at 37 °C for at least 10 min and then secured in a TA HD plus Texture Analyzer (Stable Micro Systems). Once prepared, each BSM sample was loaded into three one cubic centimeter syringes. It should be noted that while each material was prepared to the manufacturer's IFU, the materials were injected in a standardized method that in most cases varied from the manufacturer's intended delivery method.

Each filled syringe was attached to the luer lock of the cannula and injected at a rate of two millimeters per second into the cannula/test block assembly in series. Injection pressure per syringe was measured by a 30-kg load cell as the extrusion force/second (AccuFill® ($n = 5$), Beta-BSM™ ($n = 5$), HydroSet™ ($n = 5$), Pro-Dense® ($n = 4$), Cerament™ ($n = 5$), StrucSure™ CP ($n = 5$), Simplex™ P ($n = 4$), Norian™ SRS ($n = 5$)). If the third syringe in each sample was completely injected, a stylet was inserted into the cannula to inject residual BSM within the cannula.

After vacuum drying each injected foam block sample, the mass of the sample was measured to determine the mass of BSM in the foam block. Each sample was allowed to fully cure according to the manufacturers' instruction for use.

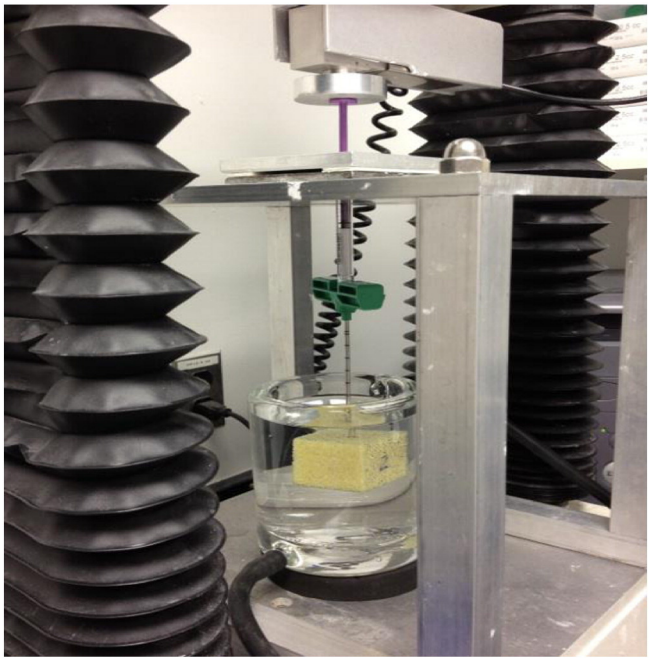

Fig. 2. The mechanical testing setup utilized.

2.5. Injection into the cadaveric bone

The AccuFill®, Beta-BSM™ and StrucSure™ materials were additionally tested in cadaveric bone blocks prepared from the femoral condyles of healthy donors (age 45–87). The cadaveric setup was used to further validate the results under the foam bone test method. Five human specimens were sectioned into 6.35 centimeters cube sections of the bone. Block setup and BSM insertion were done in the same manner as the foam and the same protocol was followed for measurements.

2.6. Micro-CT scan

The samples were analyzed by micro-CT using the μCT 35 desktop micro-CT scanner (Scanco Medical AG., Zürich, Switzerland), with the evaluation program v6.5. The samples were segmented and reconstructed using a processing language that allowed for the selection of the BSM, the cannula and the foam/bone sample. This created a better visualization of the flow pattern of the BSM within the block. Measurements were done applying the following criteria: 55 Kvp, 145 μA, with an integrated time of 400 ms/frame and a resolution of 37 μm. From

Table 2
Weights of each material at three stages of the drying process mean ± standard deviation.

Product	Wet paste g/cm^3	Hardened (pre-lyophilized) g/cm^3	Hardened (lyophilized) g/cm^3	Loss of water %
AccuFill®	1.78 ± 0.03	1.34 ± 0.03	1.24 ± 0.02	29.97
Beta-BSM™	1.34 ± 0.18	1.07 ± 0.16	0.87 ± 0.11	34.98
Cerament™	2.04 ± 0.09	1.71 ± 0.07	1.70 ± 0.07	16.90
HydroSet™	1.98 ± 0.08	1.60 ± 0.07	1.55 ± 0.07	21.77
Norian™ SRS	1.69 ± 0.01	1.18 ± 0.01	1.17 ± 0.01	31.14
Pro-Dense®	2.02 ± 0.05	1.76 ± 0.05	1.76 ± 0.05	13.14
StrucSure™	1.71 ± 0.17	1.21 ± 0.12	1.20 ± 0.12	29.65
Simplex™ P	1.09 ± 0.14	1.06 ± 0.14	1.06 ± 0.14	2.10

Loss of water was calculated based on change in weight from wet past to lyophilized hardened.

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the images obtained, we were able to obtain BSM volume (CV); foam or tissue volume (TV), and volume fraction (CV/TV).

2.7. Statistical analysis

The difference among the tested cement samples was evaluated with the use of ANOVA with a post-hoc analysis. A p-value of $p < 0.001$ was considered significant for the specific pair wise comparison. The data were expressed as the mean and standard deviation.

3. Results

3.1. Injection of the cement

Many of the CaP BSM materials were not able to maintain their physical properties under pressure and experienced a phase separation where the liquid component separated from the powder component rendering the material uninjectable with the powder portion remaining within the injection syringe (Fig. 3). This phase separation occurred with the Beta-BSM™, Pro-Dense®, Cerament™, HydroSet™, and Norian™ materials. In each case, the load cell reached the allowable maximum force.

The cement weights were determined and the corresponding loss of water was calculated. As expected, the Simplex™ (hydrophobic) lost the least amount of water and the CaP-based cements (hydrophilic) lost the most water. The lyophilized, hardened weights were used to determine the hypothetical weight increase in the experimental blocks when three cubic centimeters of cement was introduced. However, several materials began to extravasate from the entry hole around the sides of the cannula with the removal of the needle from the injection site. In these cases, while we were able to inject the material, it did not stay in the model fracture site (Fig. 4). The extravasated BSM was removed from the top of the block prior to lyophilizing and determining the final weight of the test block.

3.2. Mechanical testing of the foam samples

The mean injection force and maximum injection force were captured for each material. Within each sample, the curve of the mean and maximum injection forces was collected for each of the three syringes. With the first one-cubic centimeter syringe, the injection force required to inject Cerament™ crossed the max threshold. At the introduction of the second one-cubic centimeter syringe, Beta-BSM™, Pro-Dense®, HydroSet™ and Norian™ all reached the maximum force. Although the test setup used a 30-kilograms load cell, the machine had the capability to measure an additional 20% load, allowing for the max load to be 36 kg. In each of these cases, the material powder began to separate from its hydration solution due to the injection force. The third one-cubic centimeter injection syringe of HydroSet™ and Norian™ could not be injected due to material curing. Only in AccuFill®, StrucSure™ and Simplex™ were all three cubic centimeters of material able to be injected. AccuFill® and StrucSure™ showed similar mean injection force for syringes 1 and 2 but were statistically different ($p < 0.001$) with StrucSure™ being statistically higher in syringe 3. Additionally, AccuFill® showed statistically significantly ($p < 0.001$) lower maximum injection force than all materials tested on all syringe runs except the first cc of StrucSure™. StrucSure™ did not interdigitate into the foam as readily, causing the force to increase over the course of injecting syringes. Although Simplex™ performed well, there was a statistically significant difference ($p < 0.001$) where Simplex™ had a higher maximum injection force required to inject each cc except in comparison with StrucSure™ for all three cc runs, but was not different from Beta-BSM™ and Pro-Dense® in the third syringe.

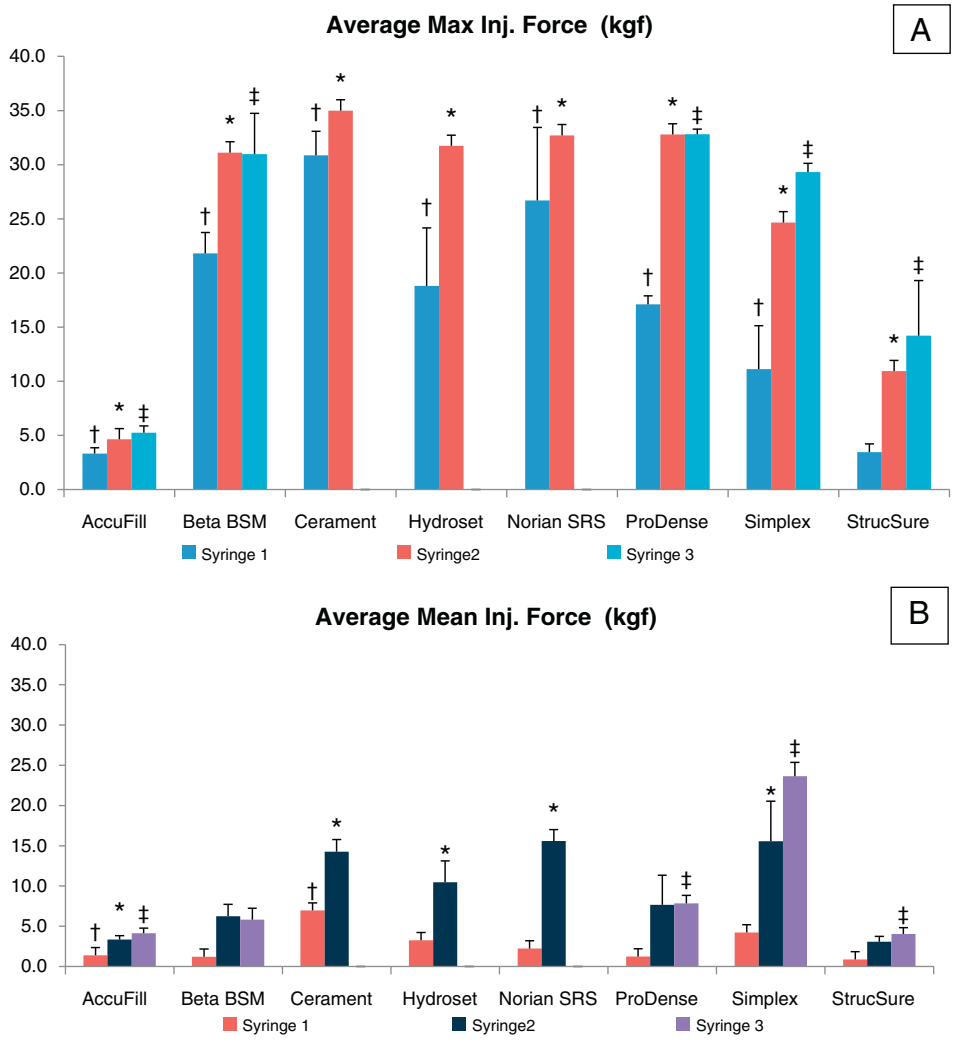

Fig. 3. Injection force evaluation. A) Average maximum. B) Mean injection forces for each syringe run of all materials tested. †Significantly different from injection using AccuFill® with syringe 1 ($p < 0.001$). *Significantly different from injection using AccuFill® with syringe 2 ($p < 0.001$). ‡Significantly different from injection using AccuFill® with syringe 3 ($p < 0.001$).

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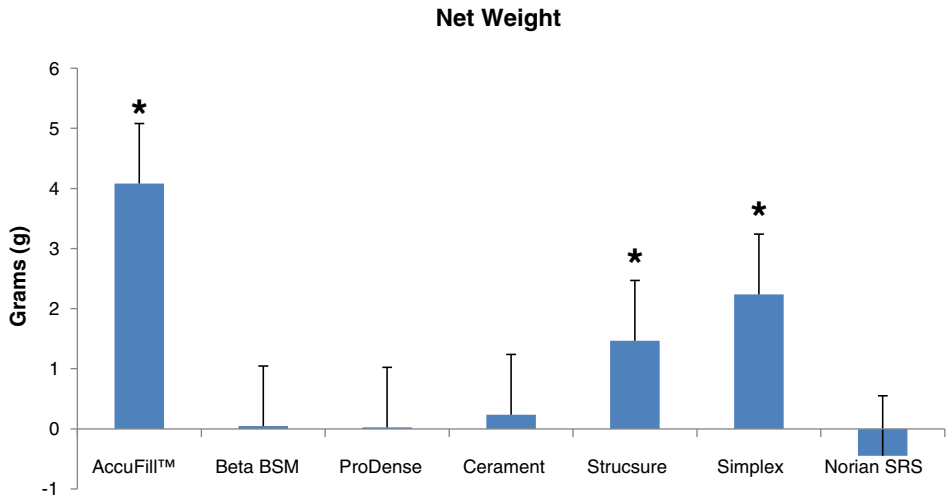

Fig. 4. Net weight. *Significantly different from AccuFill® ($p < 0.001$).

3.3. Cadaveric samples

In the cadaveric samples, only AccuFill® and Beta-BSM™ were used to confirm the model. With regard to mean injection force and maximum injection force, there was no statistical difference between the cadaveric samples and the foam samples for either material.

3.4. Measurements for net weight

The net dry weight of the BSM present was calculated. Any BSM material that extravasated from the path of the channel created for the cannula (Fig. 5) was removed from the top of the block prior to drying and weighing. In the samples where material extravasated from the injection site, a small amount of the foam may have been removed along with the BSM. The dry weight of AccuFill® at 4.07 g was statistically different than all other materials tested. Simplex™ at 2.24 g and StrucSure™ at 1.47 g were statistically different than the AccuFill® but were also different from all other materials tested. The remaining materials had an average dry weight of less than 1.00 g.

Using dry weight measurement, we were able to determine that the entire (101%) expected mass of AccuFill® remained inside the block (4.07 g injected vs. 4.02 g expected) and was statistically different than all of the other materials. 29.6% of Simplex retroejected from the insertion point as only 2.24 g of an expected 3.18 g was found inside the block. StrucSure™ similarly saw some extravasation where the 3.60 g expected after injection of three cubic centimeters, the average was only 1.47 g (41%) inside the block. The remaining products showed <5% of the expected material inside the foam. The weight findings for Norian™ were slightly negative likely due to a small amount of the foam being removed along with the extravasated BSM.

3.5. Micro-CT scan

The micro-CT analyses confirmed the observations seen during mechanical testing. Only AccuFill®, StrucSure™, and Simplex™ demonstrated a notable volume injected into the block and interdigitated into the architecture (Fig. 6). The computational analysis of the micro-CT reconstructions were able to provide the fraction of space occupied by the BSM (CV) to total volume of the foam block (TV) thereby yielding the percentage of BSM (CV/TV). The average volume of material was: AccuFill® 12.7%, StrucSure™ 5%, and Simplex™ 6.5%, and the remaining materials were all less than one percent. AccuFill® was statistically different ($p < 0.001$) than all other materials. Simplex™ and StrucSure™ were not statistically different from each other but were statistically different to all the other materials (Fig. 7).

4. Discussion

The compressive strength of trabecular bone is highly dependent on the location, the apparent density, and the bone mineral content [4,7,15]. Bone BSMs are widely used in order to reconstruct and add stability to affected areas where the trabecular bone is compromised by disease state. The ideal material would also have strength properties similar to the surrounding trabecular bone and would be able to be remodeled over time without affecting the mechanical properties of the tissue.

Human joints are susceptible to osteoarthritis degeneration from disease, trauma, and long-term repetitive use. In the knee, the cartilage and subchondral bone are affected by a variety of diseases such as traumatic osteochondral defects, osteochondritis dissecans, osteonecrosis, and osteoarthritis [1]. A growing understanding of the pathophysiology of knee osteoarthritis has led researchers to redefine osteoarthritis as a degeneration of both the articular cartilage and subchondral bone.

Bone marrow lesions (BMLs) are micro-trabecular fractures that occur in osteoarthritis rather than osteoporotic bone related to impaired healing potential. When patients do not exhibit severe degenerative changes in the knee one possible treatment option to alleviate pain is to treat the underlying defects of the subchondral bone by a procedure described as Subchondroplasty® [2]. The goal of the procedure is to fill the bone lesion area with a bioactive BSM, which can be remodeled into the healthy bone over time. For this type of procedure, one should select a BSM that can not only fill a closed void, but also provide the strength needed to sustain a healthy bone structure.

The most common commercially available bone material substitutes were tested to compare their ability to inject into a closed environment

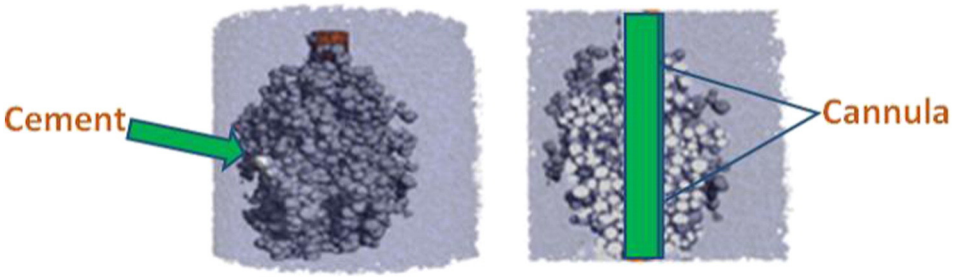

Fig. 5. Image of one of the AccuFill® samples within the simulated trabecular bone in a full view and cut at the zero-plane.

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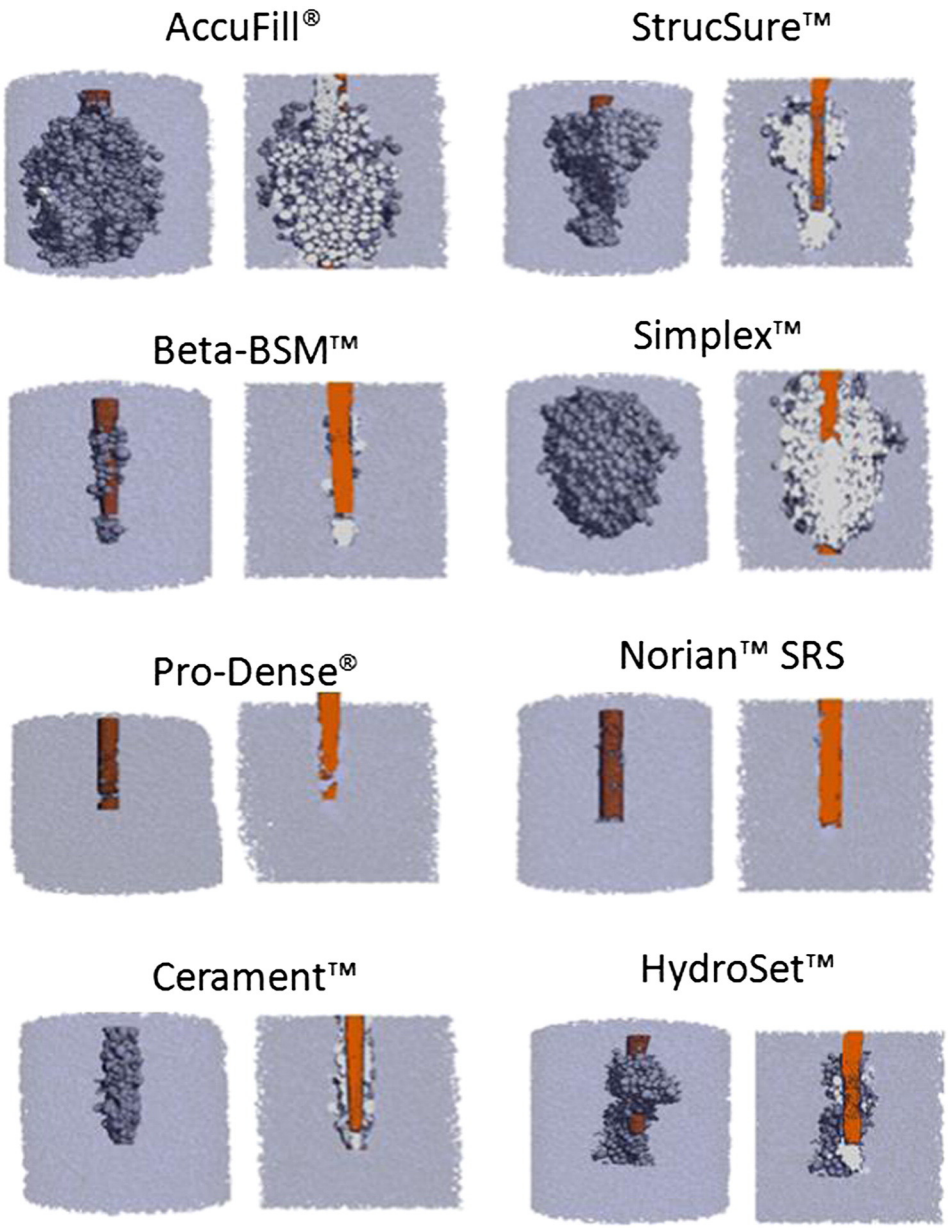

Fig. 6. Representative micro-CT reconstructions of each BSM material. Micro-CT image of the foam samples both as a whole and cut at the zero-plane.

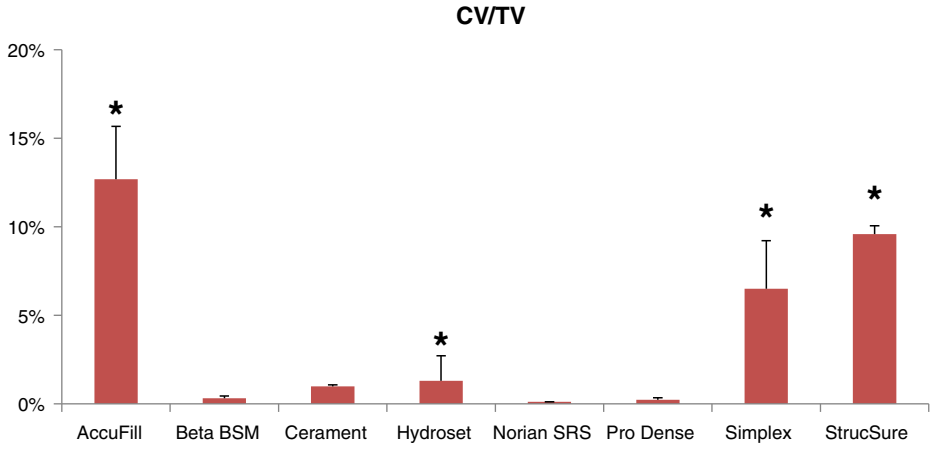

Fig. 7. BSM volume per tissue/foam volume (CV/TV). *Significantly different from AccuFill® ($p < 0.001$).

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under pressure. The limitation of our study is that the foam blocks used in testing are not identical to the pathologic trabecular bone with BMLs. In addition, the cadaveric samples did not have BMLs. However, the foam block model was shown by comparison to cadaveric samples as a valid model to compare commercially available bone BSMs in a closed structure. The comparative analysis shows that the eight materials tested performed differently both in the volume able to be introduced and the material's ability to interdigitate into the architecture. Although all the materials are understood as injectable BSMs, only AccuFill®, Simplex™ and StrucSure™ were able to flow into the closed structure. The test model was the foam because the quality and structure of cadaveric samples can vary greatly and innately have too much variability to compare between BSM materials.

Beyond the basic ability to inject into the bone, the amount of material able to be introduced is important because the BSM must stabilize the fracture area or support the void space during the healing process. The amount of material desired changes with the defect size. In this model, we defined a desired injection amount as three cubic centimeters of material, and only AccuFill® was observed to have attained the desired volume of material implanted inside the foam. Further, all the other materials either reach the maximum injection force of our apparatus or showed increasing injection force required to implant each subsequent cubic centimeter. As greater volumes of BSM would be needed for larger defects, the maximum injection force would continue to increase possibly outside of a clinically safe level.

Further investigation will be required to understand the mechanical properties of the BSMs over time in a closed environment. However, this study demonstrated that in a closed fracture environment, AccuFill® performed superior to the other BSMs tested with the lowest injection forces, the highest volume injected, the greatest area covered by material injected, and finally without an exothermic reaction. Also, the "flowability" pattern within the foam sample shows that AccuFill® was able to navigate the void space without damaging the structure with the applied force.

5. Conclusions

The "injectability" of classic cements was always considered to be a function of viscosity and could easily be manipulated to achieve the desired defect fill. This investigation of the performance of materials in a small void model under pressure has shown that not only classic cement, PMMA, but also most commercially available BSM materials are not directly governed by viscosity but are more related to their chemical composition. Future material development will need to focus not only on open, large bony voids, but also smaller applications where interdigitation is crucial.

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