ORIGINAL ARTICLE

# Polylactide-co-glycolide Fiber–Reinforced Calcium Phosphate Bone Cement

*William D. Losquadro, MD; Sherard A. Tatum, MD; Matthew J. Allen, PhD, Vet MB; Kenneth A. Mann, PhD*

**Objective:** To compare the strength of polylactide-co-glycolide fiber–reinforced calcium phosphate bone cement (FRC) with nonreinforced calcium phosphate bone cement (NRC) subjected to simulated dural pulsations in defects larger than 25 $cm^2$.

**Methods:** Seven NRC and 7 FRC specimens were set in both medium (37.5 $cm^2$) and large (50.0 $cm^2$) model skull defects while subjected to simulated dural pulsations. Specimens were removed after 24 hours and analyzed using 3-point flexural testing.

**Results:** All 14 FRC specimens maintained structural integrity during extraction and testing. Only 2 of 7 (29%) medium specimens and 2 of 7 (29%) large NRC specimens survived setting. The mean (SD) energy to peak force (in newton millimeters [Nmm]) of the medium and large NRC specimens was 0.88 (0.83) and 3.00 (3.54) Nmm, respectively, compared with 28.97 (16.52) and 49.91 (38.10) Nmm for the medium and large FRC specimens. The material strength (in megapascals) of the medium and large NRC specimens was 0.17 (0.15) and 0.39 (0.33) MPa, respectively, compared with 3.73 (0.99) and 2.62 (1.34) MPa for the medium and large FRC specimens. The energy to peak force and material strength of the medium and large FRC specimens were significantly greater than for the corresponding NRC specimens; results were not statistically significant between medium and large FRC specimens.

**Conclusions:** Fiber-reinforced calcium phosphate bone cement exhibits superior structural integrity and material strength than NRC when subjected to unshielded simulated dural pulsations. Further studies are needed to evaluate the biophysical parameters of FRC in vivo.

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An ideal material for craniofacial reconstruction would be abundant, have mechanical properties comparable to native bone, and osteointegrate by intimately bonding with its surroundings. Furthermore, this material would osteoconduct osteoprogenitor cells, osteoblasts, and blood vessels; osteoinduce formation of osteoblasts from osteoprogenitor cells; and osteoconvert to bone. Inasmuch as no such material exists, autologous bone remains the standard for craniofacial grafting. However, its drawbacks are limited supply, harvest-associated patient morbidity, and unpredictable resorption. Thus, new alloplastic bone substitutes continue to be developed and tested.

The extracellular matrix of native bone is composed of approximately 30% organic and 70% inorganic compounds by weight. The inorganic component contains hydroxyapatite, dahllite (the carbonated form of hydroxyapatite), sodium, magnesium, and other trace components. Hydroxyapatite grafts are biocompatible and bond directly to adjacent bone without fibrous encapsulation.[1]

The first hydroxyapatite grafts developed were brittle ceramic blocks that were difficult to carve and fixate. These are manufactured by sintering, a process in which precipitated clay or compacted powder is heated at high temperature until particles adhere and solidify in a single mass. These grafts osteointegrate but exhibit minimal osteoconversion. Hydroxyapatite granules mixed with various carriers are easier to contour within defects but are associated with gravitational migration and minimal bone replacement. Hydroxyapatite grafts are also synthesized from marine coral. Under high heat and pressure, the coralline calcium carbonate is chemically replaced by calcium phosphate while maintaining the complex 3-dimensional structure of the coral. The porosity of these coralline implants enables robust tissue ingrowth but imparts non–weight-bearing structural fragility that is difficult to contour.[2] Calcium phosphate bone cements were developed to improve on the limitations of solid hydroxyapatite implants.

Nonceramic calcium phosphate bone cement was developed in the early 1980s. Kits usually consist of 2 or more calcium phosphate powders and a liquid such as water or sodium phosphate; these materials are mixed intraoperatively, and the resultant paste can be easily contoured within irregular defects. It quickly sets via an isothermic reaction at physiologic pH.[3] Variable amounts and types of hydroxyapatite are formed, depending on the specific product. Like ceramic hydroxyapatite grafts, calcium phosphate cements directly osteointegrate with surrounding bone.

Calcium phosphate bone cements have been used in numerous craniofacial applications including orbital floor repair[4]; temporal, malar, and genial augmentation[5]; mandibular defect repair[6,7]; and cranioplasty.[8-11] Its unrestricted supply and absence of donor-site morbidity are especially useful in pediatric cranioplasty. It is important, however, to shield the material from dural pulsations in all but the smallest defects. Unshielded implants fail to set properly, are prone to disintegration, and may elicit an inflammatory response in particulate form.[12,13] Shielding is usually accomplished via titanium or resorbable mesh. In larger defects, the mesh also acts as a tray to facilitate cement contouring.

Calcium phosphate bone cements are currently approved for defects only 25 $cm^2$ or smaller. Reported complications when using cement in larger defects include little replacement by native bone and diffuse cement fracturing.[14] Thus, recent efforts have been focused on modifying both the mechanical and biological properties of calcium phosphate cements.

Various products have been mixed with bone cements to induce more robust bone replacement[15,16]; additional attempts have been made to improve microbial resistance[17] because infection has proved problematic in some applications.[18] Efforts to enhance mechanical properties include the addition of carbon, nylon, polypropylene, and polylactide-co-glycolide fibers.[19-22] The addition of fibers to cement increases flexural and tensile strength while simultaneously decreasing compressive strength. To date, no fiber-reinforced cements (FRCs) have been used clinically.

The Norian CRS (Cranial Repair System) Fast Set Putty (Synthes, Inc, West Chester, Pennsylvania) consists of monocalcium phosphate, α-tricalcium phosphate, and calcium carbonate powder. When mixed with sodium phosphate solution, it sets in approximately 3 to 6 minutes. The resulting compound is a low-order crystalline apatite containing 85% to 90% dahllite with 5% carbonate, remarkably similar to the 4% to 6% carbonate found in the dahllite of native bone.

In the present study, we used Norian CRS Fast Set Putty reinforced with polylactide-co-glycolide fibers. Preliminary work with this product has revealed superior flexural strength compared with standard Norian CRS Fast Set Putty in 25-$cm^2$ defects.[23] Both cements exhibited a statistically significant decrease in strength when subjected to simulated dural pulsations. However, the fiber-reinforced cement subjected to pulsations remained as strong as the nonreinforced cement (NRC) set without pulsations. The objective of this study was to further analyze the mechanical properties of FRC compared with NRC when subjected to simulated dural pulsations in defects larger than 25 $cm^2$. We hypothesized that FRC would maintain structural integrity in defects larger than 25 $cm^2$ even while unshielded from pulsations.

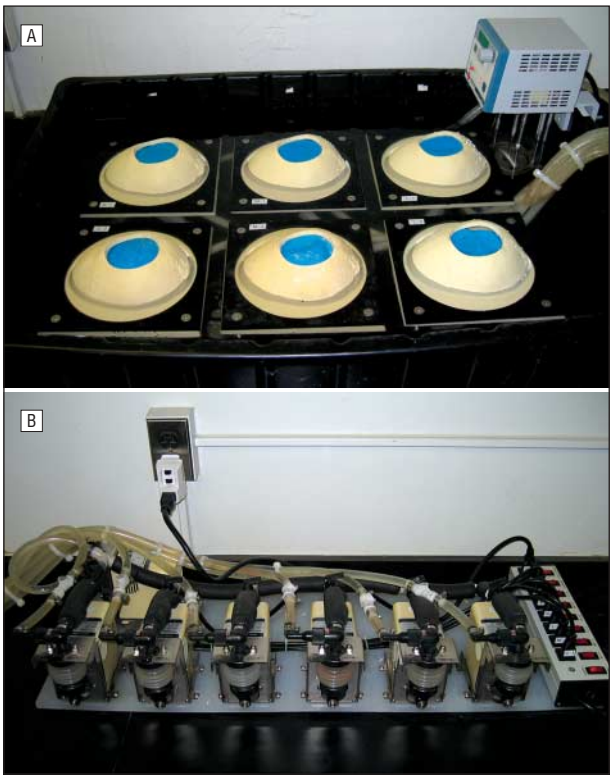


**Figure 1.** Dural pulsation model (A) and pump assemblage (B).

## METHODS

A custom dural pulsation model designed and manufactured by Synthes, Inc, was used for specimen preparation (**Figure 1**). The model consisted of 6 anatomically correct adult skulls and dura made of solid foam polyurethane and silicone, respectively (Sawbones; Pacific Research Laboratories, Inc, Vashon Island, Washington). Each skull was attached to an individual pump and filled with water sealed from the external environment. To simulate a surgical wound environment, the skull model assemblage was housed in a closed water bath maintained at a constant 37°C and 95% to 100% relative humidity using a circulating water heater. Water within the bath reached the base of the skull model but did not bathe the defect.

The NRC used in the study was Norian CRS Fast Set Putty (Synthes, Inc). The FRC consisted of Norian CRS Fast Set Putty with 3% polylactide-co-glycolide fibers by weight. Fibers were 1 mm in length and 16 μm in diameter. Fiber composition was 82% polylactide and 18% polyglycolide.

Seven NRC and 7 FRC specimens were each set in skull models with circular defects of 37.5 $cm^2$ (medium) and 50.0 $cm^2$ (large) centered over the vertex (**Figure 2**). A 15-mL and a 5-mL NRC kit were required for each medium skull defect, and two 15-mL kits were required for each large skull defect. Two 10-mL FRC kits were required for each medium defect, and three 10-mL kits for each large defect. The cement powder and solution (sodium phosphate for the NRC and sodium hyaluronate for the FRC) were mixed vigorously with a handheld spatula in a plastic bowl for 45 to 90 seconds per product instructions. The resultant paste was placed within each defect using

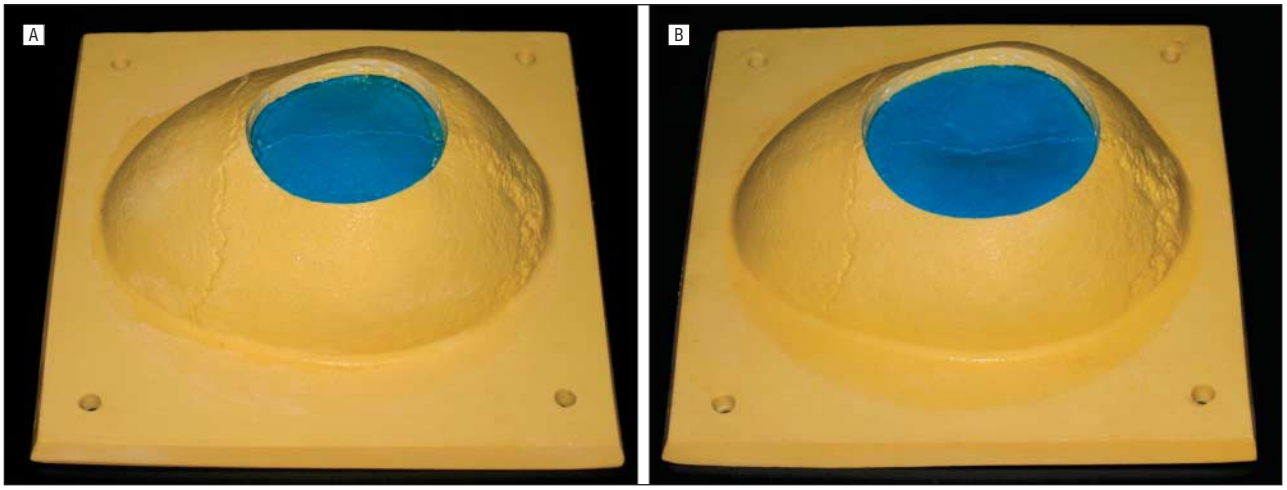


**Figure 2.** Skull models with defects of 37.5 $cm^2$ (A) and 50.0 $cm^2$ (B).

**Figure 3.** Calcium phosphate cement within model skull defect.

the handheld spatula while subjected to 67 dural pulsations per minute (**Figure 3**). On the basis of intraoperative observations, pulsations were calibrated for 1.7 to 2.0 mm of displacement. Specimens were covered with a silicone sheet and cotton gauze reaching into the water bath to simulate soft-tissue coverage. Specimens were extracted from the skull models after 24 hours. Extraction was performed by loosening a small segment of the specimen from the model defect edge with a dental carver and prying the specimen free with a dental spatula. Because of the anatomical curvature of the skull model, specimen shape approximated a spheroid cap, that is, a section cut from the top of a flattened sphere.

Three-point flexural testing until failure was performed using a computer-controlled Q-Test materials testing machine (MTS Systems Corp, Eden Prairie, Minnesota) with a 45-mm span and 1-mm/min crossbeam speed (**Figure 4**). Testing of the complete structure was performed because this was thought to be more appropriate for describing overall construct strength. After fracture, the length of the fracture plane and its thickness at 3 random points were measured.

Peak force (in newtons), energy to peak force (in newton millimeters [Nmm]), and stiffness (in newtons per millimeter) were directly measured using the materials testing machine. Bending moment (Nmm), the force multiplied by the distance from the axis of rotation at which the structure bends, was calculated using the formula (peak force)(span/2). The second moment, a measurement of the structure's resistance to bending, was calculated using the formula (1/12)[(fracture length)(average fracture thickness$^3$)]. Material strength (in megapascals) was calculated using the formula [(bending moment/2)(average fracture thickness)(second moment)].

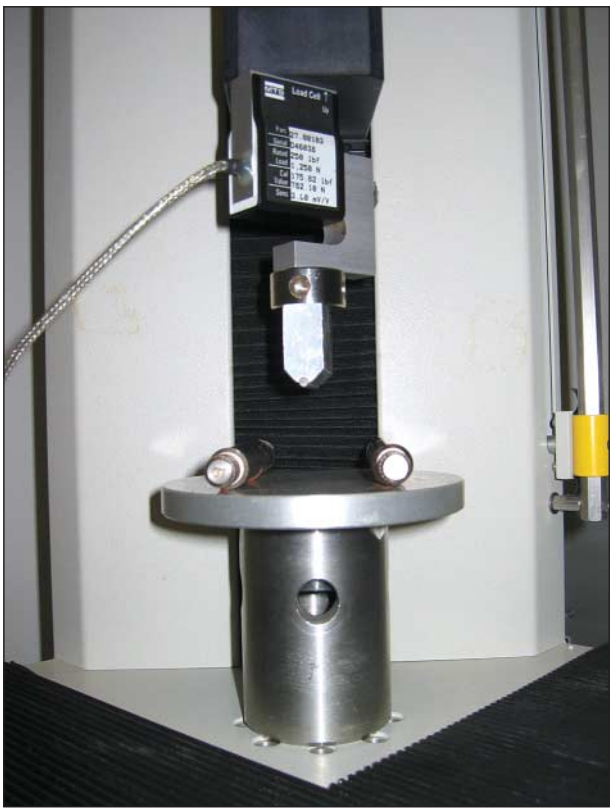

**Figure 4.** Materials testing machine used for 3-point flexural testing.

Energy to peak force and material strength were our primary outcome measures. Energy to peak force is a measure of the strength of the entire structure. Material strength represents the intrinsic cement flexural strength, in contrast to the sum structural strength measured by the energy to peak force. Statistical analysis was performed using the *t* test. Statistical significance was set at $P \leq .05$.

## RESULTS

Each of the 7 medium and 7 large FRC specimens survived setting, extraction, and testing preparation intact.

Two of 7 (29%) medium and 2 of 7 (29%) large NRC specimens survived setting; the remaining specimens crumbled and could not be tested (**Figure 5**).

The mean (SD) energy to peak force was 0.88 (0.83) and 3.00 (3.54) Nmm for the medium and large NRC specimens, respectively, vs 28.97 (16.52) and 49.91 (38.10) Nmm for the medium and large FRC specimens. Both the medium ($P=.004$) and large ($P=.02$) FRC specimens exhibited significantly greater energy to peak force compared with their NRC counterparts (**Table**).

The mean material strength of the surviving medium and large NRC specimens was 0.17 (0.15) and 0.39 (0.33) MPa, respectively. The mean material strength of the medium and large FRC specimens was 3.73 (0.99) and 2.62 (1.34) MPa, respectively. Both the medium ($P<.001$) and large ($P=.005$) FRC specimens were significantly stronger than their NRC counterparts. Mean energy to peak force ($P=.22$) and mean material strength ($P=.10$) were not statistically significant between the medium and large FRC specimens.

## COMMENT

Autogenous bone is an ideal material for craniofacial grafting. However, its limited supply, harvest-associated morbidity, and unpredictable resorption within large defects has necessitated continuous development and testing of alloplastic alternatives. Hydroxyapatite is the main inorganic component of bone and, thus, an obvious choice for implantation. Ceramic hydroxyapatite blocks, either sintered or coralline, require difficult intraoperative carving to fill defects; hydroxyapatite granules mixed with other materials is easier to contour but tends to settle in a gravity-dependent manner. Calcium phosphate cement was developed to mitigate these problems. Its handling properties and ability to set quickly, isothermically, and at physiologic pH are a major alloplastic advancement. It was enthusiastically adopted by craniofacial surgeons, in particular for use in cranioplasty.

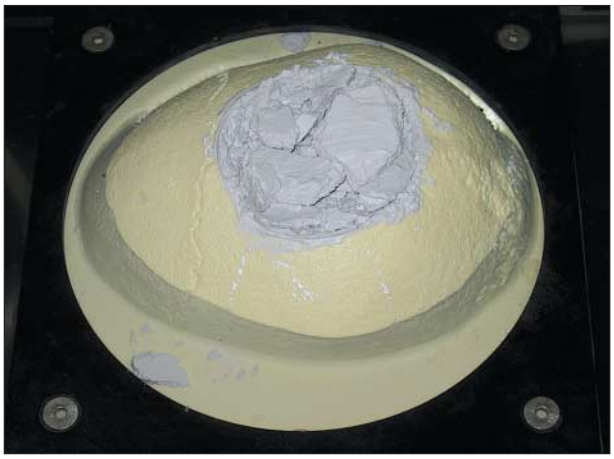

**Figure 5.** Crumbled calcium phosphate cement after 24 hours of simulated dural pulsations.

Recent use of calcium phosphate cements has been tempered by concerns about material strength and resorption.[14,24] Concerns about strength are related to both setting and impact resistance. In early reports, cement failure during setting was attributed to fluid exposure[25-27] or possible interference of dural pulsations.[28] The replacement of water with lightly acidic solutions such as sodium phosphate enabled shorter setting times and, thus, diminished the effects of fluid exposure. Dural pulsations, however, remain problematic.

Fragmentation of cement set directly on the dura has been observed and led to the recommendation that defects larger than 5 $cm^2$ in greatest diameter be shielded.[5,10] Experimentally, the introduction of dural pulsations decreased the material strength of NRC and FRC by 71% and 35%, respectively.[23] Titanium mesh is often fashioned into a rigid tray that facilitates cement contouring and setting unhindered by dural pulsations. Concerns about titanium migration or growth restriction in the pediatric population have led some to use resorbable mesh underlays instead. Regardless of whether shielding is used, calcium phosphate bone cements are not currently approved for defects larger than 25 $cm^2$.

In an effort to improve the mechanical properties of calcium phosphate bone cements, multiple additives have been examined but not used clinically. Many are nonresorbable, and their effect on native bone replacement is unknown. In an attempt to balance the seemingly conflicting objectives of increased strength and complete osteoconversion, the FRC uses resorbable polylactide-coglycolide fibers.

The results of the present study indicate that FRC exhibits superior strength compared with NRC when subjected to dural pulsations. Only 4 of 14 (29%) NRC speci-

**Table. Mechanical Analysis of Medium and Large Cement Specimens**

| Specimen | Viability, No. (%) | Mean (SD) | | | | |
|---|---|---|---|---|---|---|
| | | Peak Force, N | Stiffness, N/mm | Bending Moment, Nmm | Energy to Peak Force, Nmm | Material Strength, MPa |
| Medium, 37.5 $cm^2$ | | | | | | |
| NRC | 2/7 (29) | 5.54 (5.24) | 19.3 (10.75) | 124.54 (117.89) | 0.88 (0.83) | 0.17 (0.15) |
| FRC | 7/7 (100) | 110.47 (26.87) | 248.01 (88.22) | 2420.89 (680.01) | 28.97 (16.52) | 3.73 (0.99) |
| *P* value | | <.001 | <.001 | <.001 | .004 | <.001 |
| Large, 50 $cm^2$ | | | | | | |
| NRC | 2/7 (29) | 18.73 (19.62) | 80.03 (72.79) | 421.43 (441.34) | 3.00 (3.54) | 0.39 (0.33) |
| FRC | 7/7 (100) | 106.27 (54.28) | 208.59 (91.89) | 2290.43 (1174.27) | 49.91 (38.10) | 2.62 (1.34) |
| *P* value | | .01 | .17 | .02 | .02 | .005 |

Abbreviations: N, newtons; Nmm, newton millimeters; MPa, megapascals.

mens survived skull model extraction completely intact; this supports clinical observations that unshielded dural pulsations interfere with cement setting. Because of the extensive fracturing and crumbling, these specimens could not undergo further quantitative testing. In contrast, all FRC specimens within both medium and large defects maintained structural integrity.

Both the energy to peak force and material strength were significantly greater for the FRC specimens compared with the NRC specimens. This is consistent with findings of other studies of permanent and absorbable FRCs. Xu and Quinn[21] noted a 3-fold increase in flexural strength in calcium phosphate cement reinforced with larger polylactide-co-glycolide fibers. The medium and large FRC specimens in the present study exhibited 22- and 7-fold greater material strength, respectively, than their NRC counterparts. However, substantial differences in fiber composition, length, and size; cement composition; and testing parameters between studies render direct quantitative comparisons difficult.

An additional benefit of FRC compared with NRC is improved handling characteristics. The more viscous consistency of the mixed paste facilitated defect filling and contouring. This is most likely a result of the substitution of hyaluronate for phosphate in the solution, although the fibers' contribution to viscosity is unclear. Furthermore, an automated pneumatic mixer and injection device is available for most calcium phosphate bone cements. This provides a more uniform product that may nullify any advantage obtained during manual mixing.

Limitations of the present study include the difficulty of true clinical simulation. The dural pulsation displacement of 1.7 to 2.0 mm is based on estimates of intraoperative observations; to our knowledge, no measurements of dural amplitude have been published. In addition, the surgical site environment cannot be precisely recreated in vitro. Nevertheless, these factors do not diminish the qualitative observations herein.

Clearly, FRC is stronger than NRC after 24 hours of dural pulsations, although how that strength might change with time as the polylactide-co-glycolide fibers resorb is unknown. One might hypothesize that only peripheral areas in direct contact with tissue will begin to degrade at implantation. Fibers sequestered in the implant are unlikely to resorb until reached by native bone or vascular ingrowth. As fibers resorb, there is likely to be implant strength degradation. The rate of implant weakening would ideally be balanced by osteoconversion so that implant structural integrity is maintained.

The relationship between fiber degradation and osteoconduction is another area of interest. Despite reports of complete osteoconversion in smaller defects, clinical experience with larger NRC implants reveals little evidence of bony ingrowth beyond the periphery.[14] Osteoconduction seems to depend on pore size, and this varies not only between the ceramic and cement forms of hydroxyapatite but among the different cement compositions themselves. The minimum pore diameter necessary for substantial bony ingrowth is reportedly 100 μm.[29] Larger pores are found in sintered or coralline hydroxyapatite but not calcium phosphate cements. The median pore diameter of Norian CRS Fast Set Putty (Synthes, Inc) is approximately 30 nm.[30] It is unclear whether the addition of the resultant defects created by fiber resorption in the FRC will support substantial osteoconduction.

In conclusion, the results of this preliminary study suggest that polylactide-co-glycolide fiber–reinforced calcium phosphate cement exhibits superior strength compared with nonreinforced calcium phosphate cement. This additional strength enabled the material to set unshielded from simulated dural pulsations in our artificial cranioplasty model. Further studies of this cement in vivo are needed to characterize its strength over time and osteoconduction.

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**Author Contributions:** Dr Losquadro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Losquadro and Tatum. *Acquisition of data:* Losquadro, Allen, and Mann. *Analysis and interpretation of data:* Losquadro, Allen, and Mann. *Drafting of the manuscript:* Losquadro. *Critical revision of the manuscript for important intellectual content:* Losquadro, Tatum, Allen, and Mann. *Statistical analysis:* Losquadro, Allen, and Mann. *Administrative, technical, and material support:* Losquadro. *Study supervision:* Tatum.
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