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BIOLOGICALLY STRUCTURED MATERIALS

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ABSTRACT

In this paper bio-tissue mathematical modeling serves as a central repository to interface design, simulation, and tissue fabrication. Finite element computer analyses will be used to study the role of local tissue mechanics on endochondral ossification patterns, skeletal morphology and mandible thickness distributions using single and multi-phase continuum material representations of clinical cases of patients implanted with the traditional protocols. New protocols will be hypothesized for the use of the new biologically techno-structured hybrid materials.

Keywords: Biologically Structured Materials; Techno-structured materials Hybrid materials; Biotechnology; Bioengineering; Biomaterials, Bioactive scaffolds, Biomimetics, Endochondral ossification patterns; Finite Element Analysis, Osteointegration, Skeletal morphology, Tissue mechanics

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1. INTRODUCTION

Biomimetics, biomechanics, and tissue engineering are three multidisciplinary fields that have been contemplated in this research to attain the objective of improving prosthetic implants reliability. Since testing and mathematical methods are closely interlaced, a promising approach seemed to be the combination of in vitro and in vivo experiments with computer simulations (in silico). An innovative biomimetics and biomechanics approach, and a new synthetic structure providing a microenvironment, which is mechanically coherent and nutrient conducive for tissue osteoblast cell cultures used in regenerative medicine, are presented.

The novel hybrid ceramic-polymeric nanocomposites are mutually investigated by finite element analysis (FEA) biomimetic modeling, anatomic reconstruction, quantitative-computed-tomography characterization, computer design of tissue scaffold. The starting base materials are a class of innovative highly bioactive hybrid ceramic-polymeric materials set-up by the proponent research group that will be used as a bioactive matrix for the preparation of in situ bio-mineralized techno-structured porous nanocomposites.

This study treats biomimetics, biomechanics and tissue engineering as strongly correlated multidisciplinary fields combined to design bone tissue scaffolds. The growth, maintenance, and ossification of bone are fundamental and are regulated by the mechanical cues that are imposed by physical activities: this biomimetic/biomechanical approach will be pursued in designing the experimental procedures for in vitro scaffold mineralization and ossification. Bio-tissue mathematical modeling serves as a central repository to interface design, simulation, and tissue fabrication.

Finite element computer analyses will be used to study the role of local tissue mechanics on endochondral ossification patterns, skeletal morphology and mandible thickness distributions using single and multi-phase continuum material representations of clinical cases of patients implanted with the traditional protocols. New protocols will be hypothesized for the use of the new biologically techno-structured hybrid materials.

It is known that the field of interdisciplinary research of materials for biomedical applications is structured and calibrated today in the bone repair

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study, which is basically its basis.

The bones are considered to be a biological hybrid material composed of an organic component, collagen, and an inorganic nanocrystalline hydroxyapatite component. Both phases integrate on a nanoscale so that morphological and physical variables such as crystal size, nano-orientation, short-order order between the two components determine the characteristics of its nanostructure and therefore the mechanical properties of the different types of bone Frost, 1964, 1990, 2004).

Based on bone regeneration criteria, new bioactive biomaterials have been developed. These materials are expected to favor the formation of bone tissue by stimulating the proliferation and differentiation of osteoblasts (SCHIRALDI et al., 2004; AVERSA et al., 2016a; AVERSA et al., 2016b; AVERSA et al., 2016c; AVERSA et al., 2016d; AVERSA et al., 2017a; AVERSA et al., 2017b, 2019; SYED et al., 2017).

The use of nanostructured materials similar to natural bone tissue is one of the most promising options for bone healing. Nanotechnologies for the implementation of organo-inorganic hybrid materials offer excellent chances to improve the performance of existing conventional bone implants (AVERSA et al., 2016a; AVERSA et al., 2017).

Current research evaluates the evolution of polymer-polymer hybrids for bone tissue repair, as well as chemical procedures that control the nanostructuring of materials.

1.1. The objective of the paper is inherent in the following scientific fields;

- biomechanics and human biophysical bone,
- Biomimetics: nanotechnology in medicine for materials inspired by nature
- Bioactive scaffolds favoring osteointegration in nanocomposite and hybrid porous structural matrices

1.2. Biofidelity advances

Recent studies of the mandible (SCHWARTZ-DABNEY; DECHOW 2003, APICELLA et al., 2010; AVERSA et al., 2016a; AVERSA et al., 2016b) and FEM modeling of teeth (SORRENTINO et al., 2007, APICELLA et al., 2015).

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Knowing the mechanical and adaptive features of the bone is an essential issue in designing new biomimetic prostheses to replace a bone with minimal biological and biomechanical invasiveness.

Biomimetics is the science that investigates such aspects and can be considered the natural junction between biology and engineering. This competence convergence allows the development of biological principles and models to produce bio-inspired materials that can be used to fully design prosthetic tissues and systems.

New generations of concepts could be generated by the conscious investigation of biomimetics, which can provide clinical tools to restore the structural, biomechanical and aesthetic integrity of bone functions.

Recent advances in cellular and molecular biology and material engineering science (nanotechnology) have established that biomimetics and tissue engineering are developed to improve the integral integration of prosthetic and restorative implants (AVERSA et al., 2016a; AVERSA et al., 2016b; AVERSA et al., 2016c; AVERSA et al., 2016d; PERILLO et al., 2010; ANNUNZIATA et al., 2010).

Since last century, parts of our body have been replaced with artificial prostheses. The materials used for these devices were chosen not to produce adverse responses in contact with human body tissues and physiological fluids.

The criteria for choosing a specific biomaterial were related to its biocompatibility and functionality, which could be directly associated with interfacial bone/implant interactions at a nanometric level. Only in the 1990s, the study of these interference effects was improved by the use of thin nanometer layers and surface changes.

It then generated a great commercial interest in the orthopedic market of adopting new modified implants of nanoparticles that promote soft and soft tissue engineering.

1.3. New classes of Biomaterials

There are several ways in which living tissues can react to synthetic implant materials, but are essentially limited to their response to the interface material

Three main terms could describe the behavior of biomaterials defined by Jones et al (2012), Hutmacher (2000) and Hoppe (2011).

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Namely, tissue responses are divided into:

- Bioinert
- Bioresorbable
- Bioactive

A further classification of ceramic biomaterials can be made according to their reactivity to physiological fluids;

- bioinert, such as Alumina for dental application;
- bioactive, such as hydroxyapatite used as a coating on metallic implants,
- The active surface, such as bio-glass or A-W bottles,
- bio-resorbed, such as tri-calcium phosphate

Further improvement of these properties can be accomplished using nanostructured bioceramics that can be used as interactive materials, helping natural tissues heal by promoting tissue regeneration and restoring physiological functions (SCHIRALDI et al 2004; MANO et al., 2004; MORALES-HERNANDEZ et al., 2012; MOURIÑO et al., 2012).

This approach has been studied in this study to develop a new generation of nanostructured bio-ceramic-polymeric hybrids that can be used in a wider range of medical applications (PETRESCU; CALAUTIT, 2016a; PETRESCU; CALAUTIT, 2016b; PETRESCU et al., 2015; PETRESCU et al., 2016a; PETRESCU et al., 2016b; PETRESCU et al., 2016c; PETRESCU et al., 2016d; PETRESCU et al., 2017; PETRESCU et al., 2018).

Porosity is one of the keys to the success of these materials and is increasingly adopted when a narrowing of the bones is required and strong implant stability.

1.4. Tissue engineering new perspectives

For several years, tissue engineering has benefited from the combined use of live stem cell intake in three-dimensional ceramic scaffolds. This strategy is completed to provide healthy cells directly to the damaged site (BONFIELD et al., 1981; HENCH, 1993; HENCH, 2002; HENCH, 2010).

By combining the traditional bio-ceramic implant with the already assimilated

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knowledge of stem cell growth and differentiation in clinically and productively developed osteogenic strategies.

Stem cells developed in ceramic nanobiocomposites should be adopted in the case of extensive bone repair with excellent prospects of good functional recovery and integration of the hybrid scaffold with bone.

Synthetic Hydroxyapatite (HAp) has been described in the literature as an attractive material for bone implants (KIM et al., 2004; MORALES-HERNANDEZ et al., 2012).

Since its adoption, the most common and simplest method of producing synthetic HAp is the solid reaction between calcium and phosphate ions, resulting in the formation of powdered compounds which can be sintered and recovered at elevated temperature to form a compact polycrystalline structure Julien 2007).

The HAp bioactivity is governed by processing parameters, such as the initial compounds, the size of the crystalline granules, their purity, and the ratio of calcium to phosphorus atoms. In particular, nanocrystals have shown improved bioactivity due to their large surface area. The use of hydroxyapatite with nanoparticles has been proposed as a valid solution for the consolidation of low strength polymer scaffolds.

The use of HAp nanoparticles for new classes of implants, biocompatible coatings, and high strength nanocomposites can be developed (GORUSTOVICH et al 2010).

1.5. Biomimetics

A general feature of several tough natural hybrid materials, such as bones, sea urine teeth, pearls, is the strong nanometric interaction between inorganic and organic phases.

This feature allows the organic phase to act as a nanometric scale as a plastic energy dissipation network that inhibits crack propagation (high resistance); s, in situ synthesis techniques, have been adopted to mimic naturally occurring processes. In particular, precipitation of hydroxyapatite (or other crystalline compounds) in a polymeric matrix was considered a viable route to produce

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biomimetic composites.

1.6. Organic-Inorganic Hybrid Biomaterials

A bioinspired material development approach considering the formation of self- assembling hybrid organic-inorganic will favour the use of hybrids in biomedical applications. The high versatility of these hybrids offers main functional and structural advantages that lead to the possibility to tailor-design materials in terms of shape, and chemical and physical properties.

1.7. Bioengineering and Bioactive scaffolds

For nanotechnology nanomaterials, nanotechnology is increasingly adopted for emerging applications such as coating systems or three-dimensional coating systems (tecto) (AVERSA et al., 2016a; Karageorgiou et al., 2005; SORRENTINO et al., 2007). Critical, micro and nanotechnologies show the potential to be used to produce advanced models for fundamental studies, such as tissue engineering structures or bio-molecular devices.

The ideal material for bone skeletons has always been a hot topic for research. An ideal skeleton should provide a sufficiently rigid but durable mesh to temporarily replace the damaged bone. At the same time, it should be able to biodegrade after the formation of new tissues and integrate it fully (MONTHEARD et al., 1992; KABRA et al., 1991; PELUSO et al., 1997; SCHIRALDI et al., 2004).

Amorphous nanoparticles were synthesized in the laboratory. A new class of polymer-ceramic hybrid materials simulating the mechanical behavior of the bone were used as potential candidates for scaffolding (SYED et al., 2017).

The result of these self-assembled nanostructured composites was micro-foamed and tested as a new preimplantation skeleton that can accommodate osteoblast growth factors or stem cells to differentiate osteoblasts.

1.8. Biofidelity models and FEM analysis

Understanding the biological mechanisms of healthy and healthy bone growth is an iterative process between biology and engineering. During this process, knowing that reverse engineering of a biological system can have positive feedback in the field of biology, allowing for a more complete and secure understanding of the potential path for further development of applied medical

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engineering.

The most important question is how clinician interference with biological systems can be optimized to improve treatment options so as to increase treatment efficiency and lead to a more stable outcome.

The use of new diagnostic and engineering tools such as those used in our research (for example, CT and CTM CT segmentation and solid CAD reconstruction) can detail the anatomy of soft and soft textures in a very precise manner as a small standard deviation. Therefore, the integration of biological knowledge and clinical possibilities is essential. A more reliable and biophysical model begins with biomechanical modeling of bones, ligaments and alveolar bone, using Finite Element Analysis to gain insight into the biological response to changing biomechanical circumstances.

Because current tests and numerical methods are closely related, a methodological approach is to combine in vitro and in vivo experiments with computer simulations (in silico). There are, however, a number of stimulus points involved in creating and realizing the mathematical model. The concurrent interaction of several variables that influence the prosthetic system was investigated by simulation in the mathematical modeling of finite elements.

Finite Element Analysis (FEA) involves the subdivision of a geometric model into a finite number of elements, each with specific mechanical properties. The variables to be investigated are guessed with mathematical functions. Specific mathematical software evaluates the distribution of stresses and stresses in response to changing charging conditions.

A complete assessment of the mechanical behavior of a solid or prominent biological structure can be made, even in the case of non-homogeneous organisms. When properly validated by in vivo or in vitro testing, finite element analysis is useful in defining optimal recovery criteria and material selection criteria while allowing for potential fracture prognosis in limited circumstances.

2. METHODS AND MATERIALS

2.1. Materials

The hydrophilic matrix for amorphous silica amorphous filler (Aerosil 300

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Degussa, Germany) of 7 nm with a specific surface area of 2 n-hydroxyethyl methacrylates (HEMA), Sigma-Aldrich Chemicals Co., was used. 300 m2g-1. The initiator of the radical polymerization reactions used as azoisobutyronitrile (AIBN) obtained from Fluka (Milan, Italy). HEMA monomers were mixed with 10% by volume of silica. The degassed resin was poured into 2.5 mm thick flat molds and polymerized at room temperature, controlled at 60 ° C for 24 hours. Another end of 1 hour at 90 ° C was finally made on the nanocomposite plates.

Microporosity was induced in the dense material by first balancing the samples in pure ethyl alcohol and then rapidly extracting the alcohol absorbed by balancing into distilled water. During the rapid extraction of alcohol and counter-diffusion, a microporosity occurs in the ceramic-polymer hybrid material, evidenced by the intense bleaching of the treated system.

2.2. Finite Element Analysis (FEA)

Segmentation of medical images was derived from CT using the Mimics software (Materialize, Belgium) to process a medical image to the patient. As reported at the top of Figure 1, CT processing has led to a solid 3D solid model of anatomy and bone structure.

The combined use of Mimics and 3-Matic software (Materialize, Belgium) has been used to obtain solid 3D models and Finite Element Analysis (FEA).

External bone geometry was reconstituted by generating a three-dimensional volume that interpolates CT scans. The results were then imported into the 3Matic software for surface and solids optimization, finite element modeling and material properties of different sections of the bone according to the characteristics of the literature (BEAUPRE; HAYES, 1985; REILLY; BURNSTAIN, 1974; REILLY; BURNSTAIN, 1975; HUISKES et al., 1987; SCHWARTZ et al.; DECHOW, 2003; TÖYRÄSA et al., 2001).

Bone stress can be modulated by choosing skeletal swollen thickness for healthy bone growth. In vivo tests performed using these modified oral implants confirmed the improved ability of these implants to promote early osteointegration (GRAMAZZINI et al., 2016).

Biomimetic/biomechanical approach: Ceramic-polymer hybrid design and bulk design to improve osteointegration Bioprotective devices are widespread

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rehabilitation therapy in clinical practice in many areas of rehabilitation surgery such as dentistry, maxillofacial surgery, orthopedics. The bone and implant interface has been studied for many years as we try to move from bioinert to bioactive biomaterials.

In fact, the histological analysis carried out in these years does not allow confirmation of possible contact theories, junction systems, and others. But there is fluid contact between the osteocyte channel and the implant surface. Bioactive biomaterials could favor and amplify differentiation from an osteoblastic phenotype that occurs during healing of surgical wounds caused by the implant, with better osteointegration at shorter times. Recent studies describe the characteristics of nanostructured materials that could promote osteointegration:

- Carbon and alumina nanostructures, which mimic nano-dimensional geometry of hydroxyapatite, increase osteoblastic activity and thus produce larger bone deposits when applied to orthopedic implants.
- nanostructured biomaterials that mimic the bioactivity of hydroxyapatite crystals favor the adhesion and production of alkaline phosphates in osteoblast-like cells

Therefore, further studies on these materials could bring better and shorter healing to promote protocols to ensure early and immediate loading. The composition and the surface properties appear to be important because they seem to modulate the response of the osteoblast cells affecting tissue healing (DAVIS et al. 1991; GRAMAZZINI et al., 2016; AVERSA, 2016b).

The implanted tissue adjusts its composition and architecture to its functional load (APICELLA et al., 2011; APICELLA et al., 2015). Therefore, a key to the success of the titanium implant to integrate into the bone appears to be whether bone remodeling is correct or not on the periphery of the implant (AVERSA et al., 2016b).

Figure 1 shows the result of "in vivo" experiments performed on dental implants placed in rabbit white femur. In particular, the experiment described in Aversa et al. (2016b) consisted of assessing the osteoinductivity and osteoconductivity of the Ti implant surfaces without a 100-microns thin-layer ceramic-polymer hybrid material.

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Bone implantation or bone thickening (COMERON, 1986), which is defined as the percentage of bone implants for biomimetically implanted implants and not covered by the six-month in vivo test, shows a significant improvement in approximately 100% growth over two months, and 30% after 6 months.

The reconstruction of the bone micro-CT bone around the implant was validated using the physiological distributions of the calculated FEA strains. Maps of the maps surrounding the bone around the implant confirmed the critical role of the Ti-Bone bioactive interface.

Osteoblast proliferation and bone growth in the implanted rabbit femur are clearly favored and accelerated by the presence of the hybrid nanostructure layer.

The biomechanical approach utilizing adaptive bone properties describes the biomimetic behavior of the proposed preimplantation hybrid scaffold as it can predict bone resorption surfaces (elements of the FEA model with strains below the lower physiological boundaries were deleted in the image) as shown in the in vivo implant micro reconstruction microtubule on the right side of Figure 1).

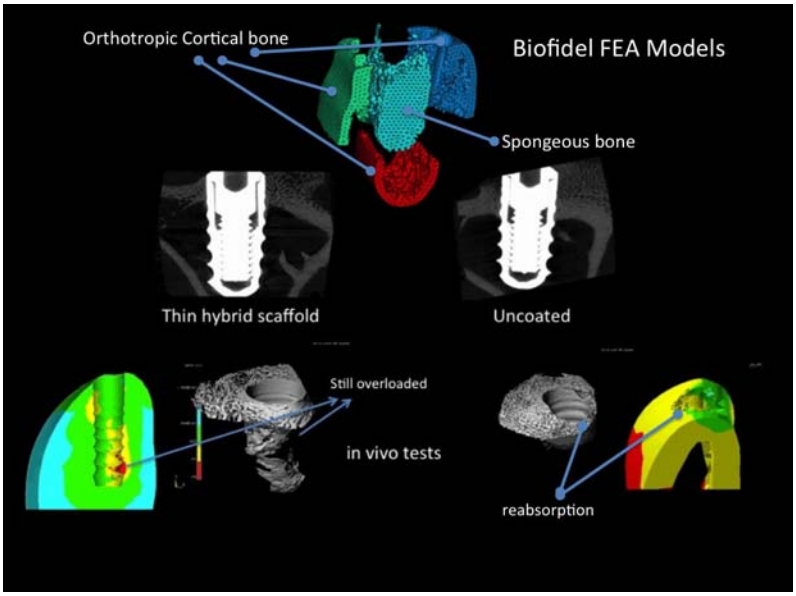

Figure 1: in silico and in vivo validation for Osteoconduction of Titanium implants coated with a nanostructured hybrid osteoactive (left side) and without (right).

Research has shown that mechanical stimulation can have a profound effect on the differentiation and development of mesenchymal tissues.

Figure 2 illustrates the adaptive properties and strain threshold values for healthy bone growth.

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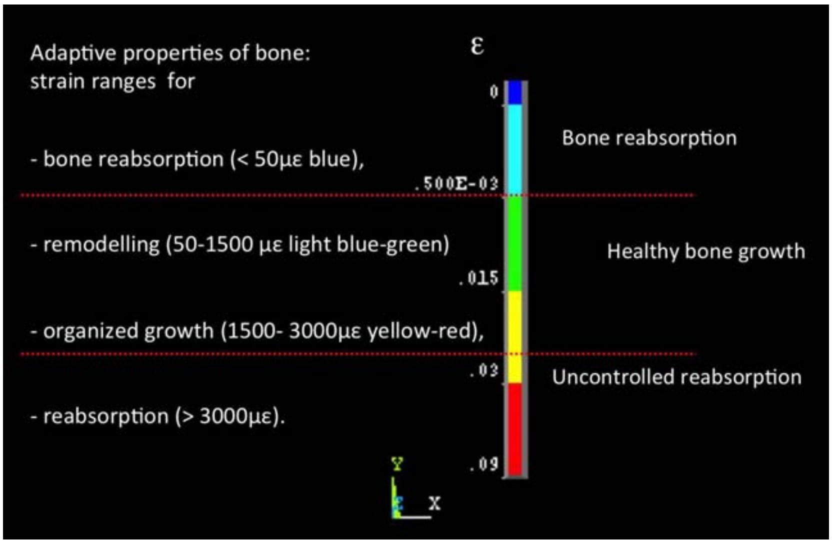

Figure 2: Adaptive window of bone physiology: Structural adaptations to mechanical usage

Source: Frost (1990)

According to Frost (1990), which quantified Wolff (1892) above (> 3000 micro epsilon) and below (<50 micro epsilon) of critical strain levels, bone growth is impaired. In the mild strain region, healthy bone growth and regeneration is favored. In fact, in order to maintain implant stability during pregnancy, it is of major importance for bone-forming osteoblasts to promote an extracellular matrix in the immediate vicinity of the implant. Osteointegration mechanisms to be considered in biofidel models

Osteointegration of implants is essential for the rehabilitation of the prosthesis. Achieving and maintaining stable functional anchylosis has the following morpho- structural characteristics, namely:

- direct contact between bone and implant in the absence of the idoneous tissue interface;
- the existence of the primary bone in contact with the surface of the biomaterial;
- deposition, externally to the primary bone, of the lamellar secondary bone in contact with the titanium surface;
- increase in preimplantation bone density compared to the normal bone region of the region;
- Increase in medullary spaces, which is required to evacuate the metabolic requirements of less involved tissues in the region in the dissipation of the

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load;

- Compact bone condensation, which may be related to the load propagation patterns determined by the specific morphology of the implant;
- organizing a strong trabecular structure that is radially removed from the compact preimplantation bone;
- the presence of a bone crystal wall at the level of the subepithelial conjunctiva, which may allow junctional tropism and the formation of the liquid epithelium.

The mature matrix, which has been described to occur in dental and orthopedic clinical trials, is expected to provide mechanical stability of the implant even in the early osseointegration phase (primary stability). In fact, due to the hydrophilic nature of the hybrid material, high fluid levels are absorbed from the external fluid medium, resulting in significant swelling and an initial increase in the volume of hybrid glass material (Figure 3).

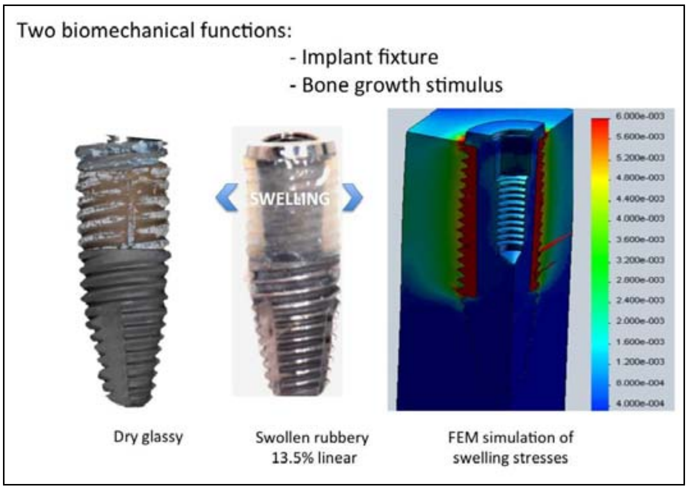

Figure 3: Mechanisms of primary stability and osteoinduction improvements in Hybrid swellable scaffold modified Titanium implant. Glassy dry scaffold (left)

The biomechanical and biomimetic active scheme has two biomechanical functions, the first being strictly related to stabilization of the prosthetic system after implantation (the prosthesis can be loaded one hour after implantation), while the second function is associated with stimulation of bone growth exerted by implanting the bone surface from around her.

The volumetric expansion of the scaffolding can be effective in improving

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the stability of the primary implant, confirming the high bioactivity of the nanocomposite material tested (Figure 4), (PETRESCU; PETRESCU, 2019; PETRESCU, 2019).

The presence of the inflatable implant component, which is supported by the upper part of the Ti core of the implant, increases the removal torque after implantation when the system is in the presence of organic fluids.

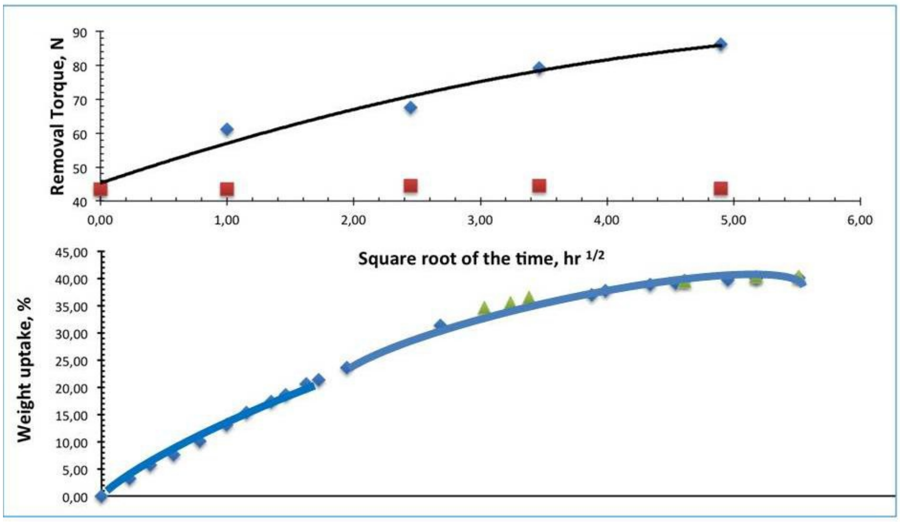

Figure 4: Physiological fluid uptake (bottom) and implant stability improvement (top) of Hybrid swellable scaffold modified Titanium implant.

The removal time, measured at different times after implantation, actually increased by more than 100% to 24. In addition, even after one hour, the removal torque already increased from 43 to 62 N (an improvement of approximately 25%). It has been described in a previous paper (AVERSA et al., 2016b) that improved retention has immediately followed the spinning kinetics of the hybrid material scaffold (bottom of Figure 4).

This increase in implant stability is due to the strong compression strains generated in the swollen rubber hybrid scaffold, as can be deduced from the map of the stained strains reported on the right side of Figure 3 (the red color of the implant hybrid insert). The implant is then constrained in its socket by the external bone, which then increases the retention and stability of the implant. Applying a larger removal torque for explants is, therefore, necessary to increase the experimentally measured inflation rate.

Furthermore, the constraint bone is subject to expansion strains as indicated by the colored map of the Von Mises strains reported in Figure 3. The color scale

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used for this map is the same as that reported in Figure 2, the physiology in which healthy growth and induction correspond to colors of yellow and green and blue and red to bone reabsorption.

The surrounding bones are subjected to healthy bone deformation at a distance equivalent to the diameter of the implant. In this toroidal volume surrounding the implant, an osteoinductive effect and a faster osteointegration of the implant are expected.

A micro-computer tomography confirmed these expectations. Figure 5 shows the micro CT of these volumes.

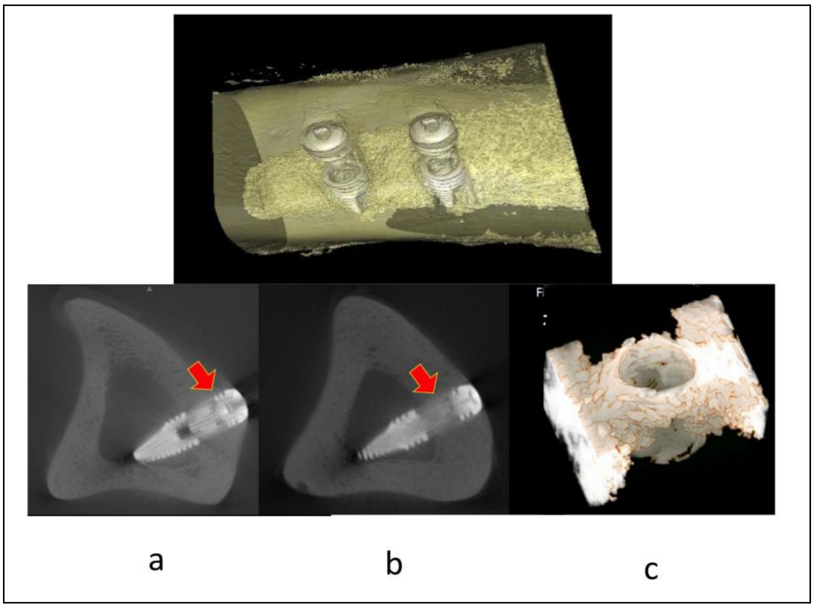

Figure 5: The Bone to Implant Contact (BIC) and the relative bone density have shown similar characteristics at cortical (a) and medullar levels (b), Bone near to the implants shows similar characteristics (c)
Souce: Gramanzini et al. (2016)

The upper part of the figure reports bone reconstruction and external implants, while the lower part shows the 3D reconstruction of the volume surrounding an implant.

BIC and relative bone density had similar characteristics at cortical (a) and medullary (b) levels indicating good osteointegration of the initial bone implant. The newly formed bone near the implanted implants has similar characteristics to the preceding (c), indicating the biomechanical stimulation effect of the swollen and swollen hybrid material.

Traditional bone prostheses are mainly made of metals and ceramics with

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remarkable strength and stiffness, but with high physiological invasiveness.

These implants, which are expected to serve for a longer period of time, without failure or surgical revision, although they guarantee mechanical and functional wood, occur frequently physiologically and mechanically with the human bone. Failures and lack of long-term reliability result from incomplete integration of the personal characteristics of the bones and the patient with local physiology.

To reduce implant invasiveness, a biomimetic approach is suggested; the implant is expected to have an "equivalent stiffness" (the combination of the elastic modulus of the material and the prosthetic shape) that matches that of a bone area where it is implanted.

The bone modulus varies in size from 4 to 30 GPa, depending on the bone type and the direction of measurement (bone orthotropy). Current implant implants are isotropic with higher rigidities than bone (for example, between 160 and 210 GPa for titanium and steel alloys) that greatly alter the physiological distribution of bone stress.

This behavior prevents the transfer of biomechanically modified stress to the adjacent bone, resulting in bone resorption around the implant and, consequently, weakening of the implant (this effect is called stress reduction).

This unwanted biomechanical invasiveness is due to the fact that the bones are functional and structural complex entities composed of less rigid, open and dense and rigid materials that are combined to provide rigidity both in orthotropic forces and in cortical bone forces. Equivalent to the three-dimensional properties of bone tissue should be truly necessary for implanted prostheses to achieve complete integration into the host bone tissue (AVERSA et al., 2019).

However, for the replacement and regeneration of soft tissues and osteoconductive and powerful mechanisms, porous and ceramic metallic biomaterials and polymeric systems and other metals have been proposed (TAYLOR et al., 2007; PARFITT, 1983;; PARFITT, 1994; MARTIN et al., 1998).

From a biomechanical point of view, the structure must be rigid enough to support physiological tasks, but should not drastically exceed the stiffness of the replaced bone to avoid stress shielding. Attaching the implant to the surface or to the bone matrix should be improved by alternatives to reduce stress protection.

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Clinical efficacy and long-term reliability of bone prostheses have been thoroughly investigated by analyzing finite elements to clarify the causes of the new replacement of invasive restoration (GRAMANZINI et al., 2016; AVERSA et al., 2016a; AVERSA et al., 2016b).

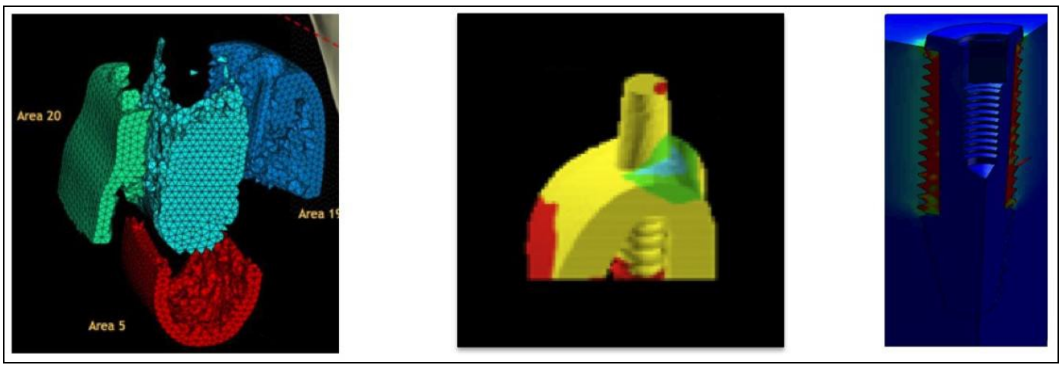
Figure 6 summarizes the main methodological steps used in these studies: (a) biophysical bone for investigation, (b) highlighting and weighing fractured bone macroanalysis, (c) stress of microanalyses and strains on the bone-implant interface. The peak values and regions of adaptive bone properties are shown in Figure 6d where unused, healthy and overloaded regimens are reported in Figure 6d (FROST, 1990).

Bone prosthesis interference was recognized at two magnitude levels, namely a micro scale (bone-implant interface, Figure 6c) and a macro scale (Figure 6b).

The first small scale (Figure 6c) explains the biological and micro-mechanical interactions of the synthetic biomaterial with bone-forming cells and highly adaptive adaptive properties, while the second on a macro scale (Figure 6b) determines the complete biomechanical functionality of the implant material and the ability to restore the distribution of the biologic stress state in the prosthesis.

Osteoblasts under specific biochemical and mechanical stimuli mature and turn into osteocytes that mineralize the bone. The activity of osteoclasts under conditions that were not stimulated mechanically after prostheses could induce bone reabsorption in this new state of mechanical equilibrium.

Figure 6d shows the adaptive bone properties that are in the coupling between bone formation and bone reabsorption.



(a) (b) (c)

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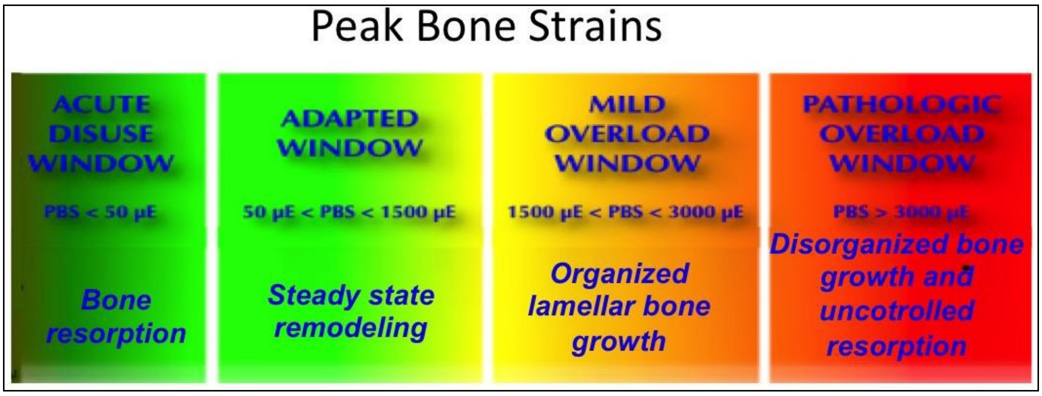

(d)

Figure 6: Finite element analysis tools for biomechanical and biomimetic investigation: (a) Biofidel models of the bone, (b) Macro Finite element analysis of the implanted bone for definition of the stresses and strains physiological modifications, (c) Micro Finite Element Analysis at the bone-implant interface, (d) Strain limits for bone adaptive properties.
Source: Frost (1998)

This process refers to bone formation in which osteoclast reabsorption via osteoclasts and renewed osteoblast generations of precursors dynamically replace dynamics (Figure 7).

The coupling can then be considered a complex mechanism of dynamic remodeling involving interactions of different types of cells and control stimuli. Mechanical stimulation should include physiological levels of the strain (Figure 6d) between 50m and 3000m (APICELLA et al., 2011; APICELLA et al., 2015; AVERSA et al., 2009). Over 50 years of osteocyte activity predominate, resulting in bone resorption of between 1500 and 3000 m, a slight increase in lamellar bone, predominantly over 3000, with uncontrolled bone growth or resorption.

3. RESULTS AND DISCUSSION

In the case of bone, which is a structural biological material that undergoes a mechanically induced continuous renewal (Figure 7), the remodeling process is controlled by a dynamic balance involving osteoclasts (linking bone cells) and homeostatic renewal osteoblasts.

Osteoblasts under specific biochemical and mechanical stimuli may actually mature and turn into osteocytes that mineralize the bone. Instead, osteoclastic activity under conditions that were not stimulated mechanically after the prosthesis (ie in the stress release area) could induce bone reabsorption in this new state of bio-mechanical balance (Figure 7).

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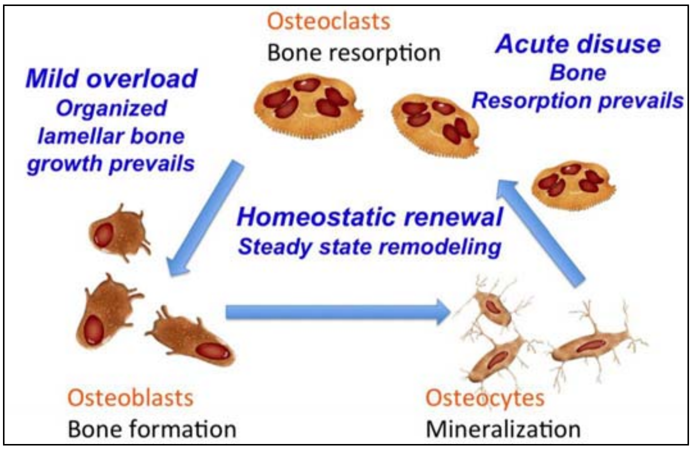

Figure 7: Bone homeostasis mechanism involving Osteoblast, Osteocyte and Osteoclast cells

Thus, in order to favor biomechanical integration and a longer maintenance period, a customized material, which carries a great combination of high strength and stiffness that fits the bone, must be used. The use of trabecular scaffolds and cortical bone to mimic behavior and colon have been proposed to recreate the distribution of macroscopic stress and bone deformities but requires a necessary micro-biomimetic interface that interacts with osteoblast osteoblasts.

Nanomaterials Ceramic-polymer nanoparticles based on hydrophilic and ceramic polymers are potential candidates for new customizable biomaterials that will be used to cover porous phosphorus structures. The hybrid layer that comes into contact with bone can be customized by choosing nanophysics content and mechanical properties to achieve the biomechanical characteristics necessary to increase thickening of the osteoinductive bone in the porous structure of the metallic prosthesis.

These resulting hybrid systems have the basic mechanical and biological properties that favor local healthy local generations. Specific and adjustable properties that simulate bone tissue that acts on the interface guide microparticle, leading to bone marrow growth and integration into host bone tissue. The main reasons for using the skeleton are therefore to provide a bone formation environment, maintain space and support the skeleton of the skeleton during the repair process.

New biomaterials that possess hybrid characteristics can be obtained by using nanometers in polymeric matrices (AVERSA et al., 2016a; AVERSA et al., 2017a; AVERSA et al., 2017b), especially carbon nanofillers such as fullerenes and

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carbon nanotubes have been proposed to increase strength and stiffness nanocomposite materials. Although the use of carbon diamond nanofilm can further improve these properties, some technological challenges in production technology should be overcome.

Graphite is only one of allotropic carbon forms and is thermodynamically stable at ambient temperatures and pressures, while the diamond is another stable allotrope carbon at high pressures and at a temperature present in a metastable state at ambient and similar conditions (PETRESCU; CALAUTIT, 2016 a-b).

Differences in the stability of allotropic forms are a consequence of the large energy barrier separating the graphite Sp2 (left in figure 8) and diamond sp3 configuration (even in figure 8), which requires high temperatures and pressures in the presence of the transformation catalyst.

However, an additional equilibrium parameter involving the surface becomes critical and significant for the distribution of the equilibrium energy to the nano dimension: Gibbs free energy is drastically influenced by the presence of surface energy input, modifying the phase diagram of the thermodynamic equilibrium (BADZIAG et al., 2003; BARNARD et al., 2003; BARNARD; STERNBERG, 2007; VIECELLI et al., 2001).

Atomic models (PETRESCU; PETRESCU, 2019; PETRESCU, 2019) have demonstrated that nanodiamonds with 3 nanometers with tetrahedral hydrocarbons are more stable than polyaromatic graphite under ambient conditions (BADZIAG et al., 1990; AVERSA et al., 2016a; AVERSA et al., 2016b; AVERSA et al., 2016c; AVERSA et al., 2016d).

The presence of a more complex structure, generated at the nano-diamond interface, opens up new interesting technology applications. Cuboctodic structures of 1.03 to 3.0 nm with onion structure characterized by the passage from Sp3 to Sp2 carbon at their surfaces were observed by Barnard and Sternberg (2007).

A reversible reverse phase transformation in a nanodiamond-graphite cluster was observed by Xiao et al. (2014) appear in this morphological transition interface, which leads to daily bucky formation, characterized by a diamond core, a graphical case (schematized in Figure 9) (BARNARD; STERNBERG, 2007). Such graphite nano- diamond surfaces can be modified using graphite carbon chemistry

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to form cyclohexane functional systems such as Diels-Alder cycle reactions between a conjugated diene and dienophiles (JARRE et al., 2011).

The nano-crystalline Sp2 and Sp3 Carbon structures open up a new perspective for future technological development in structural biomedical applications. The nanocrystalline particles produced by the detonation of carbon explosive materials (DANILENKO, 2004, GREINER et al., 1988; OZAWA et al., 2007; CHANG et al., 2008) exhibit characteristic dimensions of 3-5 nm. Lubricants, galvanic coatings, polymer nanoparticles, polishing systems, and niche applications recently used for electronics, emission devices, catalysts and combustion cells as nanocomposite membranes that lead protons for the application of detonating nanodiamonds have been proposed.

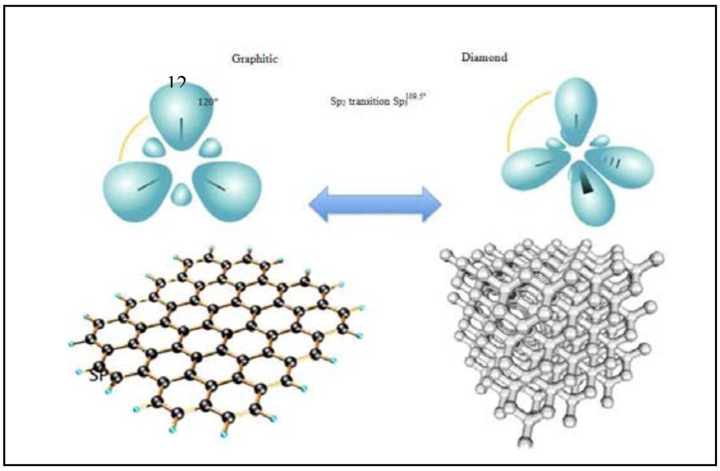

Figure 8: Left) Graphite (SP2 hybridization) and Right) Diamond (SP3 hybridization) Carbon allotropic forms

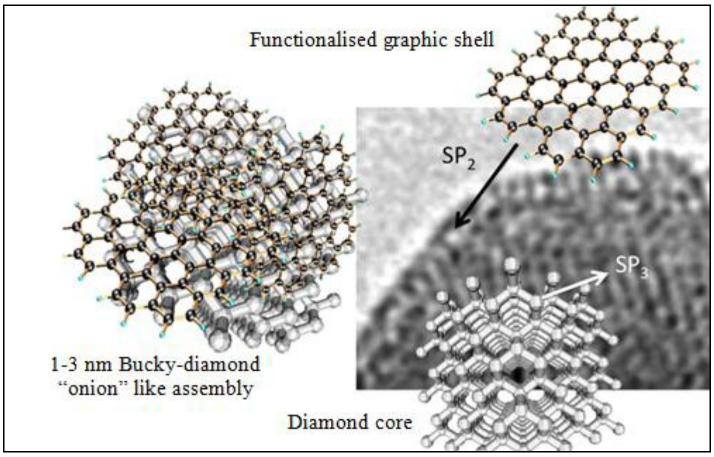

Figure 9: Bucky-Diamond "onion" like cluster (left side): Nano-diamond core (lower right side) with external graphitic shell (upper right side) and TEM of a detonation nano-diamond atomic structure (right side)

However, preliminary clinical and biochemical investigations have shown that

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these detonating nano-diamonds are biocompatible and non-toxic, opening up new biomedical applications, taking into account both the variety of surface chemical light and the intrinsic mechanical characteristics.

The detonation of nano-diamonds, characterized by different levels of purity and the presence of unwanted functional groups/elements, can not be directly appropriate for biomedical applications in which chemical purity and chemical uniformity of the surface (LAI; BARNARD, 2011a; LAI; BARNARD, 2011b). After raw production, these materials are subjected to purification procedures.

A simple method uses surface oxidation and different levels of purity and surface properties can be obtained. Oxidation carried out at elevated temperatures in an air/ozone atmosphere can lead to a purification of the carbon fraction not present as diamond up to 95% by weight (OSSWALD et al., 2006; SHENDEROVA et al., 2011).

Oxidation of nano-diamond surfaces other than elimination of unwanted functional compounds forms oxygen-containing groups (the blue dots in Figures 8 and 9) such as anhydrides and carboxylic acids (SHENDEROVA et al., 2011) which are suitable for the polarization of hydrogen or polar with the appropriate species.

By purifying air/ozone, we can work on the very reactive and hydrophilic surface of the carboxylate, which is very suitable for biomedical applications (KRUEGER et al., 2008; KRUEGER et al., 2006).

However, the toxicity of nano-diamonds remains controversial and is a real concern. In vitro and in vivo analyses are required to evaluate characteristics such as mechanical and physiological behaviors in vivo (SCHRAND et al., 2009a; SCHRAND et al., 2009b; ZHANG et al., 2011; YUAN et al., 2010).

Although biocompatibility and negative effect have also been described in the literature on the use of nano silica particles, our published investigations have shown that nano-composite and hybrid materials made by combining amorphous silica nanoparticles have reached a high level of biocompatibility, and micro-nanoparticles and p-HEMA.

These hydrogel hybrid nanocomposites have been tested for water sorption, water swelling, and isotonic saline and for fibroblasts and osteoblasts as a cellular response with adhesion, distribution and morphology tests. The presence of

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polymer-bound silica makes these biomaterials excellent only for pHEMA. Good properties of osteoinduction were also observed for the differentiation of stem cells from the dental pulp Marrelli et al. (2015).

These self-assembled nanostructured composites were also tested as a peri-implanter scheme to match osteoblast growth factors or stem cells for osteoblast differentiation (MARRELLI et al., 2015). This effect was mainly determined by micro-mechanical stress and the voltage generated at the bone/implant interface.

These new hybrid materials have been shown to be able to stimulate biomechanical bone growth within the range of physiological strains that allow for healthy growth to allow for complete early and organized integration of the implant into the receiving bone. Creating ideal scaffolds for bones is a growing argument for research. Such an ideal framework should provide a rigid and elastic mesh to temporarily replace damaged bone function while creating a bioactive substrate for bone regeneration, integrating it fully (MONTHEARD et al., 1992; KABRA et al., 2017; AVERSA et al., 2017a; AVERSA et al., 2017b).

4. PREPARATION OF MATERIALS

The 3 nm detonation nanoparticles (Aldrich, ≥97%) with a specific surface area of 400 m2g-1 were used as bioactive filling agents. Nanodiamond hydrophilization was performed (SHENDEROVA et al., 2011; AVERSA et al., 2016a; AVERSA et al., 2016b; AVERSA et al., 2016c; AVERSA et al., 2016d). The surface graft decomposition followed by functionality consists of the aggregate dispersion of ~ 20 nm. Treatment of hydrogen at high temperatures leading to nanoparticles Nanoparticles Nanoparticle nanoparticles of 2-4 nm was isolated by centrifugal isolation at> 10,000 rpm (SHENDEROVA et al., 2011).

The nanodispersion was mixed with 2-hydroxyethyl methacrylate monomers (HEMA) (Sigma-Aldrich Chemicals Co., St. Louis, MO, USA). The suspension of HEMA nanomaterials (Figure 10) was radically polymerized in the presence of the azoisobutyronitrile thermal initiator (AIBN, Fluka Milano, Italy).

4.1. The nanocarbon content was prepared at 2 and 5% by volume.

The degassed reactive suspension was first transferred to 2.0 mm thick flat molds and then polymerized at 60 ° C for 24 hours. Finally, a cure at 90 ° C was obtained.

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4.2. Finite Element Analysis (FEA)

Solid models of dental implants were generated using the Solidwork 2016 software. The titanium implant and the hybrid material replacing one part were molded. The FE model was obtained by importing solid models into ANSYS rel. 9.0 FEM software (Ansys Inc. Houston) using the IGES format. The volumes were linked to tetrahedral elements, resulting in a 3D FE model consisting of 31,240 elements and 35,841 nodes. The precision of the model was verified by the convergence test.

4.3. Mechanical characterization

The effect of elasticity measurement on the dried, swollen and pendulous p-HEMA nanostructure was performed using a DTM METTLER-TOLEDO mechanical shear modulator (Zurich, Switzerland). The elastic and viscous components of the shear modulus were measured with a constant frequency in an isothermal state. The samples were vacuum dried at 60 ° C for 24 hours before testing. In the shear test mode, discs of 10 mm diameter and 2 mm thick discs are placed between three steel plates forming a symmetrical sandwich. An isothermal scan was performed at 37 ° C in a nitrogen purged medium. Deformation control was set at 10 µm and a force limit of 0.9 N was applied at an oscillating frequency of 10 Hz (AVERSA et al., 2019).

The presence of the oxidized functional detonated nanodiamond in the monomer reaction mixture favors the self-orientation of HEMA polar monomers (Figure 10). The nanoparticles are in fact characterized by the presence of oxygen-containing groups leading to a preferred orientation and self-assembly of the HEMA hydroxyl group monomers on the nanoparticle sizing surface (left side of Figure 10).

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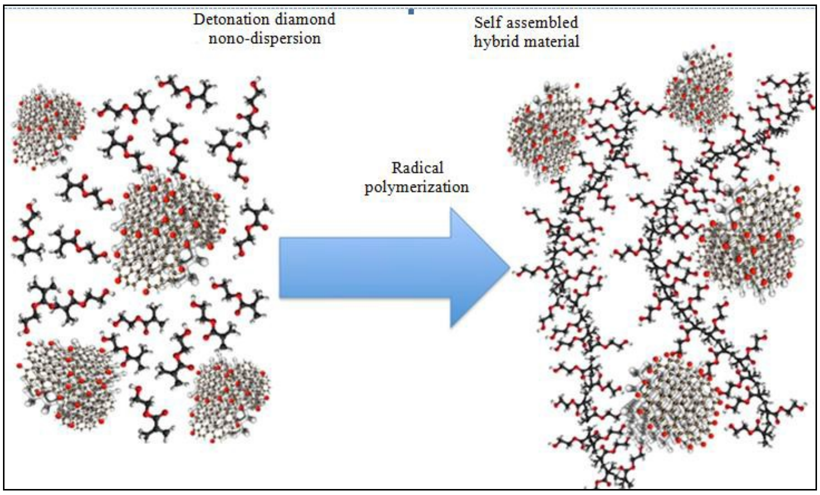

Figure 10: Self-assembly of HEMA monomers in presence of functionalised Detonation Nano-diamond (left side) and hypothesized Nanodiamonds pHEMA self assembled hybrid nanocomposite (right side)

Nanosilica hybrid Nanocomposites have been described in a previous paper (Aversa et al., 2016a) to show the self-assembled analog behavior that led to the formation of nanostructured hybrid materials. Similarly, functional nanopowder that does not contain oxygen binding atoms (red in Figure 10) and functional HEMA functional groups can produce monomer.

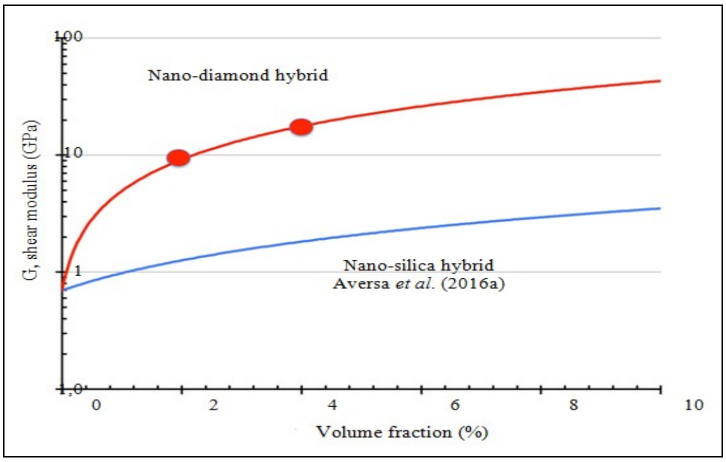

Figure 11: Camparison of mechanical shear properties on amorphous nanosilica and crystalline nano-diamonds-pHEMA hybrid nano-composite

The polymerization of these silicates from HEMA / silica gel leads to the formation of a nanostructured hybrid material exhibiting specific and specific properties, such as improved mechanical stiffness and biocompatibility (AVERSA et al., 2016a; PETRESCU et al., 2016a; PETRESCU et al., 2016b; PETRESCU et al., 2016c).

Applying this model of nanostructure formation to the nanodiamond / HEMA suspension polymerization, a similar improvement in mechanical properties and

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biocompatibility is expected. However, improved mechanical properties are expected to be more relevant due to the high and high shear force (Azo technology).

The stiffness of the synthetic diamond may be up to 15 times higher than that of silicon, i.e. from the shear modulus of about 450 GPa Vs about 30 GPa (Azo). By acting as a filler or hybrid formation, nano-diamond detonation could generate the mechanical behavior of similar nanoparticle hybrids (AVERSA et al., 2016a), the behavior of pure variation according to the volume fraction of hybrid diamond nanoparticles in the material could be assessed.

As described by Aversa et al. (2016a) aims at balancing PHEMA hybrid nano- silicas in physiological solutions. Water molecules that bind to polymeric hydrophilic groups induce a significant plasticization of the nanocomposite (in our case, a 16% by volume nanocomposite) that reduces the shear modulus of the dried initial samples from 8-9 GPa to 0.01- 1, 1 GPa 6, (AVERSA et al., 2016d; AVERSA et al., 2019).

The compositional dependence of PHEMA impulse shear modulus is not described by the classical Halpin-Tsai equation (HALPIN; KARDOS, 1976) valid for particle composites, but a linear dependence is observed. These findings confirmed the hybrid character of pHEMA nano-silica compounds.

On the other hand, the same stiffness can be achieved at a much lower volumetric loading by using the nanodiamond, i.e., between 1 and 5% in the dry state.

Figure 10 shows a schematic of self-assembled PHEMA nanodiamonds, while Figure 11 compares the shear modulus that can be obtained using nanoparticulate amorphous particles and nano-diamond crystalline particles. The red points are the 2 and 5% nano-diamond shear modulus, measured in the shear mode using a dynamic mechanical tester (AVERSA et al., 2017b).

These preliminary tests have confirmed our estimated theoretical values for hybrid configurations. Therefore, the adaptive properties of the bones can benefit from the use of biomechanical and biomechanical materials (biomimetics).

"In vivo" Evaluation of bioactivity and osteoinduction of implants

The in vivo study aimed at assessing the bioactivity and osteoinductivity of the ceramic-polymer hybrid scaffold was presented by Aversa et al. (2016d).

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Unmodified titanium dental implants and siliconized nano-hybrid implants were tested for 2 months at the laboratory hamster femur. Micro-tomography was performed to evaluate bone density and distribution around the implant (AVERSA et al., 2019).

The biomechanical and active osteoinductive characteristic of hybrid materials is summarized in Figure 12, in which microscopic microscopy and bone reconstruction and biomechanical analysis by finite element analysis are compared for the same active (left) and non-right biomechanical implants.

Active biomechanical coverage (100 microns) demonstrated that it is able to transfer the physiological strains necessary to avoid stress protection and bone resorption in the vicinity of the implant neck (the green cross section of Figures 12a-12c).

The explant implant (on the right side of Figure 12) shows a significant bone resorption process in the same area (red circulating in Figures 12d-12f), which was correctly predicted using the biofilm model (Figure 6b) for the final bone implant figure 12f).

FEM analysis in the same area of the hybrid biomaterial coated implant predicted a more physiological stress distribution due to the active biomechanical interface that stimulates osteoblast growth (Figure 12c).

Commercial 2-hydroxyethyl methacrylate was purchased from Sigma-Aldrich Chemicals Co., (St. Louis, MO, USA). Smoke silicon dioxide (Aerosil 300 Degussa, Germany) with an average diameter of 7 nm and a specific surface area of 300 m2 g-1 was used as a bioactive filler. The initiator, α-α 'azoisobutyronitrile (AIBN), was purchased from Fluka (Milan, Italy). HEMA monomers with an increasing amount of chemical silica (4 to 30% by volume) were mixed. The resin was poured into 2 mm flat plates, polymerized in an air circulation oven set at 60 ° C for 24 hours and finally treated at 90 ° C for 1 hour.

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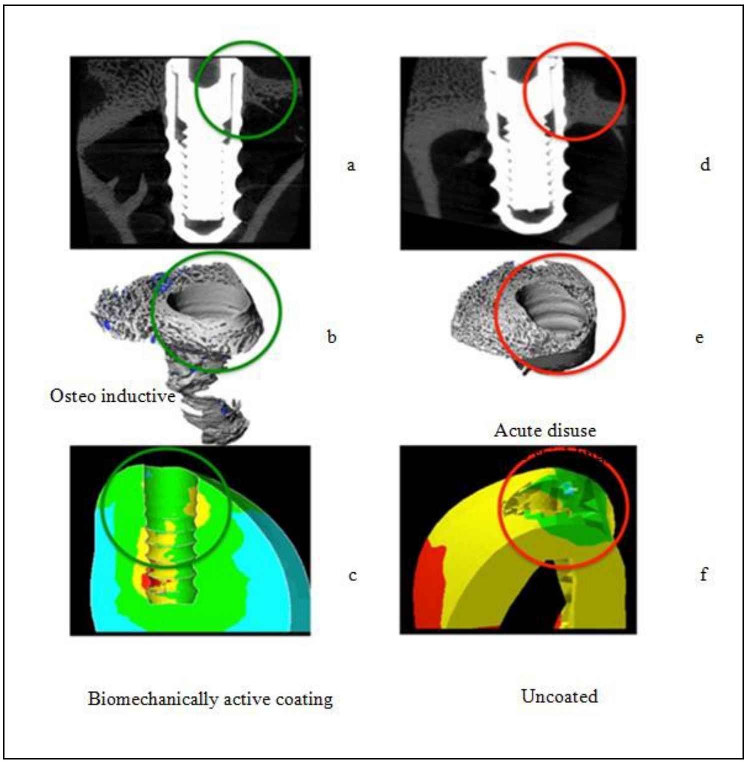

Figure 12: Comparison of “in vivo” and Finite Element Biomechanical Analysis results on a dental implant with and without the biomechanically and osteoinductive hybrid coating

Planar samples were used for sorption and swelling experiments with aqueous isotonic saline (0.15 M NaCl). The aqueous solution absorbed in the initially dried samples was determined at equilibrium by gravimetric measurements in a 0.1 mg Mettler Toledo balance sheet (Milano, Italy). Advanced inflation left in the abnormal sorption of sample II was monitored by measuring the time of thickness of the non- deposited residual glass core. The sorption and balance swelling experiments were performed at 37 ° C (thermostatic water bath) until the monitoring of the constant weight absorption monitoring (100 hours) was monitored.

Solid dental implant models were created using the Solidwork 2007 software. Titanium implant and hybrid material replacing one part were molded. The FE model was obtained by importing solid models into ANSYS rel. 9.0 FEM software (Ansys Inc. Houston) using the IGES format. The volumes were linked to tetrahedral elements, resulting in a 3D FE model consisting of 31,240 of 309 elements and 35,841 nodes. The precision of the model was verified by convergence tests.

Measurement of the elastic modulus by sampling the hybrid nanocomposite and the swollen p-HEMA hybrid was performed using a mechanical shear

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METTLER-TOLEDO (DMA) (Zurich, Switzerland). The elastic and viscous components of the shear modulus were measured with a constant frequency in an isothermal state. The samples were vacuum dried at 60 ° C for 24 hours before testing. In shear mode, discs of 10 mm diameter and 2 mm thick discs are placed between three steel plates forming a symmetrical sandwich. An isothermal scan at 37 ° C was carried out in a nitrogen purged medium. The deformation control was set at 10 µm and a force limit of 0.9 N was applied at an oscillating frequency of 10 Hz.

The in vitro study aims to evaluate the potential of nanomaterials to improve the nanomaterials of nanomaterials Nanomaterials Nanomaterials (AVERSA et al., 2016b; SORRENTINO et al., 2007; SORRENTINO et al., 2009). Both the test body and the control body were randomly assigned to four groups; each test group consisted of 9 implants, while each control group consisted of three fixed elements. Insertion values ranging between 43.4 and 44.5 and between 44.2 and 45.7 Ncm were recorded in the control and control group.

In groups 1 through 4 and in groups 5 to 8, the implants were removed after 1, 6, 12 and 24 hours. The values of the removal torque were recorded as described above. The in vivo study aims at assessing the bioactivity and osteoinductivity of the ceramic-polymer hybrid scaffold. Dental prostheses Unmodified titanium and modified and coated prostheses were implanted into the rabbit femur and eliminated after two months. The micro-calculus tomography was performed on the explanted femur, and the bone density and distribution on the implant was evaluated.

Our research aims at designing a completed biomimetic dental implant to stimulate normal OB growth in adaptable mandibular bones. To achieve this result, both a suitable biomimetic scheme material and an external implant screw piece should be designed.

The biomimetic feature of our hybrid materials has been investigated for both mechanical properties and swelling properties. The physiological behavior of the bone material to be imitated from the bioactive material of the scaffold refers to the following aspects:

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Mechanical properties (dry and swollen) Bioactivity (in vivo implant)

The PhEMA nanocomposite hybrid components with a concentration of 4 to 30 percent silicon dioxide volume were mechanically mechanically mechanically tested isometric, operating in a nitrogen atmosphere at 10 Hz and 37 ° C predominantly viscous viscosity of all compositions. The measured shear modulus is shown in Figure 13. The measured shear modulus of PHEMA-Nanosilica composites does not follow the classical Halpin-Tsai equation for particulate composites (the ascending line shown in Figure 13).

A linear dependence of the shear modulus values on the progressive loading of nano silicon was observed. This unexpected behavior indicates the hybrid nature of PHEMA nano-silica composites.

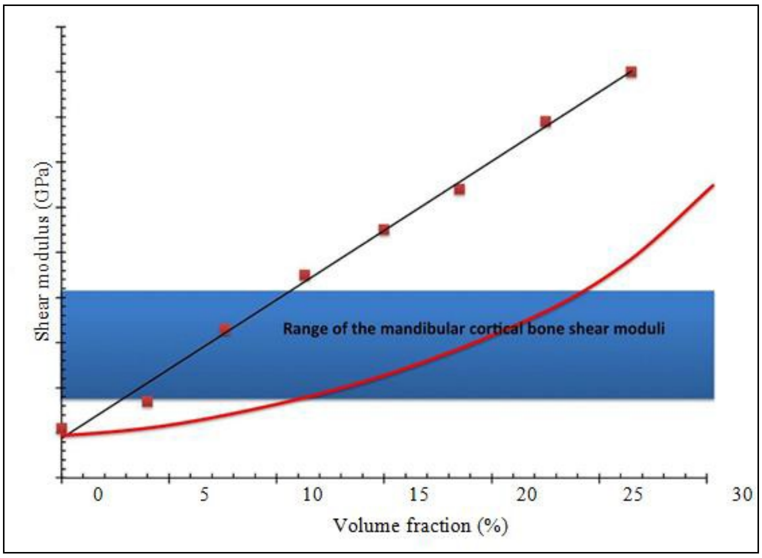

Figure 13: Shear moduli of the hybrid nanocomposites at different nano silica filler loading. The theoretical Halpin-Tsai curve is reported for comparison in the figure

To determine the appropriate nanofiller / p-HEMA ratio of the appropriate potential hybrid nanocomposite, the requirements of the target properties are: Similar to bone rigidity during implantation.

Shear modulators comparable to those of cortical bone were measured dry for nano silicon fractions ranging from 4 to 12%. A 5% volume fraction was then chosen for sample preparation and FEA simulations (AVERSA et al., 2016b; AVERSA et al., 2016; AVERSA et al., 2016c; AVERSA et al., 2016d; AVERSA; APICELLA, 2016).

Elastic modulating (traction test) ranging from 2-20 MPa (strain-curing effect)

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was measured for the swollen hybrid composite (5% by volume). This value becomes comparable to that of the tense periodontal ligament under the same conditions as articular cartilage.

The 5% hybrid nano-composite swells dramatically in isotonic aqueous solution, raising 50% of its dry weight while reducing the shear modulus to 2-3 MPa (measured in DMA at 10 Hz). Such a phenomenon is associated with plasticization of the water-induced polymer that reduces the transition temperature of the polymer glass below the test temperature 311. The sorption behavior was investigated in a 0.15 M isotonic isotonic isotonic solution maintained at 37 ° C by hybrids of glass with a volume fraction of 5% both for the weight absorption of the solution and for the swollen kinetics.

After exposure to the aqueous solution, 2 mm thick coated PHEMA glass plates begin to swell with a clear face dividing the outer rubber portion and the untreated glass core. The thickness of the correct glass progressively reduces the front feed through the sample. A measure of the swollen kinetics, which was reported in Figure 14 based on the square root of time, is given by the rate of reduction of the glass core as a function of time.

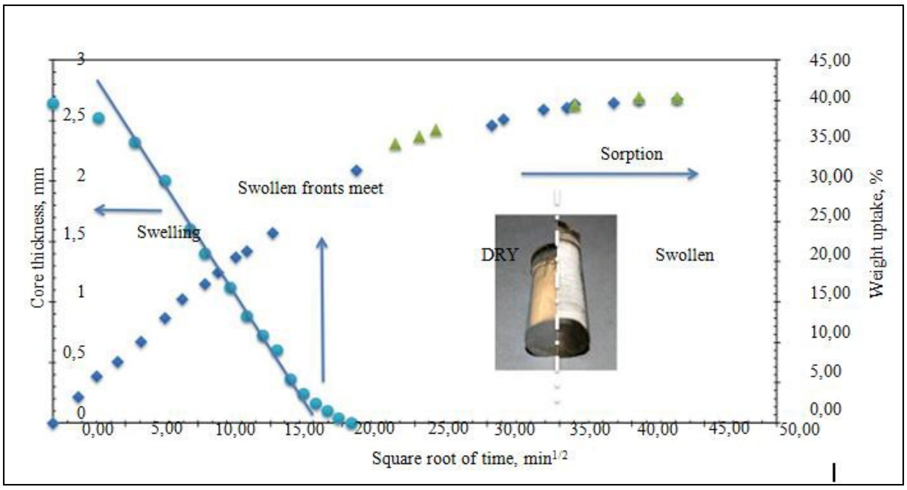

Figure 14: Swelling and sorption kinetics of a 5% by volume hybrid nanocomposite in 0.15M NaCl water solution (isotonic)

The swollen face has initially advanced at a constant rate, according to the relaxed relaxed relaxed mechanism of anomalies, indicated as "case II sorption".

An initial linear inflation rate is approximately 0.10 mm per hour. Since the swelling continues, however, the diffuse resistance develops into the exfoliated outer skin, resulting in diffusion-controlled swelling of the remaining glass core.

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When inflated fronts meet, the weight gain of the samples is about 27% but continues to increase to a balance of 40%. This is due to complete balancing through the thickness of the sample.

At steady state, a 14.5% increase in sample thickness and a 50% increase in volume were measured. These values were used to evaluate by simulating the analysis of finite elements the dimensional changes that appear in the complex geometry of the modified dental implant described in the following paragraph.

The use of the active and biocompatible biomechanical interface has been "engineered" to reproduce bone distribution compatible with the biomimetic. Intervals of physiological strains and adaptive bone properties are reported. There are superior surfaces (> 3000 m) (<50 m) that do not favor healthy bone growth. The variable tension of adaptive bone growth is bone resorption (<50 m), remodeling (50- 1500 m), organized growth (1500-3000 m), resorption (> 3000 m).

Biomimetic aspects are investigated using hybrid osteoconductive nano-composite coupled with FEM modeling of swelling and deformation of the hybrid material. The proposed solid CAD model of the new ceramic-polymer modified implant is shown in Figure 15.

Two biomechanical functions were considered during implant design: fixation of the implant and stimulation of bone growth. A portion of the Ti screw was replaced by the hybrid nano-composite that maintains the continuity of the outer yarns, while the interior, in which the remaining Ti core is conical through the threaded tip, has a thickness of between 0.5 and 0.8 mm.

This thickening of the hybrid ceramic-polymer hybrid nanocomposite produces, following inflation, a progressive volumetric increase of the peak. The scaffold should play two biomechanical functions: one structural as part of the fixation device and one bioactive as a stimulation stimulus of the bone. From a physiological point of view, stretching the periodontal ligament causes the new bone to fall into the toothbrush. Since the modulus of elasticity of the swollen scaffold was comparable to that of the periodontal ligament, the analysis of the finite element confirmed that swelling of the nanocomposite could act as a biomechanical entry of bone growth.

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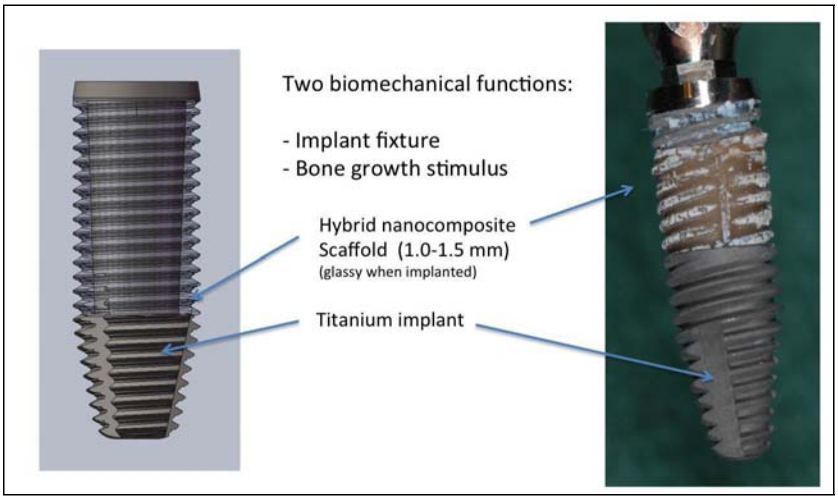

Figure 15: Thick elastic scaffold hybrid material mimicking periodontal ligament functions in the Biomimetic implant: CAD solid model and a prototype for use in "in vivo" tests of the new ceramic-polymeric modified Titanium implant

Figure 16 shows the results of a finite element analysis performed on the new implant simulating the swelling of the polymer-ceramic polymer insert in a physiological fluid: displacements up to 0.2 mm were calculated (after 8 hours depending on the swelling velocity of 0.1 mm / h). This occurrence favors fixation and stabilization of the prosthetic device after implantation (the first biomechanical function).

Moreover, since remodeling is not triggered by the main stress but by dynamic loads (not static charges) on remodeling, a positive growth stimulus is due to the presence of a deformed hybrid at a physiological compression of 5-30 m; and stress stress during bone healing and integration of the bone implant (second biomechanical function), (AVERSA et al., 2016a; AVERSA et al., 2019).

The blooming of the ceramic-polymer hybrid insert then sets the implant into the bone and creates an active biomechanical interface for bone augmentation. Bone stress was modulated by choosing a skeletal swollen thickness for healthy bone growth. The in vivo tests performed using this new modified oral implant confirmed the improved ability of these implants to promote early osteointegration.

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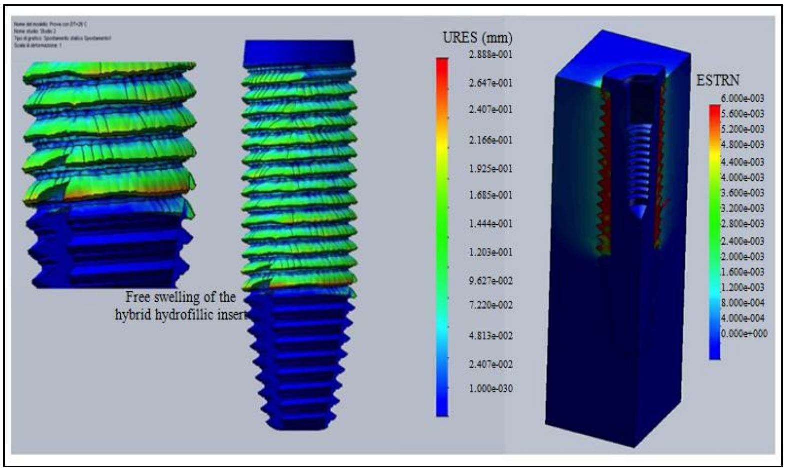

Figure 16: Displacements (URES) in mm and strains (ESTRN) of the hybrid ceramic-polymeric insert undergoing physiological fluid free and constrained swelling after implantation

This in vitro study aimed at assessing the possibility of improving the primary stability of oral implants through three-dimensional schemes consisting of a hybrid polymeric material of nanocomposite ceramic materials.

In the test groups, mean withdrawal rates increased progressively over time (diamond points) ranging from 61.2 after 1 hour to 86.2 Ncm after 24 hours, showing how swelling of the scaffold improved the stability of the primary implant. In contrast, in control groups (squares), the average values of the removal torque were between 43.7 and 44.9 Ncm.

Figure 17 compares the average growth of the removal torque and the sorption/inflation kinetics.

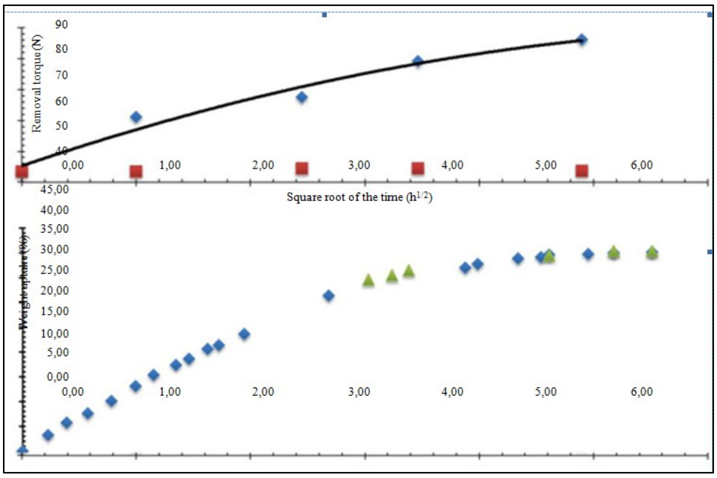

Figure 17: Comparison between the kinetics of after implantation removal torque increases and physiological fluid uptakes in modified implants undergoing swelling

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The results of the Micro CT scan are shown in Figure 18. Thin hybrid implants showed two main differences between osteoinductivity and bioactivity compared to unmodified implants:

- avoiding bone resorption in the cortical bone surrounding the implant neck
- improving osteoinduction in the bone marrow

Immediate titanium implants showed significant bone resorption in the cortical bone.

This effect may be related to the biomechanical stimulation of incorrect cortical bones outside the range of 50-3000 m. To avoid this undesirable effect due to a proper mechanical stimulus induced by the interface of the hybrid bioactive hybrid material.

Furthermore, bone growth on the implant surface (the left implant in Figure 18) is due to the osteoinductivity of the hybrid skeleton material tested (AVERSA et al., 2016b; AVERSA et al., 2016c; AVERSA et al., 2016d).

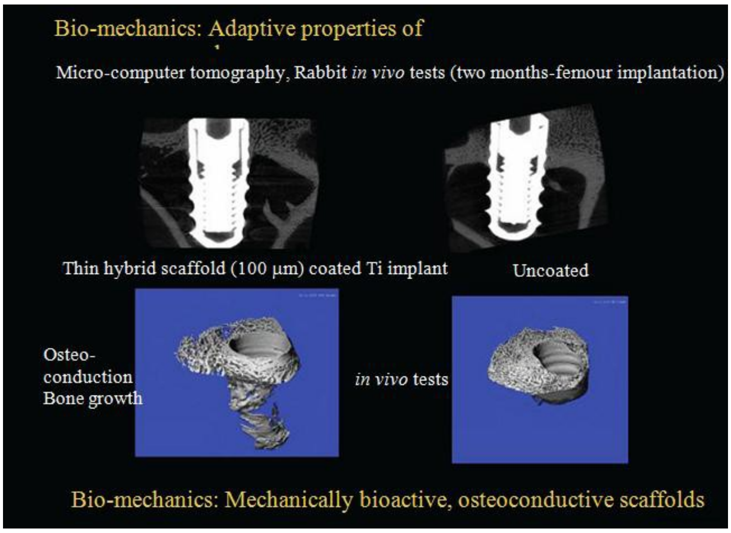

Figure 18: Biomechanicanics in adaptive morphology of the bone and osteoinduction in the hybrid scaffolding materials

Biomaterials Today's science is a very interdisciplinary field that plays a central role in the development of tissue engineering applications involving close collaboration between biologists, chemists, material engineers, physicists and clinicians who have researched in this area at a favorable level to new development systems. Regenerative medicine has developed a lot and will guarantee many pat- to-bed applications (MONTHEARD et al., 1992; FILMON et

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al., 2002; DAVIS et al., 1991; KABRA et al., 1991; APICELLA et al., 1997; PELUSO et al., 1997; CHOW et al., 2010).

Biomimetic Ability (APICELLA; HOPFENBERG, 1982; APICELLA et al., 2010; ; APICELLA et al., 2011; APICELLA et al., 2015; AVERSA et al., 2009; PERILLO et al., 2010; PETRESCU et al., 2015; SCHWARTZ-DABNEY; DECHOW, 2003; TÖYRÄSA et al., 2001; FROST, 1990; GRAMANZINI et al., 2016; HOLLEY et al., 1970; NICOLAIS et al., 1984; AVERSA et al., 2016a).

The new hybrid nanoparticles are prepared by polymerizing the hydroxy-ethyl- methacrylate monomers filled with detonating nanotubes (up to 5% by volume). This material absorbs water and swells in aqueous physiological solutions (up to 40-45% by weight), transforming it into glassy and rubbery conditions. Low levels of non- diamond loads can improve the mechanical properties of hybrid materials.

Hydromechanically compatible hybrid hydrogels can be used as scaffolding materials to increase stress adaptation mechanisms to micro and macro prostheses.

The introduction of active biomechanical interfaces will improve biomimetic implantation while reproducing the biomechanical functions of cartilage and ligaments (APICELLA; HOPFENBERG, 1982; APICELLA et al., 2010; APICELLA et al., 2011; APICELLA et al., 2015; AVERSA et al., 2009; PERILLO et al., 2015; SCHWARTZ-DABNEY; DECHOW, 2003, TÖYRÄSA et al., 2001; FROST, 1990; GRAMANZINI et al., 2016; HOLLEY et al., 1970; NICOLAIS et al., 1984).

The use of metallic microtrabecular prostheses (AVERSA et al., 2016c; AVERSA et al., 2016d) coated with ceramic-polymeric hybrid scaffolds (AVERSA et al., 2016d) was proposed to recreate macro and micro-distribution of stresses and deformations in the bone.

The development of polymer hybrid nanocomposites has been proposed in recent studies (AVERSA et al., 2016b; AVERSA et al., 2016c; AVERSA et al., 2019). These hybrid materials can induce the mechanical and biological properties needed to promote healthy local generations.

The innovative features of a biomimetic approach are that the prosthesis is now designed to replace the joint, damaged by various causes, but does not stimulate tissue regeneration. Also, the average length of a prosthesis is about

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10/15 years, while the new "biomimetic prosthesis" will last longer, estimated at 20/25 years.

This is very important because the average life span has increased significantly, increasing the number of orthopedic surgeries and health and social care costs.

A biomimetic/biomechanical approach has been developed in the design of a new modified dental material with bioactive ceramic hybrid material for biomechanical stimulation and potential improvement of the mineralization and ossification of the scaffold.

A polymer (pHEMA) filled with silica nanoparticles (4-6% by volume) was chosen as biomimetic material.

This material swells (approximately 14% linear) in the presence of an aqueous physiological solution (when in an aqueous biological environment), raising up to 50- 30% by weight of water (depending on the nano-silicon load) of glass and soft rigid and rubber. The mechanical behavior of the proposed hybrid materials is comparable to that of the bone when vitreous and cartilage (ligaments) when it is rubber after swelling.

The bio-imitative properties of this very osteoconductive biomaterial have been used to develop a new bio-dental implant. The new concept is driven by the consideration that a bioactive interface between the implanted bone and the prosthetic device is generated when the material is able to stimulate the implant surrounding the bone in the physiological range of the strain for healthy bone remodeling and organized growth (50-3000).

The use of mechanically-compatible hybrid hydrogels as scaffolding materials is expected to increase prosthetic adaptation mechanisms that introduce active interfaces that improve the implant biomimetic while reproducing the biomechanical functions of cartilage and ligaments. The adaptive properties of biomimetic biomaterials (compatible with biomechanics and bioactive) are combined with new prostheses (AVERSA et al., 2016a; AVERSA et al., 2016b; AVERSA et al., 2016c; AVERSA et al., 2016d).

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5. CONCLUSIONS

It is necessary to develop new biomaterial technologies to produce scaffolds and bone substitutes that could play a fundamental role in bone regeneration. Bone forms must exhibit specific intrinsic characteristics to function as a replacement of the actual bone, respecting biological, mechanical and geometric constraints.

5.1. These features include:

- Biological Requirements - Computerized schemes should allow cell adhesion and homogeneous distribution, growth of regenerative tissue, and ensure the passage of nutrients and chemical signals. This achievement was achieved by controlling the scaffold porosity;
- Mechanical requirements - Schemes must maintain mechanical and hardness properties that allow osteoblastic colonies to have physiologically and bio-actively controlled deformations. This was done by correctly modifying the composition of the ceramic-polymer composition (in our case, 10% by volume amorphous nano-silica).

The combination of clinical observation of traditional implantation behavior will be used to validate the bio-fidelity of FEM models, while the comparison of in vitro simulated in vitro growth of osteoblastic colonies would allow us to explore many new ideas in the design, design, and fabrication of new structure nanostructured cellular cells with increased functionality and increased cellular interaction.

This proves to be particularly useful in the direct design and manufacture of the complex skeletal scaffold.

The new type of biomimetic implants can find applications in the knee, ankle, hip, shoulder and orthopedic column.

Another area of application of biomimetic schemes is surgical oncology to support and facilitate bone regeneration, resulting in massive losses due to primitive and metastatic tumor removal interventions.

The prosthetic system could allow for better functional recovery by

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promoting bone recreation to ensure good maintenance even if it will have an impact on the quality of life of the individual patient severely affected by the oncological pathology underlying it.

The biomimetic solution combining a metal support structure (to guarantee load resistance) an osteoinductive and biomechanically active bone (which promotes bone regeneration) finds replication in all surgical treatment areas involving bone removal and requires regenerative stimulation of the resected tissue. In fact, the concentrated bone marrow contains growth factors and mesenchymal stem cells that can specialize in bone cells, cartilage cells, and tendons.

A biomimetic/biomechanical approach has been developed in the design of a new dental material modified with hybrid ceramic hybrid material for biomechanical stimulation and potential mineralization and ossification of the scaffold.

Polymer (pHEMA) filled with nano silica particles (4-6% by volume) were chosen as biomimetic material. This material swells (approximately 14% linear) in the presence of an aqueous physiological solution (when in an aqueous biological environment), raising up to 50-30% by weight of water (depending on the nano- silicon load) of glass and soft rigid and rubber.

The mechanical behavior of the proposed hybrid materials is comparable to that of the bone when it is glassy and cartilage (ligaments) when it is rubber after swelling.

The bio-imitative properties of this very osteoconductive biomaterial have been used to develop a new bioactive dental implant.

The new concept is driven by the fact that the bioactive interface of the scaffold between the implanted bone and the prosthetic device is generated when the material is able to stimulate the implant surrounding the stem to reshape the healthy bone and increase growth (50-3000).

The use of mechanically-compatible hybrid hydrogels as scaffolding materials is expected to increase prosthetic adaptation mechanisms that introduce active interfaces that improve the implant biomimetic while reproducing the biomechanical functions of cartilage and ligaments; (Adaptive properties of

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biomimetic biomaterials biomechanically and bioactive compatible of biomass, combined with new prostheses).

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