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Osteoporosis in Microgravity Environments

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1. Introduction

All life on earth has evolved in, and via the adaption to, the presence of gravity. This includes humans who branched off from a distant ancestor about five to seven million years ago. On April 12, 1961, one such human---Yuri Gagarin of the Soviet Union---took off in Vostok 3KA for the first trip into outer space. Since then, numerous trips to the moon, the Skylab, and within the Space Shuttle have followed. With the recent completion of the International Space Station, the current focus is set on very long duration crewed missions to the station, the establishment of a potential lunar outpost, and possible exploration of Mars.

As more and more humans head to space for longer and longer periods of time---out of desire or necessity---significant challenges will be faced. The *technological* challenges will undoubtedly be met. The past fifty years have taught us that given adequate time and financial resources nearly any technological hurdle can be jumped. The *biological* challenges are far greater. As noted, all human life on earth has evolved via adaption to gravity and long-term exposure to microgravity takes its toll; especially on the musculoskeletal, cardiovascular, sensory-motor, and immune systems.

In this chapter, we will review the known effects of long-term microgravity on the skeletal system, examine what is as-yet unknown, and explore possible interventions that might be used to address these effects.

2. The impact of microgravity at the cellular level

2.1 Osteoporosis on earth

Osteoporosis occurring on earth in the presence of normal gravity is most often associated with aging and most significantly impacted by peak bone mass and the rate of bone loss thereafter. Peak bone mass is generally achieved while humans are in their early thirties and subsequent bone loss is impacted not only by aging and menopause (women), but by hereditary predispositions, exogenous factors (such as alcohol, smoking, inactivity, malnutrition, prescription medications, etc.), and disease states (such as endocrine disorders, renal disorders, rheumatologic disorders, etc.). Each of these causes results in a final common pathway leading to osteoporosis---an imbalance between bone formation and bone resorption. Fractures, primarily of the proximal femur ('hip'), vertebral bodies, and distal radius ('wrist') are significant risks and, as other chapters in this text have outlined, represent important causes of morbidity and potential mortality.

Osteoblast and osteoclast uncoupling is the primary source of this excessive resorption and biomechanical fragility of bone. If the cause can be determined, then reasonable solutions aimed at such uncoupling can be offered to address the problem. Bispohosphonates and, more primitively phosphate, can impede osteoclastic resorption. Calcium, Vitamin D, calcitonin, estrogen, exercise, smoking and alcohol restriction, and avoidance of particular medications can help halt bone loss. Fluoride (no longer used), parathytoid hormone, and aggressive exercise might result in bone mass gain.

2.2 Osteoporosis in microgravity

Osteoporosis occurring as a result of microgravity is, from the perspective of the organism down to the lowest biological level, *different* than that encountered on earth.

2.2.1 Cytoskeletal alterations

Microgravity appears to significantly alter the cellular cytoskeleton. Proper cytoskeletal structure allows intracellular proteins to participate in important functions such as mitosis, cell motility, intracellular transport, and organization of organelles. Actin filaments, intermediate filaments, and microtubules are the key elements and they serve as a highly organized dynamic scaffold on which intracellular processes take place.

In microgravity, cellular structure, intracellular organization, and micro-fluid dynamics are altered[1]. Disruption of normal biochemical and physiological processes follows. Clement and Slenzka[2] have demonstrated that the spatial relationships between cellular organelles and structures are abnormal. And He[3] and Crawford-Young[4] have demonstrated that cellular cytoskeletal and microfilament dynamics are anomalous and might well be the source. Thus DNA replication, RNA transcription, protein migration, and ionic and molecular transport are perturbed.

2.2.2 Mesenchymal stem cells

The impact of these intracellular changes is felt by mesenchymal stem cells (MSC). MSC---present in adult life in the periosteum of bones and within the bone marrow---differentiate into osteoblasts following appropriate signaling and presence within the proper mileau. Meyers[5], Yuge[6], Huang[7], and Pan[8] (in separate studies) have demonstrated via flow cytometry, transcriptional analyses, and proteomic analyses that MSCs ability to proliferate, to differentiate into osteoblasts, and to contribute to osteogenesis is inhibited by microgravity.

2.2.3 Osteoblasts

Osteoblasts are also directly compromised. Bucaro[9] has demonstrated findings that suggest that direct induction of osteoblast apoptosis occurs in microgravity. Apoptosis is differentiated from usual cell necrosis (where cells swell, burst and die) by characteristic intracellular changes including nuclear condensation and shrinkage and cytoplasmic vacuolization. Observed osteoblastic apoptosis likely results from cytoskeletal changes.

Additionally, Colleran[10] has noted that the cephallic fluid shift experienced by humans in microgravity might alter interstitial fluid pressures and flows and, given that osteoblasts survive somewhat tenuously in low flow areas, these shifts might result in cell functional compromise or death.

3. The impact of microgravity at the systemic level

Systemically, microgravity induces osteoporosis via the above noted unique cellular changes *coupled* with an environment of nearly non-existent mechanical stresses where normal weight-bearing and the normal response of bone to proliferate accordingly (Wolff's Law) is altered. And this alteration differs than, say, that seen with immobilization. While patients placed in body casts and on bed rest (fully non-weightbearing) will suffer from osteoporortic changes, the amount of calcified bony tissue lost over three months is generally about 3%, tends to then level off at about three months (no further loss), and tends to be reversed with resumption of weight-bearing. In microgravity, the loss occurs at four times the rate, does not appear to level off, and appears to be much less reversible. Thus, the one-year trip to Mars is estimated to potentially result in a (devastating) greater than 25% reduction of bone mass. And this is in astronauts; predominantly male, at an age where their bone mass is at peak levels, exposed to no exogenous factors (smoking, excessive alcohol, etc.), in prime physical condition, and with no underlying disease states.

Simply, the combination of altered cellular form and function coupled with differences in bony response to microgravity systemically means that this form of osteoporosis bears relatively little relation to that seen on earth and that astronauts experience early, aggressive, continual bone loss. Predictably, systemic markers of bone resorption are greatly increased, while markers of bone formation are decreased[11] to levels rarely seen in on-earth conditions. And, importantly, it is unclear whether these changes are fully reversible upon return to earth and 'normal' gravity conditions.

4. Bone health and present day human spaceflight

Since the earliest days of human spaceflight, physiologists and NASA flight surgeons recognized the importance of exercise to maintain musculoskeletal and cardiovascular health. Owing to prolonged exposure to microgravity, Astronaut crews returning from America's first space station, Skylab, were too weak to stand upon return to earth. Exercise equipment thus became a requirement for all long duration space missions. A series of devices, including treadmills, stationary bicycles, rowing ergometers, simple resistive exercise systems and complex, reconfigurable "weight machines" have evolved in the years since, both in the Soviet-turned-Russian space program and now in the US-led International Space Station (ISS) program.

Exercise devices designed to maintain cardiovascular fitness in the absence of gravity proved to be a more straightforward engineering goal: movement against a friction wheel can easily challenge the cardiopulmonary system. Providing resistive exercise challenge to the postural musculoskeletal system of sufficient intensity and quality has only recently been accomplished aboard the ISS. The Advanced Resistive Exercise Device (ARED) uses pistons to provide smooth exercise loads, and is highly reconfigurable for a wide array of concentric and eccentric exercises.

The world record duration in space is held by Dr. Valeri Polyakov, who spent 437 consecutive days in microgravity, landing in 1995. During his endurance mission he was required to exercise up to four hours a day. Human spaceflight is very costly, but is obviously undertaken to accomplish important scientific goals in life sciences, material science, fluid and combustion physics, global environmental monitoring and many other disciplines. Even with the improved exercise countermeasures and added knowledge of

today, the overhead of spending up to two hours each and every day in space for the sole purpose of exercise is problematic.
ISS crewmembers actively work with strength and conditioning coaches throughout their preflight training. Using exercise monitoring hardware aboard ISS, these same coaches perform inflight assessments of the crew's conditioning while they are in space, and make exercise prescription modifications from Mission Control Houston, as required. Additionally, they oversee the crew's postflight physical rehabilitation, a process which may take several months to restore bone density to critical areas such as the hip and lumbar vertebral bodies.
Armed with an understanding of the whole body, cellular and subcellular processes involved in bone density maintenance in altered gravitational fields, more effective and efficient means to preserve musculoskeletal health is necessary to send humans beyond short stays aboard the ISS: Lunar outposts and expeditions to Mars are even more committing endeavors, and warrant substantial attention.

5. Future directions for research

Despite a reasonable foundation of information, much work is needed to further delineate the impact of microgravity on bones at the cellular and systemic levels. Clearly the best strategy is to conduct experimental in-vivo human studies in space, but limited access to spaceflights and limited time during flight available to dedicate to these studies renders extensive (but necessary) study unachievable[1]. Accordingly, microgravity simulation has been the primary source of basic biological scientific information including most of what has been discussed thus far in this chapter.
On the celular level, simulation can be carried out within the rotating-wall vessel (RWV); a NASA-designed tissue culture bioreactor which simulates microgravity[1]. The bioreactor rotates horizontally such that, at an ideal speed, the contents achieve relative suspension simulating microgravity via dynamic equalibrium of forces---the contained cells / tissues remain in a state of long-term, suspended free-fall. The cells / tissues retain viability by being contained along with cell-specific growth media and oxygenation via active or passive diffusion provided by a silicon rubber membrane. To date however, relatively few studies have been carried out and there is significant need for further study on the cellular level as this level may be the key to differences relative to earthly osteoporosis. Additionally, comparison with studies performed in space will be required to validate the model and to ensure that changes noted are not unique to the system itself---in-vitro cellular behavior does not always mirror real life.
On the system / organism level, research has focused on animal models; most commonly hind-limb unloading and head-down bed rest (which has also been used in human volunteer subjects)[1]. While such models provide some insight into rapid bone loss, they are not fully satisfactory given that they fail to incite the noted cellular changes associated with microgravity and gravitational forces still compress bodily tissues whereas, in true microgravity, there is negative pressure experienced by tissues. It is clear that better models need to be developed.

6. Potential future options for treatment and prevention

Current options for the prevention and treatment of osteoporosis have proven far more successful on earth than in microgravity and this is likely commensurate with the above

noted cellular anomalies encountered. Aggressive exercise by astronauts---recommended at two hours per day of heavy resistance work---has made an impact; however, freeing up time for such activities is difficult given the operational needs during missions and, as space flight expands generally, the baseline cardiovascular capabilities of travelers will be more limited. Additionally, the aforementioned cellular changes render supplements (Calcium, vitamin D, etc.), medications (bisphosphonates, etc.) and hormones (testosterone, etc.) significantly less effective in astronauts despite having a minor effect in microgravity animal models.

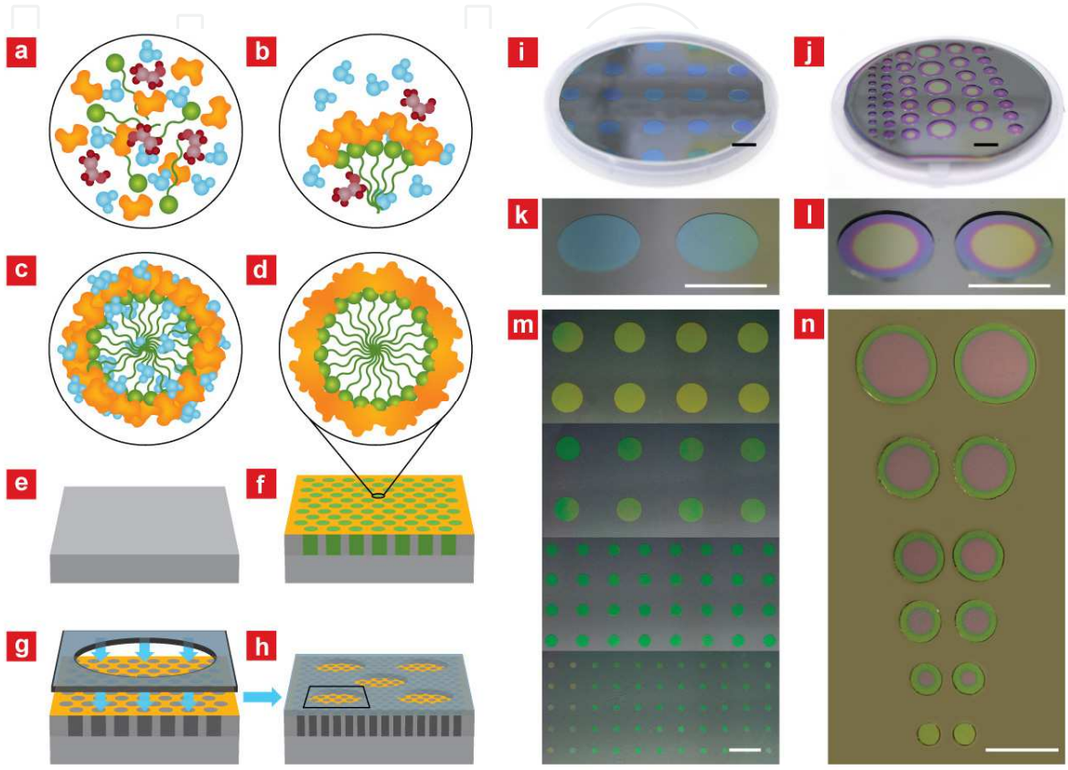
6.1 Diagnostic platforms

The identification of new diagnostic or prognostic biomarkers has been gaining attention in the field of bone disease research leading to significant benefits in terms of efficient and timely treatment. Clearly novel strategies will need to be developed, and directed both at the molecular / cellular and bony systemic levels, and will need to be long lasting and simple to administer. In our minds, the ideal platform for the development of such novel strategies will rest upon nanotechnology. The size of nanomaterials mirrors that of most biological molecules and structures allowing size-matched communication and intervention important in diagnostics and therapeutics at the sub-cellular level and felt to be the source of bone cell dysfunction in microgravity.

In this context, particular emphasis is placed on study of circulating proteome. The proteome represent the functional picture of the state of the cells because it constantly changes through its biochemical interactions with the genome and the environment. Protein turnovers and tissue microenvironment create a rich and heterogenic circulating mixture of protein fragments (low molecular weight peptidome, LMWP) that reflects both physiological and pathological processes. Despite its potential in clinical applications, profiling of the LMWP has proven to be a significant technical challenge because of the extremely high dynamic range of protein concentrations in blood and body fluids. Development of technologies that enable controlled fabrication of structure with nanoscale dimension can address the issues of the intrinsic complexity of the circulating low molecular weight peptidome [12,13]. Our group has developed diagnostic nanochannel-based lab-on-a-chip technologies [Fig 1] that can allow for the detection of the earliest signs of disease, including osteoporosis, using penny-sized discs (satisfying the need for space preservation during space flight). This device is a size-exclusion method based on mesoporous silica thin film chips able to rapidly fractionate, and selectively enrich and protect peptides and proteins from enzymatic degradation. The mesoporous silica chip were produced by the evaporation-induced self –assembly procedure under acidic conditions using triblock copolymers as structural templates [14,15].

Physical properties of mesoporous silica such as pore dimension, pore texture, and chemical surface properties such as charge and further functionalization with selective ligands can be easily controlled and tuned to enhance the ability to detect traces of molecules. The ability to fabricate nanoscale devices and materials with a high degree of precision and accuracy, in combination with the recent advances in mass spectrometry, resulted in a powerful proteomic nanoscale platform for early disease diagnosis [16]. These lab-on-a-chip based diagnostic technologies can be either used as external devices or be implanted in the body of the astronaut. Implantable chips can feature molecularly driven sensors able to measure vital signs and readily respond to specific variation by releasing counteracting molecules. Diagnostics based on readily accessible body fluids can be also used to monitor in real time

the efficacy of therapeutic interventions. In their most complex configuration these implantable devices can be considered as artificial glands that sense the status of the body and adjust to it trying to bring back homeostasis. Nanotechnology based diagnostics offer higher detection capabilities due to the reduction of the size of the sensors, the increase of their sensitivity, the absence of non-specific reactions, and the multiplexing of the multi-scale detectors that allow a wide range of intensities of the signal to be measured.



a-h, Schematic evolution of the chemical composition of the coating solution during the production of a mesoporous silica film. a, Fresh coating solution; b, Formation of micelles; c, Evaporation induced self assembly during spin-coating process; d, Zoomed in view of a pore after aging at elevated temperature. e, Bulk silicon wafer surface; f, Mesoporous silica film on a bulk silicon wafer. e-f, Cross-section of GX6 chip by SEM and TEM imaging respectively (scale bar is 500nm). i-n, images of the different chip surfaces and of the different masks that define the spotting areas.

Fig. 1. Production and assembly of MSC for proteomic applications

6.2 Delivery systems

We developed novel silicon-based theranostic nanoparticles [17-19] that have been used to achieve long-term, controlled, and targeted release of proteins and drugs that help halting or reversing osteoporosis. Among the molecules tested bone morphogenetic proteins (BMPs---which are differentiation factors that facilitate the transition of mesenchymal stem cells to osteoblasts thereby encouraging bone formation) and bisphosphonates (which inhibit osteoclasts mediated bone resorption). The finely-tuned, extended, local delivery allowed by the use of these particles means that a single treatment can be administered pre-flight with effects felt for months on end (no need to 're-dose') and might prove to prevent or treat osteoporosis of microgravity. Nanoporous silica and PLGA composites are capable of

releasing molecules in a burst or steady fashion over the course of days, weeks, or even months. These systems can also be tuned to release their payload in response to environmental stimuli (pH, temperature, blood concentrations, exposure to radiation, bone degeneration, etc.). The local delivery of antibiotics, dexamethasone, and growth factors (BMP-2) to the bone defect areas by PLGA/pSi microspheres reduced inflammation and stimulated new bone formation whilke simultaneously fighting bacterial growth. A wide variety of therapeutic and imaging agents have been successfully loaded into and released from pSi particles such as steroids [21], hormones [22], proteins[23], cancer drugs [24], or even secondary drug delivery vehicles including iron oxide nanoparticles [25], quantum dots, liposomes [26] and carbon nanotubes loaded with therapeutic drugs[18,27] to the diseased areas. In order to achieve the level of control on the release dynamics, it is possible to tailor both the pore size of the pSi during particles' fabrication or vary polymer type, molecular weight and density. Finally, the overall size of the polymer/pSi composites can also be tuned from nano level to micro level to suit certain applications by changing the polymer concentration, surfactant concentration, or the stirring speed. This hybrid system not only can reduce or abolish burst release, and prolong release kinetics, but also protect biomolecules from denaturation both during the drug loading process and while implanted in vivo. These particles have been successfully tested in different orthopedic tissue engineering applications in small and large animal models of bone fracture repair (manuscripts in preparation).

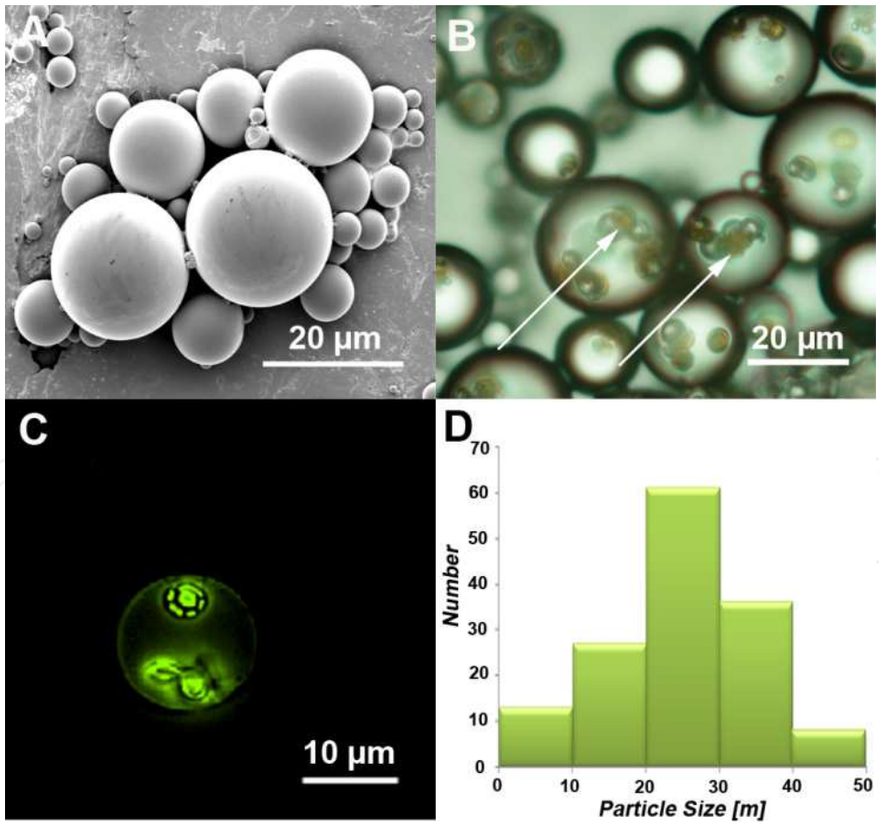


Fig. 2. Scanning electron microscopy (SEM) images of pSi particles reveals (A) uniform shape and size of particles, (B) the pore structure on the surface of the particles, and the (C) front and (D) rear surfaces of the particles.

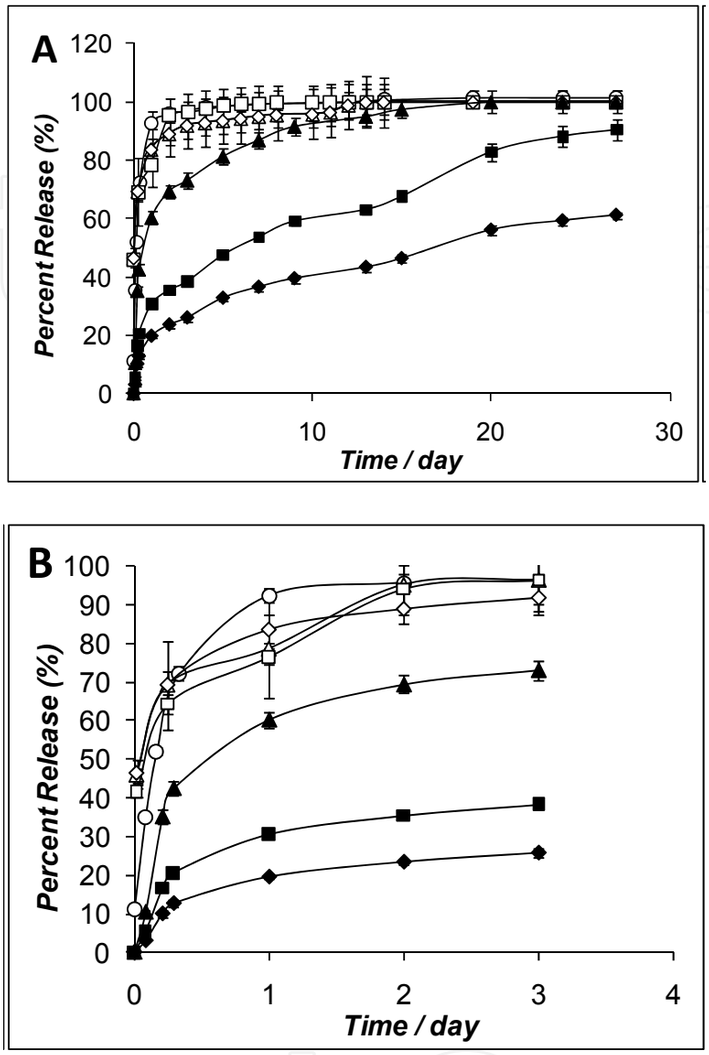


Fig. 3. Release profiles of FITC-BSA from various examined PLGA/pSi microsphere formulations. (A) Total FITC-BSA released over 27 days, (B) first three day release.

6.3 Injectable materials

Beyond these diagnostic and drug-delivery applications, our group has also developed injectable gels that employ nanotechnologies to deliver mesenchymal stem cells, platelet rich plasma, and osteogeneic factors directly to areas of bony weakness. Thus, astronauts identified to have focal osteoporosis of, say, the proximal femur, might be treated by simple focal injection affording the in-vivo, in-situ rapid regeneration of lost bony mass.

These composites have proved their osteogenic capacity in vitro and through in vivo subcutaneous implants where ectopic bone was formed. The use of bio-porogens synthesized from natural and biodegradable materials, encourages bone formation and vascularization in vivo. These porogens particles house and release MSC, recruit endogenous cells and create extracellular matrix, synergistically promoting bone formation

[28]. They also exhibit tremendous viability of MSC after cryo-preservation, allowing for long-term storage of prepared bio-porogens for immediate "on-demand" use in the clinic. Previously, we found that MSC isolated from compact bone (CB) tissue were more frequent in the total cell population and of greater colony-forming and tri-lineage differentiation potential than MSC in bone marrow (BM) (Figure 4).

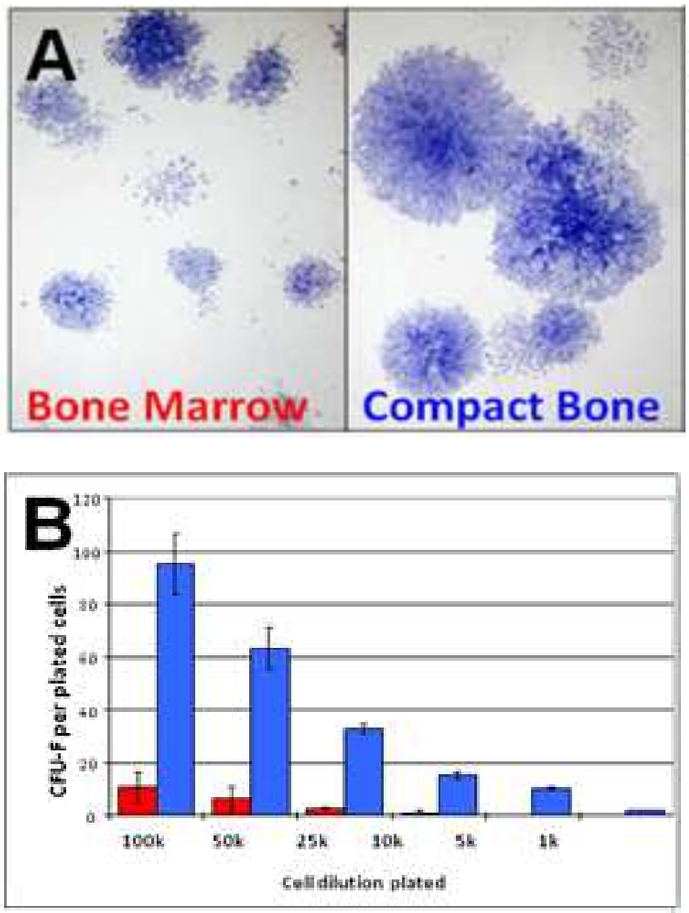


Fig. 4. MSC from compact bone (CB) produce larger and more defined colonies than those from bone marrow (BM) (A). The incidence of MSC from bulk cell populations is also nearly 10x higher in CB than BM (B).

All these biomaterials were based on the unique combination of I) nanostructured biomaterials able to mimic the extracellular matrices of either bone or cartilage with II) chemical and biochemical cues able to direct, control and preserve the phenotypes of both osteoblasts in their histological compartments. These biomaterials are made available as injectable hydrogel formulations thus reducing surgical invasiveness and improving the accuracy of the delivery to the targeted anatomical sites. Injectable composite hydrogels/pastes can be used for the spinal regions weakened by OP, with appropriate biomimetic and biomechanical characteristics.

These biomaterials can be functionalized and/or doped with chemical (e.g. strontium ions, oxygen transporters/scavangers) and biochemical (e.g. bioactive/biodocking peptides,

genes) agents able to control cell phenotype and activity. Hydrogel formulations to be examined include collagen, gelatin, alginate, self-assembling peptides, or combinations thereof. The nano-features include peptides that bind to integral growth factors such as BMP-2 and VEGF and PRP. The scaffolds may be co-implanted with mesenchymal stem cells obtained from bone marrow and adipose aspirates. Finally, we have developed ways to reinforce biocompatible polymers with nanoparticles / nanowires that greatly increase their strength allowing for the replacement of bulky, heavy metallic devices currently used for fracture repair---the light-weight, injectable polymers ideal for transport on space flights and use for the repair of osteoporotic fractures once they occur.

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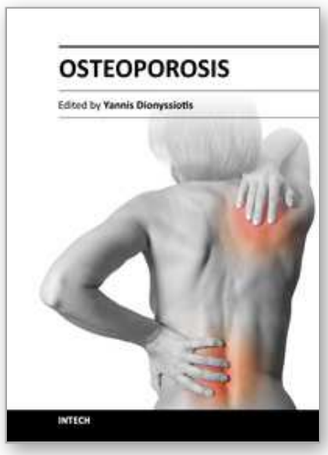

Osteoporosis

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Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral density measurements and, additionally, geometrical and mechanical properties of bone. New bone indices have been developed from biochemical and hormonal measurements in order to investigate bone metabolism. Although it is clear that drugs are an essential element of the therapy, beyond medication there are other interventions in the management of the disease. Prevention of osteoporosis starts in young ages and continues during aging in order to prevent fractures associated with impaired quality of life, physical decline, mortality, and high cost for the health system. A number of different specialties are holding the scientific knowledge in osteoporosis. For this reason, we have collected papers from scientific departments all over the world for this book. The book includes up-to-date information about basics of bones, epidemiological data, diagnosis and assessment of osteoporosis, secondary osteoporosis, pediatric issues, prevention and treatment strategies, and research papers from osteoporotic fields.

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