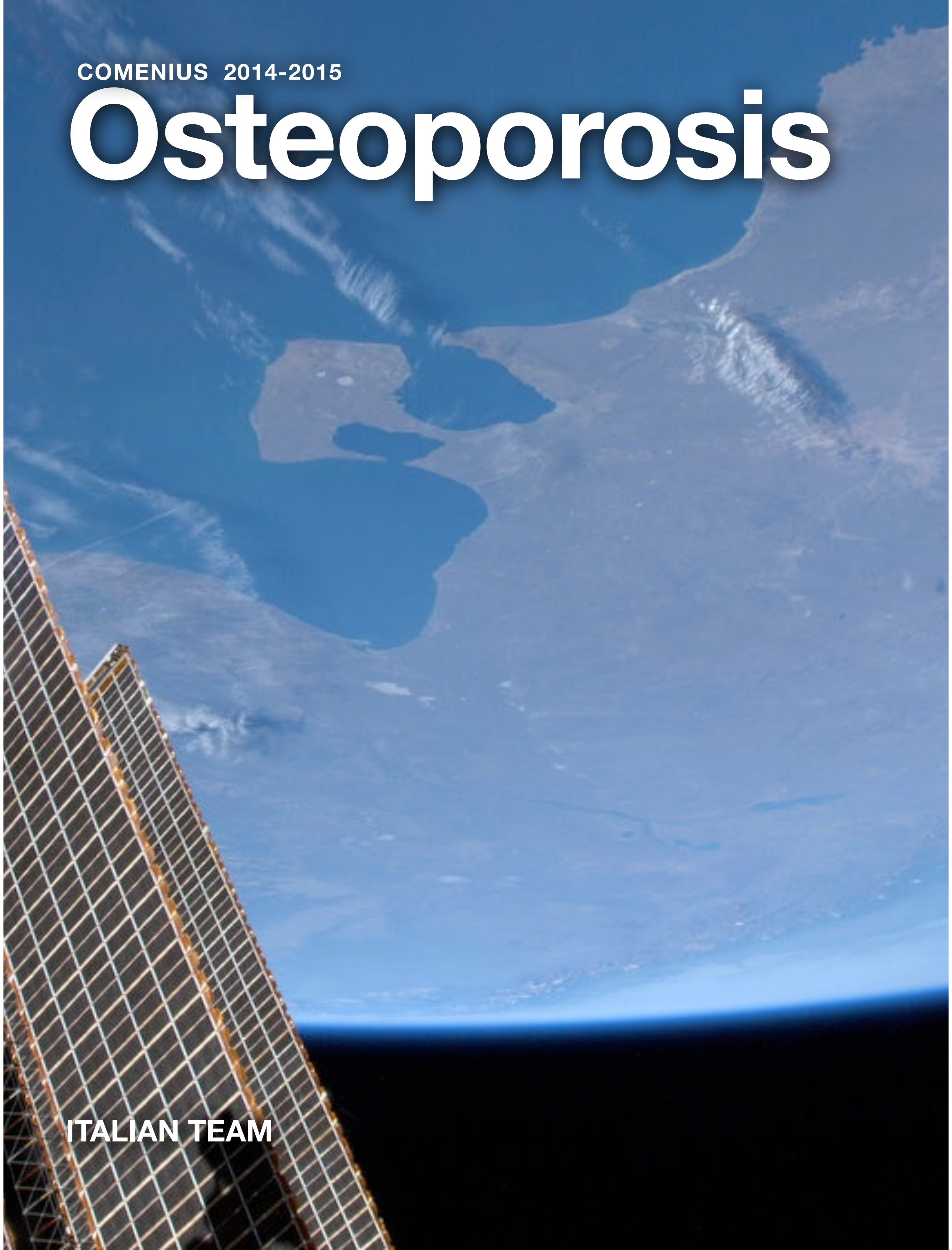
COMENIUS 2014-2015

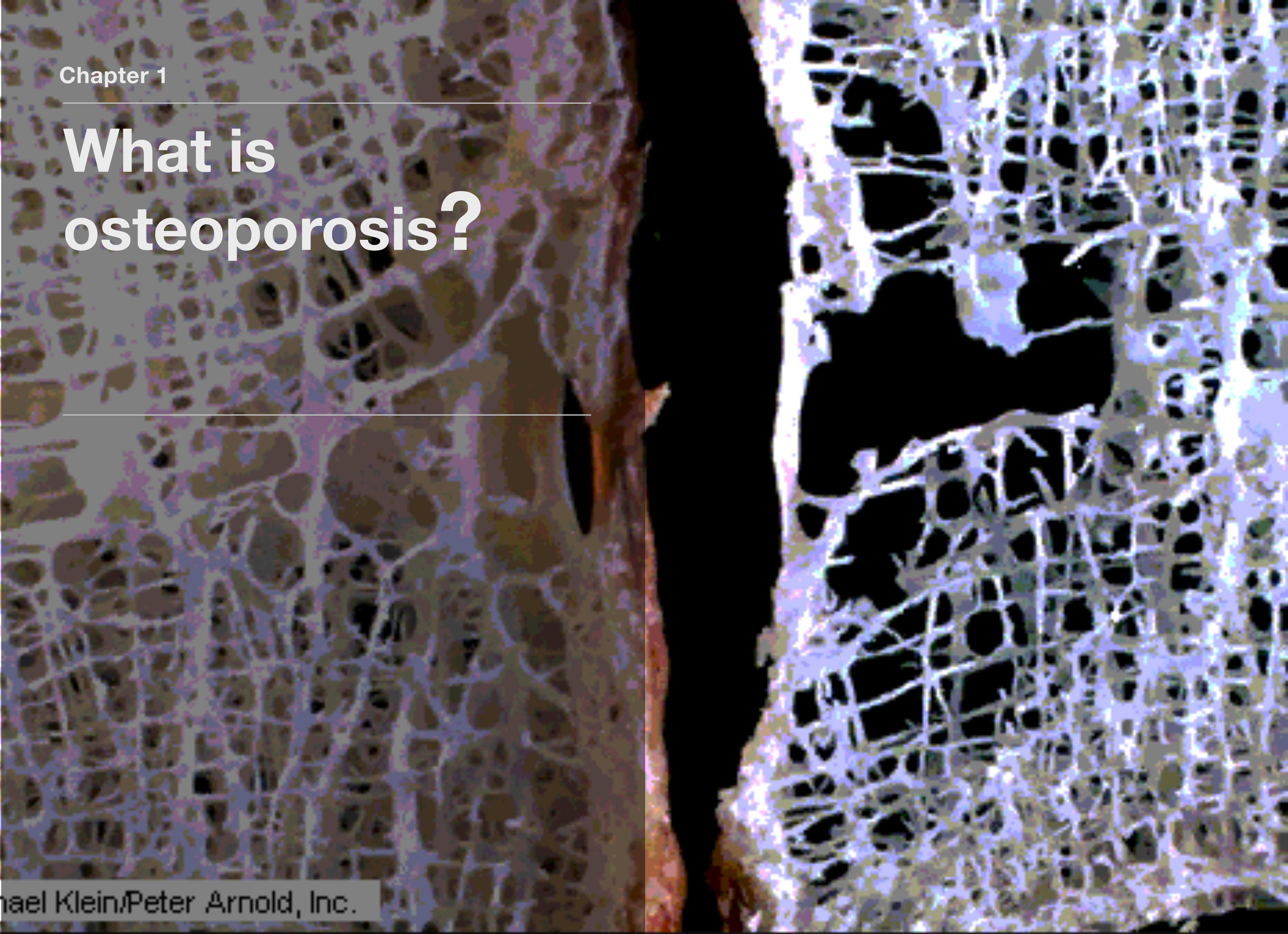
Osteoporosis



ITALIAN TEAM

Chapter 1

What is osteoporosis?



What is Osteoporosis?

Osteoporosis is a disease of the bones. It happens when you lose too much bone, make too little bone or both. As a result, your bones become weak and may break from a minor fall or, in serious cases, even fromsimple actions, like sneezing or bumping into furniture.

Osteoporosis means "porous bone." If you look at healthy bone under a microscope, you will see that parts of it look like a honeycomb. If you have osteoporosis, the holes and spaces in the honeycomb are much bigger than they are in healthy bone. This means your bones have lost density or mass and that the structure of your bone tissue has become abnormal. As your bones become less dense, they also become weaker and more likely to break. If you're age 50 or older and have broken a bone, talk to your doctor or other healthcare provider and ask if you should have a bone density test.

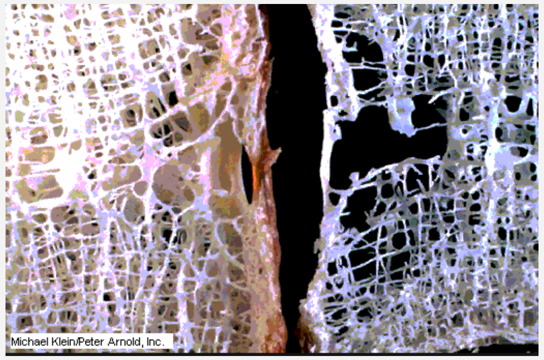
Studies suggest that approximately one in two women and up to one in four men age 50 and older will break a bone due to osteoporosis.

Osteoporosis is Serious

Breaking a bone is a serious complication of osteoporosis, especially when you're older. Broken bones due to osteoporosis are most likely to occur in the hip, spine and wrist, but other bones can break too. Broken bones can cause severe pain that may not go away. Osteoporosis also causes some people to lose height. When osteoporosis causes the bones of the spine, called vertebrae, to break or collapse, it affects your posture and causes you to become stooped or hunched.

Osteoporosis may even keep you from getting around easily and doing the things you enjoy, which may bring feelings of isolation or depression. It can also lead to other health problems. Twenty percent of seniors who break a hip die within one year from problems related to the broken bone itself or surgery to repair it. Many of those who survive need long-term nursing home care. .Osteoporosis is often called a silent disease because you can't feel your bones getting weaker. Breaking a bone is often the first sign that you have osteoporosis or you may notice that you are getting shorter or your upper back is curving forward. If you are experiencing height loss or your spine is curving, be sure to talk to your doctor or another healthcare professional right away as the disease may be already be advanced.

Immagine 1.1 Bone



left normal bone -right osteoporosis bone

Osteoporosis in microgravity

The most obvious and most immediately noticeable of gravity in our daily lives is the force of attraction that keeps us firmly on the surface of the Earth and that we experience as feeling of weight. All the laws that govern the movement are closely dependent on the gravitational field in which the motion itself is fulfilled: the fall of any body, the motion of an arrow, a bullet or all of the planets are governed by the laws of gravity. Gravity is also responsible for numerous physical phenomena, whose relationship with it is less intuitive, such as the buoyancy (or floating). The force of gravity also affects the human body, governing the capillary blood vessels, laminar flows, osmosis and many other processes, but its most obvious impact is certainly on the apparatus musculoskeletal system.

Microgravity Effects

Movement of fluid in the body
Effects on the heart and blood pressure
Vestibular problems:
Endocrine function:
Change in the composition of blood
Metabolism and tropism of the bone and muscle tissue
(http://www.youtube.com/watch?v=Jsa5Etrx3fs)

Osteoporosis in Microgravity Environments

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 andsubsequent bone loss is impacted not only by aging and menopause (women), but byhereditary predispositions, exogenous factors (such as alcohol, smoking, inactivity, malnutrition, prescription medications, etc.), and disease states (such as endocrinedisorders, 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.

Osteoporosis

Osteoclasts and osteoblasts are both kinds of bone cell. Their difference lies with their functions.

Osteoblasts are the kind of bone cells responsible for the bone formation. It is also responsible for the mineralization of the bone structure.

Osteoclasts are type of bone cells that removes bone tissue by removing the mineral matrix of the bone and dissolving the collagen part of the bone. This process is also called as bone resorption where in the bone is broken down and the mineral, for example calcium, is transferred to the blood.

Osteblasts and osteclasts regulate the amount of bone tissue. Osteoblasts forms the bone while osteoclasts reabsorbs.

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 particularmedications 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 arealtered. Distruption of normal biochemical and physiological processes follows.

Clement and Slenzka have demonstrated that the spatial relationships between cellular organelles and structures are abnormal. And He and Crawford-Young] have demonstrated that

cellular cytoskeletal and microfilament dynamics are anomalous and might well be thesource.

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,Yuge, Huang], and Pan[] (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 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 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.

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Osteoporosis in Microgravity Environments

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'sLaw) 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 osteopororttic changes, the amount of calcified bony tissue lost over three months isgenerally about 3%, tends to then level off at about three months (no further loss), and tendsto 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 fromAmerica'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 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 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 flightexpands 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.

Return Parmitano asronaute

Filmato 1.1 Running in space

Metabolism and tissue tropism bone and muscle

It is certainly one of the most important aspects of long-duration flights: the bone, no longer stressed by the load, undergoes increased catabolism, and lose 1 to 2% of the total calcium after a few weeks of microgravity resulting in osteoporosis is not ex use (similar to that by immobilization).

The loss of calcium (but not phosphorus) occurs only in bones that are normally carriers, essentially on the trabecular portion and with different recovery speed.

Serum calcium and "calciuria" increase and consequently the secretion of parathyroid hormone and the transformation of 2-5 idrossivitarnina D in 1.25 dihydroxycholecalciferol decrease which is an important regulator of calcium absorption in the gastrointestinal tract, as a consequence the intestinal transport of calcium is obstacolated and the faecal elimination increases.

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The results vary considerably from flight to flight and from person to person depending on the characteristics of the flight and on the physical exercises .

Calcitonin and the enrichment of the diet with Ca and P did not prove to be useful, unlike the diphosphonate in high doses (20 mg / kg / day), fluoride stagnoso and clodronate. Unfortunatelly the last two are poorly tolerated by

The striated muscle tissue undergoes catabolic phenomena (urinary excretion of N2, K, creatinine, amino acids and atrophy increase).

The atrophy and hypotonia are essentially the antigravity muscles (legs, neck, spine)

They need a couple of months to restore a normal function

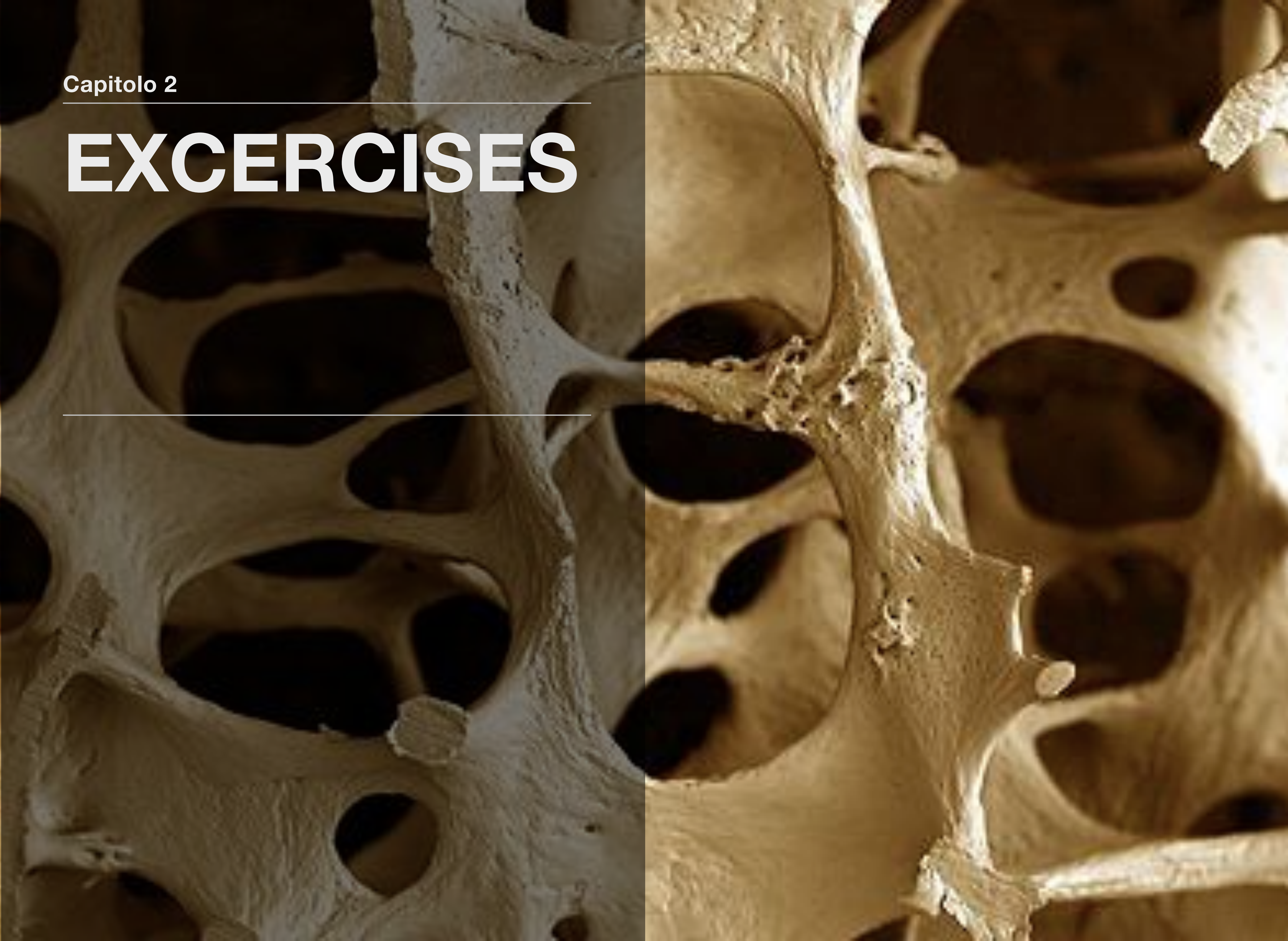
ISS astronauts daily perform exercises (2 hours) with special treadmills and bike exercises to cope with the problems mentioned above.

man.

http://www.esa.int/Our_Activities/Technology/Space_for_health/Musculo-skeletal_system_Bone_and_Muscle_loss

Capitolo 2

EXCERCISES



Interattivo 2.1 osteoporosis

Interattivo 2.2 metabolism