review article
received: 2010-04-09

UDC: 616.71:001.891

FROM SPACE FLIGHTS TO OSTEOPOROSIS

Giancarlo BILANCIO[1], Cinzia LOMBARDI[1], Massimo CIRILLO[1], Rado PIŠOT[2], Jörn RITTWEGER[3], Natale G. DE SANTO[4]

[1] University of Salerno, Department of Medicine, Baronissi, Italy
[2] University of Primorska, Science and Research Centre
Institute for Kinesiology Research, Koper, Slovenja
[3] DLR, Cologne, Germany
[4] Second University of Naples, Department of Medicine, Naples, Italy

Corresponding author:
Giancarlo BILANCIO
University of Salerno, Department of Medicine, Via Salvador Allende,
84081 Baronissi, Italy.
e-mail: giancarlo.bilancio@gmail.com

ABSTRACT

Space missions (microgravity) alter the balance between bone formation/resorption and induce bone loss. This effect represents a major limiting step in the realization of long-term space missions. A similar picture is induced by prolonged immobilization in bed (bed rest). The Osteoporosis and Muscular Atrophy project (OSMA) was a research program sponsored by the Italian Space Agency which included 35-day bed rest experiments in healthy young men. Anthropometric data of these experiments indicated the expected bone mass reduction in some segments of the leg and body mass redistribution from non-fat mass to fat mass. According to the current view, the bone mass reduction due to microgravity/bed rest is associated with the release of calcium from the bone into the bloodstream (hypercalcemia) which, in turn, lowers the secretion of parathyroid hormone and increases urinary calcium excretion. One of the main unsolved issues in this view is that hypercalcemia is mild and transient during microgravity/bed rest whereas parathyroid hormone reduction is sustained. Bone mass reduction could also be dependent on parathyroid hormone reduction as this hormone affects both formation and resorption of bone tissue. The research on the mechanisms underlying bone mass loss during microgravity/bed rest could be of help, not only to space medicine, but hopefully also for prevention and control of bone ageing and osteoporosis.

Keywords*: bed rest, space mission, microgravity, bone metabolism*

Giancarlo BILANCIO, Cinzia LOMBARDI, Massimo CIRILLO, Rado PIŠOT, Jörn RITTWEGER, Natale G. DE SANTO:
FROM SPACE FLIGHTS TO OSTEOPOROSIS, 27–34

OD POLETOV V VESOLJE DO OSTEOPOROZE

IZVLEČEK

Misije v vesolje (mikrogravitacija) spremenijo ravnotežje med kostno formacijo/resorpcijo in povzročajo izgubo kostne gostote. Ta učinek predstavlja zelo omejujoč korak v realizaciji dolgotrajnih misij v vesolje. Podoben rezultat povzroči daljša imobilizacija v postelji (t. i. „bed rest"). Projekt OSMA ali Osteoporoza in mišična atrofija je bil raziskovalni program, ki ga je sponzorirala Italijanska vesoljska agencija in je vključeval poskuse 35-dnevnega ležanja v postelji na mladih zdravih moških. Antropometrični podatki teh poskusov so pokazali pričakovano zmanjšanje kostne gostote na nekaterih predelih noge ter tudi prerazporeditev telesne mase s področja, kjer ni bilo maščob, na področje z maščobami. Glede na trenutne vidike se zmanjšanje telesne mase, ki ga povzroča mikrogravitacija/ležanje v postelji, povezuje z izločanjem kalcija iz kosti v krvni obtok (hiperkalcemija), kar pa zmanjšuje izločanje obščitničnih hormonov in povišuje izločanje kalcija z uriniranjem. Eno izmed glavnih nerešenih vprašanj ostaja, zakaj se hiperkalcemija med mikrogravitacijo/ležanjem v postelji pojavlja v blagi in začasni obliki, medtem ko je zmanjšanje obščitničnega hormona trajno. Zmanjšanje kostne gostote bi lahko bilo odvisno od zmanjšanja obščitničnega hormona, saj le ta vpliva na formacijo in resorpcijo kostnega tkiva. Raziskave o mehanizmih, ki delujejo v času izgube kostne gostote oziroma mikrogravitacije/ležanja v postelji, bi lahko bile v pomoč tako vesoljski medicini ter mogoče tudi preprečevanju in nadzoru staranja kosti in osteoporoze.

Ključne besede: *»bed rest«, misije v vesolje, mikrogravitacija, kostna presnova*

INTRODUCTION

The normal metabolism of the bone is maintained thanks to the equilibrium between formation/mineralization of new tissue and resorption of pre-existing tissue. In healthy children, teenagers, and young adults, this equilibrium is shifted toward a positive balance during growth and maturation (formation/mineralization > resorption). This equilibrium progressively shifts with ageing toward a negative balance in middle and older ages leading to a progressive loss of bone mass (formation/mineralization < resorption) (Firestein et al., 2008). Space missions alter this equilibrium and induce a substantial reduction in bone mass which is progressively more severe with the increasing duration of a mission (Smith & Heer, 2002). At present, this effect represents a major limiting step in the realization of long-term space missions. It is generally accepted that the determinant of the changes in bone metabolism during space missions are due to the lack of gravity (microgravity) and in particular due to the reduction of the gravitational load on the bone (Le Blanc, Spector, Evans & Sibonga, 2007). The bone mass reduction induced by microgravity is characterized by the loss not only of the organic component of the bone but also of its mineral content. The mineral component of the bone is hydroxyapatite, a salt which contains calcium (Ca) and phosphorus (P). Thus, a reduction in bone mass and in bone mineralization implies the inevitable release of an excess of Ca and P from the bone. As far as Ca, this excess is detectable in the urine as space missions are usually associated also with a substantial increase in urinary Ca excretion. The prolonged immobilization in bed (bed rest) is used as a model to simulate the effects of microgravity on the bone because it induces the loss of bone mass in some segments of the skeleton together with some changes in the bone metabolism with the inclusion of an increase in urinary Ca. The existence of high urinary Ca during immobilization has actually been well known in nephrology for at least 30 years (Stewart, Adler, Byers, Segre & Broadus, 1982).

THE BED REST OF THE OSMA PROJECT

The OSMA project is a multicentre program of investigation on Osteoporosis and Muscular Atrophy sponsored by the Italian Space Agency. The project included the realization of two different bed rest experiments which consisted of the continuous immobilization in bed of 10 healthy young men for a period of 35 days. The bed rest period was preceded by a week for adaptation and pre-bed rest measurements and was followed by a week for post-bed rest measurements and recovery. In these three different periods, the protocol included the collection of blood and urine samples together with measurements of anthropometry, medical parameters, and bone densitometry (Biolo et al., 2008). The design aimed to analyze the time-course of the changes induced by bed rest and, in particular, to assess if the prevailing mechanisms responsible for or associated with the reduction in bone mass vary (or not) from the early phases to the later phases of immobilization.

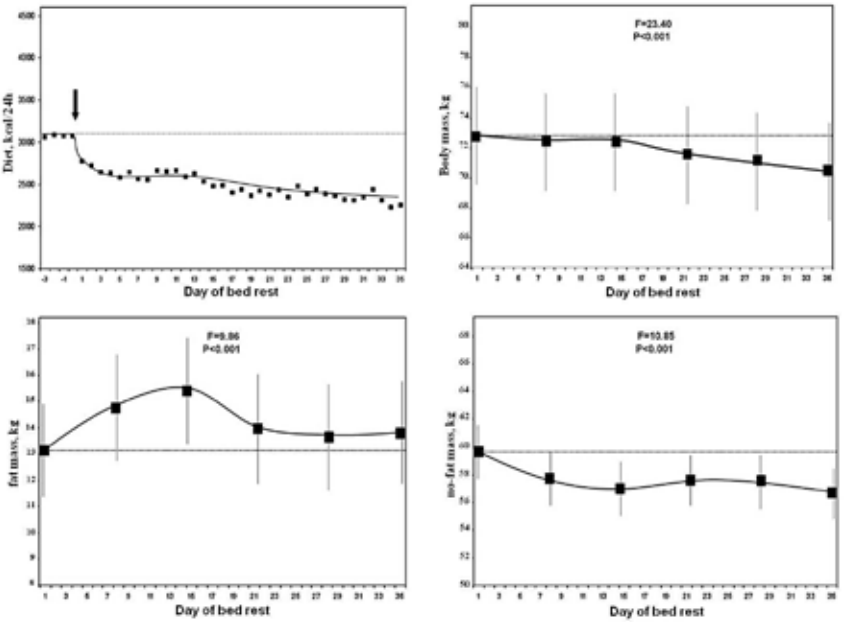

Figure 1: Descriptive data of changes in calorie intake, body mass, fat mass, and non-fat mass during first bed-rest experiment of the OSMA Project (sponsor Italian Space Agency).

Figure 1 shows calorie intake and anthropometric indices during the first experiment. Starting from the bed rest initiation, the study protocol included a reduction in calorie intake to prevent an increase in body mass and fat mass secondary to immobilization, hence, a reduction in the calorie expenditure. Body mass did not increase throughout bed rest and actually decreased in the last weeks. Despite of the lack of a body mass increase, fat mass increased indicating a re-distribution of the weight from the muscular mass to the fat mass compartment. This change was obviously due to immobilization and could not be prevented by a simple restriction of caloric intake. Figure 1 also shows that caloric intake progressively declined after day 15 of bed rest, a decline which was not designed by the protocol and reflected an uncontrolled reduction in appetite due to bed rest.

A previous paper reported the effects of this first experiment on bone densitometry (Rittweger et al., 2009). Briefly, bone mass reduction was not uniform across all segments of the leg skeleton and tended to be greater in the patella and in the tibia epiphyses (Rittweger et al., 2009). Altogether, the data confirmed that a bed rest intervention induces a negative balance mainly in the lean components of the body with inclusion of some leg segments of the skeleton. At present, there is no definite mechanism to explain these differential effects of bed rest.

BONE MASS LOSS DUE TO MICROGRAVITY / BEDREST: THE PRESENT VIEW

As stated above, one of the aims of the OSMA project was to assess if the prevailing mechanisms responsible for or associated with bone mass reduction vary (or not) from early phases to later phases of bed rest taken as a model of microgravity on Earth. In this area of research, the current view is that the loss of bone mass due to bone unloading is mainly explained by an acceleration of bone resorption (Lueken, Arnaud, Taylor & Baylink, 1993). The dissociation of this event from a compensatory increase in bone formation would lead to a progressive reduction in the organic component of the bone and in its mineralization. In other words, the exposure to microgravity or to a bed rest experiment would accelerate the physiologic process of bone ageing due to the progressive prevailing of bone resorption over bone formation. According to the view of an excess of bone resorption, the load of Ca ions available in the bone would be released from the bone into the bloodstream leading to hypercalcemia and eventually to hypercalciuria thanks to the compensatory increase in Ca excretion via the kidneys (Drummer et al., 2002). Another important piece in this mosaic is the regulation of parathyroid gland activity. Parathyroid hormone (PTH) plays a pivotal role in the control of Ca homeostasis and bone metabolism. It is well established that PTH secretion is reduced or suppressed by hypercalcemia (Potts, 2005). Therefore, the observation of PTH down-regulation during space missions or bed rest is in full agreement with the view of a primary increase in bone resorption leading to hypercalcemia and, in turn, to PTH suppression and hypercalciuria (Figure 2).

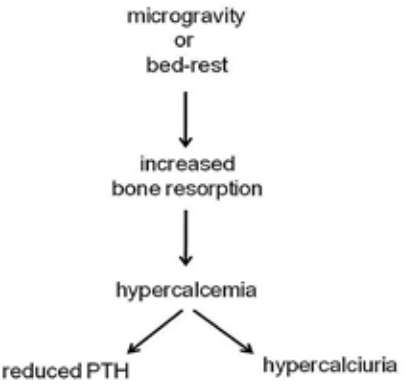

Figure 2: Present view of the chain of events linking bone unloading to alterations in indices of calcium homeostasis.

BONE MASS LOSS DUE TO MICROGRAVITY / BEDREST: THE UNSOLVED ISSUES

The main unsolved issue in the current view is that, at its best, hypercalcemia is very mild and only transient during space missions and bed rest (LeBlanc et al., 1995). In other words, a key component is lacking in the chain of events from the excess of bone resorption to PTH suppression and the excess of urinary Ca. This lack appears even more important considering that PTH suppression could have a primary role in bone mass reduction because of the favorable effects of PTH on bone metabolism. Another unsolved issue is the change in P homeostasis. As stated above, the mineral component of the bone is rich not only in Ca, but also in P. Therefore, if an excess of Ca ions is reabsorbed and released from the bone, the same should also be true for P. However, a reliable conclusion has not been achieved regarding this issue because P homeostasis has not been extensively investigated during space missions or bed rest. The largest series of data regarding P homeostasis during bed rest was reported by Zerwekh et al. who found a non-significant increase in serum and urinary P over a pre-bedrest baseline (Zerwekh, Ruml, Gottschalk & Pak, 1998). Finally, another important unsolved issue is the possibility that during space missions or bed rest experiments, early changes are different from subsequent changes (Lueken, Arnaud, Taylor & Baylink, 1993). In most physiologic and pathologic processes, a substantial change in the environmental conditions is followed first by a set of rapid effects and later by a sequence of compensatory adaptations which lead to a new equilibrium. Is this true also for bone metabolism and Ca/P homeostasis during space missions or bed rest? Does a primary excess in bone resorption exist also when space missions or bed rest experiments last for more than a few days?

BONE MASS LOSS DUE TO MICROGRAVITY / BEDREST: THE PRACTICAL IMPLICATIONS

The existence of bone mass loss during space missions or bed rest could be considered a problem of importance confined to the limits of space medicine and clinical practice for immobilized patients. This may not be the case. The available evidence suggests that bone mass reduction in those particular settings represents in many aspects an acceleration of the normal ageing of the bone. Thus, research in this field could be of help in the prevention and control of osteoporosis, a disorder which is highly prevalent in the populations of industrialized countries and results in high social and economic costs (Smith et al., 2003). In other words, as often with space research, the comprehension of the mechanisms underlying bone mass loss during space missions and bed rest could favor the development of diagnostic tools and therapeutic countermeasures of potential use also for millions of people “in the real world”.

ACKNOWLEDGEMENTS

The study was funded by the Italian Space Agency (ASI) as part of the OSteoporosis and Muscle

Atrophy (OSMA) project. Special thanks go to the participants of the bed rest study and to the Valdoltra Orthopedic Hospital (Ankaran, Slovenia).

REFERENCES

Biolo, G., Agostini, F., Simunic, B., Sturma, M., Torelli, L., Preiser, J. C., et al. (2008). Positive energy balance is associated with accelerated muscle atrophy and increased erythrocyte glutathione turnover during 5 wk of bed rest, American Journal of Clinical Nutrition. Oct; 88(4), 950–8.

Drummer, C., Valenti, G., Cirillo, M., Perna, A., Bellini, L., Nenov, V., et al. (2002). Vasopressin, hypercalciuria and aquaporin - the key elements for impaired renal water handling in astronauts? Nephron, 92(3), 503–14. Review.

Firestein, Gary, S., Budd Ralph, C., Harris Edward, D. jr., McInnes Iain, B., Ruddy, S., & Sergent, John S. (2008). Kelly's "Textbook of Rheumatology" (8th edition), Saunders Elsevier.

LeBlanc, A., Schneider, V., Spector, E., Evans, H., Rowe, R., Lane, H., et al. (1995). Calcium absorption, endogenous excretion, and endocrine changes during and after long-term bed rest. Bone, 16(4), 301S–304S.

LeBlanc, A. D., Spector, E. R., Evans, H. J., & Sibonga, J. D. (2007). Skeletal responses to space flight and the bed rest analog: a review. Journal of Musculoskeletal and Neuronal Interactions, Jan–Mar, 7(1), 33–47.

Lueken, S. A., Arnaud, S. B., Taylor, A. K., & Baylink, D. J. (1993). Changes in markers of bone formation and resorption in a bed rest model of weightlessness. Journal of Bone and Mineral Research. Dec; 8(12), 1433–8.

Potts, J. T. (2005). Diseases of the parathyroid gland and other hyper- and hypocalcemic disorders. Harrison's Principles of Internal Medicine (16th edition). McGraw-Hill. New York, 2249–2268.

Rittweger, J., Simunic, B., Bilancio, G., De Santo, N. G., Cirillo, M., Biolo, G., et al. (2009). Bone loss in the lower leg during 35 days of bed rest is predominantly from the cortical compartment. Bone, 44, 612–618.

Smith, S. M., & Heer, M. (2002). Calcium and bone metabolism during space flight. Nutrition, 18, 849–852.

Smith, S. M., Davis-Street, J. E., Fesperman, J. V., Calkins, D. S., Bawa, M., Macias, B. R., et al. (2003). Evaluation of treadmill exercise in a lower body negative pressure chamber as a countermeasure for weightlessness-induced bone loss: a bed rest study with identical twins. Journal of Bone and Mineral Research, Dec, 18(12), 2223–30.

Stewart, A. F., Adler, M., Byers, C. M., Segre, G. V., & Broadus, A. E. (1982). Calcium homeostasis in immobilization: an example of resorptive hypercalciuria. New England Journal of Medicine, May 13, 306(19),1136–40.

Zerwekh, J. E., Ruml, L. A., Gottschalk, F., & Pak, C.Y. (1998). The effects of twelve weeks of bed rest on bone histology, biochemical markers of bone turnover, and calcium homeostasis in eleven normal subjects. Journal of Bone and Mineral Research, 13,1594–601.