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# Immobilization induces a very rapid increase in osteoclast activity☆

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**Abstract**

We studied in a randomized, strictly controlled cross-over design, the effects of 6 days 6° head-down tilt bed rest (HDT) in eight male healthy subjects in our metabolic ward. The study consisted of two periods (phases) of 11 days each in order to allow for the test subjects being their own controls. Both study phases were identical with respect to environmental conditions, study protocol and diet. Two days before arriving in the metabolic ward the subjects started with a diet. The diet was continued in the metabolic ward. The metabolic ward period (1l days) was divided into three parts: 4 ambulatory days, 6 days either HDT or control and 1 recovery day. Continuous urine collection started on the first day in the metabolic ward to analyze calcium excretion and bone resorption markers. On the 2nd ambulatory day in the metabolic ward and on the 5th day in HDT or control blood was drawn to analyze serum calcium, parathyroid hormone, and bone formation markers. Urinary calcium excretion was, as early as the first day in immobilization, increased ($p < 0.01$). CTX- and NTX-excretion stayed unchanged in the first 24 h in HDT compared to the control. But already on the 2nd day of immobilization, both bone resorption markers significantly increased. We conclude from these results—pronounced rise of bone resorption markers—that already 24 h of immobilization induce a significant rise in osteoclast activity in healthy subjects. Thus, it appears possible to use short-term bed rest studies as a first step for the development of countermeasures to immobilization.


## 1. Introduction

The human skeleton is a dynamic structure that responds to changes in levels of mechanical forces [1]. In the absence of gravity, the mechanical force applied to bone is reduced. This reduced mechanical demand especially on weight-bearing bones plays an important role as stimulus for bone loss. Thereby, some people do lose more bone mass than others [2,3]. However, beside microgravity, there are many clinical conditions requiring prolonged bed rest, which are also coupled with unloading of weight-bearing bones. This also leads to a reduction in bone mass and may result in osteopenia. Therefore, 6° HDT bed rest is a commonly used model to simulate some of the effects on the musculo-skeletal system observed in spaceflight. Musculo-skeletal changes such as decrease in muscle strength and muscle mass, bone loss, increased

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excretion of bone resorption markers, and lowered levels of bone formation markers were found to be similar in bed rest and spaceflight [4].

It has been estimated that a microgravity environment or strict bed rest leads to bone loss of about 1–2% per month [4–10]. The mechanism of bone loss initiated by unloading seems to be caused by a decrease in the bone formation rate and a concurrent increase in bone resorption rate [11–14]. As a result, serum levels of bone formation markers are reduced while urinary excretion of bone resorption markers rises. Metabolic calcium balance studies reveal negative balances meaning loss of calcium from the main calcium stores, the bone [6,15,16].

Although mechanical stress is most likely one of the major stimulus for bone remodeling, other factors contribute to bone turnover as well. Nutrient supply, i.e. energy, protein, calcium, vitamin D, vitamin K and sodium are nutritional factors which contribute to a healthy adequate bone mass. Reduced calcium intake has often been found in astronauts during spaceflight [6,16–18] and may contribute to the calcium loss during the mission [16]. Nutrient supplementation may be a promising tool to contribute to a lower bone loss in space missions or bed rest. However, it is still under discussion whether high calcium intake may counteract bone loss in immobilization to the same extent as it does in postmenopausal women.

Since the era of the Russian space station MIR and the International Space Station (ISS), humans extend their stay in space to months. When we intend to explore other planets humans may be in a microgravity environment for years. One limitation of these space exploration activities is most likely the reduction of bone mass. Up to now there is no optimal countermeasure or a mixture of effective countermeasures available that can keep bone mass in unloaded weight-bearing bones.

Most of the studies on bone metabolism have been carried out in long-term bed rest [4,16,19–22], and the earliest examination in these studies was done after two weeks in HDT. The aim of the presented study was to examine the kinetics of bone turnover markers in a short-term study by using a cross-over design and applying high calcium intake.

## 2. Material and methods

The study was approved by the ethics committee of the 'Aerztekammer Nordrhein' (Nothern Rhine Medical Association), Duesseldorf, Germany.

### 2.1. Volunteers

Eight healthy, male test subjects (mean age $26 \pm 1$ y, mean body mass $70.1 \pm 1.9$ kg) gave their written informed consent to participate in the study. The subjects were nonsmokers and followed a light muscular workload before the study.

### 2.2. Study design

The study took place as a randomized, strictly controlled crossover design. Each of the two study phases consisted of two dietary adaptation days (ambulatory) and 11 days in the metabolic ward (Institute of Aerospace Medicine, German Aerospace Center (DLR), Cologne, Germany). Room temperature (24 °C) and relative humidity (50%) were kept constant during both 11-day periods in the ward. The 11-days in the metabolic ward were divided into a 4-day ambulatory period, a 6-day intervention period (either 6° HDT bed rest or control) and a recovery day. The eight subjects were randomly distributed in two groups. The first group started with the control period in the intervention phase, the second group with the bed rest period. During bed rest, all activities, including showering and body weight determination, were carried out in the horizontal position. Both study phases were identical with respect to environmental conditions, study protocol and diet.

### 2.3. Diet

Beginning with the dietary adaptation phase, the volunteers received a controlled and standardized diet consisting of 10 MJ/d, 3.5 L water/d, 200 mEq NaCl/d, 2000 mg calcium/d and 400 IU Vitamin D/d by a multivitamin preparation. Dietary protein, fat and carbohydrate intake were calculated according to the dietary reference intake values (DRI) (43), (i.e., 15–20% of the daily energy intake were administered as protein, 30% as fat and 50–55% as carbohydrates, respectively).