ISM skriftserie Nr. 62

FRAGILE BONES IN PATIENTS WITH STROKE?

Bone mineral density in acute stroke patients and changes during one year of follow up

Lone Jørgensen

Tromsø 2001

Institute of Community Medicine
University of Tromsø, Norway

ISM skriftserie
blir utgitt av Institutt for samfunnsmedisin
Universitetet i Tromsø.

Forfatterne er selv ansvarlige for sine funn og konklusjoner. Innholdet er derfor ikke uttrykk for ISM's syn.

The opinions expressed in this publication are those of the authors and do not necessarily reflect the official policy of the institutions supporting this research.

ISBN 82 - 90262 - 70 - 1
2001

Fragile bones in patients with stroke?

Bone mineral density in acute stroke patients

and changes during one year of follow up

by Lone Jørgensen

Institute of Community Medicine
University of Tromsø, Norway

Tromsø 2001

CONTENTS

ACKNOWLEDGEMENT

The first ideas related to the topics in this thesis arouse when I was working as a physiotherapist in a stroke unit. Hearing about patients who later suffered from fractures in addition to their impairments after stroke draw my attention towards the need of research in this field of rehabilitation.

I would like to thank the many who made this thesis possible and contributed to my education.

In particular, I wish to express my sincere appreciation and gratitude to Bjarne K. Jacobsen for steady guidance and constructive criticisms throughout the process. Thank you for guiding me through the difficulties of statistical analysis and other methodological problems and for scrutinising my manuscripts over and over again. Your support and continuous encouragement have been of great importance to me.

I also wish to thank Jeanette H. Magnus for her help and guidance in the initial phase of this work and for encouraging me to start as a PhD-student.

In addition to Bjarne and Jeanette, I would like to acknowledge Nicola J. Crabtree, Torgeir Engstad, Jonathan Reeve and Tom Wilsgaard, my co-authors, for their contribution, scientific advises and methodological discussions. Furthermore, I would like to thank Rolf Jorde for the valuable criticism of my papers and the treatise, and for giving me the opportunity to perform the bone mineral density measurements at The University Hospital in Tromsø. I also acknowledge Sigurd Sparr, the medical staff at the Neurologic and Geriatric Departments, and the therapists at the Physiotherapy Department at this hospital, for their help and support during the study. A special thank to Randi Sørsdal for feedback on some of the manuscripts and for fruitful discussions. Moreover, I thank Line Wilsgaard, Elin Hansen,

Grethe Hoel, Neshrin Mikkelsen and Merete Albertsen for expert technical assistance and for help by collecting and processing the data.

I also wish to express my sincere gratitude to the men and women who participated in the studies. Without their efforts, this study would not have been possible.

During the last year, I have enjoyed the good, scientific atmosphere at the Institute of Community Medicine, University of Tromsø. It has been very inspiring to be enclosed in this working environment. I am especially indebted to the members of the Tromsø Osteoporosis Study for letting me participate in their meetings and for sharing scientific knowledge.

I am also indebted to the research programme «Research on the Elderly in Tromsø» for financing my years as a research fellow as well as most of the study, and to "The Norwegian Osteoporosis Society" and The University Hospital in Tromsø for additional financial support.

Finally, I want to express thankfulness to my life companion and dearest friend Johnny, for continuous encouraging support and patience.

LIST OF PAPERS

This thesis is based on the following papers:

I Jørgensen L, Jacobsen BK, Wilsgaard T, Magnus JH. Walking after stroke: does it matter? Changes in bone mineral density within the first 12 months after stroke. A longitudinal study. *Osteoporos.Int.* 2000;**11**:381-7.

II Jørgensen L, Crabtree NJ, Reeve J, Jacobsen BK. Ambulatory level and asymmetrical weight bearing after stroke affects bone loss in the upper and lower part of the femoral neck differently: bone adaptation after decreased mechanical loading. *Bone* 2000;**27**:701-7. (Published erratum appears in *Bone* 2001;**28**:140).

III Jørgensen L, Jacobsen BK. Functional status of the paretic arm affects the loss of bone mineral in the proximal humerus after stroke. A one-year prospective study. *Calcif.Tissue Int.* 2001;**68**:11-15.

IV Jørgensen L, Engstad T, Jacobsen BK. Bone mineral density in acute stroke patients: low bone mineral density may predict first stroke in women. *Stroke* 2001;**32**:47-51.

The papers will be referred to by their Roman numerals in the text.

INTRODUCTION

Stroke

According to the World Health Organization criteria stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin".[1]

Stroke is a major cause of death and impairment in elderly people.[2;3] Data from the first stroke register in Norway, collected from 1994 to 1996 in Innherred, Nord-Trøndelag showed that the crude annual incidence risk of stroke was 3.12/1000 inhabitants aged 15 years or above. This result from Innherred, a population with a sex- and age-distribution similar to Norway as a whole, was similar to incidence rates of other Scandinavian and West European contries.[4] The incidence of stroke increased exponentially by age, and in the group aged 75-84 years the incidence rate was 21/1000 compared with 40/1000 in the group ≥85 years.[4] Based on results from this stroke register, about 10 000 first ever stroke and 3 400 recurrent stroke are expected to occur every year in Norway.[5] The study also showed that the overall 30-day case-fatality rates were 19.2% for patients with first ever stroke and 37.9% for patients with recurrent stroke.[4]

Based on data from Nord-Trøndelag, approximately 2% of the adult population over the age of 20 have had a stroke, 56% of the stroke patients regard themselves as having impaired mobility and 24% are full-time residents in an institution.[6] Other stroke related factors that may influence dependency are sensory deficits, impaired balance, impaired vision, depression and neuro-psychological problems, e.g., neglect and apraxia. Among patients surviving a stroke approximately 1/3 remain dependent with respect to ambulation and do not regain normal arm function within the first 6 months after the stroke event.[7]

Fracture

Fractures are more common in older than in younger people, and more common in older women than in older men.[8] The main age-related fractures occur in the vertebral bodies, proximal femur, proximal humerus and distal forearm. At younger age, Colles fracture of the wrist is more common than fracture of the proximal femur, but after the age of seventy, the incidence of fracture of the proximal femur increases rapidly and this fracture becomes the most common one.[8] One explanation for this change in fracture type has been related to decreased walking speed associated with an increased risk of falling to the side in old age.[9]

Fractures of the hip are more severe than the other age-related fractures. The overall annual crude incidence rate of hip fracture has been estimated to 12.1 per 1000 inhabitants (1994-1995) in Norway.[10] Like stroke, the incidence increases exponentially by age and 60% of all cases are found in people aged 80 years or more. In Sweden, the first-year mortality after a hip fracture is 20% in women and 34% in men,[11] and in a general Norwegian population (≤ 75 years) the risk of dying within 1 year after hip fracture has been estimated to be 3 to 4 times higher than in controls.[12] However, the excess mortality seems mainly to be related to persons with reduced mental status, reduced somatic health and low physical ability.[13;14]

For those who survive a hip fracture daily life may be severely restricted. Cooper, for example, points out that 40% are still unable to walk independently one year after the fracture and 60% have difficulty with at least one essential activity of daily living.[15]

Fractures in stroke patients

People who have suffered from a stroke are at increased risk of fracture, especially hip fracture [16,17] usually occurring at the paretic side.[17-20] Furthermore, it has been shown that among patients with hip fracture, 8-29% have had a stroke prior to the fracture.[18,20-22] The consequences of hip fracture are more severe in patients with previous stroke than in patients

without stroke. First, because survival is reduced and, second, because only 39% of the stroke patients who lived in their homes before the fracture are discharged back home compared with 63% of the patients without stroke.[23]

Changes in bone mass after stroke

The main reason why stroke patients are at increased risk of fracture is probably low bone mass at the paretic side (table 1) in combination with an increased risk of falling.[24-29] Although most stroke patients with hemiparesis relearn to walk,[7] many walk asymmetrically with less of their body weight through the paretic leg,[30] and this may affect bone mass. With respect to the arm, approximately 50% of the patients have reduced function immediately after the stroke event and about 1/3 do not regain normal function within the following 6 months.[7] Studies of stroke patients where bone mass of the total body has been measured describe a larger reduction of bone mineral in the paretic arm than in the paretic leg,[31-33] possibly because the leg is stimulated through weight bearing despite being paretic.

Disuse seems to be the most plausible explanation for the low bone mass both in the upper and lower extremity. The effect of decreased motor function on bone loss after stroke is, however, unclear; most studies are cross-sectional and longitudinal studies on this matter are extremely sparse with small populations followed [31-46] (table 1).

Cross-sectional studies can only evaluate the difference in bone mass between the paretic and non-paretic side. A difference may be observed if bone loss has taken place on both sides, but to a larger extend in the paretic limb, consequently leading to an underestimation of the real bone loss. A difference may, however, also be a result of bone hypertrophy of the non-paretic limb rather than bone loss at the opposite side. The true change of each side, separately, can only be examined in longitudinal studies.

When the present thesis was planned (in 1995) only one longitudinal study on stroke patients had been performed.[32] It showed that the bone mineral content (BMC) decreased by 9% in the arm and 4% in the leg within four months after stroke onset, but despite that only five patients were followed for 6 months, it was concluded that the bone loss ceased after 2-3 months.[32] Later, in 1999, another longitudinal study with 19 stroke patients was published. The patients were followed for 1 year, but included only non-ambulatory patients and the baseline bone mineral density (BMD) was measured 1 month after stroke.

Table 1. Previous studies on bone loss and the relationship to motor function after stroke (other than our own)

Type of study and author	Sample size	Time since stroke (mean/range)	Methods: Measurement technique	Methods: Anatomical site(s) measured	Results: Paretic compared to non-paretic side (or control subjects)	Results: Impaired function affects bone loss
Cross-sectional						
Hodkinson et al. (1967)[37]	14	26 (6-105) months	X-ray,	Leg	Indices of osteoporosis	No
Goodman (1971)[36]	23	2 (0.5-4) months	X-ray,	Shoulder, wrists, hands	Indices of osteoporosis	Yes
Panin et al. (1971)[41]	25	40 (7-204) months	X-ray (cortical thickness)	Humerus, radius, 3rd metacarpal	19 to 26% thinner	Yes
Denham (1973)[15]	33	3 weeks to "several" years	X-ray	2nd metacarpal	Significant bone loss	No
Naficht et al. (1975)[40]	42	3.5 (1-5) months	SPA	Forearm	6% lower BMC	Not assessed
Prince et al. (1988)[42]	74	Mean 3.6 years	Computerised X-ray densitometry	Forearm	1.4% BMC loss per year	Yes
Iversen et al. (1989)[33]	15	Range 23-38 weeks	SPA/DPA	Total arm Total leg	10% lower BMC 4% lower BMC	No
Hamdy et al. (1993)[31]	30	Mean 3 months (15 patients) Mean 121 months (15 patients)	DPA	Total arm Total leg	8% lower BMD 3% lower BMD	Not assessed
Takamoto et al. (1995)[46]	112	46 (3-254) months	DXA	Femoral neck Trochanter	7% lower BMD 10% lower BMD	Yes
del Puente et al. (1996)[34]	48	10 (1-48) months	DXA	Femoral neck	5% lower BMD	No
Sato et al. (1996)[45]	93	46 (1-267) months	Microdensitometry	Finger	Bone-mass-indices lower	Yes
Liu et al. (1999)[39]	104	Median 3 (1-9) months	DXA	Proximal humerus, distal, radius, femoral neck, calcaneus	2 to 12% lower BMD, largest in prox. humerus (continues to decrease during 3 month of rehabilitation)	Yes
Iwamoto et al. (1999)[38]	84	25 (2-130) months	Computerised X-ray densitometry	Metatarsus 1	Men 6%, women 12% lower BMD	Yes
Longitudinal		**Time followed**			**Bone loss paretic side**	
Hamdy et al. (1995)[32]	11 5	4 months 6 months	DXA	Total arm Total leg	9% BMC 4% BMC	Yes No
Ramnemark et al. (1999)[43,44]	19	1 year	DXA	Humerus Proximal femur	17% BMD 12% BMD	No

Single photon absorptiometry (SPA) Dual photon absorptiometry (DPA) Dual energy X-ray (DXA)

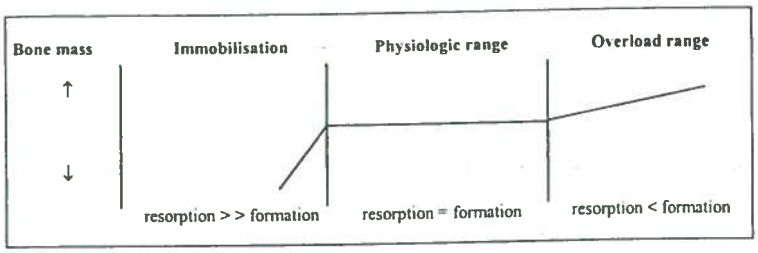
Bone adaptation

Macroscopically, bone consists of 75-80% cortical and 20-25% trabecular bone. The ratio of cortical/trabecular bone differs at different parts of the skeleton, and examples of areas with a high content of trabecular bone are the metaphyseal regions and the vertebrae, whereas examples of regions with a high content of cortical bone are the shafts of the long bone.[47] Bone is a living tissue and 5-15% of the skeleton is exchanged annually.[47] The trabecular "spongy" bone is always enveloped by cortical very "dense" bone, but because trabecular bone has a large bone surface (and contribute to most of the total bone surface) it is also a more metabolic active region than cortical bone.[48]

The proportion of the bone occupied by bone tissue is traditionally described as bone mass. During childhood and adolescence bone mass accumulate and peek in the twenties.[49] After the age of "peak bone mass" bone-resorption exceeds bone-formation resulting in a gradual annual bone loss of about 1%, in women increasing to 1-4% over the decade after the menopause.[50] Moreover, there may be an increased loss in the last decades of life.[51]

Over 100 years ago Wolf [52] suggested that bone will accommodate to the habitual stress that is imposed on it. Today it is widely accepted that bone is a highly adaptive tissue, which develops in structure and function in response to mechanical forces and metabolic demands. Several theories have been proposed to explain the mechanism; one example is the "Mechanostate Theory" by Frost.[53] Frost distinguish between modelling (referring to modelling in the formation mode) and remodelling processes, and asserts that disuse and overload have opposite effects on these two processes. Disuse activates remodelling, but inhibits modelling, leading to bone loss, whereas overload inhibits remodelling and activates formation mode modelling, leading to bone gain. Similarly, other authors describe bone adaptation as a feedback system with threshold levels of mechanical strain above or below which the adaptation begins [54,55] (figure 1).

Figure 1. Bone adaptation as a feedback system; illustration



The most extensive evidence in human studies supporting that exercise affects bone mass has so far been obtained in cross-sectional studies of athletes. Generally, physically active subjects have higher BMD than age matched sedentary controls (see reviews by Suominen,[56] Forewood,[57] Chilibeck [58]), and the osteogenic effects of training seem to be quite specific to the sites at which the mechanical strains occur.[59,60] However, as prospective exercise trials in pre- and postmenopausal women have demonstrated only modest (1-2%) improvements in bone mass,[61] the more dramatic effects of athletic activity on bone mass inferred by cross-sectional studies may reflect self-selection. Another explanation may be that exercise is more effective in adolescence (before skeletal maturity is reached) than in adults.

Like exercise, the effect of immobilisation on bone mass is site specific. As shown in a review by Järvinen [62] musculosceletal injuries (e.g., fractures) result in bone loss mainly in the regions of the skeleton related to the injury. This is also the case for patients with traumatic spinal cord injuries [63-68] and stroke patients (table 1) where the loss of bone occurs mainly in the paralysed parts of the body.

Several studies have shown that the most rapid bone loss occur during the first weeks after immobilisation; thereafter the rate is slower.[62,69-71] The extent and rate of bone mass recovery during remobilization have remained a controversial issue,[70,72,73] but it seems certain

that the time needed for recovery is clearly much longer than the time needed to reduce the bone mass, and that the recovery often seems to be incomplete.[71,74]

The bone mass present at a given time in life is determined by factors that influence the gain of bone during growth and those that influence bone loss in later life. Other factors than level of physical activity include genetics, weight in infancy, hormonal status, nutrition, several diseases and medication.[75-78]

Bone densitometry

The fundamental principle behind dual energy X-ray absorptiometry (DXA) is the measurement of the transmission of X-rays of two different photon energies through the body. This enables the masses of two types of tissue (e.g., bone and soft tissue) to be quantified. In the earlier technique of dual photon absorptiometry (DPA) a Gd-153 radionuclide source was used (which has two emissions at 44 and 103 keV). At photon energies above 100 keV there is little difference in the attenuation by bone and soft tissue, and transmission measurements reflect the total mass in the beam. Photon energies around 40 keV are ideal for the low energy beam because there is a good contrast between bone and soft tissue. Replacement of the Gd-153 source with an X-ray tube improved the performance of dual photon bone densitometers by combining high photon flux with the small focal spot size of the X-ray tube. The availability of an intense, narrow beam of radiation improved scanning time and image, and led to a concomitant improvement in precision.

Other absorptiometric techniques commonly used for measurements of bone mass beside DXA and DPA are single photon absorptiometry (SPA) and single X-ray absorptiometry (SXA). However, in terms of accuracy, precision, and radiation doses DXA seems to be the most preferable technique.[79]

Absorptiometric data can be expressed both as bone mineral content (BMC) and bone mineral density (BMD). BMD is an area density measurement (g/cm^2) derived by dividing BMC (g) by the scanned area of bone. BMD is not a measure of true density because absorptiometry provides no information about the depth of bone in the scan path. It does, however, provide a degree of standardisation for differences in body size between individuals and facilitates the comparison of an individual with a reference population. Moreover, bone mass expressed as BMD tends to be more precise than BMC,[80] an advantage in longitudinal studies.

The only methods that can measure the true volumetric density and the three-dimensional geometry of a bone directly are the quantitative computed tomography (QCT) and peripheral quantitative computerised tomography pQCT. The radiation dose of QCT is however high (~50 μSv) compared with DXA (≤ 3 μSv) whereas the radiation dose of pQCT equals the dose of DXA.[79] Measurements of the appendicular skeleton by use of pQCT may, thus, be an interesting alternative to SPA/SXA, as also separate measurements of cortical and trabecular bone can be performed by this technique.

Unfortunately, cortical and trabecular bone cannot be evaluated separately by DXA. Moreover, it is not possible to study the higher tendency for disconnection of the trabecular network as seen in osteoporotic patients[47,81] by this technique. Ultrasound may be an alternative to evaluate parts of the peripheral skeleton, as it seems to provide information about the microstructure of the bone. Ultrasound systems quantify the effect of sound distorted as it passes through bone, and is affected by e.g., trabecular orientation, spacing and quantity.[82] Usually the calcaneus is measured, but sensitivity to the presence of oedema may limit the precision,[83] as also shown in a study on stroke patients.[84]

Region of interest for measurements of bone mass

Low bone mass is related to bone strength and is a major determinant of future fracture risk.[85] Fractures are predicted best by BMD measurements from the relevant anatomical sites[86] and, thus, BMD of the femoral neck is a better predictor of hip fracture than measurements of other skeletal sites.[85]

Since the osteogenic effects seems to be site-specific to the anatomic sites at which the mechanical strains occur,[59-61] it is essential to measure bone mass at the site of loading, when one aims to evaluate the effect of physical activity or weight bearing on bone. Furthermore, as skeletal sites with a high content of trabecular bone, for example the trochanter and the proximal humerus, are expected to have the highest initial bone loss after immobilisation,[70] these regions may be of special interest when studying the early effect of disuse.

Little is known with regard to whether changes in BMD after immobilisation are uniform across the bone or whether there are regional differences, e.g., within the femoral neck. As illustrated by Pauwells,[87] the trabeculae of the cancellous tissue are usually oriented so as to resist axial deformational stresses (either from weight bearing or from muscle activity) and their number, size and distribution are related to these forces. When analysing the strains in the femoral neck, Pauwells showed that the stresses increase more strongly towards the medial (lower) border than towards the lateral (upper), and that the greatest stresses arise on the medial side of the femoral neck. The density of the cancellous tissue and the thickness of the cortex have a corresponding distribution: the cancellous tissue is denser and the cortex much thicker on the medial than at the lateral side as seen in Figure 1, paper II. Therefore, with respect to the effect of loading it must be of interest to examine changes in BMD within the femoral neck. Not only from a biomechanical, but also from a clinical point of view this question is important to investigate, as measurements of the lower femoral neck

may give us a better estimation of the impact of physical activity on BMD changes in the hip than measurements of the total femoral neck.

Low bone mass, -a risk factor for stroke?

The increased risk of fracture in stroke patients may also be related to factors other than those occurring after the stroke event. Stroke mainly occurs in the elderly population where osteoporosis is often already present. Moreover, osteoporosis and stroke share several risk factors other than age such as smoking, low physical activity and hypertension.[51;61;88-94] Low BMD and a high risk of stroke may, thus, be related, but studies on this relationship are sparse. Browner et al.[95;96] have shown that low BMD (adjusted for several potential confounders) was significantly related to stroke mortality and stroke incidence in a female population, but before our study was conducted, no data were available for men. If BMD is low in acute stroke patients, this risk factor will add to the other risk factors such as the increased incidence of falls and the increased rate of bone loss.

Thus, the aim of this thesis was to investigate changes in BMD the first year after stroke and, further, to assess whether low BMD precedes stroke:

AIMS OF THE THESIS

- to evaluate the influence of post-stroke disuse and immobility on the rate of bone loss in the proximal femur (paper I).
- to investigate whether changes in bone mineral density in the lower femoral neck (mainly influenced by compressive stresses of the hip) differ from the changes in the upper femoral neck (mainly influenced by tensile stresses) after disuse due to stroke (paper II).
- to evaluate possible changes in bone mineral density in the proximal humerus within the first year after stroke (paper III).
- to examine the possible relationship between BMD and risk of stroke in non-institutionalised elderly men and women (paper IV).

SUBJECTS

Paper I-IV

Patients

The patients in this thesis consisted of people with acute stroke admitted to The University Hospital in Tromsø (RiTø), Norway. All persons with acute stroke from Mid- and Northern Troms, a well-defined part of the county with 114 000 inhabitants, are supposed to be hospitalised to RiTø.

Stroke was defined according to the definition of the Worlds Health Organization, WHO.[1] The diagnosis was based on a doctors clinical examination, an evaluation of all available information from the hospital medical records and supported by anatomic cerebral changes on computed tomography scans.

Patients included were acute stroke patients aged ≥ 60 years, who had been able to walk without personal support prior to the stroke event. The patients included in paper I-III had to reside within a 2 hours drive from the hospital, whereas the patients in paper IV were from the municipality of Tromsø. Exclusion criteria were previous strokes affecting the sensomotoric system, unconsciousness and terminal illness, presence of osteosynthetic material in the femoral neck, a history of hip fracture, and known unilateral bone diseases affecting bone mineral density asymmetrically such as osteosarcomas and osteomyelitis. With respect to paper IV, patients with a history of previous stroke, even though this had not affected the sensomotoric system, were excluded.

The number of patients eligible, included and followed for 1 year is given in table 2. Figure 2 gives information about time of inclusion and number of patients included in the different papers. Note that not all included patients were followed for 1 year.

The patients followed in paper III (measured at baseline and after 1 year, n=28) is a subgroup of those followed in paper I (measured at baseline, 7 and 12 month, n=40), except for 2 patients who were not included in the evaluation of the latter group, because they missed the 7-month measurements.

Table 2. Number of eligible patients included and followed for 1 year (paper I-III)

Paper	Patients (n)			Time at inclusion	Walks 1 week after stroke
	Eligible	Included	Followed for 1 year		
I + II	42	42	17*	Dec 95 - Aug 97	No
	24	23	23*	June 96 - Aug 97	Yes
	66	65	40*		
III	37	37	28**	April 96 - Aug 97	No

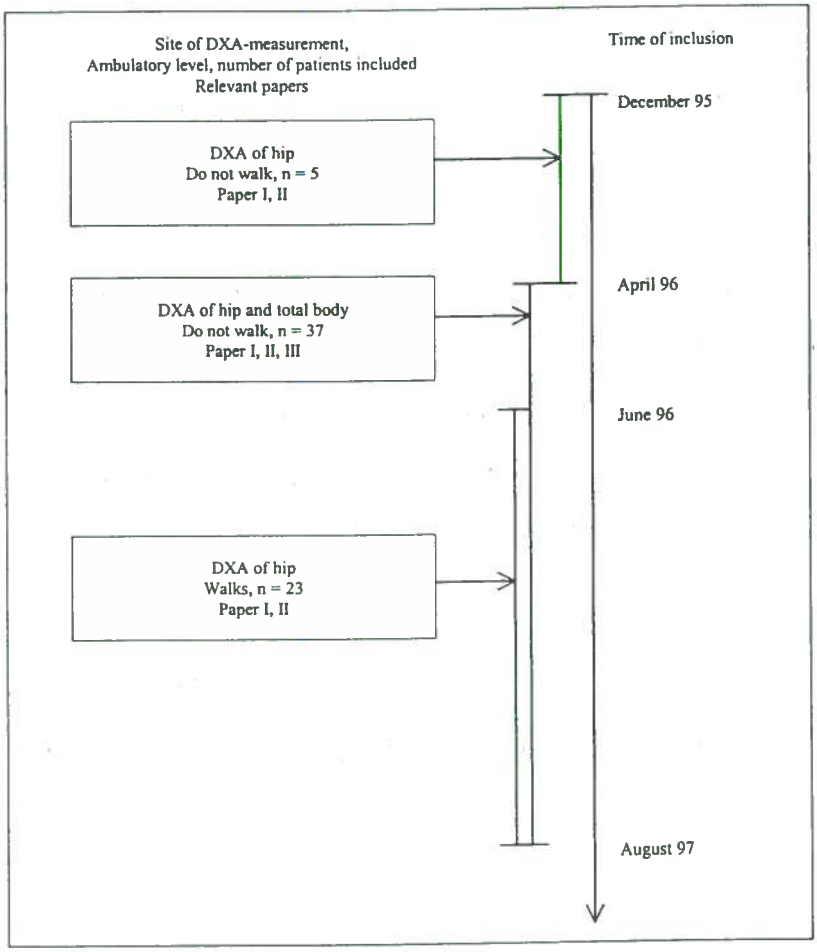
*Measured at baseline, 7 and 12 month **Measured at baseline and after 1 year

As detailed in the papers (I-III) the main causes for missing patients during follow-up were severe disease or death.

In paper IV, patients both mobile and immobile 1 week after the stroke were included in the study. Time of inclusion was June 1996 to August 1997. All but one of the 64 eligible patients accepted to participate.

With respect to paper I-III we did, unfortunately not, register the number of patients who were not eligible for the study. In paper IV, we found that 61 patients (49% of all stroke patients hospitalised to RiTø in the period of inclusion) were not eligible for the study. The cause was death, unconsciousness or severe disorientation the first week after stroke (n=30), previous strokes (n=23) or a history of hip fracture or presence of osteosynthetic material in the femoral neck (n=6). Two patients were not enrolled in the study due to femur amputation and cancer with metastasis to the bone.

Figure 2. Site of DXA-measurement in the of patients included in the study



Paper IV

Control subjects

The control subjects included in paper IV were randomly selected from the population register of Tromsø in 1998 and invited by letter to participate in the study. For each gender and 5-year age bracket we invited more than twice the number of cases in order to get a sufficient number.

Among the 404 invited possible control subjects 197 (49%) accepted to be enrolled in the study. They all stated that they had never sustained a stroke. However, to ascertain that possible unreported stroke patients were excluded, their medical hospital records were reviewed by an experienced physician (Dr. Torgeir Engstad). Six men and 3 women were found to have had a previous stroke and, thus, excluded from the analysis.

Ethics

Informed consent was obtained from each participant according to The Second Helsinki Declaration, and the trial was approved by the Regional Committee for Medical Research Ethics.

METHODS

Paper I-III

Bone densitometry

In paper I, bone mineral density (BMD) was measured using dual-energy-X-ray absorptiometry (Lunar DPX-L, version 1.3z) at both proximal femurs mean 6 days (SD 4) after the stroke, and 7 months (mean 30 weeks, SD 2) as well as 12 months (mean 52 weeks, SD 2) after the first measurement. The patients who could not walk one week after the stroke were also measured at two month (mean 8 weeks, SD 1).

The bone mineral density was determined at the femoral neck area and the trochanteric area as described in the Lunar-manual.[97] The image files were later re-analysed using a beta version of the Lunar hip strength analysis (HSA) program (version β 3.7) (paper II). In order to evaluate regional changes in femoral neck BMD, upper and lower BMD values were chosen from the HSA output (Fig 1, paper II).

In the patients described in paper III, BMD of the total body was measured using dual-energy-X-ray absorptiometry (Lunar DPX-L, version 1.3z). The first measurement was performed mean 7 days (SD 4) after the stroke followed by measurements 2 months (mean 8 weeks, SD 1), 7 months (mean 30 weeks, SD 2) and 12 months (mean 52 weeks, SD 2) later. The BMD of the head and spine were derived directly from the total body scan by use of the Lunar definitions.[97] The BMD of the proximal humerus was derived from the same total body scan by means of the region of interest (ROI) program. The proximal humerus ROI was located by using the ruler option, where the inferior part of the region was located 96 mm from the most superior part of the humerus head.

Functional tests

The patients ability to walk, the motor function of the paretic leg and arm and the degree of spasticity was assessed immediately before the BMD measurements at baseline and at two, seven and twelve months after the stroke event, weight distribution in standing after 7 months. All evaluations were done by the same investigator (LJ).

Gait

We classified the patient's ability to walk by use of the scale "Functional Ambulation Category" (FAC),[98] which has proved to be useful in stroke rehabilitation.[99] The scale assesses

the amount of human assistance rather than devices needed for ambulation, and scores from 1 (chairbound) to 6 (independent on both level and non-level surfaces). Patients who are unable to walk unless supported by another person are categorised as FAC 2-3, whereas patients who are able to walk at least 6 meters on their own are categorised as FAC 4-6.

Weight distribution in standing

Because the FAC-scale does not reflect any aspects of asymmetrical posture, we assessed the patients body weight distribution during bilateral standing using the "The Balance Performance Monitor" (BPM) (SMS Healthcare, Elizabeth House, Harlow, UK), as described in paper II. The coefficient of variation was found to be 3.6% when two measurements were performed in 10 stroke patients.

Most patients relearn to walk within the first two to three months after stroke,[100-102] and we therefore chose to use weight bearing seven months after the stroke as an integrated measure of symmetry for the period the patients were followed.

Motor function of the paretic leg and arm

The Scandinavian Stroke Scale [103;104] is a measure used to assess the neurologic status of stroke patients. The level of consciousness, eye movement, orientation, paresis of the arm, hand, and leg; facialis paresis, aphasia and gait is evaluated. In paper I and IV we used the SSS subscore for motor function of the leg, and in paper III we used the SSS subscore for motor function of the arm. These subscores are graded in five categories (0: paralysis; 2: can move but not against gravity (severe paresis); 4: raises leg/arm with flexion in knee/elbow (moderate paresis); 5: raises leg/arm straight but with reduced strength (mild paresis); 6: raises leg/arm with normal strength (no paresis).

Spasticity

Spasticity of the paretic arm was assessed according to the modified Ashworth scale[105] ranging from 0: no increase in muscle tone to 4: affected part rigid in flexion or extension.

Methods used in paper IV

BMD was measured at both proximal femurs in the same way as described in paper I, but in the analysis we used the mean values from the right and left side. The patients were measured mean 6 days (SD 4) after the stroke event.

The motor function of the paretic leg was assessed by us of the SSS-scale as described in paper I. Moreover, all participants were interviewed about their alcohol and smoking habits: were they teetotallers or not, did they smoke currently or previously. The stroke patients were asked whether or not they had used assistive devises for walking prior to the stroke and the control subjects were asked about current use of these devises.

Body weight and height was mostly measured in a standing position, except for 27 of the stroke patients, who had their height measured in a supine position, as they were unable to stand. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

The control subjects completed a questionnaire about medical history including current and previous cardiovascular diseases, cancer, diabetes and current use of medication. The same information about the stroke patients was obtained from their medical records.

Statistics

All statistical tests used in this thesis have been described in the papers (I-IV).

Briefly, paired t-tests and two-sample t-tests as well as analysis of variance and their non-parametric counterparts (Wilcoxon Signed Rank Test and Kruskal-Wallis Test for testing within-group and between-group changes, respectively) were used in paper I-III. In paper I, we also took into consideration that the measurements were repeated. In paper IV, logistic regression analysis were performed.

The data were analysed using the Windows 7.5 version of the Statistical Package for the Social Sciences (SPSS).

SUMMERY OF THE PAPERS

Paper I

Walking after stroke - does it matter? Changes in bone mineral density within the first 12 month after stroke longitudinal study

The aim of the first paper was to investigate the degree of demineralisation within the first year after stroke, and to elucidate a possible difference in patients with high versus low ambulatory levels. Forty acute stroke patients were followed (17 initially wheelchair bound and 23 initially ambulatory). BMD was measured in the proximal femur bilaterally mean 6 days, 7 months and one year after stroke onset using dual-energy X-ray absorptiometry. Ambulatory status was independently associated with changes in BMD ($p \leq 0.005$) one year after stroke. The 17 initially wheelchair bound patients had a significant 10% reduction in BMD at the paretic side and 5% reduction at the non-paretic side ($p<0.001$), whereas the 23 patients initially able to walk had a significant loss (3%) only at the paretic side ($p=0.01$). The analysis also indicated that the major reduction in BMD took place within the first 7 months. Two months after stroke 12 of the wheelchair bound patients had relearned to walk. At the paretic side the one year BMD-changes in the patients who stayed wheelchair bound, the patients who relearned to walk within the first two months, and the patients who were able to walk throughout the study were 13%, 8% and 3%, respectively, and a statistically significant trend with ambulatory level was found ($p=0.007$). This study provides clear evidence that lack of mobility and weight bearing early after stroke is an important factor for the greater bone loss in the paretic leg, but that relearning to walk within the first two month after stroke, even with support of another person, may reduce the bone loss after immobilisation.

Paper II

Ambulatory level and asymmetrical weight bearing after stroke affects bone loss in the upper and lower part of the femoral neck differently. Bone adaptation after decreased mechanical loading.

In the second paper, we focused on site specific changes in BMD within the femoral neck. We investigated the effect of walking and asymmetrical weight bearing on the loss of bone mineral in the upper and lower femoral neck. The same 40 patients described in paper I were followed. Regional BMD-changes were computed for the lower and upper femoral neck (the first is mainly influenced by compressive stresses of the hip, the latter by tensile stresses during walking). When comparing the mean BMD loss in groups of patients according to when they relearned to walk, a statistically significant trend in BMD-loss was found in the lower femoral neck on both the paretic and non-paretic side ($p<0.01$ and $p=0.01$ respectively), whereas for the upper femoral neck no significant trend was demonstrated ($p\geq0.1$). The body weight distribution during standing was assessed by use of a force-plate in 38 patients who could stand independently at the 7 months evaluation. The only significant correlation between changes in BMD and asymmetrical weight bearing was found in the lower femoral neck on the paretic side ($r=0.6$, $p<0.001$). This study shows that the reduction in BMD in the femoral neck occurs mainly in the lower part of the neck and on the paretic side. The BMD loss depends on when or if the patients relearn to walk, but also on the amount of body weight born through the paretic leg. Thus, measuring the lower part of the femoral neck may give a better estimate of the impact of gait and weight bearing than measuring the total femoral neck.

Functional status of the paretic arm affects the loss of bone mineral in the proximal humerus after stroke. A one-year prospective study.

Whereas the first two papers give information about changes in BMD in the femoral neck, we studied, in the next paper the effect of decreased arm function after stroke on bone mineral density in the proximal humerus. Twenty-five patients, initially non-ambulating, were evaluated one week after acute stroke and re-evaluated two months, seven months and one year after the stroke. Bone mineral density (BMD) of the proximal humerus was measured and the functional status of the paretic arm assessed. Furthermore, BMD of the head and spine was measured. Within one year the BMD decreased significantly in the proximal humerus at the paretic side. No significant BMD-change was found at this site of the non-paretic arm, in the spine and in the head, although the increase in bone mineral of the head approached the level of significance (+ 2%, $p=0.06$). Looking at subgroups, patients with an initial completely paralysed arm lost 27% ($p<0.001$), patients with severe to moderate paresis lost 11% ($p<0.001$), whereas patients with minor or no paresis had no significant bone loss in the proximal humerus at the paretic side after one year. A statistically significant trend with initial arm function was found both 7 month and one year after the stroke at the paretic side ($p<0.01$). Patients who were paralysed or had severe to moderate paresis both at inclusion and after one year had a larger one-year bone loss in the proximal humerus than the patients who recovered and the patients who were only minor impaired throughout the study, 25%, 8% and 5%, respectively (p-value for linear trend<0.001). We conclude that during the first year after stroke bone mineral is lost in the proximal humerus of the paretic arm, but that the loss depends on the initial degree paresis. Our results suggest that bone loss may be prevented if arm function is regained.

Paper IV

Bone mineral density in acute stroke patients. Low bone mineral density may predict first stroke in women.

Paper IV focus on the BMD before stroke. We examined the relationship between BMD and acute stroke in non-institutionalised men and women aged 60 years and older. Sixty-three stroke patients (33 women and 30 men) and 188 control subjects from the general population were included. BMD was measured using dual-energy-X-ray absorptiometry on both proximal femurs. The measurements of the stroke patients were done 6 days after the onset of stroke. The BMD of the femoral neck in the female stroke patients was 8% lower than in the control subjects (p=0.007). In men, no difference in BMD between the stroke patients and their controls was found. Women with BMD values in the lowest quartile had a higher risk of stroke than women with BMD values in the highest quartile (OR = 4.8), and the p-value for linear trend over the quartiles was statistically significant (p=0.003). The odds ratio for stroke increased 1.9 per standard deviation (0.13 g/cm^2) reduction in BMD, and the association between low BMD and stroke in women remained significant when the analysis was adjusted for potential confounders. We conclude that female, but not male, stroke patients have lower BMD than population controls. Low BMD may, thus, predict stroke in women, but low BMD may also be a marker for frail health.

GENERAL DISCUSSION

Methodological considerations

"The validity of a study is usually separated into two components: the validity of the inferences drawn as they pertain to the members of the source population (internal validity), and the validity of the inferences as they pertain to the people outside that population (external validity or generalizability)." [106]

Internal validity

Internal validity implies that the findings are not a result of bias, confounding or chance.

Bias

Bias (defined as a systematic error) may be divided into selection bias, referring to an error arrised in the process of identifying the study populations, and information or observation bias, which includes any systematic error in the measurement of information on exposure or outcome.

Selection bias

It is expected that all persons with acute stroke from Mid- and Northern Troms, a well defined part of the county with 114 000 inhabitants, are admitted to RiTø. However, although all stroke patients are supposed to be hospitalised, it has been shown (at least in an other part of Norway[4]) that exceptions may be incident stroke cases in nursing homes with small potential for rehabilitation or poor prognosis. In a recent study of stroke incidence in Nord-Trøndelag, Norway, 13.3% of the cases (fatal and not-fatal) were found outside hospital.[4] This may also be true with respect to our study; some patients resident in nursing homes before

stroke may have been eligible, but not included due to non-hospitalisation. However, as one criterion for being included was that the subjects had been able to walk prior to the stroke, we probably have not lost many eligible patients.

Eligible patients were selected according to the selection criteria previously described. Unfortunately, we are not able to supply information about how many stroke patients who were not eligible for the study except for paper IV.

With regard to the longitudinal studies (paper I-III) the participation rate was high as all but one eligible stroke patients hospitalised to RiTø accepted to be enrolled.

For logistic reasons, measurements of the total body BMD were started later than bone densitometry of the proximal femur, and only patients unable to walk at baseline were initially enrolled in the study. There is, however, no reason to expect that the patients who were not able to walk one week after the stroke in one part of the period December 1995 to August 1997 differ from stroke patients in another part of the same time period. Thus, our results with regard to the loss of BMD according to paresis, ambulatory status and time after the stroke should not be influenced by the recruitment procedure (paper I-II).

One important consideration may, however, be that a number of patients did not participate in the study for the entire year. Nevertheless, as the major cause for missing patients during follow-up was severe disease or death, and as the baseline measurements of the patients followed did not differ significantly from those of the patients not followed, the results seem representative for the type of stroke patients we have studied.

Of the stroke patients included in the case-control study (paper IV), 51% were eligible and all but one person agreed to participate. With respect to the control subjects we are quite concerned about selection bias as 51% of the invited individuals abstained to participate. This includes an unknown number who were not eligible due to e.g., previous stroke or hip fracture/osteosynthetic material in the femoral neck. The control subjects were in the letter of

invitation informed that they could only take part in the study if they had no history of stroke or hip fracture, but also that they could refuse to participate. We were not allowed to ask for reasons for non-participation. Thus, we do not know the proportion of possible controls contacted who did not take part in the study due to the exclusion criteria or for other reasons and, consequently not whether our control subjects were more or less healthy than an average same aged person without stroke. We have therefore conducted some new analysis (table 3) and compared our controls to participants in the Tromsø Study (the fourth survey, 1994/95). In this study all individuals aged 25 and above were invited to the screening and very similar or identical questions as those used in our study were posed in a self-administered questionnaire. Eighty-four percent of the subjects aged 60 and above attended. A comparison group from the population survey was constructed, consisting of subjects denying stroke and with the same sex and age (5-year age-group) distribution. The estimated response rate in this group was 77% and the results compared with those from our control group were as follows (table 3):

Table 3. Control subjects (paper IV) compared with participants of the fourth Tromsø survey study

Characteristics	Women		Men	
	Our control group	Population sample	Our control group	Population sample
BMI (kg/cm^2), mean (SD)	26.9 (4)	26.7 (5)	25.4 (3)	25.1 (3)
Current smoker	18 %	17 %	23 %	27 %
Drinks alcohol	56 %	52 %	84 %	78 %
Has diabetes mellitus	9 %	5 %	8 %	6 %
Previous myocardial infarction	9 %	8 %	23 %	14 %
Angina pectoris	21 %	15 %	18 %	18 %
Medication for hypertension	26 %	21 %	20 %	17 %

The table shows that the prevalence of risk factors for stroke in a group of subjects from the Tromsø Study and in our control group was quite similar or, if anything, somewhat higher in the latter group. Thus, our control group does not seem to be particular healthy (with high BMD), and we do not find it likely that selection bias can explain our findings.

Information bias

Bone densitometry with DXA is not time consuming, requires little co-operation from the subject, and because of its high precision it is well suited for the measurement of changes over time. Some systematic errors may, however, occur for example due to changes in body fat mass and changes in positioning between the measurements.

In 1990 Hangartner et al.[107] observed changes in BMD when fat was inhomogenously distributed over the measured area of a phantom. This observation was later confirmed by Tothill et al.[108] who performed a study to evaluate whether measures of total body BMD were influenced by changes in fat mass. The reason for questioning the accuracy of the BMD

measurements was that they had previously found that changes in total bone mineral content correlated positively with changes in body weight, whereas a loss of weight was associated with an increase in BMD. The increase in BMD arose from a reduction in measured bone area, and this was implausible since the bone area would not be expected to change. To test if fat would influence the BMD results, lard was wrapped around the limbs of volunteers (and a phantom) simulating weight changes. Spurious increases in BMC and areas were found, whereas BMD fell slightly, although there had been no true change of bone variables. The measurements were performed by use of a Hologic QDR 1000W DXA-apparatus, but in a later similar study with a Lunar DPX machine, BMD was not affected. Whether changes in fat mass could affect the projected area on the femoral neck or trochanter and, thus, BMD in these ROIs were, however, not evaluated.

It has previously been shown that fat mass of the paretic leg and arm may increase and that lean mass may decreases after stroke.[33] This was also the case in our study.[109] Thus, to evaluate possible fat related artefacts, which might have influenced our BMD-measurements in paper I, we compared the bone area of the femoral neck and the trochanter measured at baseline and one year later. The results are presented in table 4, showing that no significant changes had appeared during follow up, neither in our total population of stroke patients or in the most impaired patients (FAC 1) most prone to changes in fat mass.

TABLE 4. Mean bone area (cm^2) and standard deviation (SD) in the proximal femur at baseline and after 1 year in the paretic and non-paretic leg in all patients followed and in the most impaired patients, separately.

FAC at baseline	Anatomic site		Area at baseline mean (SD)	Area at 1 year mean (SD)	p value (paired t-test)
FAC 1-6 (n=40)	Paretic leg	Femoral neck	5.3 (0.7)	5.4 (0.7)	0.7
		Trochanter	14.1 (3.6)	14.4 (3.2)	0.4
	Non-paretic leg	Femoral neck	5.5 (0.7)	5.4 (0.7)	0.3
		Trochanter	14.2 (2.6)	14.2 (2.8)	0.9
FAC 1 (n=17)	Paretic leg	Femoral neck	5.5 (0.8)	5.5 (0.9)	0.9
		Trochanter	14.5 (4.2)	13.7 (3.9)	0.3
	Non-paretic leg	Femoral neck	5.6 (0.8)	5.6 (0.8)	0.8
		Trochanter	14.2 (2.6)	14.4 (2.8)	0.7

However, in the proximal humerus of the patients who had a paralysed arm at baseline (SSS=0) we did find indication of a decreased size of the measured area (table 5). In case this was due to an artefact the result would be an underestimation of the BMD reduction. Our results in paper III can therefore not be explained by measurement artefacts due to increased fat in the paretic arm.

TABLE 5. Mean bone area (cm^2) and standard deviation (SD) in the proximal humerus at baseline and after 1 year in the paretic and non-paretic arm in all patients followed and in the most impaired patients, separately.

SSS arm at baseline	Anatomic site	Area at baseline mean (SD)	Area at 1 year mean (SD)	p value (paired t-test)
0-6 (n=28)	Paretic arm	35.3 (6.6)	34.3 (9.3)	0.4
	Non-paretic arm	38.5 (9.2)	38.4 (9.3)	0.9
0 (n=9)	Paretic arm	38.0 (9.1)	33.3 (7.5)	0.05
	Non-paretic arm	41.2 (8.4)	39.7 (7.8)	0.5

Proper positioning of the patient is very important when bone densitometry is performed. With respect to measurements of the proximal femur, the foot block provided by the manufacturer helps to keep the leg in an optimal inward rotation of 15 degrees. It may, however, be inadequate to prevent femoral rotation completely, as the patient may still be able to rotate his ankles even though the feet are secured to the block by Velcro straps. The rotation of the femur may affect the bone mineral measurements. Goh et al.,[110] measuring fresh frozen cadaveric femurs, found that both BMD and BMC at 30 and 45 degree of internal and external rotation were higher than the values at neutral position, highest at 45 degree internal rotation. The explanation was that the femoral neck length in the scan image becomes progressively shorter when the angle of rotation is increased. This in turn increase the depth of the femur neck exposed to the X-ray beam, thus giving increased BMD and BMC readings.

The most appropriate femoral orientation for DXA scan of the femoral neck is the neutral position, which, in vivo, can be achieved rotating the legs internally 15 degree. Svendsen et al.[111] found in their in vivo study of 10 pre- and 10 postmenopausal women, that mean BMD of the femoral neck was not influenced by rotation from 0 to 45 degree inward rotation, whereas with 45 degree outward rotation the BMD increased significantly by 5% to 11%. BMD of trochanter was less influenced.

Stroke patients may over time develop strong spasticity with inward rotation, and according to Goh et al.[110] but not Svendsen et al.[111] this may, therefore, interfere with the BMD-measurements. However, the bone loss of the femoral neck is then underestimated, and this bias can therefore not explain our results (paper I). To our knowledge, no study has evaluated the effects of rotation of the arm on the BMD readings of the humerus.

In paper III, BMD of the proximal humerus, head and spine were derived from the total body scan. Whole body scans using larger pixel size than regional scans may be more prone to a certain artefact as reported by Rubenoff et al.[112] The artefact arises when pixels that include

mass. Thus, if a change in fat mass of the paretic leg is a confounder of changes in bone mass, our measurements of bone loss may have been somewhat underestimated. With respect to changes in body weight, Ramnemark et al. have shown that this does not seem to influence the changes in bone mass after stroke.[44]

Although the main reason for development of osteoporosis in patients with stroke most likely is due to the paresis and immobilisation, low intake of e.g., calcium and vitamin D may be factors influencing the bone loss. Several studies have found vitamin D deficiency after stroke [121-126] probably because malnutrition is frequent,[127;128] and because the patients may stay indoors more often. In our study, we did not examine possible differences in nutrition between subjects in the different gait- or SSS-categories. However, if the groups differed substantially with respect to food habits (e.g., intake of vitamin D) this might to some extend explain the differences between the groups consisting of subjects at different functional levels, but probably not that the bone loss was larger in the paretic than in the non-paretic leg or arm.

Warfarin is used in the treatment of patients with atrial fibrillation. It has been suggested that BMD is significantly lower in stroke patients with long-term warfarin treatment than in untreated patients, and that the difference between BMD of the paretic and non-paretic side is larger in the latter group.[129] If atrial fibrillation was present mainly among the most severely impaired patients and these patients therefore had been treated with this medication, warfarin use could contribute to our findings. However, in a study by Jørgensen et al.,[130] aiming to examine what determines recovery in patients with severe stroke, no difference was found with respect to presence of atrial fibrillation and good versus poor outcome.

From a theoretical point of view several potential confounders may be considered in paper IV. With respect to the women, BMD of the femoral neck was at least 8% lower in the stroke patients than in the control subjects, also when we adjusted for the variables in table 1 (paper IV) ($p \leq 0.01$ when the variables were entered one-by one in an univariate analysis o

variance model). In men, there were still no statistical significantly differences in BMD of the femoral neck after adjustments. Because of the limited number of cases we did not believe that it was prudent to include all variables (from table 1, paper IV) in the analysis of risk for stroke.

As discussed in the paper, the information about some of the possible confounders was not so detailed that residual confounding can be excluded. One example is information about physical activity. Because acute stroke patients often are confused, and more of our patients had aphasia or cognitive dysfunction such as amnesia, it was not possible to ask complex questions about their previous physical activity level. We considered the use of walking aids as a reasonable marker of current physical activity, but this leaves, of course, an ample room for residual confounding. This is, however, only important if a causal relationship is considered. The implications of our findings for rehabilitation are unchanged.

Power and chance

Theoretically, the sample size needed to show a BMD loss of for example 10% (e.g., a change from 1.0 g/cm^2 to 0.9 g/cm^2 (SD 0.1)) using a paired t-test has to be at least 3 (α = 0.05 and β = 0.20). Our study was therefore large enough to detect clinical significant changes within the groups followed. However, to show a difference of 10% between two groups (using a two sample t-test, and the same criteria as mentioned above) the number of people in each group has to be at least 16. The size of some of our subgroups was therefore too small to expect that significant differences between groups could be found. Nevertheless, when contrasting the groups in our one-way analysis of variance, the main results demonstrated a distinct pattern of different rates of bone-loss according to paresis and FAC or SSS status (paper I-III), which cannot be explained by lack of statistical power.

With respect to the case control study (paper IV) the minimum sample size of each group to demonstrate an OR = 2, comparing two groups (a case and a control group, 1:3) was 90:270. In our analysis of the men, we may therefore have accepted a false null-hypothesis, but regarding the women, the linear trend over the BMD quartiles cannot be related to power problems.

There is always a risk, especially when multiple comparisons are performed, that a significant result has been achieved by chance. To reduce the risk of rejecting a true null hypothesis (type I error) one may therefore adjust for multiple comparisons. However, the possibility of accepting the null hypotheses when, in fact, a difference exists (type II error) is then, simultaneously, larger. We did not adjust for multiple comparisons, first, because the statistical tests performed were a consequence of the hypothesis stated before the study was initiated, second, because an adjustment for multiple analyses may lead to more errors of interpretation when the data under evaluation are actual observations.[131]

Other considerations with respect to our measurements

Time of the 1st measurement

BMD in the patients was measured approximately 1 week after stroke onset, and one concern may be that some bone loss had occurred already within this period of time. There was, however, no difference between the BMD values of the paretic and the non-paretic side at baseline. Furthermore, as the mean bone loss after 2 months in the most impaired patients was 7% in the proximal humerus and 3% in the femoral neck (and only significant in the latter), it is unlikely that any significant bone loss took place before the first measurement.

Measurement of bone mineral density in the upper and lower part of the femoral neck

The Lunar program used to assess BMD in the upper and lower part of the femoral neck has previously been used to study BMD in healthy women and men,[132] to assess prospectively the risk of hip fracture,[133] and in a large European cross-sectional study to explore possible age related differences in BMD loss in these two parts of the neck.[134] It is, however, still an experimental software, and further studies of its validity are strongly needed.

Gait and weight distribution in standing

We classified the patient's ability to walk by use of the scale "Functional Ambulation Category". The scale assess whether the patient is able to walk 6 meters, and the amount of human assistance eventually needed when ambulating. We did not assess how often the patients were in a standing position, how often they walked and how far, which is clearly a limitation when studying the effect of weight bearing.

Our assessment of asymmetrical weight bearing is also somewhat limited. The BPM provides measurements of the left-right weight distribution only during static standing, and only during a short period of time (30 seconds). Whether the patient stands more or less asymmetrical after a longer time is unknown. Moreover, the measurement of weight distribution when standing may not be related to dynamic activities such as walking. It has been shown that improvement in the proportion of weight born by the hemiplegic limb during standing may not result in a concomitant improvement in interlimb symmetry during walking.[135] Our test of asymmetrical weight bearing may therefore underestimate the asymmetry in the patients usual gait pattern. In addition, the influence of weight bearing on the paretic leg during walking might be even more important as bone adaptation is driven by dynamic rather than static loading.[136]

SSS and spasticity

The SSS-subscore is not a specific test of muscle strength, neither is muscle performance during function directly measured. However, the test provides an overall indication of motor loss and recovery. Similar tests have previously been found to correlate with different functional tests and indexes. Feigenson et al.[137] found that weakness (mild, moderate or severe) was a powerful predictor of dressing, feeding and hygiene performance after stroke. Furthermore, Bohannon[138] points out in a review paper that the Barthel index correlates significantly with muscle weakness after stroke in several studies. A general problem in measuring muscle strength in stroke patients is, however, that it may be difficult to find a standardised position to measure the strength and that some patients cannot cooperage sufficiently. Another problem is that spasticity may interfere with the measurements.

A reliable measurement of spasticity may be difficult to obtain due to patient variability. Inter- and intra-rater agreement of the modified Ashworth scale has, however, been proved to be good when tone of the elbow flexors are tested in stroke patients.[105;139]

External validity

Based on estimations from the Tromsø population (paper IV), about half of all patients with acute stroke were eligible for our study of change in BMD in the proximal femur after stroke (paper I-II). Not eligible were e.g., patients who had been unable to walk prior to the stroke, patients with a previous stroke and unconscious patients. Their baseline BMD value may have differed from that of the patients participating in the study, but there is no reason to expect that the bone loss should differ substantially from what we found in our study population; if anything it might be even larger in the most severely impaired patients (e.g., the unconscious patients). With regard to the change in BMD in the proximal humerus after stroke (paper III), only patients who were unable to walk one week after the stroke event were included. It is possible that this has resulted in a higher mean BMD-reduction in this study group than in the average stroke patient able to walk one week after the stroke.

Other factors that may threaten the external validity of our study (paper I-III) are that stroke patients living in Northern Norway, with long winters and icy roads, may have less outdoor activities (and sunlight exposure) than people with stroke living more south. Thus, it is possible that patients who live under warmer climatic conditions have a somewhat smaller BMD-reduction than our patients.

The generalizability of our findings with regard to high stroke risk in women with low BMD (paper IV) is, as we have discussed above, open to some debate and needs conformation.

PREVIOUS STUDIES COMPARED WITH OURS

As reviewed in the introduction, very few studies have prospectively assessed changes in BMD after stroke. One study conducted in Sweden by Ramnemark et al.[43] is to some extent comparable, and the BMD loss found in the paretic and non-paretic leg in our wheelchair bound patients corresponds to the bone loss in their study. The Swedish group did, however, only include stroke patients generally immobile and the influence of motor function or ambulatory level could therefore not be examined appropriately. We included patients at different ambulatory levels and showed that ambulatory status at baseline was independently associated with the changes in BMD. Moreover, the effect of walking was further strengthened as a statistically significant trend with ambulatory level was demonstrated.

A major focus in rehabilitation of the hemiparetic stroke patient is the improvement of balance through increased loading of the affected lower limb, resulting in a more symmetric standing posture.[140-142] We showed that walking early after stroke and symmetrical weight bearing in standing is also important for preserving bone mineral in the lower femoral neck. The impact of weight bearing on BMD within the femoral neck has not been studied previously, neither in stroke patients or other types of patients. Our findings are, however, consistent with studies on physical activity showing that the osteogenic effects of training seem to be quite specific to the anatomic sites at which the mechanical strains occur.[143;144]

Osteoporosis in the paretic arm after stroke has been described previously (table 1), but the results in the studies are conflicting with respect to the relationship between arm function and bone loss. Some studies [144] find that good functional status and muscle strength are protective against bone loss,[32;42] and that spasticity is associated with bone loss on the trabecular site.[42] Other studies find no correlation between motor function and/or spasticity of the arm and demineralisation.[33;43] Also studies of patients with paresis due to a spinal cord

injury presents inconsistent results. Kirateli et al.[145] describe significantly greater bone mass in the arms of paraplegic subjects as well as quadriplegic subjects who habitually uses manual wheelchairs, but reduced bone mass in quadriplegics who are unable to use a manual wheelchair. In contrast, Garland et al.[65] find reduced arm bone mass in both quadriplegic and paraplegic patients. An explanation for the contradictionary results in these studies on both hemiplegic and spinal cord injured patients with arm paresis may be that some samples were small. This might have involved group differences in activity, muscle strength, age, or some other confounding factor which affects bone mass.

It has been discussed whether bone mineral from immobilised parts of the body may be redistributed to other parts of the skeleton. Ramnemark et al.,[43] who found a 6% significant increase in BMD in the ultradistal radius of the non-paretic arm 1 year after stroke, argued that although this BMD change most likely was due to increased physical activity, a redistribution of bone mineral from the paretic extremities might be another explanation. We did not find that BMD of the proximal humerus on the non-paretic side increased. The BMD-change in the head did, however, approach the level of significance, which may indicate that a redistribution of bone mineral may have occurred in our patients. A similar increase in bone mass of the head after immobilisation has also been found in other studies, as for example in people volunteering in long duration bed rest.[146]

Both cross-sectional and longitudinal studies of stroke patients find greater proportional losses in the upper limbs than in the lower limbs on the paretic side.[31-33,39,43,44] This may be an indication that rehabilitation aiming at regaining mobility after stroke is more effective at arresting bone loss in the lower limbs than the upper limbs. Another explanation is proposed by Kerr et al.[144] who suggests that different sites in the skeleton may have different osteogenetic thresholds for loading, and that the load thresholds for the upper limb may differ from those of the weight bearing bones of the legs.

In paper IV we found that female stroke patients had lower BMD than population controls, a result which is consistent with the results found by Browner et al.[96] However, whereas Browner et al. showed that the risk was related to BMD of the calcaneus and proximal radius, we found that it was related to BMD of the proximal femur. Moreover, compared with Browner et al. we found that the risk was somewhat higher (RR 1.9 per SD decrease in BMD vs. 1.3).[96] With respect to men, we do not believe that the relationship between BMD and stroke risk has been studied previously.

IMPLICATIONS FOR CLINICAL PRACTICE AND FURTHER RESEARCH

Exercise as treatment to prevent bone loss?

There is an ongoing discussion related to the importance of bone density measurements. Prospective studies have demonstrated a relationship between bone density and the incidence of fractures, but because of the overlap of measurements obtained from osteoporotic and control subjects, the predictive power of these absorptiometric variables may be somewhat limited.[85;147;148] However, although factors other than low bone mass, such as fall-related factors, and geometric and micro-architectural properties of the bone contribute to the risk of fracture,[149-152] low trauma fractures rarely occur in the absence of reduction in bone mass.[153;154]

The results of exercise trials aiming to increase bone mass in elderly people are rather disappointing,[155] and prevention of severe bone loss is therefore important. As we show that bone loss after stroke is related to impairment, future studies exploring if intensive exercise and/or weight bearing in a standing position early after the acute event may prevent bone loss (and fractures) are warranted. Furthermore, we need studies exploring whether different rates of bone loss within the femoral neck after immobilisation are important with respect to hip fracture. Moreover, differences in BMD of the upper and lower femoral neck may be related to type of hip fracture. Duboeuf [133] found that both upper and lower femoral neck BMD measurements were significantly predictive of trochanteric fracture, but only the upper femoral neck BMD was related to cervical fracture. Some studies,[18;20;156] but not all,[17] have found that among stroke patients trochanteric fracture may be relative more common than fracture of the femoral neck.

The advantage of exercise, next to the potential of preventing or diminishing the loss of bone, is that risk factors for falls such as low muscle mass, muscle strength, poor balance and

coordination may be influenced simultaneously.[157] Compared with individual factors, low bone mass combined with other risk factors for fracture increase fracture risk substantially.[158] Because many stroke patients not only have low bone mass, but also are at increased risk of falling,[24-29] strategies for fracture prevention should include efforts to diminish the number and severity of falls. Moreover, protection of the critical anatomic sites of the human body (especially the hip) may be worth considering. Use of external hip protectors may reduce the number of hip fractures considerably as shown in frail elderly adults.[159;160]

A positive effect of exercise on bone mass seems only to be established if sufficient calcium is available (>1000 mg/day).[161] It has been shown, at least in elderly Chinese women with an extremely low calcium intake, that calcium supplements and load-bearing exercise had a better treatment effect on BMD of the femoral neck than load-bearing exercises alone.[162] This may also be true for stroke patients where malnutrition is a frequent problem.[127;128] Moreover, vitamin D supplementation may have an effect in these patients as deficiency of this vitamin may be common and supplements may decrease the bone loss.[121-126]

A combination of exercise and bisphosphonates, known to be powerful inhibitors of osteoclastic bone resorption,[163] may be another intervention worth to explore. In spinal cord injured patients, it has been shown that both pamidronate treatment during the first 6 months and ambulatory status had significant effects on retarding the development of osteoporosis.[118] This combined effect has not been studied in stroke patients, but only recently it was shown that etidronate therapy could prevent some of the bone loss in hemiplegic patients.[164] Within 56 weeks of treatment, BMD of the 2nd metacarpal on the paretic side decreased by 2.3% in the patients treated with etidronate and by 4.5% in the placebo group. Further studies on other ROIs of the skeleton are needed.

Low BMD in acute stroke patients. Is there a cause-effect relationship?

In our case-control study we confirmed the results of the study by Browner et al.[7] by showing that women with acute stroke have lower BMD than population controls, and that low BMD may predict stroke. Longitudinal studies in men are, however, still lacking.

Although cardiovascular diseases and osteoporosis are generally considered unrelated, several studies now indicate that atherosclerosis and low BMD may be associated. In a study of postmenopausal women it was found that low bone mineral content at the menopause was a risk factor for increased mortality in later life, especially from cardiovascular disease.[165]

Vascular calcification occurs more often in women with osteoporosis.[166-168] In a study by Uyama et al.[167] a significant correlation of plaque score with total cholesterol level and low BMD was found in women, and the results suggested a relation between carotid atherosclerosis and osteoporosis. The relationship has not been studied in men. Three other studies have examined the association between aortic calcification and BMD. None of the studies included men, and the results were rather contradictionary.[166;168;169]

The association between cardiovascular disease and osteoporosis may also be related to blood pressure. In a large study of 3676 women high blood pressure at baseline predicted increased bone loss during the 3.5 years of follow-up.[88] A cross-sectional study of 47 men also showed that blood pressure was inversely related to bone mass.[170] In a recent study, Jorde et al.[171] showed that reduced intake of calcium was associated with high levels of serum parathyroid hormone (PTH). Furthermore, this was associated with moderately reduced BMD in the lumbar spine. In women, high levels of serum PTH was also associated with markedly increased blood pressure. Whether changes in blood pressure are related to changes in BMD has not been examined.

Diabetes is an established risk factor for cardiovascular diseases. Most studies, but not all, have reported low BMD values in type I diabetes,[172] and in postmenopausal women it has

been shown that while insulin-dependent patients had relatively low BMD, non-insulin-dependent patients had higher BMD than normal women.[173] Results from the Nord-Trøndelag Health Survey [174] showed that women younger than 75 years with type I diabetes or with type II diabetes of long duration had an increased risk of hip fracture. In older men, there was an increased risk associated with Type II diabetes of shorter duration. Whether the increased risk was attributed to reduced bone mass was not determined.

However, although several lines of evidence suggest a link between BMD and cardiovascular disease risk, it is at present unclear whether there is a cause-effect relationship between low BMD and high risk of cardiovascular diseases. As is may be difficult to see how BMD itself should affect the cardiovascular system, several investigators have argued against a causal relation and suggested that low BMD is rather a marker of poor general health and ageing.[6,7,10,11] Further studies are, nevertheless, needed.

CONCLUSION

This thesis highlights several clinically important questions related to bone loss the first year following stroke and with regard to bone mass at stroke onset:

Lack of mobility and weight bearing early after stroke is an important factor for the greater bone loss in the proximal femur on the paretic side. Relearning to walk within the first two month after stroke, even with support of another person may, however, reduce the bone loss after immobilisation.

The reduction in BMD in the femoral neck appears mainly to occur in the lower part of the neck and on the paretic side. It depends on when or if the patients start to walk after stroke, but also on the amount of body weight born through the paretic leg. Thus, measuring the lower part of the femoral neck may give a better estimate of the impact of gait and weight bearing than measuring the total femoral neck.

During the first year after stroke bone mineral is lost in the proximal humerus of the paretic arm, but the loss depends on the initial degree of the paresis. However, stroke patients who regain almost normal arm function within one year, despite being severely impaired initially, loose less bone mineral than patients where a severe paresis persists.

Female, but not male, stroke patients have lower femoral neck BMD than population controls. At present it is unclear if low BMD actually increases the risk of stroke in women or reflects a poor health with both high stroke risk and low BMD.

ERRATA

Paper I:

Reference 18 should be: Lindenstrøm E, Christiansen LW, Hansen BR, Nielsen BW. Reliability of Scandinavian Stroke Scale. *Cerebrovasc Dis* 1991;1:103-7.

Paper II:

Table 1, (Erratum, p 140): BMD at baseline in the lower femoral neck of the paretic leg in the patients unable to walk at 7 months should be 1.01 (0.17).

REFERENCE LIST

1. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull.World Health Organ* 1976;**54**:541-53.

2. Bonita R. Epidemiology of stroke. *Lancet* 1992;**339**:342-4.

3. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997;**349**:1269-76.

4. Ellekjær H, Holmen J, Indredavik B, Terent A. Epidemiology of stroke in Innherred, Norway, 1994 to 1996. Incidence and 30-day case-fatality rate. *Stroke* 1997;**28**:2180-4.

5. Ellekjær H. Epidemiological studies of stroke in a Norwegean population. Incidence, risk factors and prognosis. 2000. Norwegian University of Science and Technology, Trondheim. (Thesis)

6. Wyller TB, Bautzholter E, Holmen J. Prevalence of stroke and stroke-related disability in North Trøndelag county, Norway. *Cerebrovasc Dis* 1994;**4**:421-7.

7. Jørgensen HS, Nakayama H, Pedersen PM, Kammersgaard L, Raaschou HO, Olsen TS. Epidemiology of stroke-related disability. *Clin.Geriatr.Med.* 1999;**15**:785-99.

8. Melton LJ 3rd. Epidemiology of fractures. In Riggs BL, Melton III LJ, eds. *Osteoporosis. Etiology, diagnosis, and mamagement.*, pp 225-47. Philadelphia: Lippincott-Raven, 1995.

9. Cummings SR, Nevitt MC. A hypothesis: the causes of hip fractures. *J Gerontol.* 1989;**44**:M107-M111.

10. Bulajic-Kopjar M, Wiik J, Nordhagen R. Regional differences in the incidence of femoral neck fractures in Norway. *Tidsskr.Nor Laegeforen.* 1998;**118**:30-3.

11. Sernbo I,.Johnell O. Consequences of a hip fracture: a prospective study over 1 year. *Osteoporos.Int* 1993;**3**:148-53.

12. Forsén L, Søgaard AJ, Meyer HE, Edna T, Kopjar B. Survival after hip fracture: short and long-term exess mortality according to age and gender. *Osteoporos.Int.* 1999;**10**:73-8.

13. Browner WS, Pressman AR, Nevitt MC, Cummings SR. Mortality following fractures in older women. The study of osteoporotic fractures. *Arch.Intern.Med.* 1996;**156**:1521-5.

14. Meyer HE, Tverdal A, Falch JA, Pedersen JI. Factors associated with mortality after hip fracture. *Osteoporos.Int* 2000;**11**:228-32.

15. Cooper C. The crippling consequences of fractures and their impact on quality of life. *Am.J.Med.* 1997;**103**:12S-7S.

16. Kanis J, Oden A, Johnell O. Acute and long-term increase in fracture risk after hospitalization for stroke. *Stroke* 2001;**32**:702-6.

17. Ramnemark A, Nyberg L, Borssén B, Olsson T, Gustafson Y. Fractures after stroke. *Osteoporos.Int.* 1998;**8**:92-5.

18. Chiu KY, Pun WK. A prospective study on hip fractures in patients with previous cerebrovascular accidents. *Injury* 1992;**23**:297-9.

19. Mulley G, Espley AJ. Hip fracture after hemiplegia. *Postgrad.Med J.* 1979;**55**:264-5.

20. Poplingher AR, Pillar T. Hip fracture in stroke patients. Epidemiology and rehabilitation. *Acta Orthop.Scand.* 1985;**56**:226-7.

21. Gustafson Y, Berggren D, Brännström B, Bucht G, Norberg A, Hansson LI *et al.* Acute confusional states in elderly patients treated for femoral neck fracture. *J.Am.Geriatr.Soc.* 1988;**36**:525-30.

22. Gustafson Y, Brännström B, Berggren D, Ragnarsson JI, Sigaard J, Bucht G *et al.* A geriatric-anesthesiologic program to reduce acute confusional states in elderly patients treated for femoral neck fractures. *J.Am.Geriatr.Soc.* 1991; **39**:655-62.

23. Ramnemark A, Nilsson M, Borssén B, Gustafson Y. Stroke, a major and increasing risk factor for femoral neck fracture. *Stroke* 2000;**31**:1572-7.

24. Byers V, Arrington ME, Finstuen K. Predictive risk factors associated with stroke patient falls in acute care settings. *J Neurosci Nurs* 1990;**22**:147-54.

25. Davenport RJ, Dennis MS, Wellwood I, Warlow CP. Complications after acute stroke. *Stroke* 1996;**27**:415-20.

26. Dromerick A, Reding M. Medical and neurological complications during inpatient stroke rehabilitation. *Stroke* 1994;**25**:358-61.

27. Forster A, Young J. Incidence and consequences of falls due to stroke: a systematic inquiry. *BMJ* 1995;**311**:83-6.

28. Nyberg L, Gustafson Y. Patient falls in stroke rehabilitation. A challenge to rehabilitation strategies. *Stroke* 1995;**26**:838-42.

29. Sackley CM. Falls, sway, and symmetry of weight-bearing after stroke. *Int.Disabil.Stud.* 1991;**13**:1-4.

30. Brandstater ME, de Bruin H, Gowland C, Clark BM. Hemiplegic gait: analysis of temporal variables. *Arch.Phys.Med.Rehabil.* 1983;**64**:583-7.

31. Hamdy RC, Krishnaswamy G, Cancellaro V, Whalen K, Harvill L. Changes in bone mineral content and density after stroke. *Am.J.Phys.Med.Rehabil.* 1993;**72**:188-91.

32. Hamdy RC, Moore SW, Cancellaro VA, Harvill LM. Long-term effects of strokes on bone mass. *Am.J.Phys.Med.Rehabil.* 1995;**74**:351-6.

33. Iversen E, Hassager C, Christiansen C. The effect of hemiplegia on bone mass and soft tissue body composition. *Acta Neurol.Scand.* 1989;**79**:155-9.

34. del Puente A, Pappone N, Mandes MG, Mantova D, Scarpa R, Oriente P. Determinants of bone mineral density in immobilization: a study on hemiplegic patients. *Osteoporos.Int.* 1996;6:50-4.

35. Denham MJ. Progressive osteoporosis in hemiplegia. *Gerontol.Clin.(Basel)* 1973;**15**:361-5.

36. Goodman CR. Osteoporosis as early complication of hemiplegia. *N.Y.State J.Med.* 1971;71:1943-5.

37. Hodkinson HM, Brain AT. Unilateral osteoporosis in longstanding hemiplegia in the elderly. *J.Am.Geriatr.Soc.* 1967;**15**:59-64.

38. Iwamoto J, Tsukimura T, Takeda T. Bone mineral density of metatarsus in hemiplegic subjects. *Am.J.Phys.Med.Rehabil.* 1999;**78**:202-7.

39. Liu M, Tsuji T, Higuchi Y, Domen K, Tsujiuchi K, Chino N. Osteoporosis in hemiplegic stroke patients as studied with dual-energy X-ray absorptiometry. *Arch.Phys.Med.Rehabil.* 1999;**80**:1219-26.

40. Naftchi NE, Viau AT, Marshall CH, Davis WS, Lowman EW. Bone mineralization in the distal forearm of hemiplegic patients. *Arch.Phys.Med.Rehabil.* 1975;**56**:487-92.

41. Panin N, Gorday WJ, Paul BJ. Osteoporosis in hemiplegia. *Stroke* 1971;**2**:41-7.

42. Prince RL, Price RI, Ho S. Forearm bone loss in hemiplegia: a model for the study of immobilization osteoporosis. *J.Bone Miner.Res.* 1988;**3**:305-10.

43. Ramnemark A, Nyberg L, Lorentzon R, Englund U, Gustafson Y. Progressive hemiosteoporosis on the paretic side and increased bone mineral density in the nonparetic arm the first year after severe stroke. *Osteoporos.Int.* 1999;**9**:269-75.

44. Ramnemark A, Nyberg L, Lorentzon R, Olsson T, Gustafson Y. Hemiosteoporosis after severe stroke, independent of changes in body composition and weight. *Stroke* 1999;**30**:755-60.

45. Sato Y, Maruoka H, Honda Y, Asoh T, Fujimatsu Y, Oizumi K. Development of osteopenia in the hemiplegic finger in patients with stroke. *Eur.Neurol.* 1996;**36**:278-83.

46. Takamoto S, Masuyama T, Nakajima M, Seikiya K, Kosaka H, Morimoto S *et al.* Alterations of bone mineral density of the femurs in hemiplegia. *Calcif.Tissue Int.* 1995;**56**:259-62.

47. Mosekilde L. Knoglevævets biologi. Fysiologiske, kliniske og farmakologiske aspekter af relationerne mellem struktur og funktion. Denmark: Pharma Division, Ciba.Geigy A/S, 1989.

48. Akesson K. Biochemical markers of bone turnover. A review. *Acta Orthop.Scand.* 1995;**66**:376-86.

49. Heaney RP, Matkovic V. Inadequate peak bone mass. In Riggs BL, Melton III LJ, eds. *Osteoporosis. Etiology, diagnosis, and mamagement.*, pp 115-31. Philadelphia: Lippincott-Raven, 1995.

50. Gallagher JC, Goldgar D, Moy A. Total bone calcium in normal women: effect of age and menopause status. *J Bone Miner.Res.* 1987;**2**:491-6.

51. Ensrud KE, Palermo L, Black DM, Cauley J, Jergas M, Orwoll ES *et al.* Hip and calcaneal bone loss increase with advancing age: longitudinal results from the study of osteoporotic fractures. *J.Bone Miner.Res.* 1995;**10**:1778-87.

52. Wolff J. Das Gestez der Transformation der Knochen. Berlin: Hirschwald, 1892.

53. Frost HM. Bone "mass" and the "mechanostat": a proposal. *Anat.Rec.* 1987;**219**:1-9.

54. Lanyon LE. Functional strain in bone tissue as an objective, and controlling stimulus for adaptive bone remodelling. *J.Biomech.* 1987;**20**:1083-93.

55. Turner CH. Homeostatic control of bone structure: an application of feedback theory. *Bone* 1991;**12**:203-17.

56. Suominen H. Bone mineral density and long term exercise. An overview of cross-sectional athlete studies. *Sports Med.* 1993;**16**:316-30.

57. Forwood MR, Burr DB. Physical activity and bone mass: exercises in futility? *Bone Miner.* 1993;**21**:89-112.

58. Chilibeck PD, Sale DG, Webber CE. Exercise and bone mineral density. *Sports Med.* 1995;19:103-22.

59. Vuori I, Heinonen A, Sievänen H, Kannus P, Pasanen M, Oja P. Effects of unilateral strength training and detraining on bone mineral density and content in young women: a study of mechanical loading and deloading on human bones. *Calcif.Tissue Int.* 1994;**55**:59-67.

60. Heinonen A, Sievänen H, Kannus P, Oja P, Vuori I. Effects of unilateral strength training and detraining on bone mineral mass and estimated mechanical characteristics of the upper limb bones in young women. *J.Bone Miner.Res.* 1996;11:490-501.

61. Wolff I, van Croonenborg JJ, Kemper HC, Kostense PJ, Twisk JW. The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporos.Int.* 1999;9:1-12.

62. Järvinen M, Kannus P. Injury of an extremity as a risk factor for the development of osteoporosis. *J.Bone Joint Surg.Am.* 1997;79:263-76.

63. Biering-Sørensen F, Bohr HH, Schaadt OP. Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury. *Eur.J Clin.Invest* 1990;20:330-5.

64. Demirel G, Yilmaz H, Paker N, Onel S. Osteoporosis after spinal cord injury. *Spinal Cord.* 1998;36:822-5.

65. Garland DE, Stewart CA, Adkins RH, Hu SS, Rosen C, Liotta FJ *et al.* Osteoporosis after spinal cord injury. *J.Orthop.Res.* 1992;10:371-8.

66. Tsuzuku S, Ikegami Y, Yabe K. Bone mineral density differences between paraplegic and quadriplegic patients: a cross-sectional study. *Spinal Cord.* 1999;37:358-61.

67. Wilmet E, Ismail AA, Heilporn A, Welraeds D, Bergmann P. Longitudinal study of the bone mineral content and of soft tissue composition after spinal cord section. *Paraplegia* 1995;33:674-7.

68. Goemaere S, Van Laere M, De Neve P, Kaufman JM. Bone mineral status in paraplegic patients who do or do not perform standing. *Osteoporos.Int* 1994;4:138-43.

69. Young DR, Niklowitz WJ, Brown RJ, Jee WS. Immobilization-associated osteoporosis in primates. *Bone* 1986;7:109-17.

70. Minaire P. Immobilization osteoporosis: a review. *Clin.Rheumatol.* 1989;8 Suppl 2:95-103.

71. Sievänen H, Kannus P, Heinonen A, Oja P, Vuori I. Bone mineral density and muscle strength of lower extremities after long-term strength training, subsequent knee ligament injury and rehabilitation: a unique 2-year follow-up of a 26-year-old female student. *Bone* 1994;15:85-90.

72. Mazess RB, Whedon GD. Immobilization and bone. *Calcif.Tissue Int.* 1983;35:265-7.

73. LeBlanc A, Schneider V. Can the adult skeleton recover lost bone? *Exp.Gerontol.* 1991;26:189-201.

74. Kannus P, Sievänen H, Järvinen M, Heinonen A, Oja P, Vuori I. A cruciate ligament injury produces considerable, permanent osteoporosis in the affected knee. *J.Bone Miner.Res.* 1992;7:1429-34.

75. Krall EA, Dawson-Hughes B. Heritable and life-style determinants of bone mineral density. *J Bone Miner.Res.* 1993;8:1-9.

76. Salamone LM, Glynn NW, Black DM, Ferrell RE, Palermo L, Epstein RS *et al.* Determinants of premenopausal bone mineral density: the interplay of genetic and lifestyle factors. *J Bone Miner.Res.* 1996;11:1557-65.

77. Cooper C. Epidemiology of osteoporosis. *Osteoporos.Int.* 1999;9 Suppl 2:S2-S8.

78. Dempster DW, Lindsay R. Pathogenesis of osteoporosis. *Lancet* 1993;341:797-801.

79. Genant HK, Engelke K, Fuerst T, Gluer CC, Grampp S, Harris ST *et al.* Noninvasive assessment of bone mineral and structure: state of the art. *J Bone Miner.Res.* 1996;11:707-30.

80. Sievänen H, Oja P, Vuori I. Precision of dual-energy x-ray absorptiometry in determining bone mineral density and content of various skeletal sites. *J.Nucl.Med.* 1992;**33**:1137-42.

81. Mosekilde L. Age-related changes in bone mass, structure, and strength-effects of loading. *Z.Rheumatol.* 2000;**59 Suppl 1**:1-9.

82. Njeh CF, Boivin CM, Langton CM. The role of ultrasound in the assessment of osteoporosis: a review. *Osteoporos.Int.* 1997;7:7-22.

83. Johansen A, Stone MD. The effect of ankle oedema on bone ultrasound assessment at the heel. *Osteoporos.Int.* 1997;**7**:44-7.

84. Johansen A, Harris W, Stone M. Portable ultrasound assessment of bone in the elderly: Hemiparesis following stroke as a model for disuse osteoporosis. *Arch.Gerontol.Geriat.* 1997;**25**:299-304.

85. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K *et al.* Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet* 1993;**341**:72-5.

86. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;**312**:1254-9.

87. Pauwells F. Biomechanics of the locomotor apparatus. Contribution to the functional anatomy of the locomotor apparatus. Berlin: Springer-Verlag, 1980.

88. Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA. High blood pressure and bone-mineral loss in elderly white women: a prospective study. Study of Osteoporotic Fractures Research Group. *Lancet* 1999;**354**:971-5.

89. Colantonio A, Kasl SV, Ostfeld AM. Level of function predicts first stroke in the elderly. *Stroke* 1992;**23**:1355-7.

90. Jones G, Nguyen T, Sambrook P, Kelly PJ, Eisman JA. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. *BMJ* 1994;**309**:691-5.

91. Kiel DP, Zhang Y, Hannan MT, Anderson JJ, Baron JA, Felson DT. The effect of smoking at different life stages on bone mineral density in elderly men and women. *Osteoporos.Int.* 1996;**6**:240-8.

92. Nguyen TV, Center JR, Eisman JA. Osteoporosis in elderly men and women: effects of dietary calcium, physical activity, and body mass index. *J.Bone Miner.Res.* 2000;**15**:322-31.

93. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM *et al.* American Heart Association Prevention Conference. IV. Prevention and rehabilitation of stroke. Risk factors. *Stroke* 1997;**28**:1507-17.

94. Sacco RL, Gan R, Boden-Albala B, Lin IF, Kargman DE, Hauser WA *et al.* Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke* 1998;**29**:380-7.

95. Browner WS, Seeley DG, Vogt TM, Cummings SR. Non-trauma mortality in elderly women with low bone mineral density. Study of Osteoporotic Fractures Research Group. *Lancet* 1991;**338**:355-8.

96. Browner WS, Pressman AR, Nevitt MC, Cauley JA, Cummings SR. Association between low bone density and stroke in elderly women. The study of osteoporotic fractures. *Stroke* 1993;**24**:940-6.

97. Operators Manual. Madison, Wisconsin: Lunar Corporation, 1993.

98. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. *Phys.Ther.* 1986;**66**:1530-9.

99. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. *Phys Ther.* 1984;**64**:35-40.

100. Friedman PJ. Gait recovery after hemiplegic stroke. *Int Disabil Studies* 1991;**12**:119-22.

101. Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil.* 1995;**76**:27-32.

102. Olsen TS. Arm and leg paresis as outcome predictors in stroke rehabilitation. *Stroke* 1990;**21**:247-51.

103. Scandinavian Stroke Study Group. Multicenter trial of hemodilution in ischemic stroke: background and study protocol. *Stroke* 1985;**16**:885-90.

104. Lindenstrøm E, Christiansen LW, Hansen BR, Nielsen BW. Reliability of Scandinavian Stroke Scale. *Cerebrovasc Dis* 1991;**1**:103-7.

105. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther.* 1987;**67**:206-7.

106. Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincot-Raven, 1998.

107. Hangartner TN, Johnston CC. Influence of fat on bone measurements with dual-energy absorptiometry. *Bone Miner.* 1990;**9**:71-81.

108. Tothill P, Laskey MA, Orphanidou CI, van Wijk M. Anomalies in dual energy X-ray absorptiometry measurements of total-body bone mineral during weight change using Lunar, Hologic and Norland instruments. *Br J Radiol.* 1999;**72**:661-9.

109. Jørgensen L, Jacobsen BK. Changes in muscle mass, fat mass and bone mineral content of the legs after stroke. A one-year prospective study. Bone 2001. (In press)

110. Goh JC, Low SL, Bose K. Effect of femoral rotation on bone mineral density measurements with dual energy X-ray absorptiometry. *Calcif Tissue Int.* 1995;**57**:340-3.

111. Svendsen OL, Marslew U, Hassager C, Christiansen C. Measurements of bone mineral density of the proximal femur by two commercially available dual energy X-ray absorptiometric systems. *Eur J Nucl Med.* 1992;**19**:41-6.

112. Roubenoff R, Kehayias JJ, Dawson-Hughes B, Heymsfield SB. Use of dual-energy x-ray absorptiometry in body-composition studies: not yet a "gold standard". *Am J Clin Nutr.* 1993; **58**:589-91.

113. Hoshino H, Kushida K, Takahashi M, Ohishi T, Sugiyama E, Inoue T. The influence of aortic calcification on spinal bone mineral density in vitro. *Calcif Tissue Int* 1996;**59**:21-3.

114. Rand T, Schneider B, Grampp S, Wunderbaldinger P, Migsits H, Imhof H. Influence of osteophytic size on bone mineral density measured by dual X-ray absorptiometry. *Acta Radiol.* 1997;**38**:210-3.

115. Ryan PJ, Evans P, Blake GM, Fogeman I. The effect of vertebral collapse on spinal bone mineral density measurements in osteoporosis. *Bone Miner.* 1992;**18**:267-72.

116. von der Recke P, Hansen MA, Overgaard K, Christiansen C. The impact of degenerative conditions in the spine on bone mineral density and fracture risk prediction. *Osteoporos Int* 1996;6:43-9.

117. Dawson-Hughes B, Dallal GE. Effect of radiographic abnormalities on rate of bone loss from the spine. *Calcif Tissue Int* 1990;**46**:280-1.

118. Nance PW, Schryvers O, Leslie W, Ludwig S, Krahn J, Uebelhart D. Intravenous pamidronate attenuates bone density loss after acute spinal cord injury. *Arch Phys Med Rehabil.* 1999;**80**:243-51.

119. Adams WC, Imms FJ. Resting blood flow in the paretic and nonparetic lower legs of hemiplegic persons: relation to local skin temperature. *Arch.Phys.Med.Rehabil.* 1983;**64**:423-8.

120. Vogt MT, Cauley JA, Kuller LH, Nevitt MC. Bone mineral density and blood flow to the lower extremities: the study of osteoporotic fractures. *J.Bone Miner.Res.* 1997;**12**:283-9.

121. Sato Y, Maruoka H, Oizumi K, Kikuyama M. Vitamin D deficiency and osteopenia in the hemiplegic limbs of stroke patients. *Stroke* 1996;**27**:2183-7.

122. Sato Y, Maruoka H, Oizumi K. Amelioration of hemiplegia-associated osteopenia more than 4 years after stroke by 1α-hydroxyvitamin D_3 and calcium supplementation. *Stroke* 1997;**28**:736-9.

123. Sato Y, Fujimatsu Y, Kikuyama M, Kaji M, Oizumic K. Influence of immobilization on bone mass and bone metabolism in hemiplegic elderly patients with a long-standing stroke. *J.Neurol.Sci.* 1998;**156**:205-10.

124. Sato Y, Kuno H, Asoh T, Honda Y, Oizumi K. Effect of immobilization on vitamin D status and bone mass in chronically hospitalized disabled stroke patients. *Age Ageing* 1999;**28**:265-9.

125. Sato Y, Oizumi K, Kuno H, Kaji M. Effect of immobilization upon renal synthesis of 1,25-dihydroxyvitamin D in disabled elderly stroke patients. *Bone* 1999;**24**:271-5.

126. Sato Y, Kuno H, Kaji M, Etoh K, Oizumi K. Influence of immobilization upon calcium metabolism in the week following hemiplegic stroke. *J.Neurol.Sci.* 2000;**175**:135-9.

127. Dennis M. Nutrition after stroke. *Br.Med.Bull.* 2000;**56**:466-75.

128. Finestone HM, Greene-Finestone LS, Wilson ES, Teasell RW. Malnutrition in stroke patients on the rehabilitation service and at follow-up: prevalence and predictors. *Arch.Phys.Med.Rehabil.* 1995;**76**:310-6.

129. Sato Y, Honda Y, Kunoh H, Oizumi K. Long-term oral anticoagulation reduces bone mass in patients with previous hemispheric infarction and nonrheumatic atrial fibrillation. *Stroke* 1997;**28**:2390-4.

130. Jørgensen HS, Reith J, Nakayama H, Kammersgaard LP, Raaschou HO, Olsen TS. What determines good recovery in patients with the most severe strokes? The Copenhagen Stroke Study. *Stroke* 1999;**30**:2008-12.

131. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;**1** :43-6.

132. Yoshikawa T, Turner CH, Peacock M, Slemenda CW, Weaver CM, Teegarden D *et al.* Geometric structure of the femoral neck measured using dual-energy x-ray absorptiometry. *J Bone Miner.Res.* 1994;**9**:1053-64.

133. Duboeuf F, Hans D, Schott AM, Kotzki PO, Favier F, Marcelli C *et al.* Different morphometric and densitometric parameters predict cervical and trochanteric hip fracture: the EPIDOS Study. *J Bone Miner.Res.* 1997;**12**:1895-902.

134. Crabtree N, Lunt M, Holt G, Kroger H, Burger H, Grazio S *et al.* Hip geometry, bone mineral distribution, and bone strength in European men and women: the EPOS study. *Bone* 2000;**27**:151-9.

135. Winstein CJ, Gardner ER, McNeal DR, Barto PS, Nicholson DE. Standing balance training: effect on balance and locomotion in hemiparetic adults. *Arch.Phys.Med.Rehabil.* 1989;**70**:755-62.

136. Turner CH. Three rules for bone adaptation to mechanical stimuli. *Bone* 1998;**23**:399-407.

137. Feigenson JS, McDowell FH, Meese P, McCarthy ML, Greenberg SD. Factors influencing outcome and length of stay in a stroke rehabilitation unit. Part 1. Analysis of 248 unscreened patients-medical and functional prognostic indicators. *Stroke* 1977;**8**:651-6.

138. Bohannon RW. Measurement, nature, and implications of skeletal muscle strength in patients with neurological disorders. *Clinical Biomechanics* 1995;**10**:283-92.

139. Gregson JM, Leathley MJ, Moore AP, Smith TL, Sharma AK, Watkins CL. Reliability of measurements of muscle tone and muscle power in stroke patients. *Age Ageing* 2000;**29**:223-8.

140. Carr JH, Shepherd RB. A motor relearning programme for stroke. London: Heinemann Physiotherapy, 1987.

141. Bobath B. Adult hemiplegia: evaluation and treatment. Oxford: Butterworth-Heinemann, 1990.

142. Davies PM. Starting again. Berlin: Springer-Verlag, 1994.

143. Kannus P, Haapasalo H, Sievänen H, Oja P, Vuori I. The site-specific effects of long-term unilateral activity on bone mineral density and content. *Bone* 1994;**15**:279-84.

144. Kerr D, Morton A, Dick I, Prince R. Exercise effects on bone mass in postmenopausal women are site-specific and load-dependent. *J Bone Miner.Res.* 1996;**11**:218-25.

145. Kiratli BJ, Smith AE, Chen J, Perkash I. Functional ability affects bone and muscle mass after spinal cord injury. *J Bone Miner.Res.* 1995;**10**:S361.

146. Leblanc AD, Schneider VS, Evans HJ, Engelbretson DA, Krebs JM. Bone mineral loss and recovery after 17 weeks of bed rest. *J Bone Miner.Res.* 1990;**5**:843-50.

147. Cummings SR, Black DM, Nevitt MC, Browner WS, Cauley JA, Genant HK *et al.* Appendicular bone density and age predict hip fracture in women. The Study of Osteoporotic Fractures Research Group. *JAMA* 1990;**263**:665-8.

148. Gärdsell P, Johnell O, Nilsson BE, Gullberg B. Predicting various fragility fractures in women by forearm bone densitometry: a follow-up study. *Calcif.Tissue Int* 1993;**52**:348-53.

149. Ciarelli TE, Fyhrie DP, Schaffler MB, Goldstein SA. Variations in three-dimensional cancellous bone architecture of the proximal femur in female hip fractures and in controls. *J Bone Miner.Res.* 2000;**15**:32-40.

150. Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E *et al.* Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet* 1996;**348**:145-9.

151. Faulkner KG, Cummings SR, Black D, Palermo L, Gluer CC, Genant HK. Simple measurement of femoral geometry predicts hip fracture: the study of osteoporotic fractures. *J Bone Miner.Res.* 1993;**8**:1211-7.

152. Parfitt AM. Implications of architecture for the pathogenesis and prevention of vertebral fracture. *Bone* 1992;**13 Suppl 2**:S41-S47.

153. Riggs BL, Melton LJ 3rd. The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone* 1995;**17**:505S-11S.

154. Melton LJ 3rd, Wahner HW, Richelson LS, O'Fallon WM, Riggs BL. Osteoporosis and the risk of hip fracture. *Am.J Epidemiol.* 1986;**124**:254-61.

155. Wolff I, van Croonenborg JJ, Kemper HC, Kostense PJ, Twisk JW. The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporos Int* 1999;**9**:1-12.

156. Christodoulou NA, Dretakis EK. Significance of muscular disturbances in the localization of fractures of the proximal femur. *Clin.Orthop.* 1984;215-7.

157. Joakimsen RM, Magnus JH, Fønnebø V. Physical activity and predisposition for hip fractures: a review. *Osteoporos.Int.* 1997;7:503-13.

158. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE *et al.* Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N.Engl.J Med.* 1995;**332**:767-73.

159. Kannus P, Parkkari J, Niemi S, Pasanen M, Palvanen M, Järvinen M *et al.* Prevention of hip fracture in elderly people with use of a hip protector. *N.Engl.J.Med.* 2000;**343**:1506-13.

160. Lauritzen JB, Petersen MM, Lund B. Effect of external hip protectors on hip fractures. *Lancet* 1993;**341**:11-3.

161. Specker BL. Evidence for an interaction between calcium intake and physical activity on changes in bone mineral density. *J Bone Miner.Res.* 1996;**11**:1539-44.

162. Lau EM, Woo J, Leung PC, Swaminathan R, Leung D. The effects of calcium supplementation and exercise on bone density in elderly Chinese women. *Osteoporos.Int* 1992;**2**:168-73.

163. Kanis JA, McCloskey EV, Taube T, O'Rourke N. Rationale for the use of bisphosphonates in bone metastases. *Bone* 1991;**12 Suppl 1**:S13-S18.

164. Sato Y, Asoh T, Kaji M, Oizumi K. Beneficial effect of intermittent cyclical etidronate therapy in hemiplegic patients following an acute stroke. *J Bone Miner.Res.* 2000;**15**:2487-94.

165. von der Recke P, Hansen MA, Hassager C. The association between low bone mass at the menopause and cardiovascular mortality. *Am.J Med.* 1999;**106**:273-8.

166. Frye MA, Melton LJ 3rd, Bryant SC, Fitzpatrick LA, Wahner HW, Schwartz RS *et al.* Osteoporosis and calcification of the aorta. *Bone Miner.* 1992;**19**:185-94.

167. Uyama O, Yoshimoto Y, Yamamoto Y, Kawai A. Bone changes and carotid atherosclerosis in postmenopausal women. *Stroke* 1997;**28**:1730-2.

168. Vogt MT, San Valentin R, Forrest KY, Nevitt MC, Cauley JA. Bone mineral density and aortic calcification: the Study of Osteoporotic Fractures. *J.Am.Geriatr.Soc.* 1997;**45**:140-5.

169. Hak AE, Pols HA, van Hemert AM, Hofman A, Witteman JC. Progression of aortic calcification is associated with metacarpal bone loss during menopause: a population-based longitudinal study. *Arterioscler.Thromb.Vasc.Biol.* 2000;**20**:1926-31.

170. Metz JA, Morris CD, Roberts LA, McClung MR, McCarron DA. Blood pressure and calcium intake are related to bone density in adult males. *Br.J Nutr.* 1999;**81**:383-8.

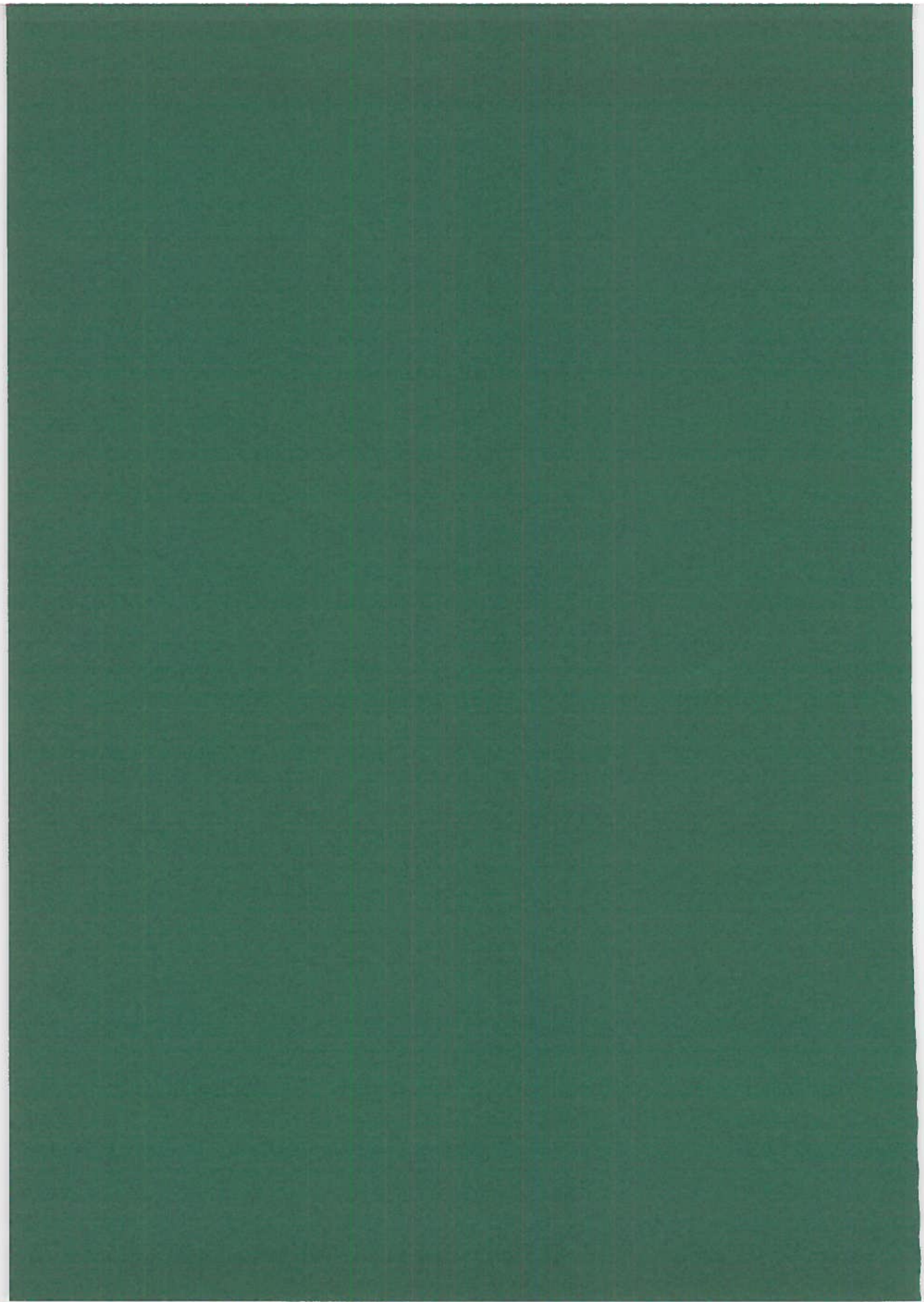
171. Jorde R, Sundsfjord J, Haug E, Bønaa KH. Relation between low calcium intake, parathyroid hormone, and blood pressure. *Hypertension* 2000;**35**:1154-9.

172. Tuominen JT, Impivaara O, Puukka P, Rönnemaa T. Bone mineral density in patients with type 1 and type 2 diabetes. *Diabetes Care* 1999;**22**:1196-200.

173. Christensen JO, Svendsen OL. Bone mineral in pre- and postmenopausal women with insulin-dependent and non-insulin-dependent diabetes mellitus. *Osteoporos.Int* 1999;**10**:307-11.

174. Forsén L, Meyer HE, Midthjell K, Edna TH. Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trøndelag Health Survey. *Diabetologia* 1999;**42**:920-5.

PAPER I



Osteoporos Int (2000) 11:381–387

Osteoporosis International

Original Article

Walking after Stroke: Does It Matter? Changes in Bone Mineral Density Within the First 12 Months after Stroke. A Longitudinal Study

L. Jørgensen, B. K. Jacobsen, T. Wilsgaard and J. H. Magnus

Institute of Community Medicine, University of Tromsø, Tromsø, Norway

Abstract. Stroke patients have increased risk of hip fractures. Nearly all fractures occur on the hemiplegic side, and reduced bone mineral density (BMD) may be an important predisposing factor. The aim of this study was to investigate the degree of demineralization within the first year after stroke, and to elucidate a possible difference in patients with high versus low ambulatory levels. Forty acute stroke patients were followed (17 initially wheelchair-bound and 23 initially ambulatory). BMD was measured in the proximal femur bilaterally at a mean 6 days, 7 months and 1 year after stroke onset using dual-energy X-ray absorptiometry. Ambulatory status was independently associated with changes in BMD ($p \leqslant 0.005$) 1 year after stroke. The 17 initially wheelchair-bound patients had a significant 10% reduction in BMD at the paretic side and 5% reduction at the non-paretic side ($p<0.001$), while the 23 patients initially able to walk had a significant loss (3%) only at the paretic side ($p=0.01$). The analysis also indicated that the major reduction in BMD took place within the first 7 months. Two months after stroke 12 of the wheelchair-bound patients had relearned to walk. At the paretic side the 1 year changes in BMD in the patients who stayed wheelchair-bound, the patients who relearned to walk within the first 2 months and the patients who were able to walk throughout the study were 13%, 8% and 3%, respectively, and a statistically significant trend with ambulatory level was found ($p=0.007$). This study provides clear evidence that lack of mobility and weight-bearing early after stroke is an important factor for the greater bone loss in the paretic leg, but that relearning to walk within the first 2 months after stroke, even with the support of another person, may reduce the bone loss after immobilization.

Keywords: Bone density; Gait; Osteoporosis; Rehabilitation; Stroke

Correspondence and offprint requests to: Lone Jørgensen, Institute of Community Medicine, University of Tromsø, N-9037 Tromsø, Norway. Tel: +47 77 66 06 51. Fax: +47 77 66 06 12. e-mail: Lone.Jorgensen@hitos.no

Introduction

Hip fractures are a serious and common complication of stroke. The incidence of hip fracture in stroke patients is 2- to 4-fold higher than in the general population [1]. Nearly all fractures occur on the hemiplegic side [2,3] and although the tendency to fall to the hemiplegic side is clearly a risk factor, reduced bone mineral density (BMD) may be another important predisposing factor [4–6]. It has been well documented that long-term bed-rest or immobility due to, for example, fractures or spinal cord injuries leads to a reduction in BMD in the lower extremities, especially during the first months of immobilization [7–10]. Earlier studies of hemiplegic patients have shown significant 4–7% differences in BMD between the paretic and non-paretic femoral neck or proximal femur [11–13]. This indicates that asymmetric weight-bearing during standing or walking may cause an accelerated bone loss at the hemiplegic side. Stroke mainly occurs in the elderly population, where osteoporosis often is already present, and an accelerated bone loss in the paretic leg may be an important factor for the increased prevalence of osteoporotic fractures in these patients. Elucidating the rate of bone loss in the hip and the influence of early mobilization is important for later interventions. No longitudinal studies on this aspect have previously been conducted.

The aim of this present 1 year prospective study was to investigate the influence of disuse and immobility on the rate of bone loss and to reveal whether early weight-bearing after stroke might prevent progressive bone loss. This was done first by examining the changes in BMD in initially completely wheelchair-bound stroke patients versus patients who could walk shortly after the stroke, and second by comparing the BMD changes in the patients who stayed wheelchair-bound, the patients who relearned to walk and the patients who were able to walk throughout the study.

Subjects and Methods

Setting

The study consisted of acute stroke patients admitted to the University Hospital in Tromsø, Norway, from December 1995 to August 1997. All persons with acute stroke from Mid- and Northern Troms, a well-defined part of the county with 114 000 inhabitants, are admitted to this hospital.

Subjects

Acute stroke patients aged 60 years or older who resided within a 2 h drive from the hospital were considered for recruitment. Patients who had not been able to walk without personal support prior to the stroke were excluded. Other exclusion criterias were few: previous strokes affecting the sensomotor system, unconsciousness and terminal illness, presence of osteosynthetic material in the femoral neck, a history of hip fracture, and unilateral bone disease affecting BMD asymmetrically, such as osteosarcoma and osteomyelitis.

Potential participants were identified among all consecutive acute stroke patients. Patients who could not walk within 1 week after stroke were recruited from December 1995 to August 1997, and patients able to walk without personal support within a week were recruited from June 1996 to August 1997. Informed consent was obtained from each participant according to the Second Helsinki Declaration, and the trial was approved by the Regional Committee for Medical Research Ethics.

Methods

Bone Mineral Density Measurements. BMD was measured using dual-energy X-ray absorptiometry (Lunar DPX-L, version 1.3z; Lunar, Madison, WI) at both proximal femora a mean of 6 days (SD 4) after the stroke, and 7 months (mean 218 days, SD 20) as well as 12 months (mean 363 days, SD 20) after the first measurement. The patients who could not walk 1 week after the stroke were also measured at 2 months (mean 57 days, SD 7). To minimize interobserver variation, all the scans were done by the same investigator (L.J.) and all were analyzed by the same technician (L.W.) who, at the time of the analysis, was not aware of the patient's paralyzed side and disability.

BMD was determined at the femoral neck area and the trochanteric area as described in the Lunar manual. The coefficient of variation (CV), determined by repeating the BMD assessment on one woman by the same investigator 10 times on different days, ranged from 1.0% (neck area) to 1.3% (trochanteric area). Furthermore, the precision was tested by measuring BMD twice in 10 patients, mean age 75 years (SD 7). The two measurements were done consecutively during the same day with an interval of a couple of minutes between the measurements. Each subject was repositioned between each scan. In this case the CV, where SD was estimated as

$$\sqrt{\Sigma(x_1 \div x_2)^2/(2N)}$$

[14], ranged from 1.7% (neck area) to 2.7% (trochanteric area).

The longitudinal drift assessed with daily phantom measurements was <1%.

Functional Tests. The patient's ambulatory level and motor function of the lower limbs were assessed immediately before the BMD measurements. We classified the patient's ability to walk using the scale Functional Ambulation Category (FAC) [15], which has proved to be useful in stroke rehabilitation [16]. The scale assesses the amount of human assistance rather than devices needed for ambulation, and scores from 1 (chairbound) to 6 (independent on both level and nonlevel surfaces). Nonambulatory patients are either wheelchair-bound (FAC 1) or unable to walk unless supported by another person (FAC 2–3), while patients categorized as FAC 4–6 are able to walk at least 6 m on their own.

The motor function of the lower limbs was assessed using the Scandinavian Stroke Scale (SSS) score [17,18]. The score is graded in five categories (0, paralysis; 2, can move but not against gravity (severe paresis); 4, raises leg with flexion in knee (moderate paresis); 5, raises leg straight but with reduced strength (mild paresis); 6, raises leg with normal strength (no paresis).

Statistical Analysis

The data were analyzed using the Windows 7.5 version of the Statistical Package for the Social Sciences (SPSS). Chi-square test was used for categorical values and Student's *t*-test for continuous variables. Analysis of variance (ANOVA) was used to compare BMD changes between FAC groups, and linear trends in reduction in BMD according to FAC group were evaluated with contrasts. ANOVA with repeated measurement design was conducted to explore the independent effects of time, functional level (FAC) and paretic/non-paretic leg for change in BMD.

Statistical correlations between FAC and SSS were evaluated using Spearman's rho (r_S).

Results

Characteristics of the Study Subjects

Of 66 eligible patients, 65 agreed to participate. Within 1 year 12 patients died, 2 decided not to continue in the study, and 2 who had been transferred to nursing homes situated more than a 2 h drive from the hospital were, at the time of the follow-up examination, too ill for the long journey. Five patients were excluded during the study: 1 had a hip fracture, 2 had new strokes and 1 had a below-knee amputation. Additionally, we excluded 4 patients in the 1 year follow-up as 3 missed the 7-month measurements due to severe illness and 1 had unsatisfactory scans.

This left us with 40 patients. Table 1 shows that there were no significant differences with regard to age, sex, side of hemiparesis and BMD baseline values between the group of patients followed for the entire year and the other group of patients.

Among the 40 patients in the study sample, 17 were wheelchair-bound (FAC 1) 1 week after the stroke and 23 were able to walk (12 with no personal support (FAC 4–6) and 11 with support from another person (FAC 2–3)). There was no significant difference between the BMD baseline values in the FAC 1 group and FAC 2–6 group ($p \geqslant 0.4$), and also no significant difference with regard to age (mean 74 years (SD 8) vs mean 75 years (SD 7) respectively, $p = 0.8$). The male/female ratio in the FAC 1 group did not differ significantly from that in the FAC 2–6 group at baseline (11/6 vs 10/13 respectively, $p = 0.2$). There were also no significant differences between the FAC 1 group and the FAC 2–6 group with respect to side of hemiparesis, smoking habits or use of medication known to affect bone metabolism and no statistically significant differences between the BMD baseline values in the paretic leg and the non-paretic leg (results not shown).

At the 2 month evaluation 12 of the 17 initially wheelchair-bound patients had relearned to walk with or without personal support (FAC 2–6), and by 7 months all but 1 had relearned to walk. The BMD baseline values of subjects who were classified as FAC 1 and FAC 2–6 at 2 months after the stroke did not differ significantly ($p>0.6$) (data not shown).

Changes in Bone Mineral Density

The BMD values decreased significantly in the 17 initially wheelchair-bound patients (FAC 1), both at the paretic and at the non-paretic side, while patients able to walk alone or supported by another person (FAC 2–6) lost bone mineral only at the paretic side (Table 2). Patients who at baseline were categorized in the FAC 1 group consistently lost more bone mineral at the paretic side compared with patients in the FAC 2–6 group ($p \leqslant 0.003$) and adjusting for gender did not change the results in BMD loss, neither for the 7 months nor for the 1 year evaluation. When contrasting the extremes, i.e., the paretic leg in the wheelchair-bound patients and the non-paretic leg in the patients able to walk at baseline, the difference in demineralization after 1 year was substantial: 10% versus 1%.

ANOVA confirmed that both ambulatory status (FAC group) ($p \leqslant 0.005$) and paretic/non-paretic status of the leg ($p \leqslant 0.02$) were independently associated with change in BMD. Furthermore, the analysis also indicated that the major reduction in BMD took place within the first 7 months and that no further statistically significant reduction in BMD was found in the last 5 months of the 1 year follow-up ($p \geqslant 0.3$) (Table 2).

We also compared the patients according to motor function of the lower limbs at baseline. As the SSS classification was highly correlated with the FAC classification ($r_S = 0.9$, $p<0.001$) the results were very similar to those shown in Table 2.

When restricting the analysis to the 17 initially completely wheelchair-bound patients (FAC 1) a significant BMD reduction of 3% in the femoral neck at the paretic side was seen already 2 months after the stroke ($p<0.05$) (results not shown in tables). At the non-paretic side the loss was 1% and not statistically significant ($p = 0.8$). Five of the patients, still categorized

Table 1. Patient characteristics at inclusion

	Patients followed for 1 year ($n = 40$)	Patients not followed for 1 year ($n = 25$)	Difference between groups: p value
Mean age, years (SD)	75 (8)	78 (7)	0.1
Sex (n; M/F)	21/19	9/16	0.2
Side of paresis (n; R/L)	19/21	10/15	0.6
Functional Ambulation Category (n; FAC: 1/2–6)	17/23	12/13	0.7
Paretic leg			
BMD (g/cm^2), mean (SD), neck	0.82 (0.15)	0.79 (0.18)	0.5
BMD (g/cm^2), mean (SD), trochanter	0.81 (0.17)	0.79 (0.22)	0.8
Non-paretic leg			
BMD (g/cm^2), mean (SD), neck	0.81 (0.15)	0.80 (0.17)	0.8
BMD (g/cm^2), mean (SD), trochanter	0.80 (0.18)	0.78 (0.22)	0.8

Table 2. Mean bone mineral density (BMD; g/cm^2) and standard deviation (SD) in the proximal femur at baseline in the paretic and non-paretic leg in stroke patients, mean changes from baseline to measurements after 7 months and 1 year according to initial Functional Ambulation Category (FAC), and p values for change in BMD from baseline and analysis of variance

Anatomic site		Ambulatory level at baseline	n	BMD at baseline mean (SD)	Change at 7 months mean (95% CI)	% change at 7 months	p value	Change at 1 year mean (95% CI)	% change at 1 year	p value
Femoral neck	Paretic leg	FAC 1	17	0.84 (0.15)	−0.07 (−0.11; −0.03)	−8	0.003	−0.08 (−0.11; −0.05)	−10	<0.001
		FAC 2–6	23	0.80 (0.16)	−0.03 (−0.04; ÷0.01)	−4	0.006	−0.02 (−0.04; −0.01)	−3	0.01
	Nonparetic leg	FAC 1	17	0.84 (0.11)	−0.02 (−0.04; −0.01)	−2	0.007	−0.04 (−0.07; −0.01)	−5	0.009
		FAC 2–6	23	0.80 (0.18)	−0.01 (−0.04; 0.02)	−1	0.5	−0.01 (−0.04; 0.01)	−1	0.3
Trochanter	Paretic leg	FAC 1	17	0.83 (0.14)	−0.06 (÷0.09; −0.03)	−7	<0.001	−0.08 (−0.11; −0.04)	−10	<0.001
		FAC 2–6	23	0.79 (0.18)	−0.03 (−0.05; −0.01)	−4	0.004	−0.02 (−0.04; 0.01)	−3	0.1
	Nonparetic leg	FAC 1	17	0.82 (0.14)	−0.03 (−0.06; 0.00)	−4	0.04	−0.04 (−0.08; 0.00)	−5	0.04
		FAC 2–6	23	0.78 (0.20)	0.00 (−0.02; 0.02)	0	0.9	0.00 (−0.03; 0.02)	0	0.9

Analysis of variance: determinants of bone mineral density loss during 1 year after stroke

Anatomic site	p values		
	Time Baseline–7 months vs Baseline–12 months	Side Paretic vs nonparetic	Ambulatory status FAC 1 vs FAC 2–6
Femoral neck	0.3	0.01	0.005
Trochanter	0.5	0.02	0.002

Table 3. Mean changes in BMD (g/cm^2) in the femoral neck from baseline to the measurement 1 year after stroke according to ambulatory level (FAC) at baseline and at 2 months

Ambulatory level	*n*	Paretic side	Nonparetic side
		Change at 12 months mean (95% CI), and % change	Change at 12 months mean (95% CI), and % change
Wheelchair-bound (FAC 1) at baseline and by 2 months	5	−0.10 (−0.19; 0.00) −13	−0.05 (−0.14; 0.04) −5
Wheelchair-bound (FAC 1) at baseline but walks (FAC 2–6) by 2 months	12	−0.07 (−0.11; −0.03) −8	−0.04 (−0.08; 0.00) −5
Walks (FAC 2–6) at baseline and by 2 months	23	−0.02 (−0.04; −0.01) −3	−0.01 (−0.04; 0.01) −1
p value for linear trend		0.007	0.2

as wheelchair-bound (FAC 1) after 2 months, had a BMD reduction of 13% at the paretic side and 5% at the non-paretic side 1 year after stroke (Table 3). Probably because of the few subjects in the analysis these changes were of marginal statistical significance. The 12 patients who relearned to walk within 2 months had lost 8% of their bone mineral in the femoral neck at the paretic side ($p = 0.002$) and 5% at the non-paretic side ($p = 0.04$) 1 year after stroke.

When we compared the 1 year BMD changes in the 5 patients who were still wheelchair-bound 2 months after stroke, the 12 patients who relearned to walk within the first 2 months, and the 23 patients who were able to walk throughout the study, a statistically significant trend with ambulatory level was found in the femoral neck at the paretic side ($p = 0.007$), but not at the non-paretic side ($p = 0.2$) (Table 3). The results for the trochanteric site were almost identical to the BMD changes in the femoral neck (results not shown).

Discussion

This study investigates two clinically significant questions in a longitudinal design: first, whether the ability to walk shortly after stroke influences the loss of bone mineral over the following year, and, secondly whether demineralization in the nonambulatory acute stroke patients was affected by whether or not they relearned to walk within the first 2 months. Our results clearly indicate that ambulatory status both immediately after the stroke and at 2 months are important.

We chose to determine the BMD in the proximal femur, since most studies conclude that measurements of this site predicts hip fracture better than measurements of other skeletal sites [6]. Earlier studies have compared the bone mineral content (BMC) of the paretic and non-paretic arm [19,20] or total BMC in the paretic versus the non-paretic leg [19,21,22]. Only three studies, two cross-sectional [11,12] and one longitudinal [13], have measured BMD in the proximal femur in hemiplegic patients. These studies show a 4–7% difference between the paretic and non-paretic leg, and are thus in agreement with our results. In the previous longitudinal study [13] the BMD loss in the paretic and non-paretic leg corresponded to the loss found in our wheelchair-bound patients, but as only stroke patients generally immobile were included, the influence of motor function or ambulatory level could not be examined appropriately. We included patients at different ambulatory levels and showed that ambulatory status at baseline was independently associated with the changes in BMD (Table 2). Moreover, the effect of walking was further strengthened as a statistically significant trend with ambulatory level was demonstrated (Table 3).

In the wheelchair-bound patients the demineralization was significant in both the paretic and the non-paretic leg, indicating that the loss of bone mineral is a result not only of the hemiparesis but also of a general reduction in physical activity. Although a bilateral BMD reduction as seen in paraplegia [8] might have been expected, we found that the loss was significantly larger in the paretic leg compared with the non-paretic leg. As stroke patients often stand with more weight on the non-paretic leg during transfers, this may explain the side-to-side difference in our wheelchair-bound patients, and as ambulant hemiplegic patients also have problems in transferring weight to the paretic leg [23], this may also be the reason why our patients who could walk at baseline (FAC 2–6) had a significant bone loss only at this side. Additionally, not solely the lack of weight-bearing but also the lack of muscle pull at the paretic side may be a possible explanation for the difference in bone loss.

The loss of bone mineral after a spinal cord injury is generally larger in the lower paralyzed limbs than the loss demonstrated in the proximal femur in the stroke patients included in our study [24]. The reasons may include the fact that patients with spinal cord injuries are often younger and that the patients commonly studied have complete lesions making weight-bearing in standing difficult. Thus, it was demonstrated in a longitudinal study by Wilmet et al. [8] that in patients with a complete lesion the bone loss in the lower limbs as a whole attained 25% by the end of the first year, while patients with a partial recovery, able to walk or

stand in an upright position, had a mean loss of 10% within 1 year.

In elderly people a mean decrease in BMD of 1–1.5% per year is expected [25,26]. We found a much higher 1 year loss in the paretic leg (up to 13%). As a BMD reduction of 10–15% compared with an age-matched norm is associated with a 50–100% increase in the risk of fracture [9], the bone loss in our population is clinical important.

The participation rate of our study was high, as only one subject eligible for participation decided not to be enrolled. One important consideration may, however, be the number of patients who did not participate in the study for the entire year ($n = 25$) versus the patients who did ($n = 40$). However, as the former group was not significantly different at baseline from the latter, the bias introduced in the study sample is probably limited. The major cause for not completing the study was severe disease or death, which was not unexpected considering the age of the participants. The rate of recurrent stroke and death following stroke was in fact low compared with earlier Scandinavian studies [27,28], probably because initially unconscious patients were not included in our study. Also, for this reason our results can not be generalized to this group of patients where an even larger amount of bone loss may be expected due to lower functional progression [29,30].

There were few stroke patients in some of the subgroups. This has hampered the analysis and reduced the statistical power. However, the main results, as presented in Tables 2 and 3, demonstrate a distinct pattern of different rates of bone loss according to paresis and ambulatory status which can not be explained by lack of statistical power.

The prospective design of our study avoids many of the potential biases inherent in previous cross-sectional studies estimating demineralization after stroke and the effect of motor function or ambulation. By using each subject as their own control, genetic and environmental determinants of bone density are controlled for. There might nevertheless be some limitations. Firstly, we only followed the patients for 1 year. The fall in BMD may continue for several years. Secondly, in the present analysis we focused on the ability to walk. Factors other than lack of mechanical stimuli, i.e., changes in the sympathetic nervous activity affecting the paretic and non-paretic side differently [31], may be of importance in hemiplegic bone loss.

In our study we were not able to examine possible differences in nutrition between subjects in the different gait categories. If the groups differed substantially with respect to food habits (i.e., differences in calcium and vitamin D intake) this might to some extent explain the differences between the groups consisting of subjects at different ambulatory levels, but probably not the fact that the bone loss was larger in the paretic than in the non-paretic leg.

Treatments of osteoporosis include the use of vitamin D and bisphosphonates (i.e., pamidronate). To our knowledge only one trial has evaluated the effect of medication on bone loss after stroke. This study showed that vitamin D and calcium supplementation prevented further decrease in BMD in patients with a long-standing stroke [32].

The effect of bisphosphonates, known to be powerful inhibitors of osteoclastic bone resorption [33], has not been evaluated in stroke patients, but in a recently published study on pamidronate treatment during the first 6 months after a spinal cord injury it was shown that both this treatment and ambulatory status had significant effects on retarding the development of osteoporosis [34]. Thus, future studies are warranted exploring whether early weight-bearing in combination with bisphosphonate treatment may be a regimen of choice to prevent bone loss and hip fractures in stroke patients.

In conclusion, this study provides clear evidence that lack of mobility and weight-bearing early after stroke is an important factor in the greater bone loss in the paretic leg. Intervention studies are needed to determine whether early mobilization with focus on exercises in a weight-bearing position can prevent or reverse bone loss in the most impaired stroke patients, as our results may suggest.

Acknowledgements. We are very grateful to the stroke patients who participated in this study, and to technician L. Wilsgaard for analyzing all the DXA scans. We also acknowledge the support of chief physician S. Sparr, MD, and the medical staff at the neurologic and geriatric medical ward, University Hospital in Tromsø. This study was financially supported by the Ministry of Health "Research on the Elderly", University Hospital in Tromsø, Norway.

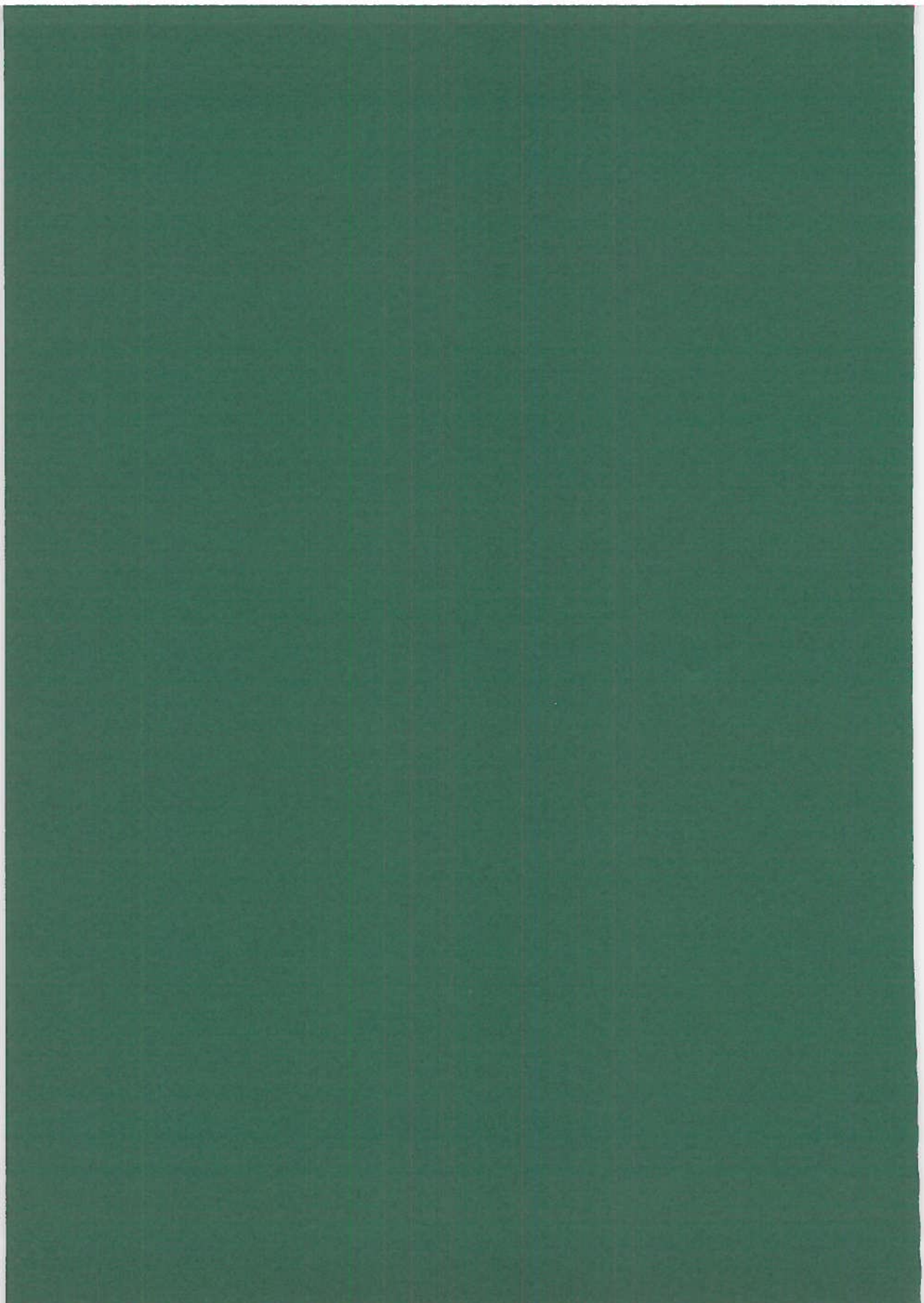
References

1. Ramnemark A, Nyberg L, Borssen B, Olsson T, Gustafson Y. Fractures after stroke. Osteoporos Int 1998;8:92–5.
2. Chiu KY, Pun WK. A prospective study on hip fractures in patients with previous cerebrovascular accidents. Injury 1992;23:297–9.
3. Mulley G, Espley AJ. Hip fracture after hemiplegia. Postgrad Med J 1979;55:264–5.
4. De Laet CE, Van Hout BA, Burger H, Weel AE, Hofman A, Pols HA. Hip fracture prediction in elderly men and women: validation in the Rotterdam study. J Bone Miner Res 1998;13:1587–93.
5. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312:1254–9.
6. Cummings SR, Black DM, Nevitt MC, Browner WS, Cauley J, Ensrud K. Bone density at various sites for prediction of hip fractures. Lancet 1993;341:72–5.
7. Zerwekh JE, Ruml LA, Gottschalk F, Pak CY. The effects of twelve weeks of bed rest on bone histology, biochemical markers of bone turnover, and calcium homeostasis in eleven normal subjects. J Bone Miner Res 1998;13:1594–601.
8. Wilmet E, Ismail AA, Heilporn A, Welraeds D, Bergmann P. Longitudinal study of the bone mineral content and soft tissue composition after spinal cord section. Paraplegia 1995;33:674–7.
9. Järvinen M, Kannus P. Injury of an extremity as a risk factor for the development of osteoporosis [review]. J Bone Joint Surg Am 1997;79:263–76.
10. Minaire P. Immobilization osteoporosis: a review. Clin Rheumatol 1989;8(Suppl 2):95–103.
11. Del Puente A, Pappone N, Mandes GM, Mantova D, Scarpa R, Oriente P. Determinants of bone mineral density in immobilization: a study on hemiplegic patients. Osteoporos Int 1996;6:50–4.

12. Takamoto S, Masuyama T, Nakajima M, et al. Alterations of bone mineral density of the femurs in hemiplegia. Calcif Tissue Int 1995;56:259–62.
13. Ramnemark A, Nyberg L, Lorentzon R, Englund U, Gustafson Y. Progressive hemiosteoporosis on the paretic side and increased bone mineral density in the non-paretic arm the first year after severe stroke. Osteoporos Int 1999;9:269–75.
14. Bots ML, Mulder PG, Hofman A, van Es GA, Grobbee DE. Reproducibility of carotid vessel wall thickness measurements. The Rotterdam Study. J Clin Epidemiol 1994;47:921–30.
15. Holden G, Gill K, Magliozoni MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. Phys Ther 1986;66:1530–9.
16. Holden G, Gill K, Magliozoni MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther 1984;64:35–40.
17. Scandinavian Stroke Study Group. Multicenter trial of hemodilution in ischemic stroke: background and study protocol. Stroke 1985;16:885–90.
18. Lindenstrøm E, Boysen G, Christiansen LW, à Rogvi Hansen B, Nielsen BW. Reliability of Scandinavian Stroke Scale. Cerebrovasc Dis 1991;23:103–7.
19. Iversen I, Hassager C, Christiansen C. The effect of hemiplegia on bone mass and soft tissue body composition. Acta Neurol Scand 1989;79:155–9.
20. Prince RL, Price RI, Ho S. Forearm bone loss in hemiplegia: a model for the study of immobilization osteoporosis. J Bone Miner Res 1988;3:305–10.
21. Hamdy RC, Moore SW, Cancellaro VA, Harvill LM. Long-term effects of strokes on bone mass. Am J Phys Med Rehabil 1995;74:351–6.
22. Hamdy RC, Krishnaswamy G, Cancellaro V, Whalen K, Harvill L. Changes in bone mineral content and density after stroke. Am J Phys Med Rehabil 1993;72:188–91.
23. Turnbull GI, Charteris J, Wall JC. Deficiencies in standing weight shifts by ambulant hemiplegic patients. Arch Phys Med Rehabil 1996;77:356–62.
24. Uebelhart D, Demiaux-Domenech B, Roth M, Chantraine A. Bone metabolism in spinal cord injured individuals and in others who have prolonged immobilisation [review]. Paraplegia 1995;33:669–73.
25. Ensrud KE, Palermo L, Black DM, et al. Hip and calcaneal bone loss increase with advancing age: longitudinal results from the Study of Osteoporotic Fractures. J Bone Miner Res 1995;10:1778–87.
26. Jones G, Nguyen T, Sambrook P, Kelly PJ, Eisman JA. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo Osteoporosis Epidemiology Study. BMJ 1994;309:691–5.
27. Indredavik B, Bakke F, Solberg R, Rokseth R, Haaheim LL, Holme I. Benefit of a stroke unit: a randomized controlled trial. Stroke 1991;22:1026–31.
28. Terént A. Survival after stroke and transient ischemic attacks during the 1970s and 1980s. Stroke 1989;20:1320–6.
29. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke: outcome assessment and sample size requirements. Stroke 1992;23:1084–9.
30. Bonita R, Beaglehole R. Recovery of motor function after stroke. Stroke 1988;19:1497–500.
31. Adams WC, Imms FJ. Resting blood flow in the paretic and nonparetic lower legs of hemiplegic persons: relation to local skin temperature. Arch Phys Med Rehabil 1983;64:423–8.
32. Sato Y, Maruoka H, Oizumi K. Amelioration of hemiplegia-associated osteopenia more than 4 years after stroke by 1α-hydroxyvitamin D_3 and calcium supplementation. Stroke 1997;28:736–9.
33. Kanis JA, McCloskey EV, Taube T, O'Rourke N. Rationale for the use of bisphosphonates in bone metastases. Bone 1991;12(Suppl 1):S13–8.
34. Nance PW, Schryvers O, Leslie W, Ludwig S, Krahn J, Uebelhart D. Intravenous pamidronate attenuates bone density loss after acute spinal cord injury. Arch Phys Med Rehabil 1999;80:243–5.

Received for publication 24 August 1999
Accepted in revised form 25 October 1999

PAPER II



Bone Vol. 27, No. 5
November 2000:701–707

ELSEVIER

Ambulatory Level and Asymmetrical Weight Bearing After Stroke Affects Bone Loss in the Upper and Lower Part of the Femoral Neck Differently: Bone Adaptation After Decreased Mechanical Loading

L. JØRGENSEN,[1] N. J. CRABTREE,[2] J. REEVE,[2] and B. K. JACOBSEN[1]

[1]*Institute of Community Medicine, University of Tromsø, Tromsø, Norway*
[2]*University Department of Medicine, Addenbrooke's Hospital, Cambridge, UK*

The aim of this 1-year prospective study of acute stroke patients was to determine the effects of walking and asymmetrical weight bearing on the loss of bone mineral in the upper and lower femoral neck. Forty patients were followed. Eight remained unable to walk, whereas 32 relearned to walk independently within 7 months (12 shortly after the stroke, 15 by 2 months, 5 by 7 months). Bone mineral density (BMD) was measured in the proximal femur within the first week after stroke and 1 year later; regional BMD changes were computed for the lower and upper femoral neck. The lower part of the femoral neck is mainly influenced by compressive stresses of the hip, the upper part by tensile stresses during walking. When comparing mean BMD loss in groups of patients according to when they relearned to walk, a statistically significant trend in BMD loss was found in the lower femoral neck on both the paretic and nonparetic sides ($p < 0.01$ and $p = 0.01$, respectively), whereas, for the upper femoral neck, no significant trend was seen ($p \geq 0.1$). In addition, the body weight distribution during standing was assessed by use of a force-plate in 38 patients who could stand independently at the 7 month evaluation. The only significant correlation between changes in BMD and asymmetrical weight bearing was found in the lower femoral neck on the paretic side ($r = 0.6$, $p < 0.001$). In conclusion, this study shows that the reduction in BMD in the femoral neck occurs mainly in the lower part of the neck and on the paretic side. The BMD loss depended on when or if the patients relearned to walk, but also on the amount of body weight born on the paretic leg. Thus, measuring the lower part of the femoral neck gives a better estimate of the impact of gait and weight bearing than measuring the total femoral neck. (Bone 27: 701–707; 2000)

Key Words: Bone mineral density (BMD); Gait; Osteoporosis; Stroke; Weight bearing.

Address for correspondence and reprints: Dr. Lone Jørgensen, Institute of Community Medicine, University of Tromsø, N-9037, Tromsø, Norway. E-mail: lone.jorgensen@hitos.no

Introduction

The incidence of hip fracture in stroke patients is two- to fourfold higher than in the general population,[33] and nearly all the fractures (80%–100%) occur on the hemiplegic side.[4,28,32]

It has been well documented that immobility leads to a reduction of bone mineral density (BMD) in the lower extremities,[14,17,23,27,35] and in an earlier longitudinal study of stroke patients we showed that the loss of bone mineral in the femoral neck was significantly higher on the paretic side as compared with the nonparetic side. The bone loss was dependent on the patient's ambulatory level at baseline and whether the patient had relearned to walk 2 months after the stroke.[19]

The level of impairment following stroke differs greatly between patients; that is, in some individuals, the ability to walk is not affected at all, others relearn to walk within a few months, and some remain completely wheelchair-bound. In addition, many ambulatory patients walk asymmetrically with less of their body weight carried through their affected leg.[2,10,16] Measurements of BMD in the femoral neck is a strong predictor of hip fractures[7,9,25] and therefore it is important to elucidate how changes in mechanical loading (length of time ambulating and asymmetrical weight bearing) might influence the loss of bone mineral.

It is unknown whether the changes in BMD after stroke are uniform across the femoral neck or whether there are regional differences. The trabeculae of the cancellous tissue are usually oriented so as to resist axial deformational stresses (either from weight bearing or from muscle activity) and their number, size, and distribution are related to these forces.[30] Pauwells[30] analyzed the strains in the femoral neck and showed that the stresses increase more strongly toward the medial (lower) border than toward the lateral (upper), and that the greatest stresses arise on the medial side of the femoral neck. The density of the cancellous tissue and the thickness of the cortex have a corresponding distribution: the cancellous tissue is denser and the cortex much thicker on the medial than on the lateral side, as seen in **Figure 1**. Therefore, if the femoral neck is remodeled according to the changes in mechanical loading one should expect to find the largest changes in BMD in the lower part of the femoral neck in patients at the lowest ambulatory level, and a stronger association between asymmetrical weight bearing and changes in BMD of the medial (lower) part of the femoral neck than in the lateral (upper) part. Not only from a biomechanical, but also from a

8756-3282/00/$20.00
PII S8756-3282(00)00374-4

Bone Vol. 27, No. 5
November 2000:701–707

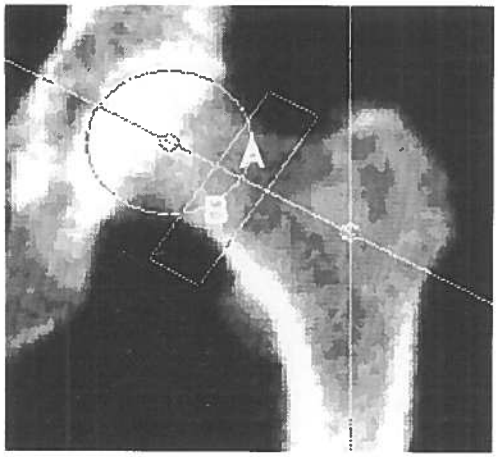


Figure 1. Image from the HSA program. (A) Upper femoral BMD ROI. (B) Lower femoral neck BMD ROI. The region is selected as the standard femoral neck ROI bisected by the neck midline.

clinical point of view this area of study is important to investigate, as measurements of the lower femoral neck may give us a better estimation of the impact of physical activity on BMD changes in the hip than measurements of the total femoral neck.

In a previous study, we showed that ambulatory status early after stroke is an important determinant of bone demineralization in the femoral neck.[19] The first aim of the present study was to investigate whether changes in bone mineral density in the lower femoral neck (mainly influenced by compressive stresses of the hip) differ from the changes in the upper femoral neck (mainly influenced by tensile stresses) according to when or if the patients started to walk after the stroke. The second aim was to examine whether asymmetrical weight bearing following stroke was associated with an accelerated bone loss, especially in the lower part of the femoral neck on the paretic side.

Subjects and Methods

Subjects

The patients and recruitment procedures have been described in detail elsewhere.[19] In brief, the patients had acute stroke, were ≥60 years of age, and lived in the county of Troms, Norway. They were recruited from December 1995 to August 1997. Patients who had not been able to walk without personal support prior to the stroke were excluded. Other exclusion criteria included: previous strokes affecting the sensomotoric system; unconsciousness and terminal illness; presence of osteosynthetic material in the femoral neck; history of hip fracture; and unilateral bone diseases affecting BMD asymmetrically, such as osteosarcoma and osteomyelitis. Informed consent was obtained from each participant according to the Second Helsinki Declaration, and the trial was approved by the regional committee for medical research ethics.

Methods

Bone mineral density measurements. BMD was measured using dual-energy X-ray absorptiometry (LUNAR DPX-L, version 1.3z, Lunar, Madison, WI). The proximal femur was measured on both the paretic and nonparetic side, on average 6 days after the stroke (SD 4 days) and again at 12 months after the first measurement (SD 20 days). To minimize interobserver variation due to repeated scannings all patients were scanned by one operator. Standard analysis, as described by the Lunar operator's manual, was initially performed to calculate the changes in neck BMD.[19] The image files were then reanalyzed using a β version of the Lunar hip strength analysis (HSA) program (version β3.7). This software has been used previously to study BMD in healthy women and men,[37] and to assess prospectively the risk of hip fracture.[11] To evaluate regional changes in femoral neck BMD, upper and lower BMD values were chosen from the HSA output (Figure 1). To assess the precision of repeated scannings, ten stroke patients (mean age 75 years) were scanned twice on the same day. All subjects were removed from the table between the scans to allow for repositioning errors. The coefficient of variation (c.v.) for the upper BMD was 3.7%, and for the lower BMD 1.1%. These figures are comparable to that obtained for the standard neck region of interest (ROI) for the same data set (c.v. = 2.1%).

Machine stability was monitored daily using the Lunar aluminum spine phantom and longitudinal changes in phantom BMD were shown to be <1% during the year.

Gait. An evaluation of the patient's gait ability was made at baseline and at 2, 7, and 12 months after stroke. We classified the patient's ability to walk by using the "Functional Ambulation Category" (FAC) scale,[15] which has proven to be useful in stroke rehabilitation.[16] The scale assesses the amount of human assistance rather than the devices needed for ambulation, and scores from 1 (chairbound) to 6 (independent on both level and nonlevel surfaces). Patients who are unable to walk unless supported by another person are categorized as FAC 2–3, whereas patients who are able to walk at least 6 meters on their own are categorized as FAC 4–6.

Measurements of weight distribution in standing. As the FAC scale does not reflect any aspects of asymmetrical posture, we assessed patients' body weight distribution during bilateral standing using the Balance Performance Monitor (BPM, SMS Healthcare, Elizabeth House, Harlow, UK). The BPM provides measurements of the left-right weight distribution, and "mean %weight-bearing" is defined as the average percentage of total body weight born on each leg during standing throughout the test. The equipment consists of two movable footplates linked to the rear of the display console and an IBM-compatible computer with DATAPRINT, v3.00 software. The measurement sensitivity for all tests was standardized for "sensitivity × 1" and with a sampling frequency of 300 Hz.

During the test the patients wore their normal shoes and were assessed while standing with one foot on each of the footplates. The feet were parallel and kept a uniform distance apart (7 cm), the medial malleoli aligned with a transverse line on the footplates. If needed, help was given to position the feet, but the standing posture was not corrected. The test lasted for 30 sec during which the patients were asked to stand still with their arms by their side and their gaze fixed on a dot on the wall at a distance of 2 meters. The BPM display was positioned away from the patient so that the subject did not receive any feedback during the test.

The precision was tested by measuring the left-right weight distribution twice in ten stroke patients, mean age 77 years (SD 7). The two measurements were done consecutively during the same day with 2–3 min intervals, and each subject was seated in a chair between each measurement. The c.v. was 3.6%.

Table 1. Mean bone mineral density (BMD, g/cm^2) and standard deviation (SD) in the proximal femur at baseline in the paretic and nonparetic leg and mean BMD changes from baseline to measurement after 1 year (95% confidence interval) in patients who could not walk at the 7 month evaluation and patients who could walk

Walks at 7 months	Anatomic site		BMD at baseline mean (SD)	Change at 1 year mean (95% CI)	p value for change	p-value for difference at lower/upper femoral neck
No (n = 8)	Paretic leg	Lower femoral neck	1.10 (0.17)	−0.14 (−0.19 to −0.09)	<0.001	0.001
		Upper femoral neck	0.61 (0.13)	−0.06 (−0.10 to −0.02)	0.01	
	Nonparetic leg	Lower femoral neck	1.07 (0.13)	−0.06 (−0.14 to 0.02)	0.1	0.3
		Upper femoral neck	0.64 (0.10)	−0.03 (−0.07 to 0.02)	0.2	
Yes (n = 32)	Paretic leg	Lower femoral neck	1.00 (0.17)	−0.03 (−0.05 to −0.01)	0.003	0.6
		Upper femoral neck	0.60 (0.17)	−0.04 (−0.07 to −0.01)	0.01	
	Nonparetic leg	Lower femoral neck	0.99 (0.18)	−0.02 (−0.04 to 0.00)	0.1	0.3
		Upper femoral neck	0.58 (0.15)	−0.01 (−0.03 to −0.01)	0.5	

As most patients relearn to walk within the first 2–3 months after stroke[13,20,29] we chose to use weight bearing at 7 months after stroke as an integrated measure of symmetry for the period the patients were followed.

Statistical Analysis

Data were analyzed using the WINDOWS 7.5 version of the Statistical Package for the Social Sciences (SPSS). The Chi-square test was used for categorical values and Student's t-test for continuous variables. Analysis of variance (ANOVA) was used to compare absolute changes in BMD between FAC groups, and linear trends in 1 year BMD changes according to FAC group were evaluated with contrasts. Because of small number of subjects in some of the subgroups, nonparametric tests were also applied (Wilcoxon signed-rank test and Kruskal–Wallis test for testing within-group and between-group changes, respectively).

Relations between individual "mean %weight bearing" and BMD changes were evaluated using Pearson's correlation coefficient, and multiple linear regression was performed to evaluate the impact of FAC group and %weight bearing to changes in BMD.

Results

Characteristics of Study Subjects

Of the 66 eligible patients, 65 agreed to participate. Within 1 year, 12 patients died, 2 decided not to continue in the study, and 2 had been transferred to nursing homes situated at a >2 h driving distance from the hospital. At the the time of follow-up examination they were too ill for the long trip. Five patients were excluded during the study: one had a hip fracture; two were immobilized due to diabetic foot ulcers and below-knee amputation; and two had new strokes. In addition, we excluded four patients as three missed the 7 month measurements due to severe illness and one had unsatisfactory scans.

This left us with 40 patients, 21 men and 19 women, with a mean age of 75 years (SD 8). Nineteen were paretic on the right side and 21 on the left side. We found no significant differences with regard to age, gender, side of hemiparesis, and bone mineral density in the femoral neck at baseline when the group of 40 patients followed for the entire year and the 15 patients not included in our analysis were compared (results not shown).

At 7 months, the distribution of the patients according to FAC category (1–6) was 1, 5, 2, 3, 9, and 20, respectively. Thus, 32 patients were able to walk with no personal support (FAC 4–6)

Table 2. Mean bone mineral density (BMD; g/cm^2) and standard deviation (SD) at baseline and mean BMD changes from baseline to measurement after 1 year (95% confidence interval) according to when patients began to walk after stroke

		Paretic side			Nonparetic side		
Time when walking	n	BMD at baseline mean (SD)	Change at 12 months: Mean (95% CI), and % change	p-value	BMD at baseline mean (SD)	Change at 12 months: Mean (95% CI), and % change	p-value
(A) Lower femoral neck							
Walked at baseline	12	0.93 (0.14)	−0.01 (−0.04 to 0.03), −1%	0.7	0.94 (0.12)	0.00 (−0.04–0.03), 0%	0.8
Walked by 2 months	15	1.04 (0.20)	−0.04 (−0.07 to −0.01), −4%	0.01	1.01 (0.23)	−0.01 (−0.03–0.01), −1%	0.4
Walked by 7 months	5	1.03 (0.12)	−0.08 (−0.14 to −0.02), −8%	0.03	1.02 (0.10)	−0.08 (−0.16–0.00), −7%	0.053
Immobile by 7 months	8	1.01 (0.17)	−0.14 (−0.19 to −0.09), −14%	<0.001	1.07 (0.13)	−0.06 (−0.14–0.02), −6%	0.1
p-value for linear trend			$p < 0.001$			$p = 0.01$	
(B) Upper femoral neck							
Walked by baseline	12	0.52 (0.14)	−0.01 (−0.06 to 0.04), −2%	0.8	0.50 (0.12)	0.00 (−0.04–0.05), 0%	0.9
Walked by 2 months	15	0.68 (0.19)	−0.06 (−0.11 to −0.02), −9%	0.01	0.63 (0.18)	0.00 (−0.03–0.02) 0%	0.9
Walked by 7 months	5	0.59 (0.11)	−0.04 (−0.10 to 0.01), −7%	0.1	0.60 (0.06)	−0.05 (−0.12–0.02) −8%	0.1
Immobile by 7 months	8	0.61 (0.13)	−0.06 (−0.10 to −0.02), −10%	0.01	0.64 (0.10)	−0.03 (−0.07–0.02) −5%	0.2
p-value for linear trend			$p = 0.2$			$p = 0.1$	

Bone Vol. 27, No. 5
November 2000:701–707

7 months after stroke, whereas 8 were still unable to walk alone (FAC 1–3). There were no significant differences between the FAC 1–3 group and the FAC 4–6 group with respect to age, gender, side of hemiparesis, use of medication known to affect bone metabolism, or baseline BMD values, and no statistically significant differences between the baseline BMD values in the paretic and nonparetic leg (results not shown).

Changes in BMD According to Gait

Baseline BMD values for the upper and lower femoral neck are presented in **Table 1**.

Both upper and lower BMD values on the paretic side decreased significantly during the first year after stroke ($p \leq 0.01$), irrespective of whether the patients could walk or not within the first 7 months. On the nonparetic side, the changes in BMD were not significant (Table 1).

In the patients unable to walk 7 months after stroke the 1 year BMD change was significantly higher in the lower femoral neck than in the upper femoral neck on the paretic side ($p = 0.001$). On the nonparetic side, and on the paretic side in the patients who walked by 7 months, no significant differences between the lower and upper femoral neck were found ($p \geq 0.3$). The immobile patients lost significantly more bone mineral in the lower femoral neck on the paretic side compared with patients who could walk by 7 months ($p < 0.001$). In contrast, there were no significant differences between the two groups (FAC 1–3 and FAC 4–6) with respect to BMD changes in the upper femoral neck ($p = 0.5$), and also, on the nonparetic side, no significant between-group changes were found (lower neck, $p = 0.1$; upper neck, $p = 0.4$).

Among the 32 patients who could walk at the 7 month evaluation, 12 had been able to do so at baseline (FAC 4–6 throughout the study), 15 had relearned to walk by 2 months (FAC 1–3 at baseline but FAC 4–6 by 2 months), and 5 by 7 months (FAC 1–3 at baseline and at 2 months, but FAC 4–6 by 7 months). Only one of the eight patients described as immobile by 7 months (FAC 1–3 at baseline, 2, and 7 months) relearned to walk by 12 months. When comparing the BMD changes between these groups 1 year after stroke, a statistically significant trend was shown for the lower femoral neck on both the paretic and nonparetic sides ($p < 0.01$ and $p = 0.01$, respectively), whereas, for the upper femoral neck, no significant trend was demonstrated ($p \geq 0.1$) (**Table 2**, parts A and B)

Correlation Between Changes in BMD and Asymmetrical Weight Bearing

At the 7 month evaluation weight bearing was measured in 38 of the patients, whereas the remaining 2 patients were unable to stand unsupported. The 32 patients who could walk independently were standing with significantly more of their body weight on the paretic leg compared with the 6 immobile patients who, although not able to walk independently, could stand unsupported for 30 sec ("%weight bearing" mean 35% vs. mean 48%, $p = 0.003$). The amount of load on the paretic leg also depended on when the patients relearned to walk, with increasing asymmetry in the patients who walked late or stayed immobile $p = 0.001$ (for linear trend) (**Table 3**).

The correlation between asymmetrical weight bearing and BMD changes in the lower as well as the upper femoral neck, measured in the 38 patients who could stand unsupported by 7 months, is presented in **Figure 2**. The only significant correlation between "%weight bearing" and change in BMD was that with the lower femoral neck on the paretic side ($r = 0.6$, $p < 0.001$).

Multiple linear regression analysis confirmed that both the time the patients started to walk and the amount of weight borne through the leg independently affected the 1 year change in BMD in the lower femoral neck on the paretic side ($p = 0.003$ and $p = 0.02$, respectively). In contrast, no significant effects of when the patients started to walk or "%weight bearing" were found in the lower femoral neck on the nonparetic side ($p = 0.1$ and $p = 0.4$, respectively). Also, in the upper femoral neck, no statistical significant effects with regard to the time patients began to walk or the amount of weight bearing were found either on the paretic side ($p = 0.4$ and $p = 0.7$, respectively) or on the nonparetic side ($p = 0.3$ and $p = 0.8$, respectively). These results changed only slightly when adjusting for gender, age, and right or left paresis, both at the lower femoral neck on the paretic side ($p = 0.006$ and $p = 0.03$, respectively) and for the other sites ($0.3 < p < 0.8$).

Because of the small number of subjects in some of the patient groups, we also applied nonparametric tests. All the patterns of BMD loss presented in the tables were confirmed, and all associations that were statistically significant ($p < 0.05$) when *t*-tests were applied remained statistically significant, with *p*-values ranging from 0.003 to 0.04.

Table 3. Mean percent weight on the paretic leg at 7 months in 38 patients who were able to stand independently, according to when they began to walk after the stroke

Time when walking	n	% weight on the paretic leg mean (SD)
Walked by baseline	12	51 (6)
Walked by 2 months	15	48 (11)
Walked by 7 months	5	43 (10)
Immobile by 7 months	6	35 (10)
p-value for linear trend		0.001

Discussion

To our knowledge no previous study has evaluated the effect of immobilization or asymmetrical weight bearing on BMD changes in the lower vs. the upper femoral neck region of interest (ROI). We have shown previously that ambulatory status after stroke is an important factor for the loss of bone mineral in the femoral neck.[19] We now demonstrate that BMD loss after immobilization is site-specific even within the femoral neck, with a greater loss in the lower than in the upper part. The bone loss in the lower femoral neck on the paretic side is related to when (if at all) the patients begin to walk after stroke as well as to asymmetrical weight bearing when standing.

The local loss of bone mineral in the femoral neck on the paretic side may be a result of both diminished muscle activity and decreased weight bearing. No muscles attach to the femoral neck itself, but several muscles acting on the hip during normal gait may influence BMD of the femoral neck indirectly. Thus, BMD of the lower femoral ROI may be affected by muscles inserting into the lesser trochanter, whereas muscles inserting into the greater trochanter may affect mainly the upper ROI. However, as all muscles of the hip on the paretic side are more or less impaired in hemiplegic patients, the net loss of mechanical loading within the femoral neck due to the lack of muscle contractions may be difficult to predict. In the present study we found that the most impaired patients have extensive significant BMD loss in both ROIs. The loss of bone mineral is, however, greater in the lower than in the upper ROI and one possible explanation is that, in addition to the loss of muscle pull, subjects who are unable to walk hardly get any effect of weight-bearing attributable to ground reaction forces. According to Pauwells[30]

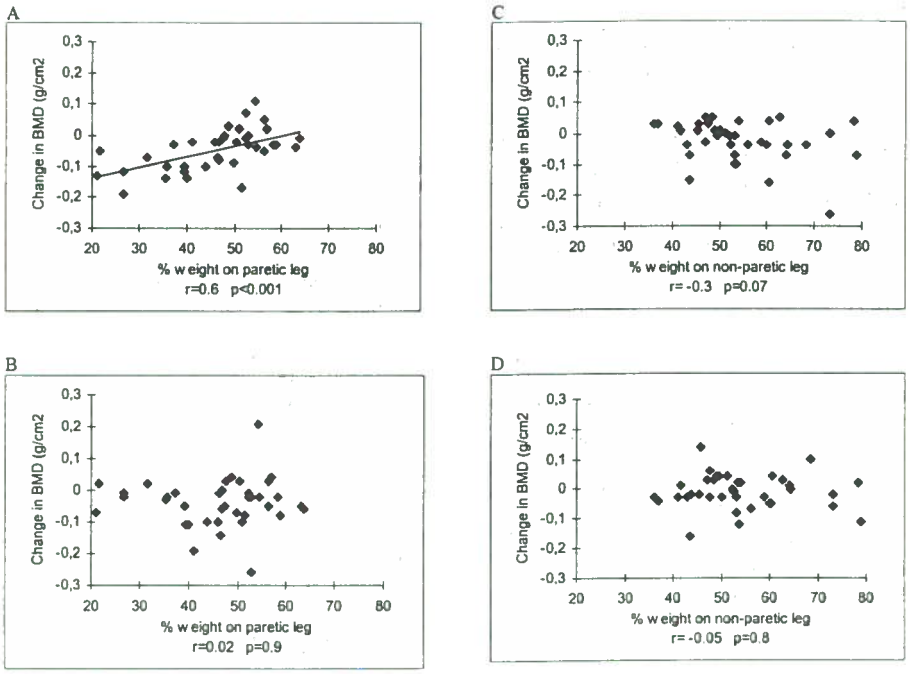


Figure 2. Relations between individual mean %weight bearing at 7 months and BMD changes from baseline to 1 year in 38 stroke patients able to stand unsupported at 7 months after stroke. (A) Lower femoral neck, paretic side. (B) Upper femoral neck, paretic side. (C) Lower femoral neck, nonparetic side. (D) Upper femoral neck, nonparetic side. Each symbol represents one subject. The line indicates the linear relationship; r is the Pearson's correlation coefficient.

and Lotz et al.[24] compression stresses within the femoral neck are mainly transmitted through the base of the femoral neck and the medial intertrochanteric region during gait, and these theoretical models may thus explain why we noted nonuniform bone loss. We believe that our results further support these theories, as we have also shown that changes in weight bearing affect BMD in the lower part of the femoral neck more than the upper part (Figure 2). In addition, our findings are consistent with studies on physical activity showing that the osteogenic effects of training seem to be quite specific to the anatomic sites at which the mechanical strains occur.[21,22]

It may be argued that BMD loss in the lower femoral neck, as opposed to the upper region, is caused in part by the differences in baseline BMD values (highest in the lower neck). We demonstrated, however, a pattern in bone loss from similar baseline values, which cannot be explained by differences in BMD baseline values (Table 2). In contrast, the pattern in the lower femoral neck on the paretic side related distinctly to the interval before the patient began to walk, whereas the upper did not.

The lower femoral neck consists of relatively more cortical than cancellous bone than the upper part,[30] and one may therefore speculate that the demineralization is influenced by the different proportions in types of bone tissue. A decrease of BMD in the weight-bearing skeleton occurs generally, however, more rapidly in trabecular bone compared with cortical bone, at least during the first months of immobilization.[26] Therefore, according to this theory, we should have found the largest demineralization in the upper part of the neck, which was not the case.

Among all groups of patients compared with respect to ambulatory status, the greatest bone loss (mean 14%) was found in the lower part of the femoral neck on the paretic side in those still immobile after 7 months (Tables 1 and 2). Because these patients were not able to walk independently we also expected to find a demineralization in the nonparetic leg. However, the loss of 5%–6% was not statistically significant ($p \geq 0.1$), most probably due to the small sample size and large sample variations. As the BMD loss was significantly larger on the paretic side compared with the nonparetic side, some loss of bone mineral on the latter side may have been prevented through activities other than walking (e.g., asymmetrical weight bearing during transfers). Standing with less body weight on the paretic leg necessarily associates with more weight through the nonparetic leg. Still, we did not find increased BMD values on the nonparetic side in any group of patients, regardless of ambulatory level, and the most reasonable explanation for this is the patients were generally physically inactive.

A major focus in rehabilitation of the hemiparetic patient is the improvement of balance through increased loading of the affected lower limb, resulting in a more symmetric standing posture.[1,3,8] We have shown that walking early after stroke and symmetrical weight bearing during standing are also important for preserving bone mineral in the lower femoral neck.

The total bone loss in humans after the age of peak bone mass is estimated to be approximately 1%–5% per year,[12,18] and the observed loss (mean 14% in the lower femoral neck on the paretic side) must therefore be considered high and clinically relevant. Duboeuf et al.[11] found that both upper and lower femoral neck BMD measurements were significantly predictive

of trochanteric fracture, but only upper femoral neck BMD was related to cervical fracture. However, some studies,[5,6,31] but not all,[33] have found that, among stroke patients, trochanteric fracture may be relatively more common than fracture of the femoral neck.

One possible limitation of our study is that the measurement of weight distribution between the two legs on the force platform is static, which may not relate to dynamic activities such as walking. Improvement in the proportion of weight born on the hemiplegic limb during standing may not result in a concomitant improvement in interlimb symmetry during walking.[36] Our test of asymmetrical weight bearing may therefore underestimate the asymmetry in our patients' usual gait pattern. In addition, the influence of weight bearing on the paretic leg during walking might be even more important, because bone adaptation is driven by dynamic rather than static loading.[34]

Only one subject eligible for our study decided not to participate, and the major cause for missing patients during follow-up was, as expected, severe disease or death. Thus, the results seem representative for the type of patients we studied. However, we believe that our findings underestimate the BMD reduction among average stroke patients, because initially unconscious, highly impaired stroke patients were not included in the study.

A second consideration is the modest number patients in some of the subgroups, which means that the power of the study to demonstrate statistically significant differences is only moderate. It is therefore likely that the nonsignificant reduction in BMD found in many of our analysis would have been significant if more patients had been included. However, the main results, as presented in Tables 1 and 2, demonstrate a distinct pattern of different rates of bone loss according to ambulatory status, which cannot be explained by lack of statistical power.

In conclusion, this study highlights several clinically relevant questions with respect to bone loss during the first year after stroke: The reduction in BMD in the femoral neck occurs mainly in the lower part of the neck and on the paretic side; it also depends on when or if the patients start to walk after stroke, but also on the amount of body weight placed on the paretic leg. Thus, measuring the lower part of the femoral neck gives a better estimate of the impact of gait and weight bearing than measuring the total femoral neck.

As for preventing bone loss after stroke, the importance of relearning to walk symmetrically as soon as possible after stroke is underlined by these findings.

Acknowledgments: The authors acknowledge the support of the chief physician, S. Sparr, M.D., and the medical staff at the Departments of Neurology and Geriatrics, University Hospital, Tromsø. This study was financially supported by "RiTø's Research Foundation, University Hospital, Tromsø; and the Norwegian Osteoporosis Society, Oslo and the research program "Research on the Elderly in Tromsø" financed by The Ministry of Health's Research on the Elderly, University Hospital, Tromsø, Norway.

References

1. Bobath, B. Adult hemiplegia: Evaluation and Treatment, 3rd Ed. Oxford: Butterworth-Heinemann; 1990.
2. Brandstater, M. E., Bruin, H., Gowland, C., and Clark, B. M. Hemiplegic gait: Analysis of temporal variables. Arch Phys Med Rehabil 64:583–587; 1983.
3. Carr, J. H. and Shepherd, R. B. A Motor Relearning Programme for Stroke, 2nd Ed. London: Heinemann; 1987.
4. Chiu, K. Y. and Pun, W. K. A prospective study on hip fractures in patients with previous cerebrovascular accidents. Injury 23:297–299; 1992.
5. Chiu, K. Y., Pun, W. K., Luk, K. D., and Chow, S. P. A prospective study on hip fractures in patients with previous cerebrovascular accidents. Injury 23: 297–299; 1992.
6. Christodoulou, N. A. and Drekatis, E. K. Significance of muscular disturbances in the localization of fractures of the proximal femur. Clin Orthop 187:215–217; 1984.
7. Cummings, S. R., Black, D. M., Nevitt, M. C., Browner, W. S., Cauley, J., and Ensrud, K. Bone density at various sites for prediction of hip fractures. Lancet 341:72–75; 1993.
8. Davies, P. M. Starting Again. Berlin: Springer; 1994.
9. De Laet, C. E., Van Hout, B. A., Burger, H., Weel, A. E., Hofman, A., and Pols, H. A. Hip fracture prediction in elderly men and women: Validation in the Rotterdam study. J Bone Miner Res 13:1587–1593, 1998.
10. Dettman, M. A., Linder, M. E., and Sepic, S. B. Relationship among walking performance, postural stability, and functional assessment of the hemiplegic patient. Am J Phys Med Rehabil 66:77–90; 1987.
11. Duboeuf, F., Hans, D., Schott, A. M., Kotzki, P. O., Favier, F., Marcelli, C., Meunier, P. J., and Delmas, P. D. Different morphometric and densitometric parameters predict cervical and trochanteric hip fracture: The EPIDOS Study. J Bone Miner Res 12:1895–902; 1997.
12. Ensrud, K. E., Palermo, L., Black, D. M., Cauley, J., Jergas, M., Orwoll, E. S., Neuitt, M. C., Fox, K. M., and Cummings, S. R. Hip and calcaneal bone loss increase with advancing age: Longitudinal results from the study of osteoporotic fractures. J Bone Miner Res 10:1778–1787; 1995.
13. Friedman, P. J. Gait recovery after hemiplegic stroke. Int Disabil Studies 12:119–122; 1991.
14. Garland, D., and Stewart, C. Osteoporosis after spinal cord injury. J Orthop Res 10:371–378; 1992.
15. Holden, G., Gill, K., and Magliozoni, M. R. Gait assessment for neurologically impaired patients. Standards for outcome assessment. Phys Ther 66:1530–1539; 1986.
16. Holden, G., Gill, K., Magliozoni, M. R., Nathan, J., and Piehl-Baker, L. Clinical gait assessment in the neurologically impaired: Reliability and meaningfulness. Phys Ther 64:35–40; 1984.
17. Järvinen, M. and Kannus, P. Injury of an extremity as a risk factor for the development of osteoporosis. Review. J Bone Jt Surg [Am] 79:263–276; 1997.
18. Jones, G., Nguyen, T., Sambrook, P., Kelly, P. J., and Eisman, J. A. Progressive loss of bone in the femoral neck in elderly people: Longitudinal findings from the Dubbo Osteoporosis Epidemiology Study. Br Med J 309:691–695; 1994.
19. Jorgensen, L., Jacobsen, B. K., Wilsgaard, T., and Magnus, J. H. Walking after stroke: Does it matter? Changes in bone mineral density within the first 12 months after stroke. A longitudinal study. Osteopor Int. 11:381–387; 2000.
20. Jørgensen, H. S., Nakayama, H., Raaschou, H. O., and Olsen, T. S. Recovery of walking function in stroke patients: The Copenhagen Stroke Study. Arch Phys Med Rehabil 76:27–32; 1995.
21. Kannus, P., Haapasalo, H., Sievanen, H., Oja, P., and Vuori, I. The site-specific effects of long-term unilateral activity on bone mineral density and content. Bone 15:279–284; 1994.
22. Kerr, D., Morton, A., Dick, I., and Prince, R. Exercise effects on bone mass in postemenopausal women are site-specific and load-dependent. J Bone Miner Res 11:218–225; 1996.
23. Leblanc, A. D., Schneider, V. S., Evans, H. J., Engelbretson, D. A., and Krebs, J. M. Bone mineral loss and recovery after 17 weeks of bed rest. J Bone Miner Res 5:843–850; 1990.
24. Lotz, J. C., Cheal, E. J., and Hayes, W. C. Stress distributions within the proximal femur during gait and falls: Implications for osteoporotic fracture. Osteopor Int 5:252–262; 1995.
25. Marshall, D., Johnell, O., and Wedel, H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Br Med J 312:1254–1259; 1996.
26. Mazess, R. B. and Wheldon, G. D. Immobilization and bone. Calcif Tissue Int 35:265–267; 1983.
27. Minaire, P. Immobilization osteoporosis: A review. Clin Rheumatol 8:95–103; 1989.
28. Mulley, G., and Espley, A. J. Hip fracture after hemiplegia. Postgrad Med J 55:264–265; 1979.
29. Olsen, T. S. Arm and leg paresis as outcome predictors in stroke rehabilitation. Stroke 21:247–251; 1990.
30. Pauwells, F. Biomechanics of the Locomotor Apparatus. Contribution to the Functional Anatomy of the Locomotor Apparatus. Berlin: Springer; 1980.
31. Poplingher, A. R. and Pillar, T. Hip fracture in stroke patients. Epidemiology and rehabilitation. Acta Orthop Scan 56:226; 1985.
32. Poplingher, A. R. and Pillar, T. Hip fractures in stroke patients. Epidemiology and rehabilitation. Acta Orthop Scand 56:226–227; 1985.

33. Ramnemark, A., Nyberg, L., Borssén, B., Olsson, T., and Gustafson, Y. Fractures after stroke. Osteopor Int 8:92–95; 1998.
34. Turner, C. H. Three rules for bone adaptation to mechanical stimuli. Bone 23:399–407; 1998.
35. Wilmet, E., Ismail, A. A., Heilporn, A., Welraeds, D., and Bergmann, P. Longitudinal study of the bone mineral content and soft tissue composition after spinal cord section. Paraplegia 33:674–677; 1995.
36. Winstein, C. J., Gardner, E., McNeal, D. R., Barto, P. S., and Nicholson, D. Standing balance training: Effect on balance and locomotion in hemiplegic adults. Arch Phys Med Rehabil 70:755–762; 1989.
37. Yoshikawa, T., Turner, C. H., Peacock, M., Slemenda, C. W., Weaver, C. M., Teegarden, D., Markwardt, P., and Burr, D. B. Geometric structure of the femoral neck measured using dual-energy x-ray absorptiometry. J Bone Miner Res 9:1053–1064; 1994.

Date Received: February 22, 2000
Date Revised: June 27, 2000
Date Accepted: June 27, 2000

ELSEVIER

Bone Vol. 28, No. 1
January 2001:140

ERRATUM

Correction to Ambulatory Level and Asymmetrical Weight Bearing After Stroke Affects Bone Loss in the Upper and Lower Part of the Femoral Neck Differently: Bone Adaptation After Decreased Mechanical Loading, by L. Jørgensen, N. J. Crabtree, J. Reeve, and B. K. Jacobsen, Bone 27:701–707; 2000.

As the result of a production error, Tables 1 and 2 were printed incorrectly. The corrected versions appear below. The publisher regrets the error.

Table 1. Mean bone mineral density (BMD, g/cm^2) and standard deviation (SD) in the proximal femur at baseline in the paretic and nonparetic leg and mean BMD changes from baseline to measurement after 1 year (95% confidence interval) in patients who could not walk at the 7 month evaluation and patients who could walk

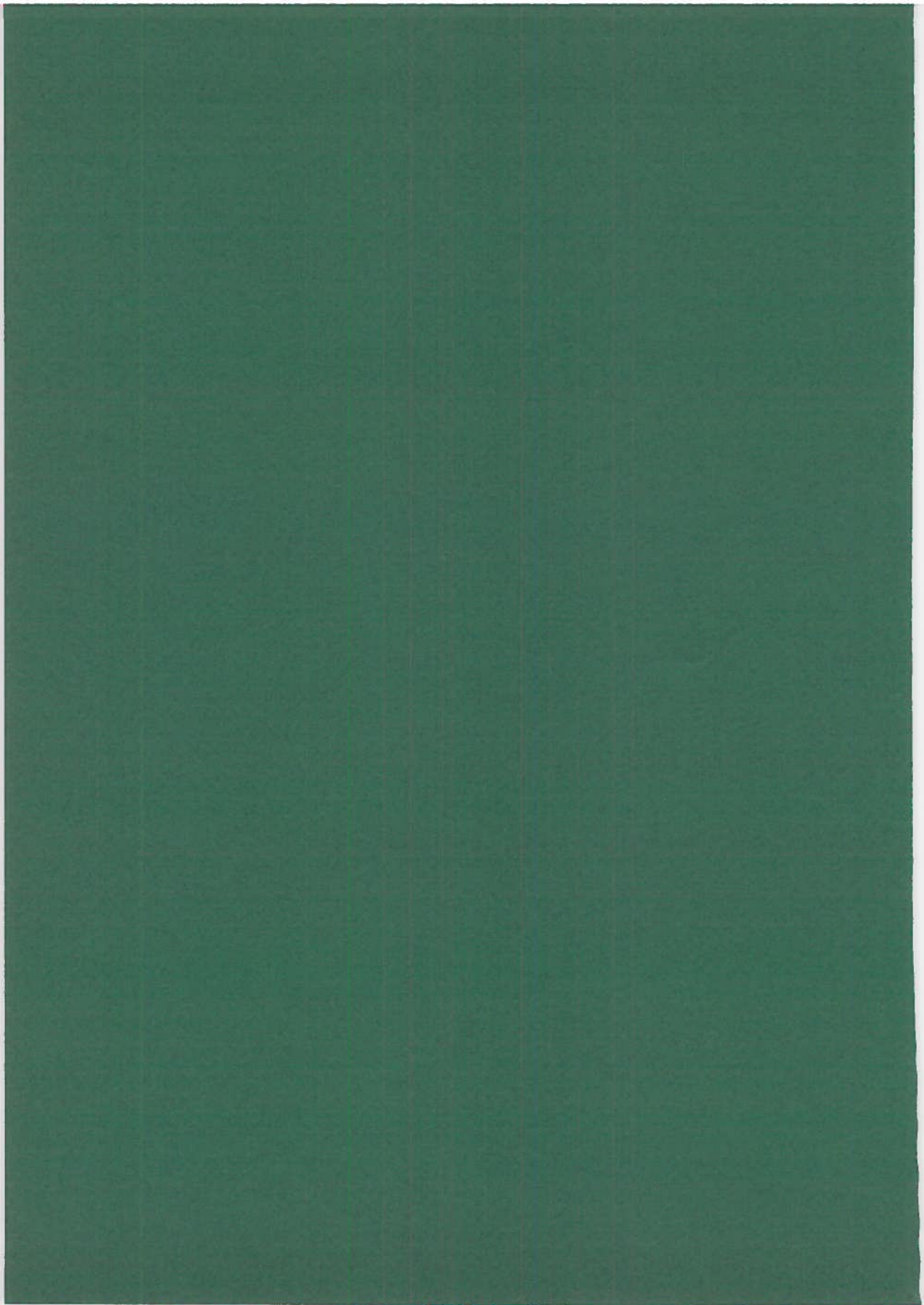
Walks at 7 months	Anatomic site		BMD at baseline mean (SD)	Change at 1 year mean (95% CI)	p-value for change	p-value for difference at lower/upper femoral neck
No (n = 8)	Paretic leg	Lower femoral neck	1.10 (0.17)	−0.14 (−0.19 to −0.09)	<0.001	0.001
		Upper femoral neck	0.61 (0.13)	−0.06 (−0.10 to −0.02)	0.01	
	Nonparetic leg	Lower femoral neck	1.07 (0.13)	−0.06 (−0.14 to 0.02)	0.1	0.3
		Upper femoral neck	0.64 (0.10)	−0.03 (−0.07 to 0.02)	0.2	
Yes (n = 32)	Paretic leg	Lower femoral neck	1.00 (0.17)	−0.03 (−0.05 to −0.01)	0.003	0.6
		Upper femoral neck	0.60 (0.17)	−0.04 (−0.07 to −0.01)	0.01	
	Nonparetic leg	Lower femoral neck	0.99 (0.18)	−0.02 (−0.04 to 0.00)	0.1	0.3
		Upper femoral neck	0.58 (0.15)	−0.01 (−0.03 to 0.01)	0.5	

Table 2. Mean bone mineral density (BMD; g/cm^2) and standard deviation (SD) at baseline and mean BMD changes from baseline to measurement after 1 year (95% confidence interval) according to when patients began to walk after stroke

		Paretic side			Nonparetic side		
Time when walking	n	BMD at baseline mean (SD)	Change at 12 months: Mean (95% CI), and % change	p-value	BMD at baseline mean (SD)	Change at 12 months: Mean (95% CI), and % change	p-value
(A) Lower femoral neck							
Walked at baseline	12	0.93 (0.14)	−0.01 (−0.04 to 0.03), −1%	0.7	0.94 (0.12)	0.00 (−0.04 to 0.03), 0%	0.8
Walked by 2 months	15	1.04 (0.20)	−0.04 (−0.07 to −0.01), −1%	0.01	1.01 (0.23)	−0.01 (−0.03 to 0.01), −1%	0.4
Walked by 7 months	5	1.03 (0.12)	−0.08 (−0.14 to −0.02), −8%	0.03	1.02 (0.10)	−0.08 (−0.16 to 0.00), −7%	0.053
Immobile by 7 months	8	1.01 (0.17)	−0.14 (−0.19 to −0.09), −14%	<0.001	1.07 (0.13)	−0.06 (−0.14 to 0.02), −6%	0.1
p-value for linear trend			$p < 0.001$			$p = 0.01$	
(B) Upper femoral neck							
Walked by baseline	12	0.52 (0.14)	−0.01 (−0.06 to 0.04), −2%	0.8	0.50 (0.12)	0.00 (−0.04 to 0.05), 0%	0.9
Walked by 2 months	15	0.68 (0.19)	−0.06 (−0.11 to −0.02), −9%	0.01	0.63 (0.18)	0.00 (−0.03 to 0.02), 0%	0.9
Walked by 7 months	5	0.59 (0.11)	−0.04 (−0.10 to 0.01), −7%	0.1	0.60 (0.06)	−0.05 (−0.12 to 0.02), −8%	0.1
Immobile by 7 months	8	0.61 (0.13)	−0.06 (−0.10 to −0.02), −10%	0.01	0.64 (0.10)	−0.03 (−0.07 to 0.02), −5%	0.2
p-value for linear trend			$p = 0.2$			$p = 0.1$	

8756-3282/01/$20.00
PII S8756-3282(00)00460-9

PAPER III



Calcif Tissue Int (2001) 68:11–15
DOI: 10.1007/s002230001165

Calcified Tissue International

Functional Status of the Paretic Arm Affects the Loss of Bone Mineral in the Proximal Humerus after Stroke: A 1-Year Prospective Study

L. Jørgensen, B. K. Jacobsen

Institute of Community Medicine, University of Tromsø, Tromsø, Norway

Received: 17 December 1999 / Accepted: 5 July 2000 / Online publication: 23 February 2001

Abstract. The aim of this study was to evaluate the effect of decreased arm function after stroke on bone mineral density (BMD) in the proximal humerus. Twenty-five patients were evaluated 1 week after acute stroke and reevaluated 2 months, 7 months, and 1 year after the stroke. BMD of the proximal humerus was measured and the functional status of the paretic arm was assessed. Within 1 year the BMD decreased significantly in the proximal humerus at the paretic side. No significant BMD change was found at the nonparetic side. Patients with an initial completely paralyzed arm lost 27% ($P < 0.001$), those with severe to moderate paresis lost 11% ($P < 0.001$), and patients with minor or no paresis had no significant bone loss in the proximal humerus at the paretic side after 1 year. A statistically significant trend with initial arm function was found both 7 months and 1 year after the stroke at the paretic side ($P < 0.01$). Patients who were paralyzed or had severe to moderate paresis both at inclusion and after 1 year had a larger 1-year bone loss in the proximal humerus than the patients who recovered and these who had only minor impairment throughout the study, 25%, 8%, and 5%, respectively (P-value for linear trend <0.001). We conclude that during the first year after stroke bone mineral is lost in the proximal humerus of the paretic arm, but that the loss depends on the initial degree of paresis. The loss may be prevented if arm function is regained.

Key words: Arm function — Bone mineral density — Osteoporosis — Rehabilitation — Stroke

Fractures due to osteoporosis are commonly localized to the hip, the proximal humerus, and the distal part of the radius. In stroke patients fractures are also frequent in these areas, especially at the paretic side [1]. Measurements of bone mineral density (BMD) are considered to be good predictors for these fractures, but only a few studies on changes in BMD in the arm due to immobilization have been performed. In cross-sectional studies of patients with frozen shoulder or rotator cuff ruptures the greatest bone loss in the arm was found in the proximal humerus [2, 3], most severely in patients with the lowest shoulder function [3]. Studies of stroke patients in which densitometry of the total body has been conducted describe a larger reduction of bone mineral in the paretic arm than in the paretic leg [4–6], possibly because the leg is stimulated through weight bearing despite being paretic. Moreover, as skeletal sites with a high content of trabecular bone have the highest initial loss of bone mineral after immobilization [7], a large decrease in BMD in the proximal humerus at the paretic side in stroke patients may be expected. To our knowledge this issue has not been examined in any previous study.

Thus, the aim of the study was to quantify possible changes in BMD in the proximal humerus within the first year after stroke, and to evaluate the effect of decreased arm function on this skeletal site.

Correspondence to: L. Jørgensen

Subjects and methods

Every acute stroke patient admitted to The University Hospital in Tromsø, Norway, from April 1996 to August 1997 was considered for this study. All persons with acute stroke from mid- and northern Troms, a well-defined part of the county with 114,000 inhabitants, are admitted to this hospital.

Subjects

All acute stroke patients aged 60 years or older and still wheelchair bound after 1 week were eligible for recruitment. Patients who lived more than a 2-hour drive from the hospital, and those who had not been able to walk prior to the stroke were excluded. Other exclusion criteria were previous strokes affecting the sensomotoric system, unconsciousness and terminal illness, and unilateral bone diseases affecting BMD asymmetrically such as osteosarcomas and osteomyelitis. As changes in BMD of the hip were also studied [8], patients with osteosynthetic material in the femoral neck and those with a history of hip fracture were also excluded. Informed consent was obtained from each participant according to The Second Helsinki Declaration, and the trial was approved by the Regional Committee for Medical Research Ethics.

Methods

Bone Mineral Density Measurements

Bone mineral density (BMD, g/cm^2) was measured using dual energy X-ray absorptiometry (DXA) (Lunar DPX-L, version 1.3z). The first measurement was performed at a mean of 7 days (SD 4, range 1–16) after the stroke followed by measurements 2 months (mean 8 weeks, SD 0.5, range 7.5–10), 7 months (mean 30 weeks, SD 2, range 25–33), and 12 months (mean 52 weeks, SD 2, range

Table 1. Mean BMD (g/cm^2) and SD in the proximal humerus, spine, and head and mean BMD changes from baseline to the measurement after 1 year (95% CI) (n = 28)

Anatomic site		BMD at baseline Mean (SD)	Change at 1 year Mean (95% CI)	% Change at 1 year	*P*-value	Difference paretic/nonparetic side *P*-value
Proximal humerus	Paretic side	0.85 (0.17)	−0.14 (−0.18; −0.10)	−17	<0.001	<0.001
	Nonparetic side	0.87 (0.18)	−0.02 (−0.05; 0.01)	−2	0.1	
Spine		1.27 (0.18)	−0.02 (−0.06; 0.01)	−2	0.1	
Head		1.96 (0.18)	+0.03 (0.00; 0.06)	+2	0.06	

48–58) later. To minimize interobserver variation, all the scans were done by the same investigator (LJ) and all were analyzed by the same technician (LW), who, at the time of the analysis, was not aware of the patient's paralyzed side and disability.

BMD of the head and spine were derived directly from the total body scan using Lunar definitions. BMD of the proximal humerus was derived from the same total body scan by means of the region of interest (ROI) program. The proximal humerus ROI was located by using the ruler option where the inferior part of the region was located 96 mm from the most superior part of the humerus head.

The coefficient of variation (CV; SD/mean) was determined by measuring BMD twice in 10 stroke patients (5 men, 5 women, mean age 74 years, SD 7), with functional levels ranging from severe to no paresis. The two measurements were done consecutively during the same day with repositioning between each scan. CV was estimated to be 3.3% and 2.4% for the proximal humerus at the paretic and nonparetic side, respectively. For both the head and the spine, CV was estimated at 1.4%. The longitudinal drift assessed with daily phantom measurements was <1%.

Functional Tests

The motor function of the paretic arm was assessed immediately before the BMD measurements by use of the Scandinavian Stroke Scale (SSS) Score [9,10]. The score is graded in five categories (0: paralysis; 2: can move but not against gravity (severe paresis); 4: raises arm with flexion in elbow (moderate paresis); 5: raises arm straight but with reduced strength (mild paresis); 6: raises arm with normal strength (no paresis). Spasticity was assessed according to the modified Ashworth scale [11] ranging from 0: no increase in muscle tone to 4: affected part rigid in flexion or extension. Both spasticity as well as the degree of paresis (SSS) was evaluated by the same investigator (LJ).

Statistical Analysis

The data were analyzed using the Windows 7.5 version of the Statistical Package for the Social Sciences (SPSS). Chi square test was used for categorical values and Students *t*-test for continuous variables. Analysis of variance (ANOVA) was used to compare BMD changes between SSS groups, and linear trends in reduction in BMD according to SSS group were evaluated with contrasts. Because of the few subjects in some of the subgroups, nonparametric tests were also applied (Wilcoxon Signed Rank Test and Kruskal-Wallis Test for testing within-group and between-group changes, respectively).

Statistical correlations between SSS and the changes in BMD, and SSS and spasticity were evaluated using Spearman's rho (r_s).

Results

Characteristics of Study Subjects

All eligible patients (n = 37) agreed to participate. Within 1 year, six patients died, one decided not to continue in the study, and two had been transferred to nursing homes situated more than a 2-hour drive from the hospital. At the time of the follow-up examination, they were too ill for the long drive. The remaining 28 patients (18 men, 10 women) had a median SSS arm score of 2 (range 0–5) at baseline. There were no statistically significant differences with regard to gender or any of the BMD baseline values in the group of patients not followed for the entire year and the group who completed the 1-year examination ($P \geq 0.1$, results not shown), but the former group was somewhat older [mean 80 years (SD 9) and mean 75 years (SD 7), respectively, $P = 0.07$]. None of the patients had a history of fracture in the proximal humerus.

Changes in BMD

In the proximal humerus at the paretic side BMD decreased significantly during the first year, and SSS at baseline correlated significantly with the 1-year loss of bone mineral ($r_s = 0.7$, $P < 0.001$). At the nonparetic side the change in BMD was not significant; also, in the spine and head no significant changes were found after 1 year (Table 1). The increase in BMD of the head did, however, approximate the level of conventional statistical significance.

Twenty-five patients completed the 2-month, 7-month, and the 1-year examination, and three patients missed either the 2- or 7-month measurements because of severe illness. We compared the BMD loss in the proximal humerus in the nine patients who were completely paralyzed at baseline (SSS group 0), the 11 patients with severe to moderate paresis (SSS groups 2–4), and the five patients with only minor or no paresis (SSS group 5, 6) (Table 2). There were no significant differences between the SSS groups with respect to the BMD baseline values ($P \geq 0.2$, results not shown), but after 7 and 12 months there was a significant bone loss at the paretic side in the SSS 0 group and SSS 2–4 groups ($P \leq 0.05$), with the largest loss in the completely paralyzed patients (SSS = 0). A statistically significant relation was found between the initial arm function (baseline SSS group) and the reduction in BMD after 7 months and after 1 year at the paretic side, whereas no trend in BMD loss with respect to SSS at baseline was demonstrated

in the nonparetic side (Table 2). Although the paucity of our data hampered the ability to draw clear conclusions, they may indicate that the loss in BMD at the paretic side in patients with low SSS (0) reaches a plateau after 7 months.

One year after the stroke there was a strong correlation between the changes in BMD in the proximal humerus at the paretic side and the SSS score evaluated by 1 year (r_s = 0.8, $P < 0.001$). Also, spasticity in the arm and SSS correlated significantly ($r_s = -0.8$, $P < 0.001$).

Fifteen patients were paralyzed or had severe to moderate paresis of the arm both at inclusion and after 1 year (SSS 0–4), eight patients categorized to the SSS 0–4 group at baseline recovered within a year, and five patients were only slightly impaired or not impaired at all throughout the study (SSS 5–6). The three groups did not differ significantly with regard to the baseline BMD values in the proximal humerus ($P \geq 0.8$). The patients who regained arm function had a lower BMD loss at the paretic side compared with the patients who did not recover, and a statistically significant relation between the function of the arm and the 1-year reduction in BMD was found at the paretic side ($P < 0.001$) but not at the nonparetic side ($P = 0.9$) (Table 3).

All associations that were statistically significant ($P < 0.05$) when *t*-tests were used were also statistically significant when nonparametric tests were used. Furthermore, the same *P*-values as displayed in the tables were found.

Table 2. Changes in BMD (g/cm²) in the proximal humerus from baseline to the measurement 2 months, 7 months, and 1 year after stroke according to functional status of the paretic arm at baseline

	Paretic side			Nonparetic side		
Functional status of paretic arm	Change at 2 months Mean (CI 95%), % change	Change at 7 months Mean (CI 95%), % change	Change at 1 year Mean (CI 95%), % change	Change at 2 months Mean (CI 95%), % change	Change at 7 months Mean (CI 95%), % change	Change at 1 year Mean (CI 95%), % change
SSS: 0 (n = 9)	−0.07 (−0.15; 0.02) −7	−0.22 (−0.32;−0.12)[a] −23	−0.25 (−0.32; −0.17)[b] −27	−0.03 (−0.10; 0.04) −3	+0.01 (−0.05; 0.06) +1	−0.02 (−0.07; 0.02) −2
SSS: 2–4 (n = 11)	−0.02 (−0.06; 0.02) −2	−0.06 (−0.11; −0.01)[a] −6	−0.09 (−0.13; −0.06)[b] −11	−0.01 (−0.06; 0.05) −1	−0.01 (−0.05; 0.04) 0	−0.05 (−0.10; 0.01) −4
SSS: 5–6 (n = 5)	−0.01 (−0.09; 0.06) −1	−0.01 (-0.08; 0.06) −1	−0.04 (−0.12; 0.05) −4	−0.01 (−0.06; 0.05) −1	−0.03 (−0.12; 0.06) −4	0 (−0.07; 0.06) 0
p-value for linear trend	0.2	0.001	<0.001	0.6	0.4	0.6

P-value for changes within the group: [a]<0.05, [b]<0.001

Discussion

In this study we found a significant demineralization of the proximal humerus at the paretic side and a strong correlation between this loss of bone mineral and the motor function of the arm (SSS). Within only 1 year BMD decreased by 25% in the paretic arm in the most impaired patients, a reduction that is clinically relevant as it increases the risk of a future fracture.

Osteoporosis in the paretic arm after stroke has been described previously [4–6, 12, 13], but the results in these studies conflict with respect to the relationship between arm function and bone loss. Prince et al. [12] found that a good functional status was protective against bone loss; additionally, spasticity was associated with bone loss at the trabecular site. In other studies no correlation was found between motor function and/or spasticity of the arm and demineralization [4–6, 13].

We found that the functional status of the paretic arm at baseline predicts the changes in BMD in this arm and that the most impaired patients have a large and continuous bone loss. For the first time we show that stroke patients who regain almost normal arm function within 1 year, despite being severely impaired initially, lose less bone mineral than patients with a persistently severe paresis.

Should patients having moderate paresis (SSS = 4) be classified together with patients having severe paresis (as done in Table 3) or with patients having minor impairment?

Table 3. Mean changes in BMD (g/cm^2) in the proximal humerus from baseline to the measurement 1 year after stroke according to arm function (SSS) at baseline and at 1 year

		Paretic side	Nonparetic side
SSS paretic arm	n	Change at 1 year Mean (95% CI), % change	Change at 1 year Mean (95% CI), % change
Paralysis or severe to moderate paresis (SSS 0–4) at baseline and by 1 year	15	−0.22 (−0.27; −0.17) −25	−0.01 (−0.04; 0.03) 0
Paralysis or severe to moderate paresis (SSS 0–4) at baseline but minor impaired (SSS 5–6) by 1 year	8	−0.06 (−0.10; −0.03) −8	−0.06 (−0.13; 0.00) −7
Minor impaired (SSS 5–6) at baseline and by 1 year	5	−0.04 (−0.12; 0.05) −4	0.00 (−0.07; 0.06) 0
P-value for linear trend		<0.001	0.9

We found that re-categorizing the patients with SSS = 4 from the group of low function to the group of good function gave essentially the same pattern, as shown in Table 3.

Although factors other than the lack of mechanical stimuli may be of importance after immobilization, the local effect is most likely the most significant, considering that the bone loss at the disused side is more evident than the changes over the whole body. Thus, with respect to the paretic arm, the loss of bone mineral probably results mainly from the lack of muscle pull, whereas for the paretic leg, decreased ground-reaction forces may be an additive and perhaps even more important factor [8]. Moreover, as the BMD change in the head approached the level of significance, the increase in this area indicates that a redistribution of bone mineral may have occurred. A redistribution of bone mineral due to immobilization has also been suggested in previous studies where similar results were found, as for example in people volunteering for long duration bed rest [14].

In our study, all 37 eligible patients agreed to participate. One important consideration is, however, that while 28 patients completed the 1-year evaluation, 9 did not. Still, as the former group was not significantly different at baseline from the latter, the bias introduced in the study sample is probably limited. The major cause for not completing the study was severe disease or death, which was not unexpected considering the age and morbidity of the participants. Initially unconscious patients and patients who were able to walk immediately after the stroke were not included; for this reason our results cannot be generalized to all stroke patients.

There were few stroke patients in some of the subgroups. This has hampered the analysis and reduced the statistical power. However, the main results, as presented in Tables 2 and 3, demonstrate a distinct pattern of different rates of bone loss according to the functional status of the paretic arm, which cannot be explained by lack of statistical power.

Conclusion

Although clinical trials are necessary for determining the benefit of an intervention, our results indicate that the loss of bone mineral in the proximal humerus of the paretic arm may be prevented if the function of this arm is regained.

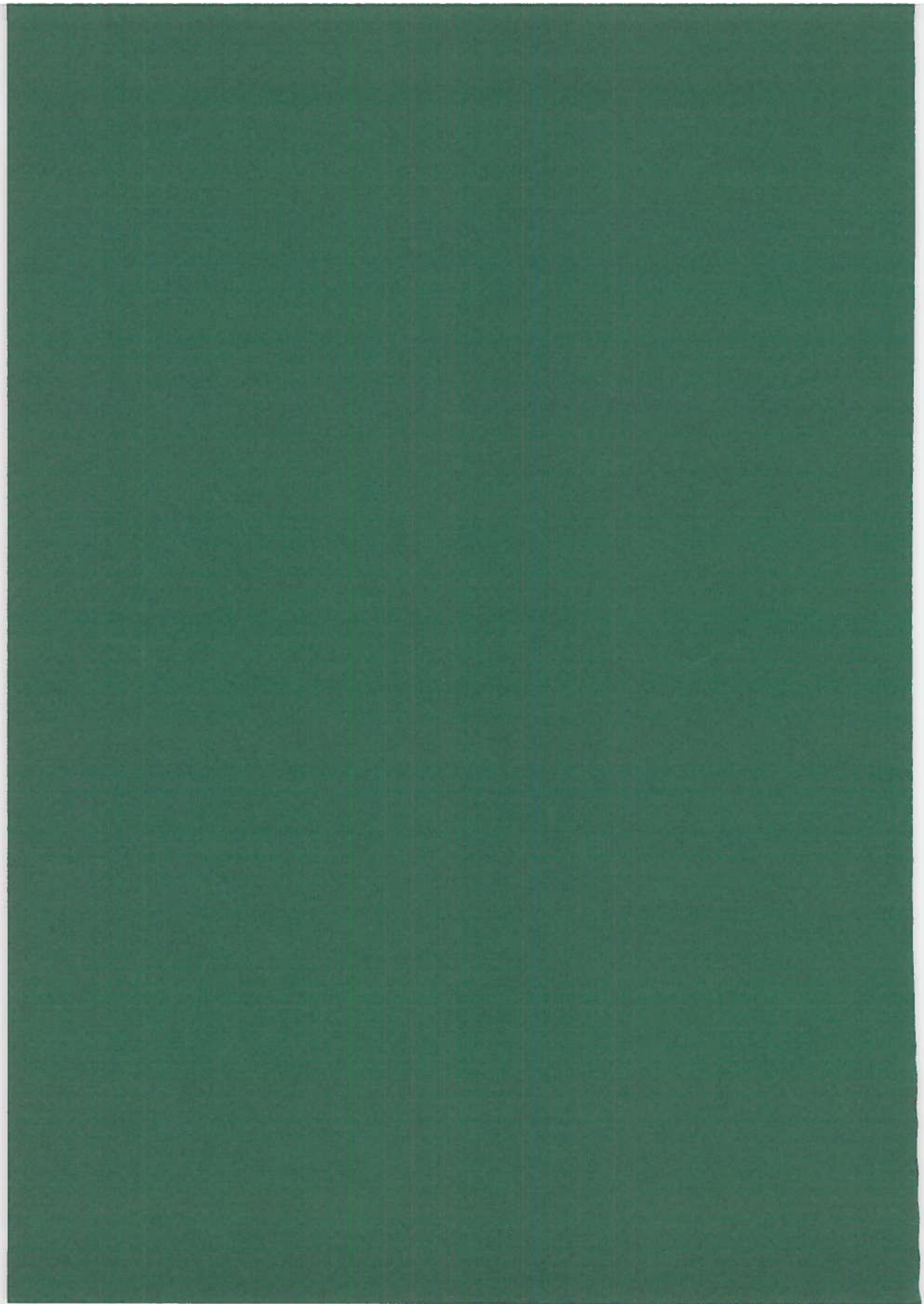
Acknowledgments. We are grateful to technician L. Wilsgaard for analyzing all the DXA scans. We also acknowledge the support of chief physician S. Sparr and the medical staff at the Departments of Neurology and Geriatrics University Hospital, Tromsø. This study was financially supported by the Ministry of Health «Research on the Elderly», University Hospital, Tromsø, Norway.

References

1. Ramnemark A, Nyberg L, Borssen B, Olsson T, Gustafson Y (1998) Fractures after stroke. Osteoporos Int 8:92–95
2. Leppala J, Kannus P, Sievanen H, Jarvinen M, Vuori I (1998) Adhesive capsulitis of the shoulder (frozen shoulder) produces bone loss in the affected humerus, but long-term bony recovery is good. Bone 22:691–694
3. Kannus P, Leppala J, Lehto M, Sievanen H, Heinonen A, Jarvinen M (1995) A rotator cuff rupture produces permanent osteoporosis in the affected extremity, but not in those with whom shoulder function has returned to normal. J Bone Miner Res 8:1263–1271
4. Iversen E, Hassager C, Christiansen C (1989) The effect of hemiplegia on bone mass and soft tissue body composition. Acta Neurol Scand 79:155–159
5. Hamdy RC, Krishnaswamy G, Cancellaro V, Whalen K, Harvill L (1993) Changes in bone mineral content and density after stroke. Am J Phys Med Rehabil 72:188–191
6. Hamdy RC, Moore SW, Cancellaro VA, Harvill LM (1995) Long-term effects of strokes on bone mass. Am J Phys Med Rehabil 74:351–356
7. Minaire P (1989) Immobilization osteoporosis: a review. Clin Rheumatol 8 (suppl 2):95–103
8. Jørgensen L, Jacobsen BK, Wilsgaard T, Magnus JH (2000) Walking after stroke: Does it matter? Changes in bone mineral density within the first 12 months after stroke. A longitudinal study. Osteoporos Int 11:381–387
9. Scandinavian Stroke Study Group Multicenter trial of hemo-

dilution in ischemic stroke: background and study protocol. Stroke 16:885–890
10. Lindenstrøm E, Boysen G, Christiansen LW, Hansen BR, Nielsen BW (1991) Reliability of Scandinavian Stroke Scale. Cerebrovasc Dis 1:103–107
11. Bohannon RW, Smith MB (1987) Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 67:206–207
12. Prince RL, Price RI, Ho S (1988) Forearm bone loss in hemiplegia: a model for the study of immobilization osteoporosis. J Bone Miner Res 3:305–310
13. Ramnemark A, Nyberg L, Lorentzon R, Englund U, Gustafson Y (1999) Progressive hemiosteoporosis on the paretic side and increased bone mineral density in the nonparetic arm the first year after severe stroke. Osteoporos Int 9:269–275
14. Leblanc AD, Schneider VS, Evans HJ, Engelbretson DA, Krebs JM (1990) Bone mineral loss and recovery after 17 weeks of bed rest. J Bone Miner Res 5:843–850

PAPER IV



Bone Mineral Density in Acute Stroke Patients

Low Bone Mineral Density May Predict First Stroke in Women

Lone Jørgensen, MSc; Torgeir Engstad, MD; Bjarne K. Jacobsen, PhD

Background and Purpose—Osteoporosis and stroke share several risk factors, including age, smoking, low physical activity, and hypertension. Thus, low bone mineral density (BMD) and high stroke risk may be related. We examined the relationship between BMD and acute stroke in noninstitutionalized men and women aged ≥60 years.

Methods—Sixty-three stroke patients (33 women and 30 men) and 188 control subjects from the general population were included. BMD was measured by using dual-energy x-ray absorptiometry at both proximal femurs. The measurements of the stroke patients were performed 6 days after the onset of stroke.

Results—The BMD at the femoral neck in the female stroke patients was 8% lower than in the control subjects ($P=0.007$). In men, no difference in BMD between the stroke patients and their controls was found. Women with BMD values in the lowest quartile had a higher risk of stroke than women with BMD values in the highest quartile (OR 4.8), and the probability value for linear trend over the quartiles was statistically significant ($P=0.003$). The OR for stroke increased 1.9 per SD (0.13 g/cm^2) reduction in BMD, and the association between low BMD and stroke in women remained significant when the analysis was adjusted for potential confounders.

Conclusions—Female, but not male, stroke patients have lower BMD than population controls. Low BMD may predict stroke in women. (***Stroke*. 2001;32:47-51.)**

Key Words: bone mineral density ■ osteoporosis ■ risk factors ■ stroke, acute

Osteoporosis and stroke share several risk factors, such as age, smoking, low level of physical activity, and hypertension.[1-9] Low bone mineral density (BMD) and a high risk of stroke may thus be related, but studies on this relationship are sparse. Browner et al[10,11] have shown that low BMD is significantly related to stroke mortality and stroke incidence in a female population, but no data are available for men. An examination of the association between BMD and stroke is of clinical importance for 2 reasons. First, if BMD is low in acute stroke patients, it may be an important explanatory factor for the increased risk of hip fracture in stroke patients.[12,13] This risk factor will thus add to other known risk factors, such as the increased incidence of falls[11-13] and the increased rate of bone loss.[14-16] Second, low BMD may predict stroke.

The purpose of the present study was to examine the relationship between BMD and acute stroke in a case-control study among noninstitutionalized men and women aged ≥60 years.

Subjects and Methods

Cases

The stroke patients included in this study were identified from among all acute stroke patients aged ≥60 years from the municipality of Tromsø, Norway, consecutively admitted to The University Hospital in Tromsø from June 1, 1996, through August 31, 1997. This hospital is the only one in the area, and all persons with acute stroke from the municipality are admitted to this hospital.

Stroke was defined according to the definition of the World Health Organization, WHO.[17] The diagnosis was based on a doctor's clinical examination and an evaluation of all available information from the hospital medical records and was supported by anatomic cerebral changes on CT scans. A specialist in internal and geriatric medicine at the University Hospital (T.E.), blinded to the BMD measurements, validated all stroke diagnoses. Patients who had not been able to walk without personal support before the stroke and patients who were unable to answer simple questions, including informed consent, were excluded. Other exclusion criteria were history of previous stroke, unconsciousness and terminal illness, presence of osteosynthetic material in the femoral neck, and history of hip fracture.

Among a total of 125 stroke patients admitted to the hospital, 64 were eligible for the study and 63 agreed to participate. Five of them had intracerebral hemorrhages. Sixty-one patients (49%) were not eligible for the study because of death, unconsciousness, or severe disorientation during the first week after stroke (n=30); previous strokes (n=23); or a history of hip fracture or presence of osteosynthetic material in the femoral neck (n=6). Two patients were not enrolled in the study because of femur amputation and cancer with metastasis to the bone.

Controls

The control subjects were randomly selected from the population register of Tromsø in 1998 and invited by letter to participate in the study. For each gender and 5-year age bracket, we invited more than

Received July 28, 2000; final revision received September 6, 2000; September 14, 2000.

From the Institute of Community Medicine, University of Tromsø, Norway.

Correspondence to Lone Jørgensen, Institute of Community Medicine, University of Tromsø, N-9037 Tromsø, Norway. E-mail Lone.Jorgensen@hitos.no

Stroke is available at http://www.strokeaha.org

TABLE 1. Characteristics of the Study Groups and Difference Between Cases and Controls

Characteristic	Women			Men		
	Cases (n=33)	Controls (n=101)	*P*	Cases (n=30)	Controls (n=87)	*P*
Age, mean (SD), y	77 (8)	76 (8)	0.3	75 (8)	75 (8)	0.9
BMI (kg/cm^2), mean (SD)	26.1 (5)	26.9 (4)	0.4	24.1 (3)	25.4 (3)	0.05
BMD neck (g/cm^2), mean (SD)	0.723 (0.14)	0.792 (0.12)	0.007	0.902 (0.13)	0.899 (0.15)	0.9
Smoking			0.7			0.5
Current smoker	9 (27%)	18 (18%)		8 (27%)	20 (23%)	
Ex-smoker	4 (12%)	17 (17%)		18 (60%)	48 (55%)	
Never-smoker	17 (52%)	55 (55%)		1 (3%)	12 (14%)	
Unknown	3 (9%)	11 (11%)		3 (10%)	7 (8%)	
Drinks alcohol	20 (61%)	57 (56%)	0.7	21 (70%)	73 (84%)	0.1
Uses walking aids	10 (30%)	19 (19%)	0.2	5 (17%)	6 (7%)	0.2
Has diabetes mellitus	6 (18%)	9 (9%)	0.2	2 (7%)	7 (8%)	0.9
Previous myocardial infarction	6 (18%)	9 (9%)	0.1	9 (30%)	20 (23%)	0.4
Angina pectoris	5 (15%)	21 (21%)	0.6	6 (20%)	16 (18%)	0.8
Medication for hypertension	15 (46%)	26 (26%)	0.03	10 (33%)	17 (20%)	0.1

twice the number of case patients in order to obtain a sufficient number. The letter of invitation contained information about the aim of the study, the criteria for exclusion (ie, hip fracture, presence of osteosynthetic material in the femoral neck, and stroke), and the fact that transportation to the hospital on the day of the examination would be provided if the attendees were unable to travel on their own.

Among the 404 invited possible control subjects, 197 (49%) agreed to be enrolled in the study. All of them had a medical record in the hospital, and to exclude possible unreported stroke these records were all reviewed by an experienced physician (T.E.). Six men and 3 women were found to have had a previous stroke and were thus excluded from the analysis.

Informed consent was obtained from all participants according to the Second Helsinki Declaration, and the Regional Committee for Medical Research Ethics approved the trial.

Methods

All participants were interviewed about their alcohol and smoking habits: whether they were teetotalers, and whether they smoked currently or had smoked previously. The stroke patients were asked whether they had used assistive devices for walking before the stroke, and the control subjects were asked about current use of these devices. Body weight and height was mostly measured in a standing position, except for 27 of the stroke patients who had their height measured in a supine position, as they were unable to stand. The body mass index (BMI) was calculated as the weight (in kilograms) divided by the square of the height (in meters). Stroke severity was assessed by use of the Scandinavian Stroke Scale (SSS),[18–19] in which the patients are categorized into 5 groups according to degree of leg paresis, ranged from paralysis (SSS score of 0) to no paresis at all (score of 6).

The control subjects completed a questionnaire about medical history, including current and previous cardiovascular diseases, cancer, diabetes, and current use of medication. The same information about the stroke patients was obtained from their medical records. Antihypertensive medication use until the stroke event was considered indicative of hypertension among the cases. Current self-reported use of antihypertensive drug was considered a marker of hypertension among the controls.

BMD was measured by using dual-energy x-ray absorptiometry (Lunar DPX-L, version 1.3z) at both proximal femurs, and BMD of the femoral neck area was determined according to the Lunar manual. In the analysis we used the mean values from the right and left side. All the measurements were done by 2 operators (L.J. and E.H.), and all the scans were analyzed by the same technician (L.W.). The interoperator precision (SD/mean) was 2.2%, tested by measuring BMD twice in 10 of the participants (mean age 67 years). The 2 measurements were done consecutively during the same day, with an interval of 2 to 3 minutes. Subjects were repositioned between each scan by the operators.

The longitudinal drift assessed with daily phantom measurements was <1%.

Statistical Analysis

To test differences between the case and control groups, χ^2 test, the Fisher exact test or Student 2-sample *t* test was used. Statistical correlations between SSS and BMD were evaluated by using the Spearman rho (r_s).

For men and women separately, the control subjects were divided into quartiles with respect to the BMD values, and the case patients were categorized according to these quartiles. ORs for stroke in the different quartiles as well as with a 1-SD change in BMD were estimated by use of logistic regression analysis. Adjustments were done for potential confounders found to be related to the case-control status in one or both sexes with $P \leq 0.1$.

The data were analyzed with the Windows 7.5 version of the Statistical Package for the Social Sciences (SPSS, Inc).

Results

Characteristics of the Cases and Their Controls

All the cases and all the controls were living in their own homes before the hospitalization or examination.

The patients were measured a mean of 6 (SD 4) days after the stroke onset. There was no difference between the paretic and nonparetic side with respect to BMD, and this was also true for the 14 most severely affected stroke patients (SSS score 0; mean difference between the paretic and nonparetic leg 0.009 g/cm^2; $P=0.7$).

Table 1 shows the characteristics of the cases and controls. Female stroke patients had a statistically significant 8% lower age-adjusted BMD of the femoral neck than the control

TABLE 2. Unadjusted and Adjusted ORs for Stroke Among Women and Men According to Femoral Neck BMD Quartiles

	Women				Men			
BMD Quartiles*	Cases, n	Controls, n	OR, Mean (95% CI)	Adjusted† OR Mean (95% CI)	Cases, n	Controls, n	OR, Mean (95% CI)	Adjusted† OR Mean (95% CI)
1	19	26	4.8 (1.4–15.9)	6.6 (1.8–24.8)	6	21	0.9 (0.3–3.1)	0.6 (0.1–2.3)
2	6	25	1.6 (0.4–6.2)	1.8 (0.4–7.4)	6	22	0.9 (0.3–3.0)	0.6 (0.2–2.4)
3	4	24	1.1 (0.2–4.8)	1.6 (0.3–7.5)	11	22	1.6 (0.5–4.8)	1.4 (0.4–4.7)
4	4	26	1.00	1.00	7	22	1.00	1.00
P for linear trend			0.003	0.003			0.6	0.2

*BMD range for women: ≤0.707, 0.708–0.777, 0.778–0.873, ≥0.874; BMD range for men: ≤0.780, 0.781–0.884, 0.885–1.010, ≥1.011.
†Adjusted for BMI, alcohol drinking, previous myocardial infarction, and medication for hypertension.

subjects ($P=0.007$) and statistically significant lower BMD than the male patients ($P<0.001$).

There was no correlation between stroke severity assessed by SSS and the BMD ($r=0.01$, $P=0.9$ and $r=0.2$, $P=0.3$ for women and men, respectively).

Women with BMD values in the lowest quartile had a significant 4.8 times higher risk of stroke than women with BMD values in the highest quartile, and the probability value for linear trend over the quartiles was statistically significant ($P=0.003$) (Table 2). Each SD decrease in BMD (0.13 g/cm^2) was associated with a 1.9-fold increase in stroke. Among men, no statistical significant relationship between BMD and stroke was found (Table 1 and 2).

Adjustments of the difference in BMD between the stroke patients and their controls with respect to the possible confounders displayed in Table 1, one by one or in concert, did not reduce the OR estimates for women or the overall conclusions (Table 2). If anything, the inverse relationship in women was strengthened, but due to wide 95% CIs, we concluded that no important effect of the adjustments was observed.

Discussion

In the present study we found that female stroke patients had lower BMD in the femoral neck than did population controls, a result consistent with those of Browner et al.[10,11] They showed that low BMD in the calcaneus and proximal radius (but not in the distal radius) was associated with an increased stroke risk in women (RR 1.3 per SD decrease in BMD), whereas we found that the risk was somewhat higher.

We measured BMD in the proximal femur, which is the most relevant region of interest to evaluate with respect to the risk of hip fracture.[20–22] Consequently, if low BMD is already present at stroke onset, the severe bone loss thereafter[14–16] puts the female stroke patients at a particularly high risk of hip fracture. The result of the present study, therefore, has considerable clinical implications regardless of what the causal relationship might be.

We did not find any relationship between stroke risk and low BMD in men; to our knowledge, this topic has not been studied previously. Although Johansson et al[23] did show that BMD was a strong predictor of total mortality in men as well as women, the number of fatal stroke was too low to evaluate the relationship between BMD and stroke mortality.

Because of our study design, some bias cannot be excluded. First, the BMD in the patients was measured 6 days after stroke onset. In a previous longitudinal study, we showed that patients who were completely wheelchair-bound had a significant 3% BMD loss in the femoral neck on the paretic side and a nonsignificant 1% loss on the nonparetic side 2 months after stroke.[14] The BMD difference of 8% between the female cases and their controls cannot, therefore, be explained by the bone loss that may have occurred between stroke onset and the BMD measurement 1 week later. Furthermore, there was no difference between the BMD values of the paretic and the nonparetic legs. This also indicates that no change in BMD had taken place before the measurement.

Second, there may be a bias connected to the enrolment of the control subjects. Only one eligible stroke patient refused to participate in the study, whereas 51% of the invited controls abstained, including an unknown number of individuals who were not eligible due to eg, previous stroke or hip fracture/osteosynthetic material in the femoral neck. The control subjects were told in the letter of invitation that they could participate in the study only if they had no history of stroke or hip fracture, but also that they could refuse to participate without giving any reason for this decision. Thus, we do not know the proportion of possible controls contacted who did not take part in the study due to the exclusion criteria or for other reasons. We did expect that a higher proportion of the cases had used walking aids prior to the stroke, because physical disability has been identified as a predictor of stroke,[6] but we cannot exclude the possibility that the frailest controls abstained to participate even though they were offered free transportation to the examination. On the other hand, it is also possible that control subjects were more likely to respond if they were ill and therefore wanted to participate in a medical research study. If so, the prevalence of risk factors may be overestimated and the BMD in the controls most probably underestimated. In particular, some female control subjects with known osteoporosis may have participated to have their BMD assessed, but as a consequence this would reduce the mean BMD in the control women and thus cannot explain our results. When we excluded women with

known osteoporosis from our analysis, the difference in mean BMD in female stroke patients and controls was unchanged. We have also compared data from our control group with data from a population survey in Tromsø, which had a 77% response rate. The prevalence of risk factors in this group was similar to or even lower than that given for the control group in Table I. Thus, the controls in our study were not a particular healthy group of people. In conclusion, we do not find it likely that selection bias can explain our findings.

The information about current use of medication and current and previous diseases were obtained from the medical records of the stroke patients, whereas the control subjects answered a questionnaire. This may have introduced response bias and hampered effective control for confounders. It is, nevertheless, reassuring that we found more people with previous myocardial infarction and more use of medication for hypertension among the stroke patients, although only the difference in use of medication for hypertension in women was statistically significant. Unfortunately, the information about some of the possible confounders (eg, physical activity, smoking, and alcohol) was not so detailed that residual confounding can be excluded. However, this is of major importance only if a causal relationship between low BMD and stroke is considered.

At present, it is unclear whether there is a cause-and-effect relationship between low BMD and high risk of stroke. Previous investigators have argued against a causal relation and suggested that low BMD is, rather, a marker of poor general health and aging.[10,11,23] There are, however, several possible links between osteoporosis and stroke, because both conditions may be related to estrogen deficiency, diabetes, hypertension (and use of medication to treat hypertension), low level of physical activity, and smoking.[3-9,24-27] Moreover, high blood pressure, an established risk factor for stroke, has been associated with increased bone loss at the femoral neck in elderly women.[9]

A salient finding in our study was the inverse relationship between BMD and stroke in women but not in men. This may indicate that estrogen deficiency may play an important part in this relationship. Estrogen replacement may reduce the risk of both stroke and osteoporosis, although the results are inconsistent.[24,28] Because we considered the medical records of the cases (from which information about medication was extracted) to be unreliable with respect to information about use of estrogens, it was impossible to adjust for this medication. However, when persons known to use estrogen were excluded, the mean BMD value of the controls was essentially unchanged.

In conclusion, we found that female, but not male, stroke patients have lower BMD than population controls. Our results confirm the findings of previous studies about women and provide for the first time information about the relationship in men. We call for new studies to confirm or refute these findings, also because our study has limited statistical power. At present, it is unclear whether low BMD actually increases the risk of stroke or reflects poor health with both high stroke risk and low BMD. We believe that it is premature to reject a causal relationship; sometimes the biological understanding comes after the epidemiological finding. In any case, because female stroke patients have a low BMD (for whatever the reason), this emphasizes even more the need for an aggressive attitude in poststroke rehabilitation.

Acknowledgments

The study was financially supported by the research programme Research on the Elderly in Tromsø, financed by The Ministry of Health and Social Affairs, Norway. We are very grateful to the participants in this study. We acknowledge the support during the study of chief physician Sigurd Sparr, MD, at the Department of Geriatric Medicine, University Hospital of Tromsø, and the medical staff of the Neurologic and Geriatric departments. We thank Line Wilsgaard and Elin Hansen for their expert technical assistance with the BMD measurements. We also thank Neshrin Mikkelsen and Merete Albertsen for their help in collecting and processing the data.

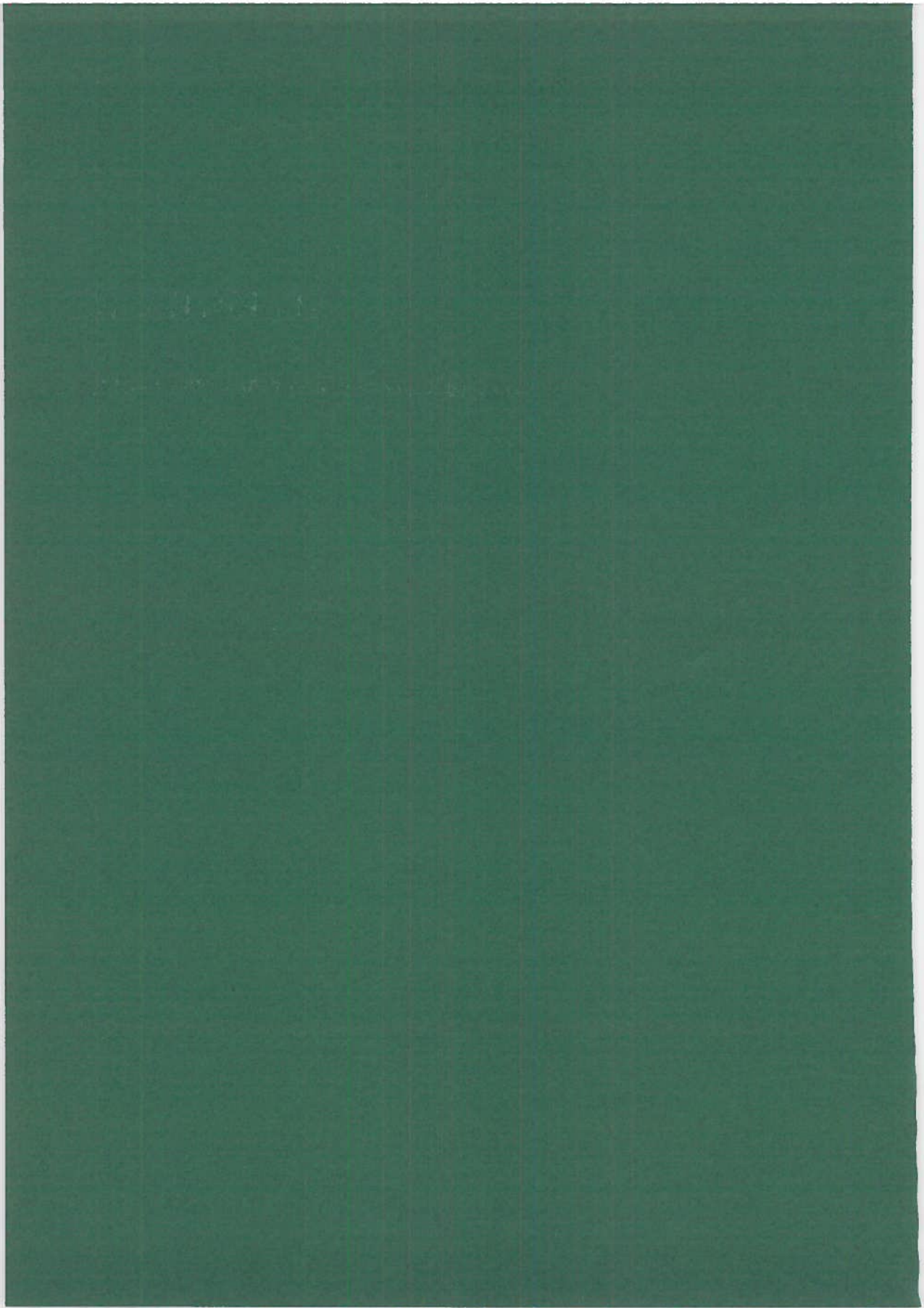
References

1. Ensrud KE, Palermo L, Black DM, Cauley J, Jergas M, Orwoll ES, Nevitt MC, Fox KM, Cummings SR. Hip and calcaneal bone loss increase with advancing age: longitudinal results from the Study of Osteoporotic Fractures. *J Bone Miner Res*. 1995;10:1778–1787.
2. Jones G, Nguyen T, Sambrook P, Kelly PJ, Eisman JA. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo Osteoporosis Epidemiology Study. *BMJ*. 1994;309:691–695.
3. Kiel DP, Zhang Y, Hannan MT, Anderson JJ, Baron JA, Felson DT. The effect of smoking at different life stages on bone mineral density in elderly men and women. *Osteoporos Int*. 1996;6:240–248.
4. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, Goldstein LB, Gorelick PB, Howard G, Kittner SJ, Manolio TA, Whisnant JP, Wolf PA. American Heart Association Prevention Conference IV: prevention and rehabilitation of stroke: risk factors. *Stroke*. 1997;28:1507–1517.
5. Sacco RL, Gan R, Boden-Albala B, Lin IF, Kargman DE, Hauser WA, Shea S, Paik MC. Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke*. 1998;29:380–387.
6. Colantonio A, Kasl SV, Ostfeld AM. Level of function predicts first stroke in the elderly. *Stroke*. 1992;23:1355–1357.
7. Wolff I, van Croonenborg JJ, Kemper HC, Kostense PJ, Twisk JW. The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporos Int*. 1999;9:1–12.
8. Nguyen TV, Center JR, Eisman JA. Osteoporosis in elderly men and women: effects of dietary calcium, physical activity, and body mass index. *J Bone Miner Res*. 2000;15:322–331.
9. Cappuccio FP, Meilahn E, Zmuda JM, Cauley JA, for the Study of Osteoporotic Fractures Research Group. High blood pressure and bone-mineral loss in elderly white women: a prospective study. *Lancet*. 1999; 354:971–975.
10. Browner WS, Seeley DG, Vogt TM, Cummings SR for the Study of Osteoporotic Fractures Research Group. Non-trauma mortality in elderly women with low bone mineral density. *Lancet*. 1991;338:355–358.
11. Browner WS, Pressman AR, Nevitt MC, Cauley JA, Cummings SR. Association between low bone density and stroke in elderly women: the study of osteoporotic fractures. *Stroke*. 1993;24:940–946.
12. Ramnemark A, Nyberg L, Borssén B, Olsson T, Gustafson Y. Fractures after stroke. *Osteoporos Int*. 1998;8:92–95.
13. Ramnemark A, Nilsson M, Borssén B, Gustafson Y. Stroke, a major and increasing risk factor for femoral neck fracture. *Stroke*. 2000;31: 1572–1577.
14. Jørgensen L, Jacobsen BK, Wilsgaard T, Magnus JH. Walking after stroke: does it matter? Changes in bone mineral density within the first 12 months after stroke: a longitudinal study. *Osteoporos Int*. 2000;11: 381–387.
15. Ramnemark A, Nyberg L, Lorentzon R, Olsson T, Gustafson Y. Hemiosteoporosis after severe stroke, independent of changes in body composition and weight. *Stroke*. 1999;30:755–760.
16. Hamdy RC, Moore SW, Cancellaro VA, Harvill LM. Long-term effects of strokes on bone mass. *Am J Phys Med Rehabil*. 1995;74:351–356.
17. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ*. 1976;54:541–553.

18. Scandinavian Stroke Study Group. Multicenter trial of hemodilution in ischemic stroke: background and study protocol. *Stroke*. 1985;16:885–890.
19. Lindenstrøm E, Boysen G, Christiansen LW, à Rogvi Hansen B, Nielsen BW. Reliability of Scandinavian Stroke Scale. *Cerebrovasc Dis*. 1991;1: 103–107.
20. De Laet CE, Van Hout BA, Burger H, Weel AE, Hofman A, Pols HA. Hip fracture prediction in elderly men and women: validation in the Rotterdam study. *J Bone Miner Res*. 1998;13:1587–1593.
21. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ*. 1996;312:1254–1259.
22. Cummings SR, Black DM, Nevitt MC, Browner WS, Cauley J, Ensrud K, Genant HU, Palermo L, Scott J, Vogt TM. Bone density at various sites for prediction of hip fractures. *Lancet*. 1993;341:72–75.
23. Johansson C, Black D, Johnell O, Oden A, Mellstrom D. Bone mineral density is a predictor of survival. *Calcif Tissue Int*. 1998;63:190–196.
24. Paganini-Hill A. The risks and benefits of estrogen replacement therapy: Leisure World. *Int J Fertil Menopausal Stud*. 1995;40(suppl 1):54–62.
25. Tuominen JT, Impivaara O, Puukka P, Ronnemaa T. Bone mineral density in patients with type 1 and type 2 diabetes. *Diabetes Care*. 1999;22:1196–1200.
26. Christensen JO, Svendsen OL. Bone mineral in pre- and postmenopausal women with insulin-dependent and non-insulin-dependent diabetes mellitus. *Osteoporos Int*. 1999;10:307–311.
27. Wasnich RD, Davis JW, He YF, Petrovich H, Ross PD. A randomized, double-masked, placebo-controlled trial of chlorthalidone and bone loss in elderly women. *Osteoporos Int*. 1995;5:247–251.
28. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women: Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*. 1998;280:605–613.

APPENDIX A

Declaration of consent for the stroke patients



FORESPØRSEL OM Å DELTA I FORSKNINGSPROSJEKT

Informasjon og samtykke-erklæring for forsøkspersonene i prosjektet: "Osteoporoseutvikling hos pasienter med apoplexia cerebri"

Hensikten med undersøkelsen:
Mange eldre mennesker har øket risiko for å falle og brekke lårhalsen. Dette kan blant annet skyldes osteoporose, en nedgang i bentettheten i knoklene, populært kalt "benskjørhet".

Vi ønsker med denne undersøkelsen å finne ut, om det skjer en endring i bentetthet hos pasienter som har fått slag, og om dette i så tilfelle har sammenheng med deres fysiske funksjon, f.eks. om de kan gå.
Øket kunnskap på dette område kan være en hjelp i forhold til veiledning av pasienter, pårørende og helsepersonell, når det gjelder opptrening etter lammelser på grunn av slag.

Forespørselen rettes til slagpasienter over 60 år som innlegges på RiTø.
Kontaktperson i forhold til prosjektet er: Lone Jørgensen, Høgskolen i Tromsø, Avd for Helsefag.

Beskrivelse av undersøkelsen og risiko-vurdering:
De pasienter som samtykker i å delta i undersøkelsen vil i løpet av få dager få utført en bentetthets-måling.
Bentetthetsmålingen er en undersøkelse som er helt smertefri og uten komplikasjoner.
Ved undersøkelsen brukes det en lav røntgendosering, som tilsvarer 1/20 av et vanlig lunge-bilde. Undersøkelsen varer i alt 30 minutter.
Du kan godt ha klær på deg under undersøkelsen, men ikke klær som inneholder knapper eller materiale av metall.

Bentetthets-undersøkelsene og funksjonsvurderingen vil bli gjentatt etter to måneder etter syv måneder og etter et år i forbindelse med vanlige kontroll-undersøkelser på RiTø.

Fra din journal ønsker vi å hente ut følgende data: diagnoser, alder, høyde, vekt, bosted og medikamentforbruk. Du vil i tillegg bli spurt om dine røyk- og alkoholvaner.

Samtykke-erklæring:
Det er frivillig å delta i undersøkelsen, og du kan når som helst trekke deg uten å angi grunn og uten at det på noen måte berører forholdet til helsepersonell eller prosjektets medarbeidere.
Likeledes kan du når som helst be om å få slettet de opplysninger som er registrert om deg.
Dette gjelder også etter at prosjektet er avsluttet.
Opplysninger innhentet i forbindelse med prosjektet vil etter prosjektavslutning oppbevares ved en institusjon som er godkjent av Datatilsynet.

Jeg er blitt forklart pasientinformasjonen, og samtykker i å delta i studiet.
Jeg har mottatt egen kopi av informasjons- og samtykkeerklæringen.

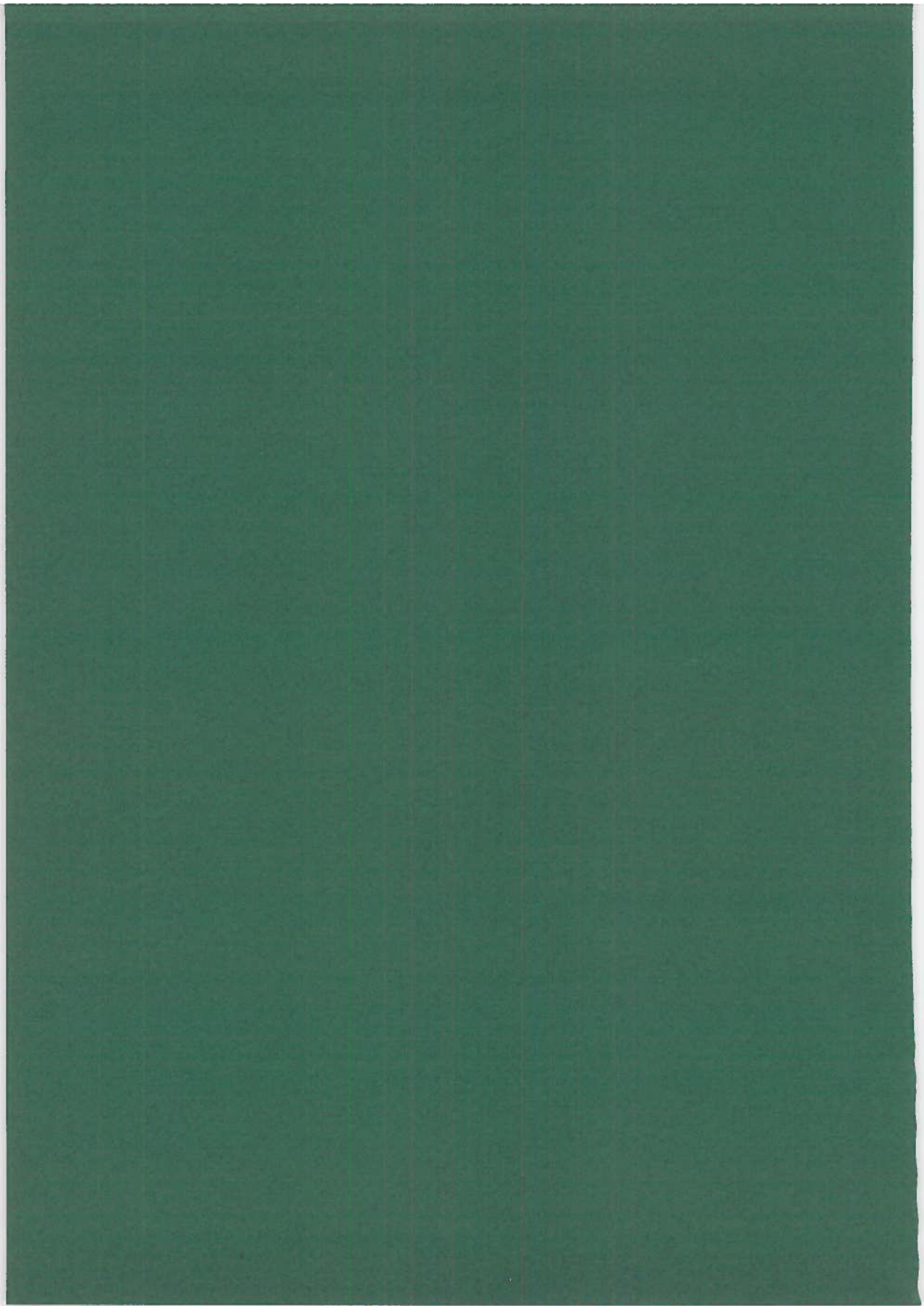
.....

Sted Dato Underskrift pasient

APPENDIX B

Declaration of consent for the control subjects

Questions and questionnaire (paper IV)



FORESPØRSEL OM Å DELTA I FORSKNINGSPROSJEKT

VIL DU VÆRE KONTROLL-PERSON ?

Informasjon og samtykke-erklæring for kontroll personene i prosjektet:
"Benskjørhet hos pasienter med slag"

Hensikten med undersøkelsen:
Mange eldre mennesker har økt risiko for å falle og brekke lårhalsen. Dette kan blant annet skyldes osteoporose, en nedgang i bentettheten i knoklene, populært kalt "benskjørhet".
Vi ønsker med denne undersøkelsen å sammenlikne bentettheten hos personer som ikke har hatt slag (kontroll-personer) med pasienter som har hatt slag.
Økt kunnskap på dette område kan være en hjelp i forhold til veiledning av pasienter, pårørende og helsepersonell, når det gjelder opptrening etter lammelser på grunn av slag.

Fra Folkeregisteret er du ved loddtrekning valgt ut til å deltage i en undersøkelse som kontroll-person. Kontroll-personene må være over 60 år og må kunne gå.
De må **ikke** ha hatt **hjerne-slag, kunstige hofteled** eller **tidligere lårhalsbrudd.**

Kontaktperson i forhold til prosjektet er:
Lone Jørgensen, Høgskolen i Tromsø, Avd for Helsefag (tlf: 776 60651), eller
Elin Hansen, Forskningsposten RiTø, tlf 776 27348.

Beskrivelse av undersøkelsen og risiko-vurdering:
Hvis du samtykker i å delta i undersøkelsen, vil du i løpet av høsten 1998 få utført en bentetthetsmåling på RiTø. Undersøkelse tar ca. 45 min og er helt smertefri og uten komplikasjoner. Det brukes en lav røntgendosering, som tilsvarer 1/20 av et vanlig lungebilde.
Du kan godt ha klær på deg under undersøkelsen, men ikke klær som inneholder knapper eller materiale av metall.
Ca to måneder etter undersøkelsen vil du få brev om hvordan resultatet av bentetthetsmålingen var. Hvis du har lav bentetthet vil vi gi deg anbefalinger om tiltak og eventuelt be deg kontakte din faste lege.

Ut over bentetthetsundersøkelsen registrerer vi om du går med eller uten hjelpemidler, din høyde, vekt, tidligere arbeide, hvordan du vurderer din helse og funksjonsevne samt eventuelle tidligere sykdommer og nåværende medikamentbruk.

Vi vil gjerne høre om du ønsker å delta i denne undersøkelse, og ber deg derfor returnere ditt svar i vedlagte svarkuvert (porto er betalt).

De som har svart ja til å delta vil høsten 98 få tildelt time pr. brev for undersøkelsen. Alle transportkostnader til og fra RiTø blir dekket. De som ikke kan benytte offentlig transportmiddel får tilbud om å bli hentet og kjørt hjem i drosje.

Hvis du ikke vil være med og ikke vil at vi purrer på svar, kan du krysse av i Nei-rubrikken. Vi har kun adgang til å purre en gang.

Sett kryss i den ruten som passer

ja, jeg ønsker å delta ☐

nei, jeg ønsker ikke å delta ☐

Undersøkelsen er ikke forbundet med smerte eller ubehag, det blir ingen venting på sykehuset og du skal kun møte denne ene gangen.

For deg som ønsker å delta,
vær vennlig å oppgi ditt telefon-nummer: .....

Når prosjektet er avsluttet og resultatene bearbeidet vil du få tilsendt litt informasjon om dette

Samtykke-erklæring:
Det er frivillig å delta i undersøkelsen. Du kan la være å delta eller svare på enkelte spørsmål, og du kan trekke deg fra undersøkelsen når som helst uten å angi grunn og uten at det vil få noen negative konsekvenser for ditt forhold til helsevesenet. Likeledes kan du når som helst be om å få slettet de opplysninger som er registrert om deg. Dette gjelder også etter at prosjektet er avsluttet. Når informasjonen om deg benyttes vil det ikke være mulig å identifisere deg som person.
Opplysninger innhentet i forbindelse med prosjektet vil etter prosjektavslutning oppbevares ved en institusjon som er godkjent av Datatilsynet.

Jeg er blitt forklart pasientinformasjonen, og samtykker i å delta i studiet.
Jeg har mottatt egen kopi av informasjons- og samtykkeerklæringen.

.....

Sted Dato Underskrift

SPØRGSMÅL

Røyking:

	ja	nej
Røyker du daglig for tida?	☐	☐

	antal år
Hvis du har røykt daglig tidligere, hvor længe siden er det siden du sluttet?	☐
Hvor mange år tilsammen har du røykt daglig?	☐

Alkohol:

	ja	nej
Er du total avholdsmann/-kvinne?	☐	☐

Ganghjælpemiddel:

	ja	nej
Brukte du gang-hjelpemiddel før du fikk slag (pasienter)	☐	☐
Bruker du gang-hjelpemiddel nå (kontroller)	☐	☐

Pas.nr.....

SPØRRESKJEMA TIL KONTROLL PERSONER

TIDLIGERE ARBEID OG ØKONOMI

Hvordan vil du beskrive det arbeidet du hadde de siste 5-10 årene før du ble pensjonist?

- **For det meste stillesittende arbeid?** ❒
  (f.eks. skrivebordsarbeid, montering)
- **Arbeid som krever at du går mye?** ❒
  (f.eks. ekspeditørarbeid, husmor, undervisning)
- **Arbeid hvor du går og løfter mye?** ❒
  (f.eks. postbud, pleier, bygningsarbeid)
- **Tungt kroppsarbeid?** ❒
  (f.eks. skogsarb., tungt jordbruksarb., tungt bygningsarb.)

Hvor gammel var du da du ble pensjonert? _____ år

OPPVEKST

Hvordan var de økonomiske forhold i familien under din oppvekst?

- Meget gode ❒
- Gode ❒
- Vanskelige ❒
- Meget vanskelige ❒

RØYKING

	ja	nei
Røyker du daglig for tida?.....	☐	☐

ALKOHOL

	ja	nei
Er du total avholdsmann/-kvinne?	☐	☐

LEGEMLIGE FUNKSJONER

Klarer du selv disse gjøremålene i det daglige uten hjelp fra andre?

	ja	med noe hjelp	nei
Gå innendørs i samme etasje.....	☐	☐	☐
Gå i trapper.....	☐	☐	☐
Gå utendørs.....	☐	☐	☐
Gå ca 500m.....	☐	☐	☐
Gå på toalettet.....	☐	☐	☐
Vaske deg på kroppen.....	☐	☐	☐
Bade eller dusje.....	☐	☐	☐
Kle på og av deg.....	☐	☐	☐
Spise selv.....	☐	☐	☐
Gjøre lett husarbeid (f.eks. oppvask).....	☐	☐	☐
Gjøre tyngre husarbeid (f.eks. gulvvask).....	☐	☐	☐
Gjøre innkjøp.....	☐	☐	☐
Ta bussen.....	☐	☐	☐

Er du avhengig av noen av disse hjeplemidlene?

	ja	nei
stokk	☐	☐
krykke	☐	☐
gåstol	☐	☐

	ja	vanskelig	nei
Kan du lese (evt med briller).....	☐	☐	☐

EGNE SYKDOMMER

Hvordan er helsen din nå? Sett bare ett kryss

- Dårlig ☐
- Ikke helt god ☐
- God ☐
- Svært god ☐

Har du eller har du hatt
Sett ett kryss for hvert spørsmål

	ja	nei
Kreftsykdom	☐	☐
Epilepsi	☐	☐
Parkinsons sykdom	☐	☐
Kronisk bronkitt	☐	☐
Benskjørhet (osteoporose)	☐	☐
Psykiske plager som du har søkt hjelp for	☐	☐
Stoffskiftesykdom	☐	☐
Sykdom i leveren	☐	☐
Grøn stær	☐	☐
Grå stær	☐	☐
Slitasjegikt (artrose)	☐	☐
Leddgikt	☐	☐
Astma	☐	☐
Diabetes (sukkersyke)	☐	☐
Hjerteinfarkt	☐	☐
Angina pectoris (hjertekrampe)	☐	☐

Har du noen gang hatt brudd ? ☐ ☐

Hvis ja, hvilken koppsdel ? _____

hvor gammel var du ved siste brudd ? alder: _____

FALL

Hvis du tenker tilbake over de siste 3 mdr.

Hvor mange gange har du falt gjennomsnittlig i løpet av en måned? ____ gange

LEGEMIDLER OG KOSTTILSKUDD

Har du det siste året periodevis brukt noen av de følgende midler daglig eller nesten daglig?

Angi hvor mange måneder du brukte dem.
Sett 0 hvis du ikke har brukt midlene.

Smertestillende..... _____mnd
Sovemedisin..... _____mnd
Beroligende midler..... _____mnd
Medisin mot depresjon..... _____mnd
Allergimedisin..... _____mnd
Astmamedisin..... _____mnd
Hjertemedisin (ikke blodtrykksmedisin)..... _____mnd
Insulin..... _____mnd
Tabletter mot diabetes (sukkersyke)..... _____mnd
Tabletter mot lavt stoffskifte..... _____mnd
Kortisontabletter..... _____mnd
Midler mot forstoppelse..... _____mnd

Kosttilskudd

Jerntabletter..... _____mnd
Vitamin D-tilskudd..... _____mnd
Andre vitamintilskud..... _____mnd
Kalktabletter eller benmel..... _____mnd
Tran eller fiskeoljekapsler..... _____mnd

	nå	før	aldri brukt
Bruker du medisin mot høyt blodtrykk?	☐	☐	☐

BESVARES BARE AV KVINNER

Hvor gammel var du da du fikk menstruasjon første gang? _____år
Hvor gammel var du da menstruasjonen sluttet? _____år

Bruker du, eller har du brukt østrogen-medisin?	nå	før	aldri brukt
Tabletter eller plaster.....	☐	☐	☐
Krem eller stikkpiller.....	☐	☐	☐

ISM SKRIFTSERIE - FØR UTGITT:

1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskættede i Sør-Varanger kommune.
   Av Anders Forsdahl, 1976. (nytt opplag 1990)

2. Sunnhetstilstanden, hygieniske og sosiale forhold i Sør-Varanger kommune 1869-1975 belyst ved medisinal-beretningene.
   Av Anders Forsdahl, 1977.

3. Hjerte-karundersøkelsen i Finnmark - et eksempel på en populasjonsundersøkelse rettet mot cardiovasculære sykdommer. Beskrivelse og analyse av etterundersøkelsesgruppen.
   Av Jan-Ivar Kvamme og Trond Haider, 1979.

4. The Tromsø Heart Study: Population studies of coronary risk factors with special emphasis on high density lipoprotein and the family occurrence of myocardial infarction.
   Av Olav Helge Førde og Dag Steinar Thelle, 1979.

5. Reformer i distriktshelsetjenesten III: Hypertensjon i distriktshelsetjenesten.
   Av Jan-Ivar Kvamme, 1980.

6. Til professor Knut Westlund på hans 60-års dag, 1983.

7.* Blodtrykksovervåkning og blodtrykksmåling.
   Av Jan-Ivar Kvamme, Bernt Nesje og Anders Forsdahl, 1983.

8.* Merkesteiner i norsk medisin reist av allmennpraktikere - og enkelte utdrag av medisinalberetninger av kulturhistorisk verdi.
   Av Anders Forsdahl, 1984.

9. "Balsfjordsystemet." EDB-basert journal, arkiv og statistikksystem for primærhelsetjenesten.
   Av Toralf Hasvold, 1984.

10. Tvunget psykisk helsevern i Norge. Rettsikkerheten ved slikt helsevern med særlig vurdering av kontrollkommisjonsordningen.
    Av Georg Høyer, 1986.

11. The use of self-administered questionnaires about food habits. Relationships with risk factors for coronary heart disease and associations between coffee drinking and mortality and cancer incidence.
    Av Bjarne Koster Jacobsen, 1988.

12.* Helse og ulikhet. Vi trenger et handlingsprogram for Finnmark.
    Av Anders Forsdahl, Atle Svendal, Aslak Syse og Dag Thelle, 1989.

13. Health education and self-care in dentistry - surveys and interventions.
Av Anne Johanne Søgaard, 1989.

14. Helsekontroller i praksis. Erfaringer fra prosjektet helsekontroller i Troms 1983-1985.
Av Harald Siem og Arild Johansen, 1989.

15. Til Anders Forsdahls 60-års dag, 1990.

16. Diagnosis of cancer in general practice. A study of delay problems and warning signals of cancer, with implications for public cancer information and for cancer diagnostic strategies in general practice.
Av Knut Holtedahl, 1991.

17. The Tromsø Survey. The family intervention study. Feasibility of using a family approach to intervention on coronary heart disease. The effect of lifestyle intervention of coronary risk factors.
Av Synnøve Fønnebø Knutsen, 1991.

18. Helhetsforståelse og kommunikasjon. Filosofi for klinikere.
Av Åge Wifstad, 1991.

19. Factors affecting self-evaluated general health status - and the use of professional health care services.
Av Knut Fylkesnes, 1991.

20. Serum gamma-glutamyltransferase: Population determinants and diagnostic characteristics in relation to intervention on risk drinkers.
Av Odd Nilssen, 1992.

21. The Healthy Faith. Pregnancy outcome, risk of disease, cancer morbidity and mortality in Norwegian Seventh-Day-Adventists.
Av Vinjar Fønnebø, 1992.

22. Aspects of breast and cervical cancer screening.
Av Inger Torhild Gram, 1992.

23. Population studies on dyspepsia and peptic ulcer disease: Occurrence, aetiology, and diagnosis. From The Tromsø Heart Study and The Sørreisa Gastrointestinal Disorder Studie.
Av Roar Johnsen, 1992.

24. Diagnosis of pneumonia in adults in general practice.
Av Hasse Melbye, 1992.

25. Relationship between hemodynamics and blood lipids in population surveys, and effects of n-3 fatty acids.
Av Kaare Bønaa, 1992.

26. Risk factors for, and 13-year mortality from cardiovascular disease by socioeconomic status. A study of 44690 men and 17540 women, ages 40-49.
Av Hanne Thürmer, 1993.

27. Utdrag av medisinalberetninger fra Sulitjelma 1891-1990.
Av Anders Forsdahl, 1993.

28. Helse, livsstil og levekår i Finnmark. Resultater fra Hjerte-karundersøkelsen i 1987-88. Finnmark III.
Av Knut Westlund og Anne Johanne Søgaard, 1993.

29. Patterns and predictors of drug use.
A pharmacoepidemiologic study, linking the analgesic drug prescriptions to a population health survey in Tromsø, Norway.
Av Anne Elise Eggen, 1994.

30. ECG in health and disease. ECG findings in relation to CHD risk factors, constitutional variables and 16-year mortality in 2990 asymptomatic Oslo men aged 40-49 years in 1972.
Av Per G. Lund-Larsen, 1994.

31. Arrhythmia, electrocardiographic signs, and physical activity in relation to coronary heart risk factors and disease. The Tromsø Study.
Av Maja-Lisa Løchen, 1995.

32. The Military service: mental distress and changes in health behaviours among Norwegian army conscript.
Av Edvin Schei, 1995.

33. The Harstad injury prevention study: Hospital-based injury recording and community-based intervention.
Av Børge Ytterstad, 1995.

34.* Vilkår for begrepsdannelse og praksis i psykiatri. En filosofisk undersøkelse.
Av Åge Wifstad, 1996. (utgitt Tano Aschehoug forlag 1997)

35. Dialog og refleksjon. Festskrift til professor Tom Andersen på hans 60-års dag, 1996.

36. Factors affecting doctors´ decision making.
Av Ivar Sønbø Kristiansen, 1996.

37. The Sørreisa gastrointestinal disorder study. Dyspepsia, peptic ulcer and endoscopic findings in a population.
Av Bjørn Bernersen, 1996.

38. Headache and neck or shoulder pain. An analysis of musculoskeletal problems in three comprehensive population studies in Northern Norway.
Av Toralf Hasvold, 1996.

39. Senfølger av kjernefysiske prøvespreninger på øygruppen Novaya Semlya i perioden 1955 til 1962. Rapport etter programmet "Liv". Arkangelsk 1994.
Av A.V. Tkatchev, L.K. Dobrodeeva, A.I. Isaev, T.S. Podjakova, 1996.

40. Helse og livskvalitet på 78 grader nord. Rapport fra en befolkningsstudie på Svalbard høsten 1988.
Av Helge Schirmer, Georg Høyer, Odd Nilssen, Tormod Brenn og Siri Steine, 1997.

41.* Physical activity and risk of cancer. A population based cohort study including prostate, testicular, colorectal, lung and breast cancer.
Av Inger Thune, 1997.

42. The Norwegian - Russian Health Study 1994/95. A cross-sectional study of pollution and health in the border area.
Av Tone Smith-Sivertsen, Valeri Tchachtchine, Eiliv Lund, Tor Norseth, Vladimir Bykov, 1997.

43. Use of alternative medicine by Norwegian cancer patients
Av Terje Risberg, 1998.

44. Incidence of and risk factors for myocardial infarction, stroke, and diabetes mellitus in a general population. The Finnmark Study 1974-1989.
Av Inger Njølstad, 1998.

45. General practitioner hospitals: Use and usefulness. A study from Finnmark County in North Norway.
Av Ivar Aaraas, 1998.

45B Sykestuer i Finnmark. En studie av bruk og nytteverdi.
Av Ivar Aaraas, 1998.

46. No går det på helsa laus. Helse, sykdom og risiko for sykdom i to nord-norske kystsamfunn.
Av Jorid Andersen, 1998.

47. The Tromsø Study: Risk factors for non-vertebral fractures in a middle-aged population.
Av Ragnar Martin Joakimsen, 1999.

48. The potential for reducing inappropriate hospital admissions: A study of health benefits and costs in a department of internal medicine.
Av Bjørn Odvar Eriksen, 1999.

49. Echocardiographic screening in a general population. Normal distribution of echocardiographic measurements and their relation to cardiovascular risk factors and disease. The Tromsø Study.
Av Henrik Schirmer, 2000.

50. Environmental and occupational exposure, life-style factors and pregnancy outcome in artic and subartic populations of Norway and Russia.
Av Jon Øyvind Odland, 2000.

50B Окружающая и профессиональная экспозиция, факторы стиля жизни и исход беременности у населения арктической и субарктической частей Норвегии и России
Юн Ойвин Удлан 2000

51. A population based study on coronary heart disease in families. The Finnmark Study 1974-1989.
Av Tormod Brenn, 2000.

52. Ultrasound assessed carotid atherosclerosis in a general population. The Tromsø Study.
Av Oddmund Joakimsen, 2000.

53. Risk factors for carotid intima-media thickness in a general population. The Tromsø Study 1979-1994.
Av Eva Stensland-Bugge, 2000.

54. The South Asian cataract management study.
Av Torkel Snellingen, 2000.

55. Air pollution and health in the Norwegian-Russian border area.
Av Tone Smith-Sivertsen, 2000.

56. Interpretation of forearm bone mineral density. The Tromsø Study.
Av Gro K. Rosvold Berntsen, 2000.

57. Individual fatty acids and cardiovascular risk factors.
Av Sameline Grimsgaard, 2001.

58. Finnmarkundersøkelsene
Av Anders Forsdahl, Fylkesnes K, Hermansen R, Lund E, Lupton B, Selmer R, Straume E, 2001.

59. Dietary data in the Norwegian women and cancer study. Validation and analyses of health related aspects.
Av Anette Hjartåker, 2001.

60. The stenotic carotid artery plaque. Prevalence, risk factors and relations to clinical disease. The Tromsø Study.
Av Ellisiv B. Mathiesen, 2001.

61. Studies in perinatal care from a sparsely populated area.
Av Jan Holt, 2001.

De som er merket med * har vi dessverre ikke flere eksemplar av.