Journal of Clinical Densitometry, vol. 9, no. 1, 78–83, 2006

1094-6950/06/9:78–83/$32.00
DOI: 10.1016/j.jocd.2005.09.001

Original Article

Densitometric and Quantitative Ultrasound Measurements and Laboratory Investigations in Wheelchair-Bound Patients

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Abstract

Skeletal status and laboratory investigations may be influenced by immobilization. Thirty-six wheelchair-bound subjects and 19 age-matched controls were evaluated using measurements of bone mineral density (BMD) at the calcaneus and forearm (PIXI, Madison, WI), amplitude-dependent speed of sound at the hand phalanges (quantitative ultrasound-DBM Sonic 1200, IGEA, Modena, Italy), carboxyterminal telopeptide of type I collagen and bone alkaline phosphatase. In the whole group and in the males, bone mineral density values were significantly lower in comparison with controls (calcaneus, forearm) and in females only for calcaneus. The duration of the disease significantly influenced the calcaneal bone mineral density data. Bone alkaline phosphatase was significantly lower in the patients than in the controls. Bone resorption had a negative influence on forearm BMD. Generally, skeletal and laboratory results were not affected by duration of the disease or reason for immobilization. In conclusion, in wheelchair-bound subjects, the skeletal status was affected and bone formation was depressed.

Key Words: Amplitude-dependent speed of sound; bone alkaline phosphatase; bone mineral density; cerebral palsy; collagen; immobilization.

Introduction

The adverse skeletal effects of immobilization have been studied extensively. Weightlessness and complete, prolonged immobilization as occurred with voluntary bed rest *(1)*, spaceflight *(2)*, or spinal cord injury *(3–5)* regularly lead to accelerated bone resorption. Under these conditions, the loss of bone mass is more pronounced in the lower, weight-bearing limbs. Studies performed in humans and animals have shown that periods of immobilization as short as 2 wk may lead to significant loss of bone mass *(6,7)*. In some previously published studies, changes in calcium homeostasis *(1,8,9)* and bone mineral density (BMD) were evaluated in immobilized patients. Quantitative ultrasound (QUS), a method of skeletal evaluation more recently introduced into clinical practice, was only rarely used to detect skeletal changes due to physical activity *(10)* or immobilization *(11)*.

Another factor influencing skeletal status, beside long-term immobilization, is disturbed motor function present in subjects with several neurological disorders. Among different neurological diseases potentially influencing skeletal status is cerebral palsy (CP). Recently it was estimated that approximately 98,000 children and young adults in the United States

Received 06/22/05; Revised 09/28/05; Accepted 09/28/05.
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are severely affected with CP and are nonambulatory *(12)*. Cerebral palsy describes a number of motor disorders characterized by impaired voluntary movement resulting from prenatal development abnormalities, or perinatal or postnatal damage occurring before the age of 5 years *(13)*. The term CP is not a diagnosis, but it identifies children with nonprogressive spasticy, ataxia or involuntary movements. Cerebral palsy syndromes are grouped into 4 main categories: (1) spastic, (2) athetoid, (3) ataxic, and (4) mixed forms. The most common is the spastic form occurring in about 70% of all cases. The spastic form of the syndrome is due to upper motor neuron involvement and may mildly or severely affect motor function. Therefore, skeletal status may be affected in CP patients. Understanding the pathophysiology of skeletal status in CP is difficult given the heterogeneity of the condition and the multitude of potentially important factors *(14)*. Obviously an impairment of physical function limiting weight-bearing exercises and/or immobilization significantly influences skeletal status. In recent studies, BMD was decreased in subjects with CP *(12,14,15)*.

The aim of this study was to assess an influence of long-term immobilization and impairment of motor functions on skeletal status and laboratory investigations in a group of young adults.

Subjects and Methods

Subjects

In the study, 36 subjects (20 males and 16 females) with a mean age of 24 yr wheelchair-bound for 17.9 ± 7.8 yr were studied and compared with 19 controls. All patients were recruited from a nursing home. The majority of subjects (21 total: 11 males and 10 females) were affected by CP. Ten males and 9 females never were able to walk independently. The shortest time of immobilization was 4 yr in females and 6 yr in males. In all cases of CP, the spastic form of the disease with paraplegia was present. The CP was diagnosed on the basis of specific features of the disease by experienced neurologists.

Other reasons for immobilization included in males: myelomeningocele (4 subjects), spinal cord injury (4 subjects), and muscular dystrophy (1 subject), and in females: flaccid paralysis of lower limbs (3 subjects), spina bifida (2 subjects), and muscular dystrophy (1 subject). Despite some differences in functional status, statistical analyses were performed with the whole group and with both sexes separately as well as in CP and non-CP patients.

A control group consisting of 19 healthy volunteers (10 males and 9 females) was recruited from students and young doctors. Both in patients and controls, no additional factors known to affect bone metabolism therapy (i.e., prolonged medication or chronic diseases) for osteoporosis or previous fractures were noted.

Clinical characteristics of patients and controls are presented in Table 1. Mean age did not differ between all patients and all controls or in gender subgroups, and some differences in regard to body size were observed. Also in subgroups divided into CP and non-CP patients, the mean age, duration of the disease, body size, and age at the onset of immobilization were not significantly different (data not shown). All female subjects (i.e., patients and controls) menstruated regularly. In order to analyze the role of disease duration, the whole group was also divided into subjects never walking independently (n = 19) with a mean period of immobilization of 23.7 ± 2.9 yr, and the rest of the patients with a mean period of immobilization of 9.7 ± 4.4 yr (n = 17). The mean age did not differ between these subgroups. The functional status of the upper limbs of the population was divided into three subgroups. In subgroup 1 (n = 13, 7 females and 6 males) the function of the upper limbs was normal. Subgroup 2 (n = 14, 7 females and 7 males) was characterized by moderately limited function; in daily living activities the upper limbs were used, but in some occasions such as washing, cleaning, etc., the help of a third person was necessary. In subgroup 3 (n = 9, 2 females and 7 males) function was limited, and only some small movements were possible (e.g., opening the door, lifting small things, etc.). A similar division was carried out according to functional status of the lower

Table 1
Clinical Characteristics of Patients and Controls (Mean ± SD)

Variable	All patients (n = 36)	Male patients (n = 20)	Female patients (n = 16)	All controls (n = 19)	Male controls (n = 10)	Female controls (n = 9)
Age (yr)	24.2 ± 3.6	25.0 ± 4.2	23.2 ± 2.6	23.1 ± 3.0	23.4 ± 4.0	22.8 ± 1.4
Weight (kg)	62.0 ± 5.0	66.8 ± 15.8	56.0 ± 11.9	66.7 ± 11.4	74.8 ± 9.1	57.8 ± 5.1
Height (cm)	157.6* ± 12.3	162.7** ± 13.0	151.1* ± 7.5	175.4 ± 85	181.3 ± 6.3	169.1 ± 5.4
BMI [kg/m^2]	24.9** ± 5.1	25.2 ± 5.4	24.5** ± 4.9	21.5 ± 2.5	22.8 ± 2.6	20.2 ± 1.5
Duration of the disease [yr]	17.9 ± 7.8	17.5 ± 8.0	18.3 ± 7.8	—	—	—

Note: Mean age does not differ significantly between patients and controls.
Abbr: BMI, body mass index.
*Versus adequate controls, $p < 0.000001$.
**Versus adequate controls, $p < 0.01$.

limbs in the subjects studied. In subgroup 1 (n = 17, 7 females and 10 males) function was moderately limited, subjects were wheelchair-bound, but 3 times a week they walked a distance of 20 to 100 meters with the help of a third person or specially designed equipment. In subgroup 2 (n = 11, 6 females and 5 males) function was limited, with no possibility of walking independently or with the help of a third person or specially designed equipment. The description of subgroup 3 (n = 8, 3 females and 5 males) was similar to subgroup 2, with underdevelopment of affected limbs in addition.

A local ethics committee gave permission for the study and all subjects who were studied provided a written agreement.

Methods

The BMD [g/cm^2] was assessed by dual-energy X-ray absorptiometry at the calcaneus and forearm (PIXI, Lunar, Madison, WI). In all subjects studied, the nondominant side was measured by one operator. Due to deformation of the calcaneus, a measurement in this site was performed in 15 males and 13 females, but the rest of the skeletal data was collected from all subjects. The coefficients of variation percent (CV%) for forearm and calcaneus measurements were 1.5% and 2.0% in healthy subjects, respectively. The CV% obtained in wheelchair-bound subjects (5 males and 5 females) were measured 5 times each with repositioning of the extremity and was 0.70% for the calcaneus and 2.39% for the forearm.

Skeletal status was also assessed by QUS measurements of proximal phalanges using the DBM Sonic 1200 (IGEA, Carpi, Italy). This unit consists of two probes mounted on an electronic caliper, one emitter, and one receiver. The receiver records the ultrasound energy after it has crossed the phalanx. We determined the amplitude-dependent speed of sound (Ad-SoS [m/s]) in the distal metaphyses of the proximal phalanges of the second through fifth finger of the nondominant hand. Speed of sound in bone tissue was calculated considering the first signal with an amplitude of at least 2 mV at the receiving probe; thus, the measured speed of sound is amplitude dependent. Acoustic coupling was achieved using a standard ultrasound gel. All measurements were done by the same operator. The CV% obtained in 15 healthy subjects (8 males and 7 females) was 0.64%, and in 10 wheelchair-bound subjects (5 males and 5 females) it was 0.43%. All measurements performed to establish precision were done by the same operator with repositioning of the extremity and were repeated 5 times.

Laboratory investigations included a bone resorption marker (carboxyterminal telopeptide of type I collagen [ICTP]) and a bone formation marker (bone alkaline phosphatase [bALP]).

The ICTP was established using Orion Diagnostica UniQ (Espoo, Finland) radioimmunoassay technique. Reference limits are: 1.4–5.2 μg/L for males and 1.6–5.3 μg/L for females, and the CV% was 5.7%. The bALP was measured using an alkaline phosphatase kit (AMP; BioSystems, Madrid, Spain) by kinetic methods, and the CV% was 10%. The normal values ranged from 28.6 to 33.0 U/L.

Statistical Analysis

The statistical analysis was performed in the whole group and for both sexes separately. To estimate whether a disease underlying immobilization had an influence on results obtained in the study, the analysis was also performed in CP and non-CP patients. Skeletal and laboratory data were also compared with respect to the duration of the disease.

All calculations of means and standard deviations were done using the Statistica program (Tulsa, OK) run on an IBM personal computer. The data distribution was established by the Shapiro-Wilk's W test. Differences between results in patients and controls were established using the Student's *t*-test for independent variables or the Mann-Whitney *U*-test in a case of non-Gaussian data distribution. Correlation analyses were performed by Pearson's correlation or Spearman correlation in a case of abnormal data distribution. The statistical significance level used was $p < 0.05$.

Results

Table 2 presents results of densitometric and ultrasound measurements in the whole group (i.e., both males and females). In the whole group and in males, BMD values were significantly lower for both calcaneus and forearm (p range, 0.02–0.0000001), and in females for only the calcaneus ($p = 0.0001$). Skeletal status was more affected in the calcaneus; in males, T-score and Z-score values were lower than in females and in the forearm. The Ad-SoS values were lower in the whole group and gender subgroups, but differences were not significantly different. In the whole group, the differences remained the same also after adjustment for body size (data not shown). The duration of the disease significantly influenced calcaneal measurements: in females negatively for Z-score ($r = -0.6$, $p < 0.05$), and in males positively for T-score ($r = 0.60$, $p < 0.05$) and Z-score ($r = 0.66$, $p < 0.001$). Fig. 1 shows correlations of calcaneal Z-score with duration of the disease in females and males.

Comparisons between skeletal and laboratory results obtained in CP and non-CP patients showed no statistically significant differences except for lower values in CP patients for Ad-SoS ($p < 0.01$) and calcaneal Z-score ($p < 0.05$). Despite different duration of the disease, also subjects never walking independently (n = 19) and the rest of the patients (n = 17) did not differ in skeletal and laboratory data (data not shown).

A correlation analysis of skeletal variables with disease duration has shown a significant correlation for forearm BMD in patients never walking ($r = 0.44$, $p < 0.05$) and in subjects affected later in life there were no significant correlations noted. The same analysis conducted in CP and non-CP subjects has shown no significant relationships.

Results of laboratory investigations are given in Table 3. Only values of bALP were significantly different in comparison with controls, being lower in all patients and in males. Laboratory data were not influenced significantly by the duration of the disease (data not shown). The only marker of bone metabolism showing correlation with skeletal variables in all

Table 2
Skeletal Measurements in Patients and Controls

Variable	All patients (n = 36)	All controls (n = 19)	*p*	Male patients (n = 20)	Male controls (n = 10)	*p*	Female patients (n = 16)	Female controls (n = 9)	*p*
Forearm BMD (g/cm^2)	0.44 ± 0.11	0.52 ± 0.07	0.01	0.43 ± 0.14	0.57 ± 0.04	0.004	0.46 ± 0.07	0.46 ± 0.06	ns (0.95)
T-score	−1.48 ± 1.83	−0.36 ± 0.82	0.01	−2.24 ± 1.93	−0.23 ± 0.69	0.004	−0.53 ± 1.18	−0.5 ± 0.97	ns (0.95)
Z-score	−1.39 ± 1.75	−0.36 ± 0.82	0.02	−2.1 ± 1.85	−0.23 ± 0.69	0.005	−0.53 ± 1.18	−0.5 ± 0.97	ns (0.95)
Calcaneal BMD (g/cm^2)	0.316 ± 0.13	0.56 ± 0.1	0.000001	0.33 ± 0.15	0.62 ± 0.06	0.00006	0.29 ± 0.1	0.51 ± 0.11	0.0001
T-score	−2.9 ± 1.51	0.005 ± 1.1	0.000001	−3.18 ± 1.7	−0.06 ± 0.72	0.00001	−2.58 ± 1.27	0.08 ± 1.37	0.0001
Z-score	−2.7 ± 1.45	0.13 ± 1.0	0.000001	−3.03 ± 1.61	0.04 ± 0.8	0.00001	−2.32 ± 1.21	0.23 ± 1.31	0.0001
Ad-SoS (m/s)	2071 ± 65	2097 ± 40	ns (0.12)	2069 ± 68	2100 ± 50	ns (0.21)	2073 ± 63	2093 ± 28	ns (0.38)

Abbr: Ad-SoS, amplitude-dependent speed of sound; BMD, bone mineral density; ns, not significant difference.

patients was ICTP. Forearm BMD, T-score and Z-score correlated with ICTP with the following *r* values: -0.53 ($p < 0.01$), −0.55 ($p < 0.01$), and −0.56 ($p < 0.01$), respectively. For males and females separately, no such correlations were found. Calcaneal BMD and Ad-SoS did not correlate with laboratory variables. In patients divided according to the kind of disease, only ICTP correlated with forearm BMD; in CP patients, *r* values ranged from –0.53 to –0.61 ($p = 0.017$–0.004), and in non-CP patients, *r* values ranged from –0.54 to –0.55 ($p < 0.05$). In patients never walking independently, the tendencies were similar as in the whole group (correlations with ICTP with *r* values from –0.51 to –0.53, $p < 0.05$), whereas in patients with shorter duration of the disease, the influence of ICTP was stronger (*r* ranged from –0.60 to –0.65, $p < 0.05$).

In controls, no significant correlations were obtained between skeletal and laboratory variables.

Discussion

Results obtained in the current study show that in wheelchair-bound subjects the skeletal status is seriously affected. An important issue of the study is that our patients were affected many years before peak bone mass was achieved. Puberty is a time in the life of humans when large increases in BMD occur during a relatively brief period *(16)*. In studies performed in adolescent females, physical activity had a beneficial influence on BMD and QUS parameters *(17,18)*. Therefore, in patients studied with a growing skeleton, immobilization and underlying disease affect the optimal peak bone mass that can be achieved.

In studies performed in CP patients, BMD values were decreased at the spine and hip *(12,14,15)*. In these studies, however, no data on skeletal measurements in upper limbs were available. Opposite results recently were noted in ambulatory children with CP and myelomeningocele in which spinal BMD did not differ from results in the controls *(19)*. This observation may suggest that an active rehabilitation program may prevent a decrease in BMD. Support for a positive role of weight-bearing physical activity is provided by a longitudinal study performed in children with spastic CP *(20)*. During an 8-month intervention, a significant increase in femoral and spine BMD was noted *(20)*.

In our patients, calcaneal BMD was significantly decreased and this is comparable with data given by Uebelhart et al *(21)*, who noted a decrease in lower limb BMD. The lack of a decrease in forearm BMD in female patients in comparison with female controls is similar to data obtained by Jones et al *(3)* who noted no change in the leg and arm BMD of spinal cord-injured males. It is difficult to explain why only the forearm BMD in females was preserved because all patients were recruited from the same nursing home and shared the similar rehabilitation program. Generally, we observed that results expressed in Z-scores were lower in males vs females also in calcaneal BMD. An important observation concerns correlations between calcaneal BMD and duration of disease, i.e., in females this was negative, and in males a positive

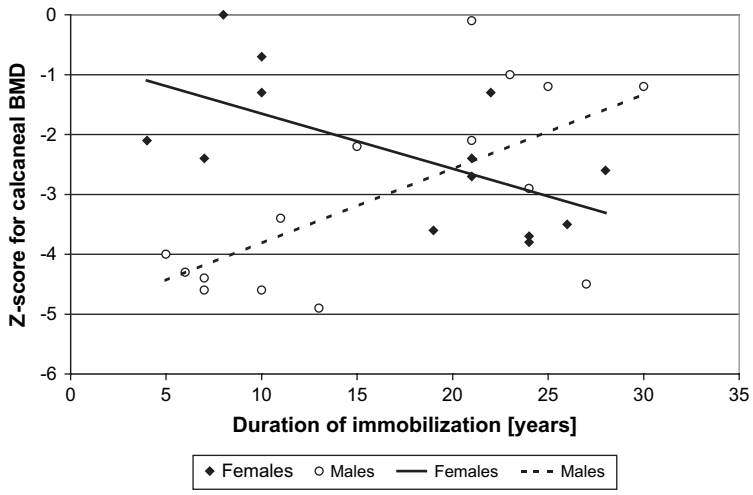

Fig. 1. Correlation between duration of immobilization and Z-score for alcaneal bone mineral density (BMD).

influence on T-score and Z-score correlations were observed. Results in males were comparable with data given by Szollar et al *(5)*, who noted a plateau for hip BMD at 19 years after spinal cord injury and then BMD at this site improved. We may hypothesize that an earlier tendency to improve calcaneal BMD observed in our male patients is due to a high trabecular content of the calcaneus. A possible explanation of different results in females is that peak values of BMD are reached earlier than in males, and maybe the process of skeletal growth is still partly present only in males. Obviously, only a prospective study may provide fully validated results and further longitudinal evaluations are in progress. In a study by Biering-Sorenson *(22)* densitometric measurements were performed in a group of 26 subjects with spinal cord lesions that occurred before 2 to 25 years. Bone mineral content of the femoral neck and the shaft was 25%, and for the proximal tibia it was more than 50% lower than normal values. The latter value is very close to the difference in calcaneal BMD between our male patients and male controls (47%). Garland et al *(23)* studied males after spinal cord injury and bone mineral loss occurred throughout the entire skeleton except the skull. Percentage differences for lower extremity were 35%–37% in comparison with data in controls, and 26% for arms. Bone mineral content, which was close to the decrease in forearm BMD was noted in our study (24%). In the study by Kannisto et al *(24)* assessing 35 adult spinal cord injuries that occurred 19 yr earlier at the age of 13 yr and the long period after injury makes this study a useful one to compare with our results. The authors obtained low femoral BMD with a mean Z-score of -2.05 and normal spinal BMD, and time since injury did not affect BMD measurements. In the study by Kannisto et al *(24)* bone ALP was in the normal range, which is different from our data, and ICTP was in the normal range, which is similar to our observations.

Quantitative ultrasound has only been rarely used to follow skeletal changes due to immobilization. Meys and Sutter *(11)* performed densitometric and ultrasound measurements at the calcaneus in 23 males after brain injury. All parameters were about 40% lower than in the controls, and a period of immobilization correlated with their values (r range, 0.4–0.6, $p < 0.001$). In the current study, we did not observe a decrease in Ad-SoS (except non-CP patients). We postulate two mechanisms explaining our results. Hand phalanges consist mostly of cortical bone and may be less sensitive to immobilization and/or good hand function in the patients studied may preserve the bone status. However, in males, the forearm BMD

Table 3
Results of Laboratory Measurements

	Whole patients (n = 36)	Male patients (n = 20)	Female patients (n = 16)	Whole controls (n = 19)	Male controls (n = 10)	Female controls (n = 9)
ICTP [μg/L]	6.05 ± 2.5	6.61 ± 3.1	5.42 ± 1.47	5.64 ± 1.73	5.93 ± 2.18	5.32 ± 1.07
bALP [U/L]	13.95 ± 11.0*	11.6 ± 4.7**	16.56 ± 15.0	29.2 ± 10.8	32.5 ± 12.7	25.5 ± 7.07

Abbr: bALP, bone alkaline phosphatase; ICTP, carboxyterminal telopeptide of type I collagen.
*$p < 0.0001$.
**$p < 0.00001$.

was diminished and further investigations are necessary. Recently, Warden et al *(25)* proved that calcaneal QUS measurements are able to assess skeletal changes due to acute spinal cord injury. However, the important limitation in the wider clinical use of QUS to monitor longitudinal changes is the relatively poor precision and longer intervals between measurements than in the case of densitometry *(26)*.

The most important observation derived from our study in regard to bone markers is the persistently suppressed bone formation, whereas bone resorption markers did not differ significantly between patients and controls. However, the role of this marker was shown in correlation analysis; ICTP significantly and negatively correlated with forearm BMD. This influence was stronger in patients with shorter periods of immobilization, which is a not an unexpected observation. Markers of bone formation: ALP *(15)* and osteocalcin *(12)* were estimated in CP patients, and mean values did not differ from values noted in controls.

Our study has several limitations. In a case-control study the natural course of changes in skeletal status and bone metabolism cannot be reliably estimated. A small number of patients and controls were studied. One of the limitations of the study may be a common analysis of patients with CP and other reasons for immobilization. However, skeletal results generally showed comparable trends. Also a lack of central DXA measurements is a limitation of the study.

In conclusion, the study showed that in wheelchair-bound subjects the skeletal status was seriously affected and bone formation was depressed. Proposed modifications in patients' management ought to include an increase in duration and intensity of physical training, especially weight-bearing exercises. The efficacy of therapy using antiresorptive drugs ought to also be clarified, and a longitudinal observation is currently in progress.

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