CE56

M-078

BONE MINERAL MEASUREMENT

SKYLAB EXPERIMENT M-078

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The observation that bone mineral is lost in patients who are either immobilized or remain in bed for extended periods of time formed the basis for the concern that large amounts of bone may be lost during long periods of weightlessness. This concern was magnified when early X-Ray densitometry studies suggested that rather large amounts of mineral could be lost during rather short periods of weightlessness (4-14 days). In the FIRST SLIDE, we have summarized the data accumulated during the early Gemini and Apollo missions. Significant losses were reported for the os calcis in the crewmen of Gemini 4 and 5 and Soyuz 3 and 9 missions and in the Commander of Apollo 7 and the Lunar Module Pilot on the Apollo 8 mission. Relatively insignificant changes were seen on Gemini 7 and in the other crewmen of Apollo 7 and 8. Very large losses of radius mineral were reported for the crewmen of Gemini 5 and the radius and ulna of Apollo 8. In a recent re-evaluation of the Gemini 4 and 5 data, errors were noted to have resulted in an approximate 6-7% over estimation of loss. I have been informed that this re-evaluation is currently in press. Even though some of this data was revised to reflect smaller losses, their general magnitude was a cause for concern.

It is necessary, however, to view these results with an appreciation of the problems inherent in the measurement techniques used. X-Ray densitometry with its attendant problems of a polychromatic energy beam, film characteristic changes, film development variables and the need for ultimate translation of film density to digital analysis, has many sources of error. These errors are magnified when steps are not taken to overcom soft tissue irregularities and changes. Many of the problems associated with a radiographic technique are amplified when measurements are to be made at a variety of locations with wide differences in temperature, humidity, power sources and equipment as was the case with the Gemini studies.

Since bed rest is the only reasonable earth simulation to weightlessness, these findings led to a series of prolonged bed rest studies of 30-36 weeks which , in addition to careful calcium balance studies, also employed a newer more precise method of estimating bone mineral in the radius, ulna and os calcis. This technique did not suffer from the uncertainties of film development and the polychromatic characteristics of the X-Ray beam.

It employed an essentially monoenergetic photon source, the 27.5 KEV X-Ray of Iodine 125 and a sodium iodide crystal scintillation detector. The NEXT SLIDE shows these essential elements mounted on a scanner yoke in direct opposition to each other and collimated so that a 3 mm. beam is similarly viewed by a 3 mm. extrance collimator on the detector. The yoke is mounted on a scanner which is able to scan a limb placed between the source and detector in a rectilinear raster pattern; out along the X axis, a Y increment and then in along the X axis. Transverse scans across a limb are made at 3 mm. longitudinal increments. Companion electronics are calibrated to accept only the primary photons that are neither absorbed nor scattered by the limb placed in the beam path. The limb to be examined is placed in devices which hold them stable and in position for scanning. SLIDE. During measurement of the os calcis the heel rests in a foot mold mounted in a plastic box filled with water to provide tissue equivalency. A fiberglass foot mold is fashioned from an impression of each subjects foot made prior to the study. The NEXT SLIDE depicts the configuration for arm scanning. In this case the arm is encased in a constant thickness of tissue equivalent material called Superstuff. Tissue equivalent material compensates for the irregular thickness of tissue covering surrounding the bone. This same configuration was used for measuring other lower extremity bones, primarily the tibia, fibula and metatarsals. During all of these studies it became clear that of the bones studied, only the os calcis demonstrated early and significant mineral loss. We will therefore direct our attention today as we did on the Apollo and Skylab crews, to results obtained from the os calcis with the radius and ulna serving as representative upper extremity bones. As shown on the NEXT SLIDE, the most distal 2 cm. portion of the radius and ulna were measured and reported as mean mineral content in grams of ash per cm. of the bone length. The NEXT SLIDE illustrates the area of central os calcis measured. The lines represent the scan rows. The mineral content of a 2 1/2 cm. section of this bone is reported in mg./cm.^{2} of hydroxyapatite.

The method of calculating is schematically illustrated on the NEXT SLIDE. The count rate of the transmitted beam through the tissue and tissue equivalent is designated as I_o^* and represents 100% transmission. Each data point through bone is designated as I. Transmission or absorbance through this segment is given as the log of the ratio I_o^*/I and the sum of these values across the bone is proportional to the mineral content in this ~~sengnet~~ segment. The standards used to convert these values to mineral content are shown on the NEXT SLIDE.

The entire system is calibrated before and after each subject scan by measuring a Witt-Cameron standard which consists of three chambers containing dipotassium hydrogen phosphate to simulate bone attenuation. The pre and post absorption values expressed in arbitrary units and the actual bone content in terms of these units is derived by linear regession against the known bone equivalency of each chamber. Further calibration of the system is obtained daily by scanning a hydroxyapitite step wedge consisting of 6 steps each of 3 different concentrations. The NEXT SLIDE illustrates the type of regression line obtained from such a calibration. On the NEXT SLIDE we summarize data obtained. From ambulatory controls studied over a period of time a variability of one S.D. of about 1.5% is observed. Therefore any change greater than 3% (2 S.D.) can be considered significant.

Using these techniques, the following observations were made:

1. As shown in the NEXT SLIDE, periods of up to 30 weeks of bed rest can result in significant mineral losses in the central os calcis. Losses up to 40% have been observed. This bone is both highly trabecular as well as weight bearing. In contrast, the radius, a primarily cortical and non-weight bearing bone, has failed to exhibit mineral losses during periods of up to 30 weeks of bed rest. It must be remembered that the os calcis contains 1/500th of the total skeletal calcium and that 20% of the skeleton is composed of trabecular bone. This accounts for about 240 gms. of the total calcium with about 3.3 gms. being in the os calcis.

2. The mean rate of whole body calcium loss was about 0.5% per month. The NEXT SLIDE illustrates the degree of urinary calcium

loss during bed rest. Urinary calcium increased in all subjects and reached a peak at about the 6th week of bed rest approximately 100mg/day greater than the basal value. A similar pattern for the calcium balance is shown on the NEXT SLIDE. The losses reached 200-300 mg./day by the 5th to 8th week and persisted throughout the bed rest period.

3. As shown in the NEXT SLIDE, little or no os calcis mineral loss was observed during the first month of bed rest, that is, -0.7% with one standard deviation limits of +1.3 to -2.7%. Mineral loss thereafter averaged about 5% per month. The two month losses are shown on the NEXT SLIDE. A mean of -6.2% is shown here for 15 subjects with one standard deviation limits of -1.3 to -11.1%. This wide variability of data was reconcilled when it was observed that the loss could be correlated with the initial 24 hour urinary hydroxyproline excretion and the initial os calcis bone mineral content. We postulated that persons with a high calcaneal mineral content and/or a low urinary hydroxyproline excretion rate would be likely to retain more mineral during bed rest. Thus the calcaneal mineral which remains at any time during bedrest would be a function of the baseline calcaneal mineral divided by urinary hydroxyproline (corrected either for body surface area or creatinine excretion). This relationship is illustrated in the NEXT SLIDE where the mineral content remaining after 11-12 weeks is shown on the ordinate and the ratio of baseline calcaneal mineral to 24 hr. urinary hydroxyproline is shown on the abscessa. We will refer to this term as the prediction term in subsequent discussion. It can be seen that a high prediction term is associated with little os calcis mineral loss and a low prediction term is associated with

larger losses. The applicability of this term to the flight situation will have to await the completion of all of the Skylab missions. We will return to this concept later.

It is clear however that the earlier reported X-Ray densitometry results did not correlate well with our bed rest results. We therefore proceeded to measure the Apollo 14, 15 and 16 crews pre and post flight. The NEXT SLIDE shows the measurement configuration used. The os calcis and forearm were measured simultaneously. The same equipment was used both pre and post flight with the exception of Apollo 14 which was a quaranteened mission. In this case, duplicate scanning devices were left in the Mobile Quaranteen Facility and the electronics were placed outside the trailer. Cabling through the bulkhead of the trailer permitted remote operation of the scanners and acquisition of data. Measurements were made 30, 14 and 5 days before flight and as soon as possible after recovery aboard the aircraft carrier , (R+0), the day after recovery (R+1) and 5 and 14 days after recovery (R+5 and R+14 respectively). As seen on the NEXT SLIDE, no significant mineral losses were observed in the radius or ulna on any of the crewmen. The ulnar mineral changes of about -3.5% in the Command Module Pilot of Apollo 15 and 16 and the Lunar Module Pilot of Apollo 16 were just at the 2 S.D. level for repetative measurements of this bone.

In the case of the os calcis only 2 crewmen of Apollo 15 had losses on R+0. The NEXT SLIDE shows that mineral regain was rapid for the Commander. Indeed, there was a return to control values on R+1.

Only the Command Module Pilot had a significant loss with gradual return to control values within two weeks. Note that changes do occur during the R+0 to R+1 period. This point has not generally been appreciated. Indeed, a gradual continuing loss for a week has been seen in some of our bedrest subjects.

These results in general were in concert with our bedrest data and supported our contention that the early Gemini data could have been in error, a point which has recently been conceded. However, the observation that at least one Apollo crewman of 9 showed a consistent loss of os calcis mineral with slow regain again points to the biological variability and the need for a prediction term to sort out this variability. Hydroxyproline values were not reported for this crewman so that the prediction term could not be applied. Preparatory to the Skylab missions, a simulated altitude test (SMEAT) was conducted in Houston over a two month period. The NEXT SLIDE shows the effect of confinement and Skylab environment upon the crewmen as compared to the non-confined controls.

No losses outside of the two standard deviation limits was observed for any of the crewmen. The increase in ulnar mineral in the Scientist Pilot is unexplained. These data however establish a baseline against which the Skylab results can be evaluated. Urinary hydroxyprolines were obtained on this crew. All had high prediction terms (37, 48 and 40 respectively).

In each of the studies at least 3 control subjects are measured along with the crew to offset any instrumental or environmental difficulties. In addition the standards previously described were measured before and after each scan. The same techniques are being employed during the Skylab missions.

The results from the first 28 day mission are shown on the NEXT SLIDE. The figures given in parenthesis are the % change from mean baseline as before. No significant losses were observed for any of the 3 bones measured and therefore no measurements were made after 6 days from recovery. The NEXT SLIDE summarizes the data obtained on the day of recovery and compares it with the control subjects (clearly, no losses are seen). It is of interest to note the slightly above baseline ulnar mineral in the Pilot, similar to that seen in the Scientist Pilot of the SMEAT test. This is however within the 2 S.D. limits of the technique. (SLIDE OFF).

Based upon all of this data we have the following evidence that the bed rest situation is a closer approximation to the flight situation with regard to bone mineral than heretofore suspected.

1) calcium balances are similar for a 30 day period with 0.3% being lost on the first Skylab mission and 0.5% being lost during a comparable period of bedrest. Both situations suggest the development of a plateau. Possibly this plateau was earlier during the SL 1/2 mission than bed rest.

2) mineral loss from the os calcis was not evident during the 28 days of the first Skylab mission, nor after 30 days of bed rest.

3) in neither situation were mineral losses seen in the radius or ulna.

If we are to accept this similarity then it would be useful to re-examine our bed rest results in the light of the prediction terms obtained in those subjects. Since no mineral losses were seen in the radius or ulna, we will confine our observations to the os calcis.

We have taken the data obtained from 15 untreated bed rest subjects and have derived the best fit polynominal for each subjects data to allow us to obtain the status of the mineral content on any desired day of bed rest. SLIDE. Based upon the mission planning for Skylab, we have obtained the os calcis mineral losses for the 28th, 59th, 70th and 84th day of bedrest and have plotted the observed mineral losses for these days against the prediction term for each bedrest subject. A least squares fit of this data to a straight line was derived and is shown here as the solid line. The stippled area describes the 2 S.D. limits for each set of data. From these graphs it is clear that the anticipated mean mineral losses for any time period can vary significantly, depending upon the prediction term appropriate for the subject. For example, at 84 days it can vary from almost no loss, down to a 20% loss.

One can reason that the bone turnover rate for each individual is different. Since the bone formation and accretion rates during the 1 G situation in healthy adult males under 50 years of age are equal as long as the calcium balance is maintained at approximately 0, if the stimulus of gravity is removed from these subjects, ~~bone formation is reduced~~ ~~and~~ bone accretion continues unopposed. Since the turnover rates vary, obviously the rate of loss for each individual in this situation will also vary. Those having a normally higher turnover rate would lose greater amounts of mineral. We believe that the person with a higher mineral content generally has a lower 24 hr. urinary hydroxyproline.

On the NEXT SLIDE we have put the mean mineral loss lines for each of the days on a single graph. It is clear that the rate of loss over the 84 days for a man with a 30 prediction term is clearly less than that for one with a 14 prediction term.

The validity of our argument will have to await the results from longer space missions. The data for the 28 day mission falls within the predicted limits but a 28 day mission alone cannot verify these assumptions.

In conclusion, we have presented data that supports the previous observations, namely, that mineral is lost from bone during bed rest and weightlessness. The similarity between the data derived from these two situations is closer than has heretofore been suspected. Losses have been minimal during missions so far undertaken. A prediction term has been proposed in an attempt to translate bed rest data into the weightless condition. Such prediction terms have also been used to evaluate the effect of various remedial measures on the calcium loss during bedrest. It therefore seems possible that these observations may be applicable to the weightless condition. The validity of this proposal must await longer space flight data.

Finally, as with most research, the finished product is the result of the work of manY. I wish to acknowledge the invaluable support of my colleagues in metabolic diseases: Drs. Donald McMillan; Charles Donaldson; Stephen Hulley and Victor Schneider and their staff who made the bed rest studies possible and to Dr. Daryl Lockwood who was instrumental in the development of the prediction term.

Furthermore, I acknowledge the support and participation of my staff in the performance of all of these studies, often under rather trying conditions and the late Charles Larsen who translated the conceptual design of the scanner into a working model, and Mr. Scott Brown who designed the electronic modules. Support from the Johnson Space Center staff and the principal coordinating scientists, Drs. Paul Rambaut and Michael Whittle were invaluable in the execution of the flight studies.

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M-078

SKYLAB SL-3

BONE MINERAL MEASUREMENT

Experiment M-078

RIGHT RADIUS

g/cm

Date	CDR	SPT	PT
6/27/73	1.323 (+0.6)	1.160 (+0.5)	1.679 (-1.2)
7/12/73	1.313 (-0.2)	1.160 (+0.5)	1.710 (+0.6)
7/23/73	1.309 (-0.5)	1.141 (-1.1)	1.709 (+0.6)
Mean	1.315	1.154	1.699
9/25/73	1.297 (-1.4)	1.156 (+0.2)	1.660 (-2.3)
9/26/73	1.319 (+0.3)	1.154 (0.0)	1.670 (-1.7)
10/2/73	1.319 (+0.3)	1.155 (+0.1)	1.684 (-0.9)

RIGHT ULNA

g/cm

6/27/73	0.693 (+0.7)	0.676 (+0.6)	0.891 (-0.2)
7/12/73	0.691 (+0.4)	0.666 (-0.9)	0.899 (+0.7)
7/23/73	0.681 (-1.0)	0.673 (+0.1)	0.890 (-0.4)
Mean	0.688	0.672	0.893
9/25/73	0.691 (+0.4)	0.661 (-1.6)	0.889 (-0.4)
9/26/73	0.702 (+2.0)	0.668 (-0.6)	0.872 (-2.4)
10/2/73	0.702 (+2.0)	0.656 (-2.4)	0.892 (-0.1)

LEFT OS CALCIS

mg/cm^2

6/27/73	473.9 (+0.3)	532.5 (+1.1)	644.8 (+1.2)
7/12/73	470.3 (-0.5)	534.8 (+1.5)	634.9 (-0.4)
7/23/73	473.9 (+0.6)	512.8 (-2.6)	632.5 (-0.8)
Mean	472.7	526.7	637.4
9/25/73	483.5 (+2.3)	516.0 (-2.0)	646.1 (+1.4)
9/26/73	482.8 (+2.1)	516.1 (-2.0)	626.5 (-1.7)
10/2/73	476.4 (+0.8)	487.9 (-7.4)	641.0 (+0.6
10/9/73		495.9 (-5.8)	

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BONE MINERAL MEASUREMENT

(SL3, Experiment M078)

Control Subjects

OS CALCIS

Date	Alexander	Brown	Kolb	LaPinta	Ullmann	Vogel	Whittle
6/20/73	524.7	-	-	498.1	-	-	-
6/22/73	-	506.8	-	-	551.5	-	-
6/23/73	-	507.0	-	509.2	551.7	-	603.2
6/27/73	-	-	-	503.4	-	617.6	-
6/28/73	508.3	-	-	-	561.1	-	612.4
7/11/73	-	-	-	497.1	562.8	-	-
7/12/73	523.2	-	-	-	-	627.0	-
7/13/73	-	-	-	-	558.4	-	591.8
7/23/73	-	514.9	449.8	490.2	-	-	597.1
7/24/73	500.1	-	-	-	-	-	-
9/21/73	-	512.9	-	-	-	-	-
9/25/73	522.6	519.8	448.9	-	-	-	612.0
9/26/73	531.8	514.4	451.0	-	-	620.9	606.6
10/1/73	-	-	451.5	-	-	-	-
10/2/73	518.1	-	-	-	-	613.8	602.3

BONE MINERAL MEASUREMENT

(SL3, Experiment M078)

Control Subjects

RADIUS

Date	Alexander	Brown	Kolb	LaPinta	Ullmann	Vogel	Whittle
6/20/73	-	-	-	1.304	-	-	-
6/22/73	1.096	1.533	-	-	1.166	-	-
6/23/73	-	1.534	-	1.307	1.174	-	1.164
6/27/73	-	-	-	1.312	-	1.485	-
6/28/73	1.100	-	-	-	1.159	-	1.159
7/11/73	-	-	-	-	1.147	-	-
7/12/73	1.088	-	-	-	-	1.510	-
7/13/73	-	-	-	-	1.158	-	1.176
7/23/73	-	1.524	1.238	1.317	-	-	1.162
7/24/73	1.099	-	-	-	-	-	-
9/21/73	-	1.541	-	-	-	-	-
9/25/73	1.106	1.536	1.228	-	-	-	1.156
9/26/73	1.110	1.543	1.241	-	-	1.512	1.163
10/1/73	-	-	1.238	-	-	-	-
10/2/73	1.102	-	-	-	-	1.468	1.154

BONE MINERAL MEASUREMENT

(SL3, Experiment M078)

Control Subjects

ULNA

Date	Alexander	Brown	Kolb	LaPinta	Ullmann	Vogel	Whittle
6/20/73	-	-	-	0.649	-	-	-
6/22/73	0.548	0.767	-	-	0.660	-	-
6/23/73	-	0.758	-	0.625	0.673	-	0.578
6/27/73	-	-	-	0.646	-	0.694	-
6/28/73	0.559	-	-	-	0.668	-	0.584
7/11/73	-	-	-	-	0.679	-	-
7/12/73	0.559	-	-	-	-	0.695	-
7/13/73	-	-	-	-	0.676	-	0.597
7/23/73	-	0.761	0.594	0.628	-	-	0.580
7/24/73	0.552	-	-	-	-	-	-
9/21/73	-	0.752	-	-	-	-	-
9/25/73	0.543	0.744	0.581	-	-	-	0.564
9/26/73	0.540	0.748	0.571	-	-	0.693	0.567
10/1/73	-	-	0.564	-	-	-	-
10/2/73	0.543	-	-	-	-	0.690	0.564

BONE MINERAL MEASUREMENT
EXPERIMENT M-078
PRE-FLIGHT SL-3
BACK-UP CREW

	Brand		Lenoir		Lind	
			Os Calcis (mg/cm^2)			
6/2 /73	740.9	(+0.8)	595.2	(+1.0)	548.0	(+1.1)
7/13/73	729.2	(-0.8)	578.6	(-1.8)	543.4	(+0.3)
7/24/73	735.0	(0.0)	594.4	(+0.8)	534.7	(-1.3)
Mean	735.0		589.4		542.0	
			Radius (g/cm)			
6/28/73	1.639	(+0.6)	1.374	(+0.5)	1.243	(-2.4)
7/13/73	1.630	(+0.0)	1.363	(-0.3)	1.285	(+0.9)
7/24/73	1.619	(-0.6)	1.363	(-0.3)	1.293	(+1.5)
Mean	1.629		1.367		1.274	
			Ulna (g/cm)			
6/28/73	0.911	(-0.9)	0.690	(+0.4)	0.643	(-0.5)
7/13/73	0.938	(+2.1)	0.686	(-0.1)	0.646	(0.0)
7/24/73	0.907	(-1.3)	0.686	(-0.1)	0.648	(+0.3)
Mean	0.919		0.687		0.646	

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PREDICTION TERM AND MEASURED MINERAL LOSSES

BEDREST SUBJECTS

	PREDICTION TERM	% CHANGE FROM MEAN BASELINE	% CHANGE FROM MEAN BASELINE	
MH	11.2	+1.0 (24)	- 7.4 (53)	
AD	13.7	+0.1 (23)	- 9.6 (51)	
RAW	14.1	-0.7	-14.0 (52)	
LG	14.8	-2.3 (31)	- 9.9 (52)	
AK	16.3	-2.6 (22)	- 9.5 (52)	
JG	18.0	-2.5 (30)	-12.9 (58)	
FK	20.5	-3.2 (31)	-10.3 (58)	
RG	20.8	-4.1 (31)	- 4.4 (45)	
FB	21.7	+0.4 (30)	- 2.2 (46)	
GF	23.7	+1.6 (35)	- 4.7 (49)	
RWR	25.7	-1.3 (30)	- 1.1 (43)	
BL	28.1	+0.1 (35)	- 5.8 (49)	
RCW	29.7	-0.7 (31)	- 0.2 (52)	
HTA	30.5	+3.3 (22)	+ 2.7 (50)	
GM	36.3	+1.0 (28)	- 3.4 (51)	
SKYLAB SL-1/2				
CONRAD	15.0	+0.5 (28)	-----	
WEITZ	30.0	+2.7 (28)	-----	
KERWIN	41.6	-0.9 (28)	-----	
SKYLAB SL-3				
BEAN	35.3	-----	+ 2.3 (59)	
GARRIOTT	27.7	-----	- 2.0 (59)	R+0
			- 7.4	R+7
LOUSMA	54.7	-----	+ 1.4 (59)	
			+ 0.8	R+7

( ) = Days of Bed Rest or Weightlessness

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