An Accurate and Reproducible Absorptiometric Technique for Determining Bone Mineral Content in Newborn Infants

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Summary

At the Bone Mineral Laboratory of the University of Wisconsin a microcomputer-based digital read-out system was designed specifically for determining bone mineral content (BMC) and bone width (BW) in newborn infants with the following features: (1) high accuracy and precision; (2) high reproducibility *in vivo*; (3) direct read-out of BMC and BW; (4) automatic data calibration; and (5) use of a low activity [¹²⁵I] source (<50 mCi). BMC and BW were determined on the left radius on a series of 114 newborn infants of all gestational ages and a curve for intrauterine bone mineral content extrapolated from the data. Accuracy of the photon absorptiometric system was assessed by measuring BMC on a series of nine small bone sections (29-212 mg/cm) and confirmed by subsequent ashing of these bone sections ($r = 0.99$). Short-term precision (weekly, coefficient of variation 1.7%) and long-term precision (monthly, coefficient of variation 2.1%) for measuring BMC were determined by multiple determinations on a four-chambered bone phantom calibrated with the bone sections. Immediate reproducibility (without repositioning the arm) for the 4-6 scans performed for each determination of BMC and BW was good with a mean coefficient of variation of 3.9% for BMC and 3.6% for BW. In 84 infants, repositioning error was determined by repeating the measurement of BMC and BW after repositioning the arm. The correlation coefficients between measurements before and after repositioning the arm were 0.97 for BMC and 0.95 for BW. BMC correlated well with gestational age ($r = 0.92$), birth weight ($r = 0.89$) and bone width ($r = 0.92$). BW also correlated with gestational age ($r = 0.84$) and birth weight ($r = 0.85$). A multiple linear regression analysis of BMC versus BW, gestational age, and birth weight was done. The correlation coefficient between the predicted BMC from these variables and measured BMC was 0.95. Photon absorptiometry can be used with high accuracy, precision, and reproducibility *in vivo* in newborn infants. BMC correlates with gestational age, birth weight, and bone width.

Abbreviations

BMC, bone mineral content

BW, bone width

IUBMC, intrauterine bone mineral content

Since the report by Minton *et al.* (9), the technique of photon absorptiometry has held promise for determining changes in bone mineral content (BMC) in the newborn, particularly in the very-low-birth-weight infant where disorders of bone mineralization are common. This previous work has not been verified nor has the accuracy or reproducibility *in vivo* of the technique been established for the small bones of the newborn infant. At the Bone Mineral Laboratory of the University of Wisconsin a microcomputer-based digital read-out system was designed specifically for determining BMC and bone width (BW) in newborn infants with

the following features: (1) high accuracy and precision; (2) high reproducibility *in vivo*; (3) direct read-out of BMC and BW; (4) automatic data calibration; and (5) use of a low activity [¹²⁵I] source (<50 mCi). Subsequently, BMC and BW were determined on a series of 114 newborn infants of all gestational ages and a curve for intrauterine bone mineral content (IUBMC) extrapolated from the data (14).

MATERIALS AND METHODS

Photon absorptiometry. BMC and BW were measured by a photon absorptiometric system in which a collimated, 2-mm diameter photon beam from a low activity, [¹²⁵I] "spent" source (20-50 mCi) passes beneath the arm (bone) to be scanned (12). A collimated scintillation detector placed over the arm was equipped with a mechanism to allow for simultaneous movement of the collimated detector and [¹²⁵I] source, with a scan speed of 0.4 mm/sec. Changes in beam intensity are due to the attenuation by bone mineral, and the integrated attenuation is proportional to the mass (mg per cm) of mineral in the scan path. The length of the scan path is proportional to the width of the bone, the bone edge being detected by a 10% decrease from the baseline count in tissue adjacent to the bone. The system includes a nuclear counting device (Baird-Atomic Model 530) and a microcomputer (Radio Shack TRS-80) with a specially designed interface for counting pulses and controlling the motor of the scanner.

All measurements of BMC and BW were made at a site on the distal left radius located by external measurement at a position $\frac{1}{3}$ of the distance from the distal end. The infant's forearm was placed in a lucite holding device, surrounded with a segment of water-filled dialysis tubing, and compressed with a lucite plate, thereby assuring a constant soft tissue equivalent material around the bone (1). A series of four to six determinations of BMC and BW were done at each site and the average value used. The radiation dose from a series of four scans did not exceed 13 mrad as measured by thermoluminescent dosimetry with lithium fluoride chips. This is comparable to the radiation dose from a pediatric chest x-ray, though the path of the scan is only 0.3 mm wide.

To determine the accuracy of the absorptiometric system, BMC was measured on a series of nine small bone sections and confirmed by subsequent ashing of these bone sections (10) (Fig. 1). Three of the bones were from premature infants, the remaining six were of avian origin. The mineral content of the bone sections ranged from 29-212 mg/cm compared to an adult range of 600-1500 mg/cm at the $\frac{1}{3}$ distal radius (7). The BMC of a normal full-term infant is about 90 mg/cm (9). There was a high correlation coefficient for the linear regression of ashed weight *versus* measured BMC, $r = 0.99$ with a standard error of estimate (S.E.E.) of 2.1 mg/cm. Subsequently, this regression line was used to calibrate a four-chambered bone phantom (precision bored plastic chambers filled with a solution of potassium phosphate) used in daily

calibration of the scanner (15). Precision of the system was determined by making multiple measurements of the bone phantom. Short-term precision of the phantom was excellent as shown by coefficients of variation of 1.7% and 0.7% for weekly determined means of BMC and BW respectively. Long-term precision (monthly determined means) was 2.1% for BMC and 0.8% for BW.

Population. Measurements of BMC and BW were made during the first week of life at a mean age of 3.0 days, in 114 Caucasian, appropriate for gestational age infants from 22–42 wk gestation. Gestational age was determined from the history of the last menstrual period and corroborated by physical examination for those infants greater than 27 wk gestational age. For those infants less than or equal to 27 wk, ultrasound (biparietal diameter) was

used as the second corroborator of gestational age. If there was more than a 2-wk discrepancy between the two determinations of gestational age, the infant was excluded from the study. All infants were admitted to the nurseries of Madison General Hospital. All were free from congenital malformations and persistent metabolic acidosis (>8 h). Sixty-seven of the infants were less than 38 wk gestational age and 30 infants were 32 wk gestational age or less. Seven of the most premature infants died within a few hours of birth and were measured within 12 h after death. A series of 4–6 scans were done on each infant and the average value used. Interassay reproducibility *in vivo* was tested in 84 infants by repositioning and remeasuring the arm, and repeating the scan on the same day. Informed consent was obtained from all parents.

RESULTS

Results for BMC and BW are shown in Table 1. Males as a group had a higher BMC than females at each gestational age, though the differences were not significant.

Immediate reproducibility (without repositioning of the arm) for the 4–6 scans performed for each determination of BMC and

Fig. 1. Weight of nine 1-cm small bone sections (three from premature infants, six of avian origin) after ashing vs bone mineral content as measured by photon absorptiometry.

Table 1. Results of radial bone mineral content (BMC) and bone width in 114 appropriate for gestational age infants from 22–42 wk gestational age

Gestational age (wk)	n	BMC (mg/cm)	S.D.	Bone width (mm)	S.D.
22	1	20.1		2.5	
24–25	3	26.3	7.7	2.9	0.5
26–27	3	32.5	11.9	3.0	0.5
28–29	6	38.6	7.9	3.5	0.5
30–31	11	43.0	7.5	3.4	0.3
32–33	14	46.9	8.0	3.7	0.5
34–35	13	54.9	11.0	4.0	0.5
36–37	16	71.4	12.1	4.5	0.4
38–39	24	92.6	14.0	5.1	0.5
40–41	19	94.1	9.6	5.3	0.6
42	4	100.1	23.9	5.2	0.9

Fig. 2. Bone mineral content as measured by photon absorptiometry in the left radius of 114 newborn infants vs gestational age.

Fig. 3. Bone mineral content vs bone width as measured by photon absorptiometry in the left radius of 114 newborn infants of all gestational ages. Dotted lines represent ± 1 S.E.E.

BW was good with a mean coefficient of variation of 3.9% for BMC and 3.6% for BW in the 114 infants. The repositioning error was small in 84 infants who were remeasured; the correlation coefficient between measurements before and after repositioning the arm was 0.97 (S.E.E. = 6.0 mg/cm) for BMC and 0.95 (S.E.E. = 0.4 mm) for BW. Reproducibility was not affected by gestational age or birth weight.

The relationship of BMC to gestational age (GA) was examined using both linear and curvilinear regression analysis. An exponential curve ($BMC = 3.47 e^{0.082GA}$) fit the data more closely ($r = 0.92$ versus $r = 0.88$) than did the linear regression ($BMC = 5.06GA - 111$). The curvilinear regression was used to define a curve that could be extrapolated to the intrauterine period (Fig. 2); however, the linear relationship was adequate over the period from 28–42 wk as has been previously reported (14). There was a linear relationship of BMC with birth weight ($r = 0.89$, S.E.E. = 12.1 mg/cm). Likewise, BW correlated with gestational age and birth weight, the correlation coefficients being 0.84 and 0.85, respectively. A high correlation (linear) was found between BMC and BW (Fig. 3). This correlation coefficient was 0.92 with an S.E.E. of 10.0 mg/cm.

Finally, multiple linear regression analysis of BMC versus BW, gestational age, and birth weight was done. The correlation coefficient between the predicted BMC from these variables and measured BMC was $r = 0.95$.

DISCUSSION

Photon absorptiometry has been shown to be a reliable, non-invasive method for determining bone mineral content. The accuracy and precision of photon absorptiometry have been demonstrated in adults (1). Conventional radiologic methods do not detect decreases in bone mineral of less than 30–40% (4, 6), and quantitative morphometric and photodensitometric methods can determine bone loss within only broad limits (10–20% error) (8). There is limited experience using computed tomography to measure bone mineral (2). Bone biopsy, tetracycline labeling, technetium scan or total skeletal biochemical analysis are not practical for serial determinations of bone mineral in neonates.

The results of photon absorptiometry in newborn infants of gestational ages from 28–42 wk including an intrauterine bone mineral curve have been reported (9, 14). But the accuracy of the system for measuring small bones has not been previously reported nor have the results for reproducibility *in vivo*. A criticism of the photon absorptiometric technique in infants has been its reproducibility, because the point of measurement on the radius is located by external measurement and the subject must not move the arm during the measurement. For isolated bone sections, it has been shown that the BMC is not affected significantly by the amount of soft tissue around the bone nor by the orientation of the bone within the soft tissue (12). For bones *in vivo*, it has been reported that rotation of the forearm affects the measurement of BMC; orientation of the upper arm does not affect measurements at the distal site (11). In this study, we have clearly demonstrated that the system is accurate for newborn infants and that measurements can be reproduced despite the inherent problems with repositioning and arm orientation.

Our results for BMC (Table 1, Fig. 2) are similar to those previously reported, despite the use of a lower activity, "spent" source (20–50 mCi versus 50–200 mCi) (9). BMC for infants 37–41 wk gestational age was previously reported to be 90 ± 9 mg/cm ($\pm$ S.E.) (9), whereas the BMC for the same gestational age range in our study is 91 ± 2 mg/cm. The linear correlation coefficient for BMC versus gestational age was 0.83 in the previous study (9) and 0.88 in the present, whereas the correlation coefficients for BMC versus birth weight were 0.82 and 0.89, respectively.

In the present study (Fig. 2), we have used a curvilinear regression to describe the relationship between BMC and gestational age and extrapolated the data to a curve of intrauterine bone mineral content. This is logical as the relationships between fetal calcium accretion and gestational age and fetal skeletal weight and gestational age are curvilinear (3, 5, 13).

The results for BW, as measured by photon absorptiometry, have not been previously reported in infants. The relationship between BMC and BW (Fig. 3) may be useful in identifying disorders of bone mineral metabolism in low birth weight infants. In such rapidly growing infants, we speculate that the bone width continues to increase due to increased matrix formation, whereas BMC may decrease or remain unchanged due to a relative decrease in deposition of bone mineral secondary to insufficient mineral intake. The technique of photon absorptiometry may thus be useful in identifying and treating infants with such nutritional problems.

In conclusion, photon absorptiometry can be used with high accuracy, precision, and reproducibility *in vivo* in newborn infants. BMC shows a high correlation with gestational age, birth weight and bone width.

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