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Proximal intestinal absorption of calcium is elevated in proportion to growth rate but not bone mass is small for gestational age piglets

Rebecca C. Mollard[a], June Kohut[a], Jinping Zhao[a], Hope A. Weiler[a,b,*]

[a]*Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, Manitoba, R3T 2N2, Canada*
[b]*Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, R3T 2N2, Canada*

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Abstract

During the first year of life, body calcium content increases faster in relation to body size than any other time during growth. Studies have shown postnatal growth and bone mineralization differences between appropriate for gestational age and small for gestational age infants. The objective of this study was to compare duodenal calcium transport using intestinal ligated loop technique in 21-day-old small for gestational age (birth weight of <1.2 kg) and appropriate for gestational age piglets (birth weight of ≥ 1.4 kg). Piglets were fed liquid formula between day 5 and 21 of life and monitored daily for weight gain. At day 21 calcium absorption was measured followed by measurement of bone mass using dual energy x-ray absorptiometry. Small for gestational age piglets had greater calcium absorption and growth rate than appropriate for gestational age piglets. Birth weight was negatively related to weight gain and calcium absorption. Weight gain was positively related to calcium absorption. Appropriate for gestational age piglets had significantly higher whole body bone mineral content than small for gestational age piglets even after correction for body size. Whole body bone mineral content was positively correlated with birth weight and negatively correlated with calcium absorption. These observations suggest that small for gestational age piglets are capable of absorbing elevated amounts of calcium in the proximal intestine in support of compensatory growth. However, at 21 days of age small for gestational age piglets are similar in size but have lower bone mass compared to appropriate for gestational age piglets.

Keywords: Intrauterine growth restriction; Calcium absorption; Piglet

1. Introduction

Infants born small for gestational age (SGA) are characterized by delayed postnatal growth [1,2] and reduced bone mass [3,4]. During the first year of life, the calcium content of the body increases faster in relation to body size than any other time during the life cycle [5]. The skeleton of an appropriate for gestational age (AGA) term newborn contains approximately 25 g of calcium and makes up approximately 1% of the infant's weight [5]. All calcium retained in the body following birth comes from the diet. Calcium metabolism involves ingestion, digestion, intestinal absorption, utilization and excretion [6]. Calcium is absorbed by both active and passive transepithelial transport [6]. Active transport is essentially localized to the duodenum, is dependent on vitamin D and changes based on calcium homeostasis and requirements during growth and pregnancy [7]. In infancy, calcium is highly absorbed at approximately 58%, as indicated by 3-day metabolic balance studies [8]. Bronner et al. [8] suggest that preterm infants absorb calcium mainly through the passive route, based on the first order kinetics observed. However, they report net balance and did not use isotope tracers to assess true absorption in contrast to net balance [8]. As well, they did not report how many infants were born SGA or AGA [8]. Calcium absorption in SGA infants has a tendency to be higher when compared to AGA infants [9]. Again, the technique used to measure absorption was whole body metabolic balances. Whether the SGA infant is capable of absorbing calcium in the duodenum at rates necessary to support rapid growth is not known. While nutritional recommendations [10] suggest increased nutritional needs to support catch-up growth, data related to the ability of the SGA

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* Corresponding author. Tel.: +1-204-474-6798; fax: +1-204-474-7593.

E-mail address: hweiler@ms.umanitoba.ca (H.A. Weiler).

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infant to absorb and utilize nutrients relative to infants born AGA is limited.

Previously, the piglet has been studied to learn of absorptive processes in infancy [11,12,13]. Based on available evidence, the pig model appears to be an appropriate model for studying digestive and absorptive processes in humans [14]. Advantages in using the pig model to study issues in human nutrition include: highly adaptive to new environments, can be weaned at birth and reared artificially, large litter size, readily available and similar anatomy and physiology to human infants [14]. Much is known about the nutrition and growth in the pig [14]. Nutritional requirements are very similar between piglets and humans in infancy and growth [15]. The SGA piglet has been characterized as a model appropriate to study questions related to human infant nutrition [16]. In addition, at birth the SGA piglet has reduced bone mass relative to the AGA piglet [17] in parallel to SGA and AGA human infants [3,4]. Thus, both the SGA piglet and human infant require substantial nutrient retention in support of rapid catch-up growth and bone mineralization. Therefore, the main objective of this study was to determine if calcium absorption in the duodenum differs between SGA piglets and AGA piglets and if it is high enough to support compensatory growth and bone mineralization.

2. Methods and materials

2.1. Animals and diet

Male piglets, born at Glenlea Swine Research Unit, University of Manitoba were transported to the housing facility at the University of Manitoba. Piglets were selected from litters [12] of 8 to 12 piglets and taken from the sow at day 3 of life. Animal care and procedures were examined by the University of Manitoba Committee on Animal Use and were within the guidelines of the Canadian Council of Animal Care [18].

The average birth weight of piglets born at this institution is 1.6 ± 0.2 kg. Using the approach for human infants, SGA was defined as 2 Standard deviation below the average weight at birth. Thus fifteen male SGA piglets, defined as piglets with a birth weight of ≤1.2 kg, and fifteen male AGA piglets, defined as piglets with a birth weight of ≥1.4 kg, were fed liquid formula (350 mL · kg^{-1} · d^{-1}) at 9 AM, 3 PM and 9 PM for 15 days (from 5 to 21 days of life) as per Weiler and Fitzpatrick-Wong [19]. Volume of formula consumption was monitored after each feed to ensure that the full 350 mL/kg was consumed on a daily basis. Piglets arrived on day 3 of life and were taught to lap formula. During the 2 days of adaptation, if a piglet did not learn to lap readily, gavage feeds were used to ensure enough formula was consumed to continue growth. The formula was based on nutritional requirements for healthy growing piglets between 3 and 10 kg as set by The National Research Council [20]. Formula (see Table 1 for composition) contained 1050 kcal/L, 60 g/L fat, 50 g/L protein, 2.1 g/L calcium, 1.4 g/L phosphorous and 4400 IU/L (0.11 mg/L) cholecalciferol.

Table 1
Composition of diet fed to piglets for 15 d

Diet Composition	Unit/L
Ingredients	
Oil Blend:	
Soybean,[1] g	23
High oleic safflower,[2] g	23
Coconut,[3] g	14
Dry Mix:	
Skim milk powder,[4] g	110
Whey powder,[5]g	35
Vitamin[6] and Mineral[7] Mix:	
dl-α-tocophyeryl acetate, mg	5
Cholecalciferol, mg	0.11
All trans-retinol acetate, mg	1
Thiamine, mg	30
Riboflavin, mg	60
Niacin, mg	440
Pantothenic acid, mg	284
Pyridoxine, mg	36
Folacin, mg	20
Vitamin B-12, mg	0.4
D-Biotin, mg	2
CaCO3, g	1
Choline Chloride, g	42.4
MnSO4, mg	40
Ferrous Sulfate, mg	167

[1] Vita Health, Winnipeg, Manitoba
[2] Bestfoods Food Service, Division of Bestfoods, Toronto, Canada
[3] Harlan Teklad, Madison, WI
[4] Parmalat Canada Production and Distribution, Winnipeg Canada
[5] Lactose reduced whey powder (as Avaonlac 134). Glanbia Ingredients, Monroe, WI
[6] Harlan Teklad, Madison, WI, for all listed except all *trans*-retinol acetate from Sigma-Aldrich Canada, Oakville, Canada.
[7] Sigma-Aldrich Canada, Oakville, Canada

2.2. Measurements

2.2.1. Growth

Weight (kg) was measured at 9 AM in non-fed state from day 0 to day 15 of study.

Weight gain (g·kg^{-1}·d^{-1}) was calculated at end of study.

Weight gain:

$$\left(\begin{array}{c}\text{weight in g on day 15—weight in g on day 0 of study} \\ \text{weight on day 0 in kg + day 15 of study in kg/2}\end{array}\right) /15 \text{ days}$$

Length (cm) was determined by measuring from tip of snout to base of tail on day 15 of study.

2.3. Calcium absorption

Calcium absorption was determined using an intestinal ligated loop technique as described previously by Weiler et al. [21]. The intestinal ligated loop technique is designed to

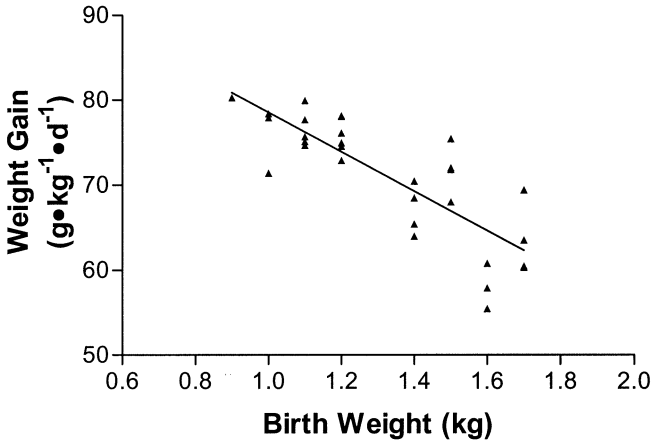

Fig. 1. Relationship between birth weight and subsequent weight gain in piglets over 15 days. r = -0.82, $P < 0.0001$, Pearson correlation, $n = 30$.

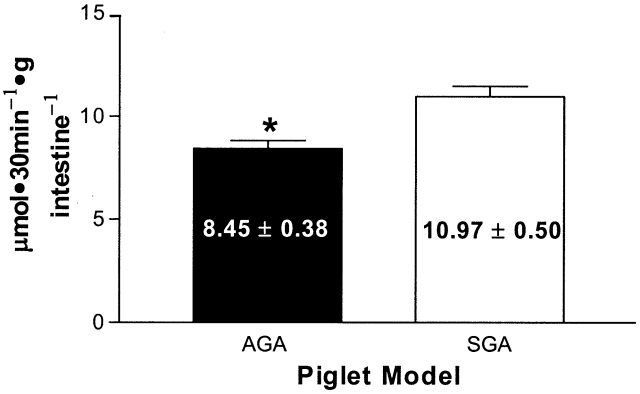

Fig. 2. Intestinal calcium absorption of AGA ($n = 15$) and SGA ($n = 15$) piglets measured by intestinal ligated loop technique after 15 days of formula feeding. * $P = 0.0004$, unpaired two-tailed *t*-test.

assess calcium absorption by testing the disappearance of a radiolabeled calcium isotope across the layers of the intestinal tract. This technique was conducted on the morning after the 15th day of study. The piglet was fasted for 12 hr and then anesthetized using sodium pentobarbital (30 mg/kg). A 5 to 10 cm section of duodenum distal to the ligament of Treitz was ligated at both ends using suture and the duodenal section was then filled with radioisotope buffer solution (pH of 7.4, mOsmol of 315) containing: ^{45}Ca (18 MBq/L; Amersham Ltd), Poly R-478 (100 mg/L; Sigma-Aldrich Ltd), mannitol (20 mmol/L; Fisher Scientific) and $CaCl_2$ (2 mmol/L; Fisher Scientific). Radioisotope buffer solution samples were taken from the ligated duodenal section every 5 min for a 30-min period. Samples were analyzed for ^{45}Ca by scintillation counting (Model LS 6000TA; Beckman Instruments Inc.). Poly R-478 was measured by UV spectrometry as described by Stahl et al. [22]. Calcium absorption was calculated according to the method of Ghishan et al. [23].

2.4. Bone mass

Bone mass was assessed at the end of the study by measuring bone mineral content (BMC) of whole body using dual energy x-ray absorptiometry (DXA; QDR 4500W series, Hologic Inc.). Whole body BMC was divided by body weight and length to account for size.

2.5. Statistical analyses

Differences among groups were detected by an unpaired two-tailed *t*-test. Relationships between variables were detected by Pearson Correlation analysis using GraphPad Prism Version 3.02 software. A *P*-value of less than 0.05 was accepted as significant. Data is expressed as mean ± standard error of the mean (SEM).

3. Results

By study design, the SGA piglets had a significantly lower birth weight - SGA had a mean birth weight value of 1.11 ± 0.03 kg compared to AGA 1.55 ± 0.03 ($P < 0.0001$). The SGA piglets had a significantly lower first day of study (5 days of age) weight, 1.41 ± 0.06 kg compared to AGA 1.88 ± 0.07 ($P < 0.0001$). However, following 15 days of study (21 days of age), there was no longer a significant difference in weight between the two groups, SGA 5.21 ± 0.20 kg compared to AGA 5.60 ± 0.21. Also, there was no significant difference in final length, SGA 53.37 ± 0.77 cm compared to AGA piglets 53.45 ± 0.70 cm. SGA piglets had a significantly higher rate of weight gain at 76.39 ± 0.65 compared to AGA 65.56 ± 1.505 $g \cdot kg^{-1} \cdot d^{-1}$ ($P < 0.0001$). A negative relationship between birth weight and subsequent weight gain over 15 days of study was found (r = -0.82, $P < 0.0001$) (Fig. 1).

As indicated using the intestinal ligated loop technique the SGA piglets had greater ($P = 0.0004$) calcium absorption than the AGA piglets (Fig. 2). A negative relationship

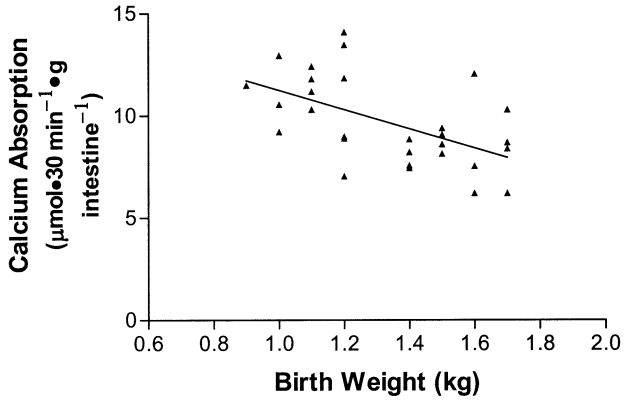

Fig. 3. Relationship between birth weight and calcium absorption in piglets following 15 days of formula feeding. r = -0.55, $P = 0.0016$, Pearson correlation, $n = 30$.

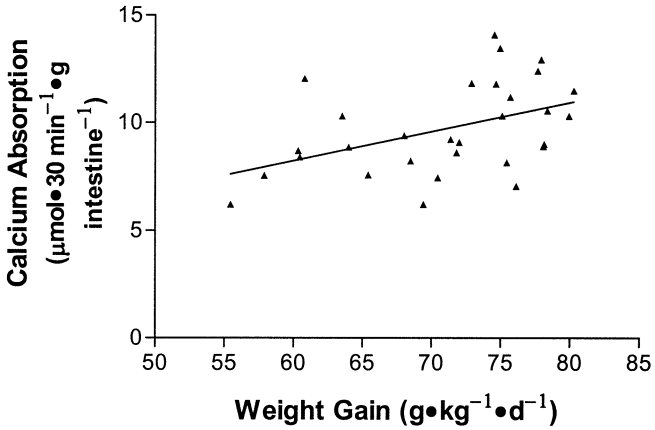

Fig. 4. Relationship between weight gain and calcium absorption in piglets following 15 days of formula feeding. r = 0.45, P = 0.0125, Pearson correlation, n = 30.

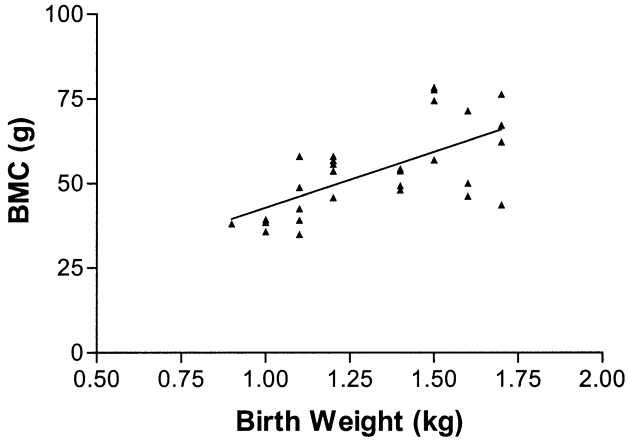

Fig. 5. Relationship between whole body BMC and birth weight in piglets following 15 days of formula feeding. r = 0.90, $P < 0.0001$, Pearson correlation, n = 30.

was also found between birth weight and calcium absorption (r = -0.55, P = 0.0016) (Fig. 3) and a positive relationship was found between weight gain and calcium absorption (r = 0.45, P = 0.0125) (Fig. 4).

AGA piglets had significantly higher whole body BMC than the SGA piglets (P = 0.0013) (Table 2). AGA piglets had significantly higher BMC following adjustment for size; BMC divided by whole body weight (P = 0.0003) and length (P = 0.0002) (Table 2). Piglet whole body BMC was positively correlated with birth weight (r = 0.64, P = 0.001) (Fig. 5). In addition, whole body BMC was negatively correlated with calcium absorption (r = -0.43, P = 0.0182) (Fig. 6). BMC was also negatively correlated with weight gain, however it did not reach significance (r = -0.28) (Fig. 7).

4. Discussion

By the end of the first three weeks of life, compensatory growth of SGA piglets yielded body size equivalent to piglets born AGA. The negative relationship between growth rate and birth weight combined with equal volumes of formula suggests greater nutrient utilization in the SGA piglets. This parallels observations in human infants. For example, Chessex et al. [24] studied very low birth weight SGA and AGA infants and observed a significant difference in weight gain between SGA (19.4 ± 0.9 g · kg^{-1} · d^{-1}) and AGA (16.8 ± 1.0 g · kg^{-1} · d^{-1}) infants fed formula. Picaud et al. [9] observed a tendency toward higher weight gain in very low birth weight SGA infants (20.7 ± 4.6 g · kg^{-1} · d^{-1}) compared to AGA infants (17.9 ± 3.2 g · kg^{-1} · d^{-1}) fed fortified mothers' milk but this difference was not significant. It has been suggested that the higher rate of weight gain found by Chessex et al. [24] and Picaud et al. [9] is related to elevated water retention in the SGA infants. It is unknown whether the SGA piglets in our study had higher water retention. However, at the end of our study there was no significant difference in length between the SGA and AGA piglets, suggesting that the weight gain was not solely due to water retention.

The growth rate of the piglets studied herein (65.56 ± 1.51 to 76.39 ± 0.65 g · kg^{-1} · d^{-1}) is much higher than that of an infant (16.8 ± 1.0 to 20.7 ± 4.6 g · kg^{-1} · d^{-1}) [9,24]. These piglets were full term SGA and AGA piglets in

Table 2
Bone mineral content of SGA versus AGA piglets

	SGA Piglet	AGA Piglets
BMC (g)	46.65 ± 2.26	60.75 ± 3.24
BMC/length (g/cm)	0.87 ± 0.04	1.13 ± 0.05
BMC/weight (g/kg)	8.96 ± 0.24	10.69 ± 0.32

Data are mean ± SEM, n = 15 per group. BMC: bone mineral content; SGA: small size for gestational age; AGA: appropriate size for gestational age.

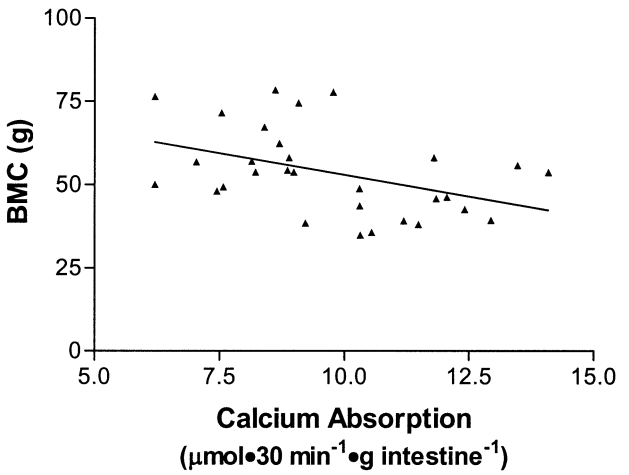

Fig. 6. Relationship between whole body BMC and calcium absorption in piglets following 15 days of formula feeding. r = -0.56, P = 00013, Pearson correlation, n = 30.

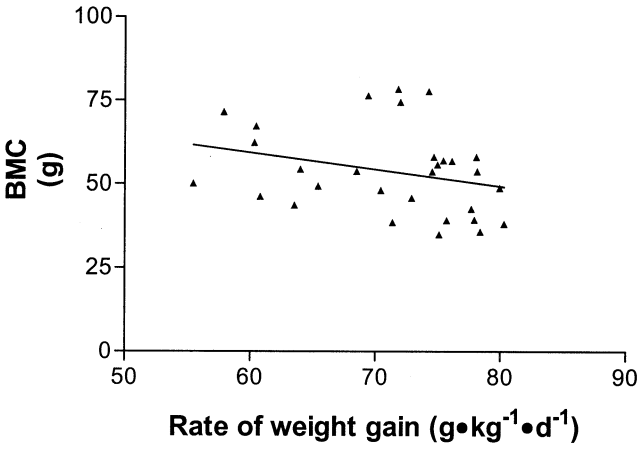

Fig. 7. Relationship between whole body BMC and weight gain in piglets following 15 days of formula feeding. r = -0.63, $P = 0.0002$, Pearson correlation, $n = 30$.

contrast to reports in human infants, who were born preterm and either SGA or AGA [11,25,26]. Minton et al. [4] found that during a 12-week postnatal period, growth rates of weight gain, length and head circumference in preterm and term SGA infants paralleled values attained by AGA infants. Thus, the SGA and AGA piglet are appropriate models to investigate nutritional interventions targeted at improving growth outcomes for the SGA human infant.

The increased growth rate in SGA piglets when compared to AGA piglets is accompanied by elevated proximal intestinal calcium transport. The advantage in studying SGA piglets is that isotope tracers in localized segments of intestine can be studied. In contrast, Picaud et al. [9] found no difference in mineral balance between SGA and AGA very low birth weight infants using net balance studies. However, they reported a "tendency" towards better calcium absorption ($P = 0.125$) and utilization ($P = 0.219$) in the SGA infants [9]. The researchers felt this may be related to better fat absorption [9]. Picaud et al. [9] also found significant positive correlation between fecal fat and fecal calcium contents. Picaud et al. [9] studied net absorption and utilization of calcium by determining calcium intake and the amount of calcium excreted in the urine and stool. In the piglets, calcium absorption was measured only in the proximinal intestine using isotopic tracers in the absence of fat and thus does not reflect whole intestinal transit or retention in the body.

At 21 days of age, SGA piglets had lower whole body BMC when compared to AGA piglets. Following adjustment for size, the SGA piglets still had significantly lower whole body BMC. In addition, whole body BMC was positively correlated with birth weight and negatively correlated with calcium absorption in both AGA and SGA piglets. Although the SGA piglets were not significantly smaller at end of study, had higher growth rates and increased proximal intestinal calcium absorption they had significantly lower whole body bone mass. This suggests that SGA piglets are able to catch up in size at a greater rate than in bone mass and that the limitation for mineralization is at the level of bone and not intestinal calcium absorption.

Active transport of calcium is developed in the proximal intestine of the young piglet [21]. The SGA piglets in this study appear to be able to up-regulate transport of calcium in support of accelerated growth, which may be sufficient to attain a BMC level comparable to AGA piglets. At 21 days of age, the SGA piglets might not have had enough time to attain a BMC level comparable to the AGA piglets. Lower BMC found in the SGA piglets supports data found in human infants. Decreased BMC has been found in term SGA infants when compared to term AGA infants at birth [3,4]. By adult age, infants born SGA and AGA have similar bone mass [26,27]. The age at which the SGA piglet and human infant catch up in bone mass is unknown.

A sub-optimal intrauterine environment associated with growth restriction has been postulated to lead to permanent metabolic programming [28]. Whether elevated calcium absorption continues in piglets or humans, recovering from growth restriction, is not clear. Calcium absorption has been found to be elevated in postmenopausal females who were born SGA [25]. The association between calcium absorption was independent of 25-hydroxyvitamin D, but not of 1,25-dihydroxyvitamin D [25]. The researchers felt their results might be explained by the significant inverse correlation between 1,25-dihydroxyvitamin D and birth weight [25]. The researchers suggested that a poor intrauterine environment leads to a permanent up-regulation or programming of adult intestinal calcium absorption [25]. Increased calcium absorption may be the result of the action of parathyroid hormone (PTH) on the hydroxylation of 25-hydroxyvitamin D. PTH stimulates the activity of the renal 1α-hydroxylase, which enhances the synthesis of 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D in the renal proximal tubule [29]. This leads to enhanced intestinal calcium absorption via stimulation of the active route. While PTH and vitamin D were not measured in the piglets, an inverse association between birth weight and intestinal calcium absorption was found in this study. Similarly, a positive relationship between growth rate and calcium absorption was observed in the piglets, suggesting that the higher the growth rate the higher the requirement for calcium.

In conclusion, our results suggest that the smaller the birth weight, the higher the calcium absorption and the faster the post-natal growth rate. Based on 1) the report of elevated calcium absorption in women born SGA and 2) our results in piglets where postnatal diets were controlled and calcium absorption elevated in SGA piglets, it appears that calcium absorption is programmed in utero. Whether greater absorption of dietary calcium is utilized for bone mineralization requires further investigation. While the rapid weight gain of the SGA piglets resulted in weight comparable to the AGA piglets at 21 days of life, further research is needed to determine whether SGA piglets

catch-up to AGA piglets in bone mass and the age at which this happens. It is important to establish the mechanism(s) behind the elevated calcium absorption by studying vitamin D and PTH levels and the metabolic response in bone.

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