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Bone metabolism compensates for the delayed growth in small for gestational age neonates

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Abbreviations: IGF-1, insulin-like growth factor 1; IGFBP3, Insulin-like growth factor binding protein 3; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor-kappaB; RANKL, receptor activator of nuclear factor-kappaB ligand; GA, gestational age; AGA, appropriate for the gestational age; SGA, small for the gestational age; LGA, large for the gestational age; GA_1, SGA versus AGA neonates; GA_2, LGA versus AGA neonates

The goal of the present study is to investigate the relationship between anthropometric and bone metabolism markers in a sample of neonates and their mothers. A sample of 20 SGA (small for the gestational age), AGA (appropriate for the gestational age) and LGA (large for the gestational age) term neonates and their 20 mothers was analyzed at birth and at exit. Elisa method was used to measure the OPG (Osteoprotegerin), RANK (Receptor activator of nuclear factor-kappaB), RANKL (Receptor activator of nuclear factor-kappaB Ligand), IGF-1 (Insulin-like growth factor 1), IGFBP3 (Insulin-like Growth Factor Binding Protein 3) and Leptin levels. Birth weight and length were positively correlated with RANKL, IGF-1 and IGFBP3 and negatively with the ratio OPG/RANKL. SGA neonates presented lower RANKL values and higher OPG/RANKL ratio while LGA neonates had higher RANK levels than AGA neonates. Positive association was shown between neonatal IGFBP3 and maternal IGF-1 values and between neonatal and maternal RANK values at birth and at exit. These results reveal a remarkable upregulation of OPG/RANKL ratio in SGA neonates, pointing out the role of bone turnover in compensating for the delayed neonatal growth.

Introduction

The skeleton is a metabolically active organ that undergoes constant remodeling throughout life. Bone, which is the main component of the skeleton, contains osteoclasts, osteoblasts, chondrocytes, adipocytes, hematopoietic and immune cells.[1] The identification of the osteoclastogenesis inducer, the receptor activator of nuclear factor-kappaB ligand (RANKL), its cognate receptor RANK, and its decoy receptor osteoprotegerin (OPG), has contributed to the great advance in the understanding of the molecular mechanisms involved in the normal physiology of the skeleton.[2] Moreover, the cytokine-like hormone Leptin, which is secreted by adipocytes, is an important candidate molecule linking changes in body composition with bone formation and bone resorption.[3]

The growth of skeleton starts in the first fetal weeks and is completed at the end of teenage. Genetic, environmental and endocrine factors influence the extent of growth. Insulin-like growth factor (IGF-1) is one of the most important endocrine factors that promote the mitosis of differentiated chondrocytes both in fetal period and in childhood. Insufficient secretion or action of IGF-1 is accompanied with reduced growth levels. During fetal period, the correspondent stimulus has not been clarified yet. In serum, 80% of IGF-1 is linked to the IGF binding protein 3 (IGFBP3), avoiding the quick renal clearance.[4]

Neonates are divided in three categories according to quartiles (A) AGA neonates who have appropriate birth weight or/and height for their gestational age, (B) SGA neonates who have small size for their gestational age and (C) LGA neonates who have large size for their gestational age. SGA neonates face increased danger of death and morbidity in the first period of life. Furthermore, SGA growth may be related to serious metabolic abnormalities that are presented in the adult life, such as metabolic syndrome and osteoporosis. Finally, SGA children often present psychosocial disadvantages and behavioral problems especially if cognitive impairment coexists.[5]

There is limited data sofar that associates neonatal anthropometric and biochemical characteristics within neonates who differ in terms of gestational age as well as in correspondance with maternal and fetal bone turnover markers. Therefore, the objective of this study is to investigate the possible relationship between neonatal anthropometric characteristics (birth weight and birth height) and highly interesting hormones and bone turnover and growth markers (Leptin, OPG, RANKL, RANK, IGF-1, IGFBP3) in a sample of new born neonates and their mothers taking into account the size for the gestational age of the neonates (AGA, SGA, LGA).

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Table 1. Maternal and neonatal general characteristics

Descriptive characteristics	SGA (N = 7)	AGA (N = 7)	LGA (N = 6)
First birth	71%	29%	33%
Age of mothers (y)	27 ± 4.6	25 ± 6	26 ± 5
Duration of pregnancy (w)	40 ± 0.45	39 ± 1.45	39 ± 0.89
Boys	71%	57%	50%
Neonatal birth weight (g)	2466 ± 157	3364 ± 318	4205 ± 103
Neonatal birth height (cm)	45 ± 1.2	50 ± 1.4	53 ± 0.98

Results

In **Tables 1 and 2** are presented basic descriptive characteristics of study participants. Data are expressed as relative frequencies for the categorical variables. Data are expressed as mean ± standard deviation; median values for the continuous variables.

Unadjusted data analysis showed that birth weight of all the neonates was inversely correlated with OPG/RANKL ratio (rho = -0.562, p = 0.010) and positively correlated with serum RANKL (rho = 0.611, p = 0.004), IGF-1 (rho = 0.573, p = 0.008) and IGFBP3 values (rho = 0.485, p = 0.030) at birth, while no association was observed with OPG (p = 0.112), RANK (p = 0.334) or Leptin (p = 0.440) levels. Respectively, the birth height of all neonates was positively correlated with serum RANKL (rho = 0.565, p = 0.010) and IGF-1 concentrations at birth (rho = 0.520, p = 0.019) while it was negatively associated with OPG/RANKL ratio (rho = -0.523, p = 0.018) (**Table 3**). According to the Kruskal-Wallis test, the different size for the gestational age influenced RANK (median = 0.114, p = 0.047), RANKL (median = 0.09, p = 0.049), the OPG/RANKL ratio (median = 47, p = 0.058) and marginally IGF-1 (median = 39.41, p = 0.062), while no statistically strong change was found in OPG (median = 3.76, p = 0.165) and IGFBP3 levels (median = 1630, p = 0.105) of the neonates at birth (**Table 4**). These correlations were also confirmed at discharge.

As residual confounding may exist, data analysis was further adjusted for gestational age and the different size for the gestational age, parameter that was found to influence the levels of RANK, RANKL, and OPG/RANKL ratio of the neonates. For this analysis two new variables were created. The first variable examined SGA neonates comparing to AGA neonates (GA_1) and the second one examined LGA neonates comparing to AGA neonates (GA_2). Therefore, multiple linear regression models were applied to test the association between RANK, RANKL, OPG/RANKL ratio (dependent outcomes) and GA_1 (SGA/AGA) and GA_2 (LGA/AGA) (independent covariates), after controlling for several potential confounders. RANK, RANKL and OPG/RANKL ratio were log-transformed because of their skewed distribution. The multi-adjusted analysis showed that SGA neonates presented lower RANKL values (Beta = -0.520, p = 0.036) and higher OPG/RANKL ratio (Beta = 0.498, p = 0.044) comparing to AGA neonates, while LGA neonates had higher RANK levels than AGA neonates (Beta = 0.593, p = 0.022) (**Table 5**).

The multiple linear regression models evaluated the association between log(RANK), log(RANKL) and log(OPG/RANKL) (dependent variables) and GA_1 (SGA/AGA), GA_2 (LGA/AGA) (independent variables) after controlling for potential confounders. The dependent variables were log-transformed because of lack of normality. Variables that were also entered in the models but showed no effect on the investigated outcomes were the number of birth (first child, second, etc) and the maternal habits (smoking, alcohol and coffee consumption).

Finally, when taking into account the mothers biochemical markers, it was found that maternal IGFBP3 and IGF-1 correlate positively at birth (rho = 0.510, p = 0.022) and at discharge (rho = 0.603, p = 0.005). Additionally, maternal RANKL, RANK and OPG/RANKL ratio at birth, correlate positively with maternal RANKL (rho = 0.599, p = 0.005), RANK (rho = 0.544, p = 0.013) and OPG/RANKL ratio (rho = 0.617, p = 0.008) at discharge, respectively. As far as the comparison of biochemical markers between neonates and mothers is concerned, a positive correlation was shown between neonatal IGFBP3 and maternal IGF-1 values at birth (rho = 0.466, p = 0.038) and at discharge (rho = 0.558, p = 0.011) as well as between neonatal and maternal RANK values at birth (rho = 0.464, p = 0.039) and at discharge (rho = 0.732, p < 0.001).

Discussion

The purpose of this study was to investigate the possible relationship between neonatal anthropometric characteristics (birth weight and birth height) and hormones, bone turnover and growth markers (Leptin, OPG, RANK, RANKL, IGF-1, IGFBP3) in a sample of new born neonates and their mothers, taking into account the size for the gestational age of the neonates (SGA, AGA, LGA).

The data analysis showed that birth weight and birth height of neonates were positively correlated with serum IGF-1, IGFBP3 and RANKL values and inversely correlated with OPG/RANKL ratio while no association was observed with OPG, RANK and Leptin levels. The positive correlation between birth weight and IGF-1 and IGFBP3 was also demonstrated in previous studies and is in line with the well described anabolic role of IGF-1.[6-8] Other studies in neonates, who also differed in terms of gestational age, showed that SGA neonates had lower, whereas LGA neonates had higher serum levels of IGF-1 and IGFBP3 than AGA neonates.[9] Moreover, a higher protein content of IGF-1 was observed in SGA compared with AGA and LGA placentas and lower contents in LGA compared with AGA placentas, suggesting that the placental IGF-1 expression may be influencing human fetal gowth.[10] The growth hormone/insulin-like growth factor 1 axis is considered to be a major determinant of bone mass acquisition and a key regulator of bone cell activity as well as crucial for fetal growth. While the effects of IGF-1 on osteoblastic development and function are well documented, it has been also proposed that when IGF-1 stimulates bone formation, it enhances bone turnover, thereby releasing molecules from activated marrow stromal cells and osteoblasts that can also lead to enhanced osteoclastogenesis and mature osteoclast activity. Several groups have shown that IGF-1 can enhance osteoclast recruitment and differentiation either directly through the IGF-1 receptor or indirectly via

Table 2. Maternal and neonatal characteristics at birth and at discharge (on postnatal day 4)

Descriptive characteristics	SGA (N = 7)		AGA (N = 7)		LGA (N = 6)	
Mothers (n = 20)	**At birth**	**At discharge**	**At birth**	**At discharge**	**At birth**	**At discharge**
OPG (pmol/l)	6.5 ± 2.9	4.2 ± 0.63	4.5 ± 1.7	4.3 ± 0.98	5 ± 2.6	3.9 ± 0.34
RANKL (pmol/l)	0.16 ± 0.20	0.05 ± 0.04	0.17 ± 0.16	0.14 ± 0.15	0.28 ± 0.38	0.75 ± 1.6
OPG/RANKL	775 ± 1760	232 ± 277	55 ± 66	67 ± 51	40 ± 41	37 ± 31
RANK (pg/mL)	0.11 ± 0.016	0.12 ± 0.02	0.11 ± 0.024	0.11 ± 0.016	0.15 ± 0.06	0.13 ± 0.036
LEPTIN (ng/mL)	40 ± 52	17 ± 13	77 ± 81	39 ± 35	45 ± 32	28 ± 20
IGF-1 (ng/mL)	286 ± 76	89 ± 56	373 ± 160	285 ± 87	424 ± 273	119 ± 79
IGFBP3 (ng/mL)	5614 ± 1838	2653 ± 798	5989 ± 1511	3471 ± 1223	6205 ± 1633	2987 ± 633
Neonates (n = 20)	**At birth**	**At discharge**	**At birth**	**At discharge**	**At birth**	**At discharge**
OPG (pmol/l)	3.9 ± 0.20	4.18 ± 0.98	4.1 ± 1.4	4.1 ± 0.46	3.7 ± 0.16	3.7 ± 0.35
RANKL (pmol/l)	0.06 ± 0.03	0.086 ± 0.04	0.14 ± 0.11	0.09 ± 0.04	0.16 ± 0.12	0.11 ± 0.04
OPG/RANKL	100 ± 94	66 ± 62	42 ± 23	57.14 ± 28.5	32 ± 16	40 ± 18
RANK (pg/mL)	0.12 ± 0.025	0.11 ± 0.008	0.10 ± 0.010	0.11 ± 0.016	0.15 ± 0.056	0.13 ± 0.03
LEPTIN (ng/mL)	10 ± 4.7	6.2 ± 1.1	18 ± 11	9.23 ± 2.29	19 ± 21	6 ± 2
IGF-1 (ng/mL)	23 ± 18	42 ± 45	50 ± 55	43 ± 44	53 ± 13	59 ± 33
IGFBP3 (ng/mL)	1420 ± 238	1412 ± 861	1706 ± 572	1237 ± 455	2200 ± 544	1590 ± 496

the RANKL expression.[11,12] These data indicate that IGF-1 may act as a coupling factor in bone remodelling by activating both bone formation and bone resorption.[13]

Additionally, it is worth further investigating, the positive association between birth weight and height of neonates with serum RANKL and the negative association with the OPG/RANKL ratio, observed in this study. In this context, the different size for the gestational age appeared to be an important parameter of neonatal bone metabolism as it affected significantly the neonatal levels of RANK, RANKL and the ratio OPG/RANKL. More specifically, SGA neonates had lower RANKL values and higher OPG/RANKL ratio comparing to AGA neonates, while LGA neonates had higher RANK levels than AGA neonates. These associations were independent of the kind and the number of birth and the maternal habits (smoking, alcohol and coffee consumption) which were considered as potential confounders in our analyses. It is noteworthy, that SGA mothers showed lower RANKL at discharge, meaning that the high OPG/RANKL ratio found in SGA neonates could be due, partly, to mothers' lower RANKL. The mother together with the placenta and the embryo should be regarded as one entity, with the physiological parameters of one, influencing the other. Overall, these findings may be explained by the fact that SGA neonates need to catch up with retarded growth and bone formation, that is why RANKL is reduced whereas the OPG/RANKL ratio is elevated, indicating the need of bone formation to predominate over bone resorption. The discovery of the RANKL/RANK/OPG system has been one of the most important advances in bone biology in the last decade. This signaling system is essential for skeletal homeostasis, and disruption of it leads to inhibition of bone resorption in vitro and in animal models of most bone diseases characterized by increased resorption. Furthermore, RANKL/RANK signaling plays important roles in tissues other than bone.[14] Although many studies describe the role of the OPG/RANKL/RANK system in adults, very little is known about these relatively novel bone metabolism markers in neonates and even less about the possible relationship between these markers in neonates and mothers.

Table 3. Unadjusted correlations between birth weight, birth height and biochemical factors of neonates at birth

N = 20 neonates	Birth weight (g)		Birth height (cm)	
	Rho	p	Rho	p
OPG (pmol/l)	-0.366	0.112	-0.413	0.070
RANKL (pmol/l)	**0.611**	**0.004**	**0.565**	**0.010**
OPG/RANKL	**-0.562**	**0.010**	**-0.523**	**0.018**
RANK (pg/mL)	0.228	0.334	0.191	0.419
LEPTIN (ng/mL)	0.183	0.440	0.074	0.757
IGF1 (ng/ml)	**0.573**	**0.008**	**0.520**	**0.019**
IGFBP3 (ng/ml)	**0.485**	**0.030**	0.411	0.072

With regard to the mothers' biochemical markers, it was shown that maternal IGFBP3 and IGF-1 correlate positively at birth and at discharge. Furthermore, neonatal IGFBP3 was significantly and positively associated with maternal IGF-1 values at birth and at discharge, while neonatal RANK was significantly and positively associated with maternal RANK values at birth and at discharge. These results indicate a common activity of neonatal and maternal bone metabolism and it is very important, as little is known so far regarding the physiological mechanisms underlying this relationship. Nevertheless, maternal and perinatal factors should be taken into account to optimize our understanding of the mechanisms by which endocrinal factors regulate fetal growth.[7]

In our study, the OPG levels did not vary neither in neonates nor in mothers serum. Uemura H et al.[15] showed that maternal

Table 4. Change in the biochemical markers of all the neonates according to their different size for the gestational age at birth

Neonates N = 20	median	25%	75%	p
OPG (pmol/l)	3.8	3.6	3.9	0.165
RANKL (pmol/l)	0.09	0.07	0.14	**0.049**
OPG/RANKL	47	27	60	**0.058**
RANK (pg/mL)	0.114	0.100	0.130	**0.047**
LEPTIN (ng/mL)	9.5	6.9	19	0.418
IGF-1 (ng/mL)	39	14	56.7	0.062
IGFBP3 (ng/mL)	1630	1245	2292	0.105

Table 5. Multiple linear regression models

Neonates N = 20	log (RANK)		log (RANKL)		log (OPG/RANKL)	
	Beta	p	Beta	p	Beta	p
GA_1 (SGA compared with AGA Neonates)	0.286	0.243	**-0.520**	**0.036**	**0.498**	**0.044**
GA_2 (LGA compared with AGA Neonates)	**0.593**	**0.022**	0.078	0.736	-0.107	0.646

OPG levels increased during pregnancy, reached a peak before birth and decreased quickly after birth, an observation that was confirmed by other reseachers as well.[16] Despite the fact that this increase of OPG in pregnancy could be accompanied by a respective decrease in bone resorption in mothers, in fact the reverse was observed by these researchers. This is why the physiological meaning of increased OPG levels during pregnancy is considered to be unknown.[17] However, some studies showed no relationship between maternal bone metabolism and neonatal bone turnover at the last stage of pregnancy.[18] On the other hand, other studies have shown the positive effects of folic acid supplementation, during pregnancy, on both maternal and fetal bone turnover markers (OPG, RANKL, osteocalcin).[19] It was also shown that different maternal factors may affect the birth weight and height of neonates such as the maternal weight before pregnancy, the extent of increase of maternal weight during pregnancy, the maternal height.[20] Additionally, it was reported that teenager pregnant women that were underweight or with low weight gain were at greater risk of SGA birth.[21]

Finally, leptin levels were also investigated in the present study as the level of circulating leptin is directly proportional to the total amount of fat in the body.[22] Although it initially seemed from the descriptive characteristics that leptin correlates with the gestational status of the neonates, there was found no statistically significant association between leptin and other anthropometric, growth or bone parameters.

This study exhibits both strengths and limitations. Among the strengths is that to the best of our knowledge this is the first study in neonates, who differ in terms of gestational age, combining analysis of the neonatal and maternal OPG, RANK, RANKL, IGF-1, IGFBP3 and leptin levels aiming at a more comprehensive approach of the neonate perinatal bone metabolism. Specifically, the downregulation of RANKL and the parallel upregulation of OPG/RANKL ratio in SGA neonates found in this study is very important, as it highlights a, first described, compensatory physiological mechanism which is activated in order to overcome the reduced growth in these neonates. With regard to the limits of this study, it should be pointed out that our sample number is not big enough to make statements in the general population. However, it is quite difficult to collect a large number of neonatal and maternal samples which would equally comprise neonates from the three gestational age categories. The future directions of research would be, apart from the confirmation of the findings in a larger prospective study, the follow-up of the neonates at a later time-point, in order to evaluate whether this mechanism of prevalence of bone formation to bone resorption is still active during the infant period. In this context, it would be interesting to further investigate the calcium absorption and excretion rates, the development or not of osteopenia, as well as the overall bone mineralization process.

Materials and Methods

Study's sample. The working sample of this project consisted of 20 mothers (27 ± 4 y, range 19–34, all Caucasian) and their 20 neonates. The maternal and neonatal blood samples were collected on fasting state (A) between the first 2–4 h after birth and (B) before discharge, on postnatal day 4, in the General Hospital of Nikaia, Athens. The collection of blood samples was performed from September 2008 to December 2009, in order to ensure that not only AGA (> 10th subtiles and < 90), but SGA (< 10th subtiles, all being IUGR) and particularly LGA (> 90th subtiles) neonates would be also included in the study. Among 20 neonates, 8 neonates were girls and 12 were boys. Their birth weight ranged from 2,160 to 4,350 g while their birth height ranged between 44 and 55 cm. Among these term neonates (the gestational age varied from 38 to 40 weeks), the first seven AGA neonates, the first seven SGA neonates and the first six LGA neonates, and their mothers, were randomly chosen to participate in this study. Other information regarding the mothers, such as the number of birth (first child, second, etc) and the maternal habits (smoking, alcohol and coffee consumption) were also recorded. Mothers with gestational diabetes were excluded from the study. All mothers who participated in the present study were informed of the purposes of the study and the protocol that would take place and they gave written consent. The study was approved by the Medical Research Ethics Committee of the Hospital and was performed in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Biochemical characteristics. The levels of OPG, RANKL, RANK, IGF-1, IGFBP3 and Leptin were determined in the 80 neonatal and maternal blood samples (20 neonates and 20 mothers each measured in two time points). The biochemical evaluation was performed in the same laboratory that followed the criteria of the World Health Organization Reference Laboratories. ELISA method was used for the quantitative determination, in duplicate in serum samples of the

participants, of human OPG and human ampli-sRANKL (BI-20402 and BI-20452, Biomedica Gruppe), IGF-1, IGFBP3 and RANK (GD100, GDb300 and DY683, R&D Systems Inc.), as well as for the determination of human Leptin concentration (KAC2281, Invitrogen Corporation).

Statistical analysis. Continuous variables are presented as mean values ± standard deviation. Categorical variables are presented as frequencies. Normality was tested using the Kolmogorov-Smirnov criterion. As the continuous variables did not present normal distribution, correlations between OPG, RANKL, RANK, OPG/RANKL ratio, IGF-1, IGFBP3, Leptin, and the other continuous variables (i.e., birth weight, birth height) were tested using the Spearman's rho correlation coefficient. For the same reason, correlations between continuous and categorical variables were tested using the Kruskal-Wallis test. Multiple linear regression models were applied to test the association between RANKL, RANK, OPG/RANKL ratio (dependent outcomes), and GA_1 (SGA/AGA), GA_2 (LGA/AGA) (independent covariates), after controlling for several potential confounders. RANK, RANKL and OPG/RANKL ratio were log-transformed because of their skewed distribution. All reported *P*-values are based on two-sided tests and compared with a significance level of 5%. SPSS 16 (SPSS Inc.) software was used for all the statistical calculations.

Conclusion

In conclusion, the association between neonatal and maternal bone and growth markers and anthropometric characteristics is of increasing scientific interest. The size for the gestational age seems to affect directly these relationships. These results reveal a remarkable upregulation of OPG/RANKL ratio in SGA neonates, pointing out the prevalence of bone formation to bone resorption in order to compensate for the delayed neonatal growth. It is a very remarkable finding, demonstrating that body physiology activates a very important molecular pathway in order to protect bones from the unfavorable consequences of the delayed growth. The findings of the present study may contribute to the better understanding of maternal and neonatal bone metabolism which may lead to the development of new preventive methods against limited intrauterine growth.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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