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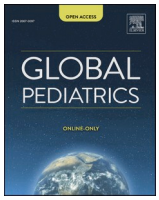

Perinatal oxidative stress and bone development in the first year of life: A preliminary study using REMS

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ABSTRACT

Background: Oxidative stress has been implicated in impairing tissue development, but its impact on early postnatal skeletal growth in humans remains poorly understood. This study investigates the relationship between perinatal redox status and bone development during infancy, using Radiofrequency Echographic Multi Spectrometry (REMS), a non-invasive, radiation-free technology for bone quality assessment.

Methods: A longitudinal observational study on a cohort of healthy, full-term neonates ($n = 65$, 29 females and 36 males) was conducted. Total antioxidant capacity (TAC) and markers of protein and DNA oxidation (advanced oxidation protein products (AOPP); 8-hydroxy-2′-deoxyguanosine (8OH-dG)) were measured in arterial cord blood at birth. Auxological parameters were collected at birth and during follow-up visits at 1, 3, 6, and 12 months. Bone quality was assessed using REMS at 3, 6, and 12 months, and results were expressed as age-adjusted Z-scores.

Results: Cord blood TAC levels showed a significant positive correlation with birth weight ($r = 0.51$, $p < 0001$), length ($r = 0.40$, $p = 0.0013$), and birth head circumference ($r = 0,42$, $p = 0,0017$). Statistical positive correlations were also found between cord blood TAC and length and weight a 1 month of age ($r = 0.51$, $p < 0.001$; $r = 0.36$, $p = 0.0067$). In contrast, higher levels of oxidative damage were inversely associated with REMS-derived Z-scores at both 6 and 12 months of life (8OH-dG vs REMS-derived Z-scores at 6 months (r=-0.23, $p = 0.02$), and AOPP vs REMS-derived Z-scores at 12 months (r=-0.33 $p = 0.022$; r=-0.64, $p < 0.001$, respectively). REMS Z-scores also showed strong internal consistency across timepoints (3 vs 6 months, $r = 0.53$, $p < 0.001$,; 6 vs 12 months, $r = 0.29$, $p = 0.046$). A significant correlation was observed between REMS Z-score and head circumference at 3 months ($r = 0.48$, $p < 0.001$).

Conclusions: Our findings suggest that perinatal oxidative balance plays a critical role in early longitudinal growth. REMS appears to be a reliable tool for tracking bone quality in infancy, with potential for future applications in pediatric bone health monitoring. Although limited to healthy infants born from physiological pregnancies, this study provides foundational data in a largely unexplored area and supports the hypothesis that fetal redox status may influence lifelong skeletal outcomes.

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1. Introduction

Enhancing bone mineral density throughout skeletal development is a key strategy for preventing osteopenia and reducing the risk of later osteoporosis.[1] The attainment of optimal peak bone mass by skeletal maturity is a critical determinant of long-term skeletal health, and various factors influencing this process can modulate an individual's lifetime risk of osteoporosis. Bone development begins in utero, with maternal health and nutritional status playing fundamental roles in shaping fetal skeletal mass and mineralization.[2] Emerging evidence indicates that oxidative stress (OS) during pregnancy can negatively affect the acquisition of peak bone mass. In animal models, melatonin—a potent antioxidant—has been shown to counteract bone loss, restore trabecular microarchitecture, and enhance bone formation.[3] These findings underscore the potential impact of free radicals in the perinatal period on skeletal development. A biochemical association between OS and reduced bone mineral density is further supported by experimental and clinical studies.[4] For instance, intra-embryonic injection of AAPH, an alkoxyl radical generator, into chicken egg albumen significantly reduces bone length, suggesting a direct detrimental effect of OS on bone growth.[5] Oxidative stress appears to primarily affect proliferative zones in developing bone. Despite these insights, the extent to which OS influences skeletal development during early infancy remains largely unknown, particularly regarding its impact on bone status within the first year of life. Radiofrequency Echographic Multi-Spectrometry (REMS) is an innovative, non-ionizing imaging technique shown to be effective in assessing bone mineral density in clinical practice, with advantages in safety and accuracy compared to traditional methods.[6] This study represents a preliminary investigation within the previously published REMS-Bone protocol in pediatric population.[7] The aim here is to explore the relationship between OS biomarkers and REMS-derived bone Z-scores in infants, as well as to examine their association with auxological parameters during the first year of life

2. Methods

This analysis is a part of a multicenter, longitudinal, prospective research project titled "Radiofrequency Echographic Multi-Spectrometry for Early Bone Health: The REMS-Bone Study Protocol" (Trial acronym: REMS-Bone) .[7] The study was approved by the local Ethics Committee (Protocol No 15,298). Specifically trained researchers obtained prospective informed consent from all participants. Written informed consent was signed by both parents. We prospectively enrolled 65 consecutively infants born at the University Hospital of Parma, starting in June 2024. Table 1 summarizes the perinatal and clinical characteristics of the study population. Each participant was followed for the first year of life through clinical and instrumental evaluations conducted at predefined time points: 48 h after birth, and at 1, 3, 6, and 12 months of age. Follow-up was completed in June 2025. Inclusion Criteria were: full-term newborns from low-risk pregnancies, absence of current or previous maternal conditions that could potentially interfere with bone metabolism (kidney or liver diseases), absence of maternal motor disabilities, no previous history of bone fractures or recent traumatic fractures (in the mother), absence of a diagnosis of osteopenia or osteoporosis according to the criteria of the Italian Society for Osteoporosis, Mineral Metabolism, and Skeletal Diseases (SIOMMMS). Newborns hospitalized from birth for specific conditions, newborns with metabolic disorders, newborns with genetic syndromes were excluded. In all enrolled patients, biological samples have been collected in arterial cord blood. Serum samples have been analyzed for biomarkers of oxidative stress:

2.1. Data acquisition procedure

At birth and at 1, 3, 6, and 12 months of age, infant length was measured using a horizontal Harpenden stadiometer, and weight was assessed with an electronic scale. Head circumference was measured using a non-stretchable measuring tape positioned above the supraorbital ridges and ears, encircling the occipital prominence.

2.1.1. Oxidative stress data

In cord serum, the following biochemical mediators involved in OS were measured: total antioxidant capacity (TAC), advanced oxidation protein products (AOPP), and 8-hydroxy-2′-deoxyguanosine (8OH-dG). In detail, TAC was evaluated by a colorimetric assay kit from Abcam (ab65329) according to the Manufacturer's instructions. Color development was monitored at 570 nm by a MultiSkan microplate reader from ThermoScientific, and TAC amount in the sample well was calculated from the Trolox standard curve. AOPP levels were assessed by a colorimetric assay kit from Abcam (ab242295). Color development was monitored at 340 nm, and sample AOPP content was calculated by referring to the chloramine standard curve. 8-OHdG quantification was performed by a competitive ELISA kit from Abcam (ab285254). Colour development was measured at 450 nm, and a standard curve (range

Table 1
Perinatal and clinical characteristics of the study population.

	Birth	1 month	3 months	6 months	12 months
Total number	65	60	55	53	49
Gender	Female 29				
Delivery mode	Male 36				
Gestational age (weeks)	Spontaneous 47				
Apgar 1	Operative. 16				
Apgar 5	C-section 7				
	39.74 (1.02)				
	8.63 (0.76)				
	9.55 (0.71)				
Weight (gr)	3360.77 (509.72)	4077.83 (561.01)	5904.00 (832.39)	7790.43 (1083.83)	10,215.31 (1252.36)
Cranial circumference (cm)	34.82 (1.62)	37.37 (1.46)	41.09 (1.55)	43.84 (1.65)	47.70 (4.46)
Length (cm)	51.14 (2.36)	54.67 (1.85)	62.01 (2.97)	68.94 (2.68)	75.45 (4.78)
Feeding					
Breast milk		$N = 31$	$N = 30$	$N = 10$	$N = 49$
Formula milk		$N = 12$	$N = 17$	$N = 8$	
Mixed		$N = 17$	$N = 8$	$N = 1$	
Weaning				$N = 34$	
TAC (mM)	73.18 (6.49)				
AOPP (μM)	198.21 (116.67)				
8OH-dG (ng/ml)	57.84 (13.15)				

Values are presented as mean ± standard deviation (SD).
Abbreviations: TAC: total antioxidant capacity; AOPP: advanced oxidation protein products; 8OH-dG: 8-hydroxy-2′-deoxyguanosine;.

1.56–100 ng/mL) was generated using a four-parameter logistic (4-PL) curve fit. The sensitivity of the assay was <0.94 ng/mL.

2.1.2. REMS Scans

REMS scans were conducted at femoral sites using a dedicated ultrasound device (EchoStation, Echolight Spa, Lecce, Italy) equipped with a 40 mm linear transducer operating at a nominal frequency of 9 MHz, following the manufacturer's guidelines. The device was provided by the manufacturer in a research-configured mode, enabling manual identification of the diaphyseal regions of interest (ROIs) for REMS analysis. Data acquisition and analysis is schematically illustrated in Fig. 1. The probe was positioned on the infant's hip to visualize the target bone interface. The operator adjusted the scan depth and transducer focus in order to have the target bone profile as much as possible in the center of the image and immediately below the focus level. After the acquisition, B-mode frames were displayed for each infant and the ROIs were identified through a semi-automatic procedure: for each considered femur profile, 4 red dots were manually placed on the image, in order to identify proximal epiphysis, metaphysis and diaphysis; then, the relevant portions of the ultrasound radiofrequency raw signals belonging to each of the three mentioned regions were automatically selected by the software and used for subsequent REMS analysis.

2.1.2.1. Configuration for data processing with REMS device. Since the REMS algorithm has been originally developed and validated for the adult population, its analytical framework and reference models are optimized to interpret bone tissue characteristics typical of adult subjects. In this study, the device was configured to operate using fixed adult values: biological sex set to female, age fixed at 50 years, body weight at 50 kg, and height at 155 cm. This standardized configuration ensured that the differences in the resulting bone mineral density (BMD) measurements are exclusively influenced by the raw ultrasound data acquired from the newborn femurs. The underlying assumption is that, although the obtained BMD values will not be significant (since they were obtained through the employment of a REMS reference models specifically developed for adult subjects), they are able to relatively rank the newborns according to their femoral bone density and therefore they can gain significance if expressed in terms of a corresponding Z-score

2.2. Statistical analysis

Descriptive statistics were used to summarize the sample characteristics, reporting means and standard deviations for continuous variables, and absolute and relative frequencies (percentages) for categorical variables. Correlation analyses were conducted to explore the relationship between oxidative stress profiles and clinical parameters, as well as to assess the feasibility of REMS-derived z-scores in evaluating skeletal development during the first year of life. Linear regression analyses based on Pearson's correlation were applied. A p-value < 0.05 was considered statistically significant. All statistical analyses were carried out using R (version 4.3.1).

3. Results

The study included 65 full-term newborns (mean gestational age 39.7 ± 1.0 weeks; mean birth weight 3360.77 ± 509.72 g). Table 1 reports the clinical characteristics of the study population and the oxidative stress markers measured in the arterial cord blood. Significant correlations were observed between the parameters of interest (with corresponding R and p values reported; Table 2).

Specifically, TAC in cord blood showed a significant positive correlation with the birth weight ($r = 0.51$, $p < 0.001$; Fig. 2a), length ($r = 0.40$, $p = 0.0013$; Fig. 2b) and head circumference ($r = 0.42$, $p = 0.0017$; Fig. 2c). A statistical positive correlation was also found between the cord blood TAC and the weight at 1 month of age ($r = 0.36$, $p = 0.0067$; Fig. 3a) and the length at 1 month of age ($r = 0.51$, $p < 0.001$; Fig. 3b). In contrast, higher levels of oxidative damage markers, 8OH-dG and AOPP, were inversely associated with REMS-derived Z-scores at both 6 and 12 months ($r = -0.33$ $p = 0.022$, Fig. 4a; $r = -0.64$, $p < 0.001$, Fig. 4b, respectively). REMS Z-scores also showed strong internal consistency across time-points (3 vs 6 months, $r = 0.53$, $p < 0.001$, Fig. 5a; 6 vs 12 months, $r = 0.29$, $p = 0.046$, Fig. 5b). A significant correlation was also observed between REMS Z-score and cranial circumference at 3 months of age ($r = 0.48$, $p < 0.001$, Fig. 6).

4. Discussion

Our study investigates the relationship between oxidative stress and bone growth in the neonatal period. One particularly interesting finding is the positive correlation between total antioxidant capacity measured in arterial cord blood and both birth length and weight. This observation aligns with existing literature, notably the study by Niu J. et al. ,[5] which demonstrated that the injection of free radicals into animal embryos resulted in offspring with shorter limb lengths. Importantly, in our cohort, the positive correlation between neonatal TAC and auxological parameters persisted at one month of age. Given that umbilical artery reflects intrauterine life, this finding further underscores the critical role of maternal nutritional status—not only in overall fetal and neonatal health, but specifically in postnatal bone growth. The data suggest that a well-supported maternal antioxidant profile may have direct

Table 2
Significant correlations between the parameters of interest (*R* and *P* values reported).

		Pearson *R*	*p*-value
Birth weight (g)	TAC (mM)	0.51	<0.001
Birth length (cm)	TAC (mM)	0.40	0.0013
Birth circumference (cm)	TAC (mM)	0.42	<0.001
1 month weight	TAC (mM)	0.36	0.0067
1 month length	TAC (mM)	0.51	<0.001
3 months circumference (cm)	Z score 3 months	0.48	<0.001
Z score 3 months	Z score 6 months	0.53	<0.001
Z score 6 moths	Z score 12 months	0.29	0.046
Z score 6 months	8OH-dG (ng/ml)	–0.33	0.022
Z score 12 months	AOPP (μM)	–0.64	<0.001

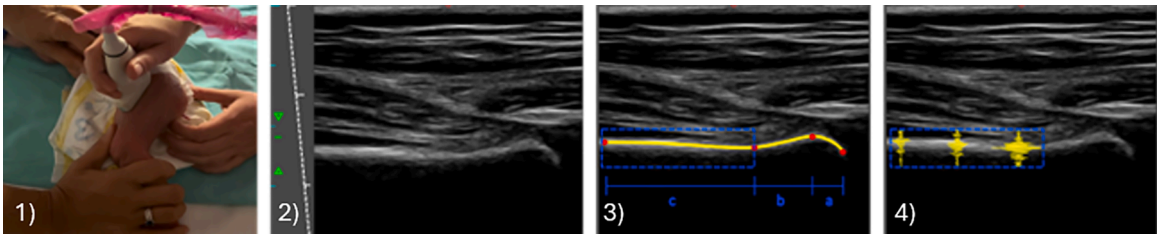

Fig. 1. ROI extraction procedure from a B-mode ultrasound image of the infant's femur. From left to right: 1) probe positioning; 2) B-Mode acquisition; 3) four manually placed red dots reference points, encompassing a) Proximal Epiphysis, b) Metaphysis, c) Diaphysis; 4) raw RF signals extracted from the diaphysis region are used for REMS analysis.

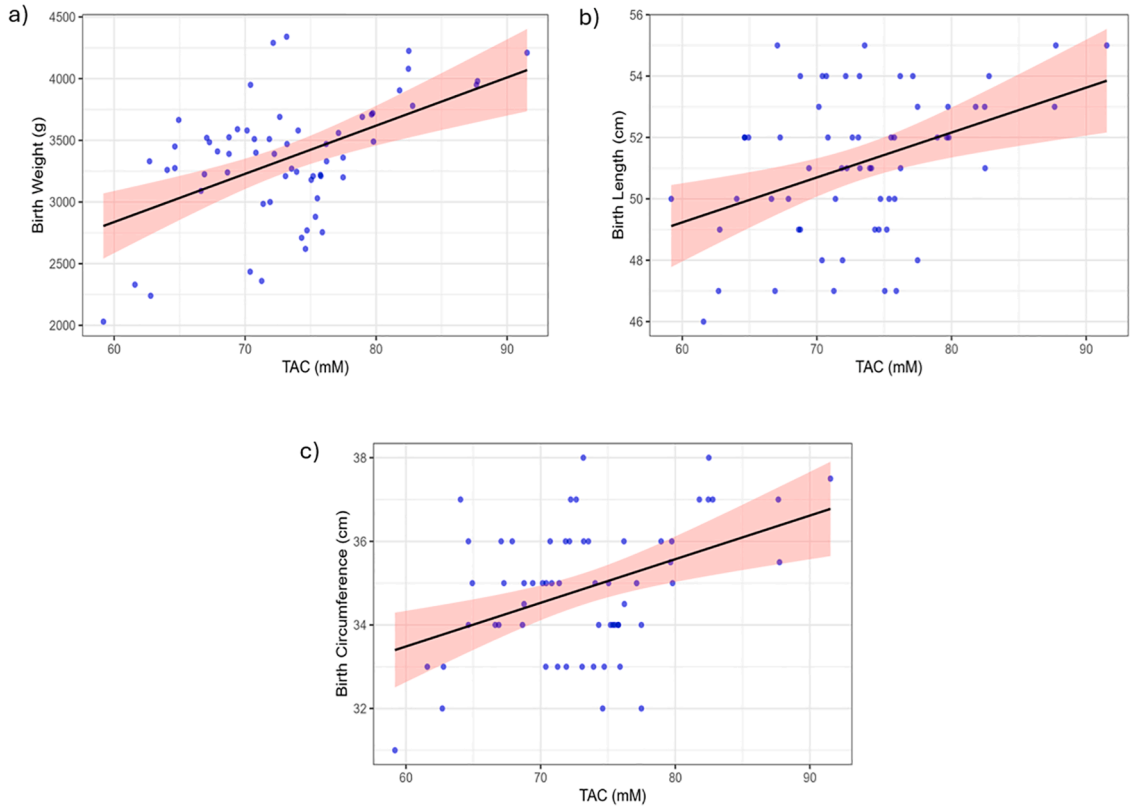

Fig. 2. Correlation between TAC and birth weight (2a); Correlation between TAC and birth length (2b); Correlation between TAC and birth head circumference (2c).

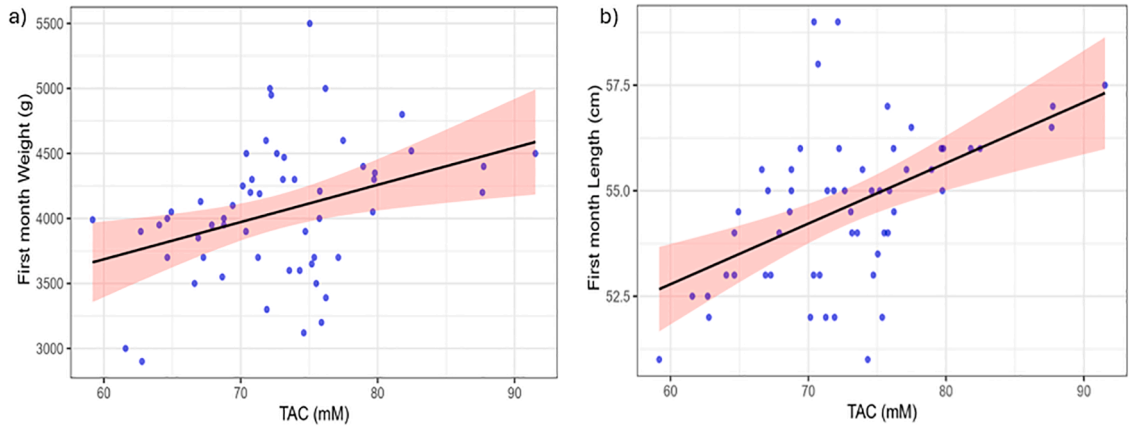

Fig. 3. Correlation between TAC and weight at 1 month of life (3a); Correlation between TAC and length at 1 month of life (3b).

implications for the skeletal development of the offspring.

From a clinical perspective, these findings highlight the potential value of monitoring and optimizing maternal antioxidant status during pregnancy as a modifiable factor to support optimal fetal growth and early skeletal development. Nutritional counseling and targeted interventions aimed at enhancing maternal antioxidant intake—whether through diet or supplementation—could represent promising strategies for improving perinatal outcomes, particularly in populations at risk for growth restriction or nutritional deficiencies.

Even more noteworthy is the application of REMS technology in this pediatric population. The Z-scores obtained at 3, 6, and 12 months showed statistically significant correlations with each other. This novel finding, being the first reported in the literature, suggests that REMS is not only feasible but also reliable for assessing bone development in infants. REMS has already been extensively validated in the elderly for the diagnosis and management of osteoporosis[8] Multiple clinical studies have demonstrated that REMS correlates strongly with DXA measurements for bone mineral density, achieving Pearson correlation coefficients above 0.93 and Cohen's kappa values of 0.82 for lumbar spine and 0.79 for femoral neck[6, 8, 9] Additionally, REMS shows high sensitivity and specificity (>91 %) in distinguishing osteoporotic from non-osteoporotic individuals, with excellent intra- and inter-operator precision (RMS-CV around 0.32–0.38 %).[6] A systematic review further confirmed the diagnostic accuracy and predictive value of the REMS fragility score for fracture risk.[10] Although our findings are preliminary, they pave the way for potential future applications of REMS as a longitudinal, non-invasive, and radiation-free method for monitoring bone health from infancy through adolescence and into adulthood.

These findings are consistent with the Developmental Origins of Health and Disease framework, which proposes that environmental

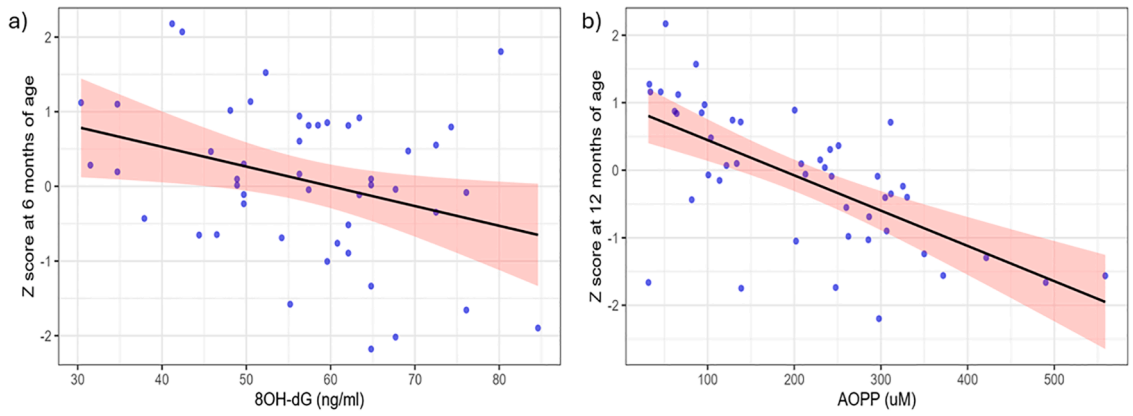

Fig. 4. Correlation between REMS-derived Z-score at 6 months and 8OH-dG levels in cord blood (4a); Correlation between REMS-derived Z-score at 12 months and AOPP levels in cord blood (4b).

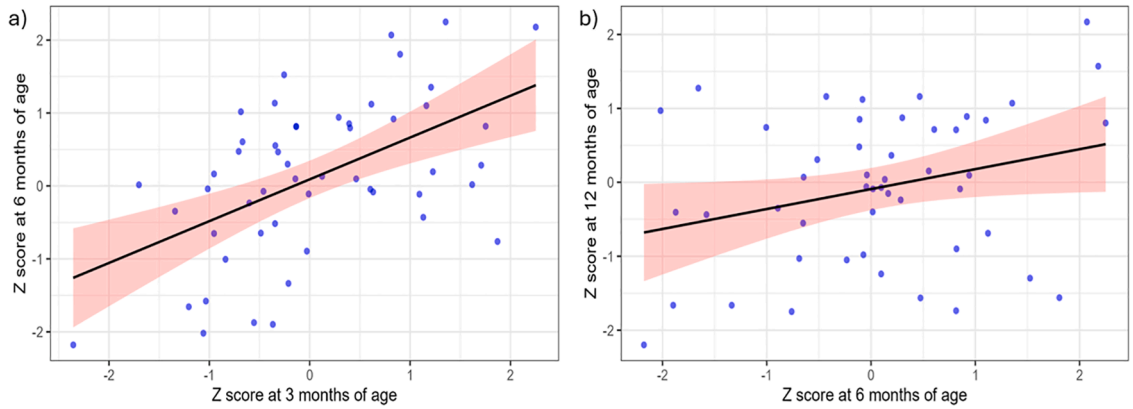

Fig. 5. Correlation between REMS-derived Z-score at month 3 and REMS-derived Z-score at month 6 (5a); Correlation between REMS-derived Z-score at month 6 and REMS-derived Z-score at month 12 (5b).

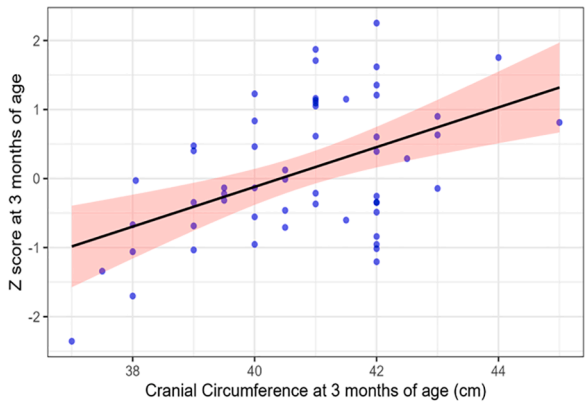

Fig. 6. Correlation between REMS derived Z-score and cranial circumference at 3 months of age.

factors during early life—including the fetal and neonatal periods—such as OS and nutritional exposures, can program long-term health trajectories and influence the risk of developing chronic conditions, including osteoporosis.[11–14]

Equally novel and compelling is the observed correlation between markers of lipid, protein, and DNA peroxidation—measured in umbilical cord blood—and REMS-derived Z-scores at 6 and 12 months of life. Specifically, our data demonstrate an inverse relationship: higher levels of peroxidative damage, and thus elevated perinatal OS, are associated with lower REMS-derived Z-scores. This finding underscores the peculiar vulnerability of the fetus and neonate to oxidative injury during critical windows of skeletal development. It also highlights the potential of REMS as a sensitive, non-invasive modality for detecting early bone quality alterations, offering unique insights not accessible through traditional imaging techniques in infancy. Our results align existing preclinical studies that have directly investigated the effects of oxidative stress on early bone development.[5,15,16] Tompkins et al.[15] showed that microinjection of hydrogen peroxide into chicken embryos down-regulated key osteogenic genes such as COL1A2, BMP, and RUNX2, resulting in significantly shorter embryos and impaired skeletal growth. Niu et al.[5] demonstrated that alkoxyl radicals can induce lipid peroxidation-mediated ferroptosis in embryonic chondrocytes by degrading SOX9, a critical transcription factor for chondrogenesis and ossification. Additionally, in a mouse model, overexpression of catalase altered redox signaling during early development, disrupting the balance between osteoblastogenesis and osteoclastogenesis and affecting both trabecular and cortical bone formation.[16]

Moreover a recent scoping review of 78 studies identified total oxidant/antioxidant status and markers such as catalase, glutathione, and ischemia-modified albumin as significantly correlated with fetal growth restriction.[17] Together, these clinical and preclinical findings converge to support the notion that OS plays a mechanistic role in shaping early skeletal development. They further strengthen the relevance of our REMS-based observations by providing a foundation in developmental bone biology. The integration of REMS in our study offers a promising tool to capture these subtle but biologically significant changes in bone quality during infancy—changes that may have

long-term implications for skeletal health throughout life.

Interestingly, we also observed a statistically significant correlation between REMS-derived Z-scores and head circumference (HC) at 3 months of age. While HC is typically considered a proxy for brain volume and neurological development,[18] its association with bone quality has not been extensively investigated. One possible interpretation is that both cranial and skeletal growth are influenced by common underlying factors such as nutritional status, endocrine signaling, and redox homeostasis during the perinatal period. It is well established that early-life growth trajectories, including HC, are sensitive indicators of developmental well-being and may reflect adequate nutrient availability and metabolic balance—conditions that also promote proper bone mineralization.[19] Moreover, synchronized neurocranial and skeletal development in infancy may suggest shared regulatory pathways or parallel environmental influences, such as oxidative stress exposure and antioxidant defense systems, which we have shown to impact bone quality via REMS-derived outcomes. This interpretation is further supported by findings from large longitudinal cohorts such as the Generation R Study, which demonstrated that postnatal growth parameters—including HC—are predictive of bone mass and architecture later in childhood[19–21]

Notably, we also found a positive correlation between TAC in umbilical cord blood and HC at birth. This observation reinforces the idea that perinatal oxidative status may have a broader influence not only on skeletal outcomes but also on brain growth and cranial development. Together, these results support the hypothesis that antioxidant protection in utero plays a crucial role in shaping multiple aspects of neonatal development, potentially through shared biological mechanisms. While these associations should be interpreted cautiously, they raise important questions regarding the interconnectedness of early organ system development and suggest novel avenues for research into how systemic oxidative balance may program both skeletal and neurological health trajectories.

4.1. Study limitations

This study represents a preliminary analysis within a larger, ongoing clinical trial and should therefore be interpreted as an initial exploration of the relationship between OS and bone development in early life. Some limitations must be acknowledged. First, the small sample size limits generalizability of the findings. Although the results provide promising insights, they should be validated in larger, independent cohorts. Second, the study design is observational and limited to a single cohort of healthy, full-term neonates without major perinatal complications. As such, no comparisons were possible with infants born preterm, or those exposed to pregnancy-related pathologies such as intrauterine growth restriction, gestational diabetes, or preeclampsia—conditions in which OS is often more pronounced. While associations between perinatal OS markers and skeletal outcomes were observed, further research, potentially incorporating interventional or mechanistic approaches, is necessary to elucidate causality. Finally, the lack of diversity in the study population, while allowing us to isolate physiological patterns under standard conditions, further restricts the applicability of our findings to broader populations. Nonetheless, we believe that starting from a well-defined, low-risk population was an important first step, particularly in a research area where human data remain extremely limited. To our knowledge, this is the first human study to explore the longitudinal relationship between perinatal OS markers and postnatal bone development using a non-invasive, radiation-free technology such as REMS.

5. Conclusion

In conclusion, our findings provide novel evidence that perinatal OS—measured through biochemical markers in umbilical cord blood—is inversely associated with early skeletal development, as assessed by REMS-derived Z-scores during the first year of life. We also demonstrate a significant correlation between total antioxidant capacity and key auxological parameters at birth, including head circumference, suggesting a broader role of oxidative balance in neonatal growth regulation.

Moreover, this study is the first to apply REMS technology in a longitudinal pediatric context, confirming its feasibility and reliability for monitoring bone quality in infancy. These results contribute to a growing body of literature suggesting that the intrauterine redox environment may play a critical role in early skeletal programming, with potential implications for lifelong bone health.

Further perspective is to involve larger and more heterogeneous populations and to explore the potential of REMS as a clinical tool in both preventive and diagnostic strategies for pediatric bone disorders.

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CRediT authorship contribution statement

Serafina Perrone: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Silvia Carloni:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Virginia Beretta:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Data curation. **Serena Benedetti:** Methodology, Formal analysis. **Elena Scarpa:** Visualization, Methodology, Investigation, Formal analysis, Data curation. **Laura Cannavò:** Writing – review & editing, Visualization, Supervision. **Chiara Petrolini:** Writing – review & editing, Visualization, Investigation. **Federica Grassi:** Visualization, Validation, Investigation. **Vincenzo Raitano:** Writing – review & editing, Visualization, Methodology. **Maria Cristina Albertini:** Visualization, Validation, Supervision, Methodology, Data curation. **Domenico Corica:** Visualization, Supervision. **Tommaso Aversa:** Visualization, Validation, Supervision. **Elvira Di Pasquo:** Visualization, Methodology, Investigation. **Maria Elisabeth Street:** Visualization, Validation. **Malgorzata Wasniewska:** Writing – review & editing, Visualization, Validation, Supervision. **Andrea Dall'Asta:** Writing – review & editing, Visualization, Validation, Supervision. **Tullio Ghi:** Writing – review & editing, Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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