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Original Article

Bony density in adolescents after surgical repair of tetralogy of Fallot: a comparative study with healthy adolescents

Carla Rego,[1] António Guerra,[1] Micaela Guardiano,[1] Patricia Esteves,[1] Jorge Pereira,[2] Álvaro Aguiar,[1] José Carlos Areias[3]

[1]*Nutrition Unit – Pediatric Service,* [2]*Nuclear Medicine Service,* [3]*Pediatric Cardiology Service, Faculty of Medicine, Hospital S. João, Porto, Portugal*

Abstract *Background:* Adverse influences arising in fetal life or immediately after birth have a permanent effect on body structure, physiology and metabolism. Evidence is now accumulating that programming of bone growth might be an important contributor to the later risk of osteoporosis. Long-term morbidity and mortality associated with tetralogy of Fallot is not completely known. The aim of the present study was to evaluate the state of the bones in adolescents after surgical repair of tetralogy of Fallot, so as to ascertain any possible repercussions of the disease on bone mineralization. *Material and methods:* We studied 34 adolescents with repaired tetralogy of Fallot, between the ages of 11 and 18 years, to establish their nutritional status, in terms of height, weight, and skinfolds, their body composition using an anthropometric method, their sexual maturity according to Tanner, and their food-habits as based on 24-hour recall. Bone density was evaluated by lumbar dual-energy X-ray absorptiometry. We included 34 healthy eutrophic adolescents, matched for gender and age, as controls. *Results:* No significant differences were observed between the patients and their controls concerning nutritional status, body composition, total energy intake and nutritional supply in macronutrients, calcium, phosphorus, magnesium and vitamin D. Bone mineral density, expressed in Z-score and g/cm^2, was significantly higher in patients with tetralogy of Fallot ($p < 0.01$). The age at the time of the first surgical procedure, or at complete surgical repair, and the total number of surgical procedures, had no significant influence on nutritional status or bone mineralization. Gender, chronological age, sexual maturity and the index of body mass are the major determinants of bone density for both samples. Obese adolescents with repaired tetralogy of Fallot had a significantly higher bone density ($p < 0.05$) compared to undernourished or euthrophic patients. *Conclusions:* Being born with tetralogy of Fallot has no significant repercussion, by the stage of adolescence, on nutritional status, pubertal progression, and accretion of bone minerals subsequent to surgical repair. Nutritional status is the major influence on the accretion of bone mass.

Keywords: Tetralogy of Fallot; bony density; adolescents

OSTEOPOROSIS IS TODAY CONSIDERED AN important cause of morbidity and mortality, and results in high medical expenditure world wide. As such, it represents a public health concern.[1]

Correspondence to: Carla Rego, Serviço de Pediatria – Hospital S. João, Alameda Prof. Hernani, Monteiro, 4202-451 Porto, Portugal. Tel: +351 22 9969786; Fax: +351 22 5505919; E-mail: carla.rego@mail.telepac.pt

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Osteoporosis and osteopenia are defined by a bone mineral density respectively lower than −2.5 and between −1 and −2.5 standard deviations of the medium value defined for a population of the same age and sex.[1] According to some authors, an increase of bone mass occurs from conception up to the end of the second or fourth decade of life.[2] Several studies show that more than nine-tenths of the peak of individual bone mass is present at 18 years,[3,4] this indicator being the largest determinant of bone mineral density by adulthood.[5] The only features that will permit a reduction of osteoporosis are the maximization

of peak bone mass during growth and development, concomitant with prevention of loss of bone mass in adult age.[5]

There is evidence that three to four-fifths of the individual value of peak bone mass is genetically determined. The capacity of phenotypic expression of this genetic potential depends on environmental factors observed during childhood and adolescence.[6,7] Current genetic markers, however, are able to explain only a small proportion of the variation of individual bone mass.[8] It is likely that environmental influences during early life, namely the state of health, appropriate supply of nutritional calcium, and normal progression of puberty and physical activity[9,10] all interact with the genome in establishing the functional level of a variety of metabolic events involved in skeletal growth. Such phenomenons are known as *programming*,[9,11] and describe persisting changes in both structure and function caused by environmental stimuluses acting at critical periods during early development.

Tetralogy of Fallot is the most frequent congenital cyanotic cardiac disease,[12] with pulmonary arterial obstruction inducing tissue hypoxia.[12] Hypoxia induces metabolic changes, with repercussion on the markers of health already seen during childhood, with variable reversibility.[13,14] Due to recent improvements in medical and surgical therapy, many children with tetralogy of Fallot are now surviving through adolescence and beyond.[15,16] The aim of the present study, therefore, was to evaluate the state of the bones in a group of adolescents who had undergone surgical repair of tetralogy of Fallot, so as to establish any repercussions of the disease on bone density.

Material and methods

Using all the patients regularly observed at the Clinic of Pediatric Cardiology of our Department, we included 187 who had undergone surgical repair of tetralogy of Fallot in a study protocol submitted as Project #59 of the Portuguese Ministry of Health, and entitled "Prediction of atherosclerotic, cardiovascular and osteoporotic risk in children and adolescents after surgical repair of Tetralogy of Fallot". For the purposes of this investigation, we selected a subsample of 34 patients aged from 11 to 18 years, and matched them for age and gender with 34 healthy eutrophic adolescents as controls.

The protocol includes:

Auxollogy, nutritional status and characterization of body composition

Weight and height were measured according to international recommendations.[17] The index of body mass, dividing weight by the square of height,[18] was calculated. Body composition was evaluated by bioelectrical impedance (Tanita®). Data from National Center of Health Statistics[19] were used for references for weight and height. Data from Hammer and colleagues[20] and Haschke et al[21] were respectively used as references for the index of body mass and fat mass.

Characterization of sexual maturity

Sexual maturity was evaluated according to the Tanner scale.[22]

Characterization of food habits

We obtained a 24 hour recall of diet for each participant. Quantification of nutrients was made according to appropriate software.[23] The Recommended Dietary Allowances of the United States Food and Nutrition Board[24] were used as reference values for nutritional supply of macronutrients, and Dietary Reference Intakes[25] for calcium, phosphorus, vitamin D and magnesium.

Evaluation of bone mineral density

The absorptiometric study was accomplished in the lumbar column (Lumbar 1–Lumbar 4) by dual-energy X-ray absorptiometry, using a Hologic QDR 1500®. The variation coefficient for repeated assays of the lumbar column was of 1.8%, and the coefficient error was 1%. The dose of received radiation was approximately 5mRem.

Statistics

Anthropometric parameters and nutrient intake where expressed respectively as Z-scores and percentages of reference values. Chi square test and multifactorial variance analysis (ANOVA) were used for comparative studies. A multiple linear regression study was also made, considering bone mineral density as a dependent variable, and the chronological age, the indicators of the nutritional status, the biological maturity and nutrients intakes as dependent variables. A p value was considered significant at the level of 0.05.

The local Ethical Committee had previously approved the study, and informed consent was obtained from parents and adolescents.

Results

All adolescents studied were born at term, and were adequate for gestational age.

No significant differences regarding nutritional status and body composition was observed between the patients and their controls, but those who had

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Table 1. Patients with tetralogy of Fallot compared to their controls for nutritional status (Z-score), fat mass (% weight), food-habits (24 h recall), Tanner stage, and bony mineral density (dual-energy X-ray absorptiometry Lumbar1–Lumbar 4) (Median and standard deviation).

		Tetralogy of Fallot	Control
Weight		−0.59 (0.51)	−0.33 (0.50)
Height		−0.21 (0.99)	−0.19 (1.02)
Body mass index		−0.33 (0.9)	−0.2 (0.4)
Fat mass		22.5 (6.7)	19.5 (4.9)
Total energy intake		96.2 (38.1)	94.3 (19.5)
Proteins		17.2 (3.9)	18.5 (4.2)
Carbohydrates		46.4 (8.6)	50.6 (7.9)
Fat		35.8 (8.7)	34.8 (6.5)
Calcium		83.9 (40.9)*	113.8 (38.4)*
Magnesium		98.9 (75.6)	104.1 (40.2)
Phosphorus		123.6 (59.2)	124.2 (46.1)
Vitamin D		20.2 (29.4)	32.5 (23.4)
Tanner stage (%)			
<3	Female	8.8	5.9
	Male	11.8	14.7
≥3	Female	38.2	41.2
	Male	41.2	38.2
Bone mineral density		1.08 (0.17)*	0.89 (0.15)*
Z-score bone mineral density		−0.059 (1.8)*	−1.31 (1.3)*

Total energy intake expressed in % Recommended Dietary Allowances; Proteins, carbohydrates and fat expressed in % of total energy intake; Calcium, phosphorus, magnesium and vitamin D as % Dietary Reference Intakes; * $p < 0.01$

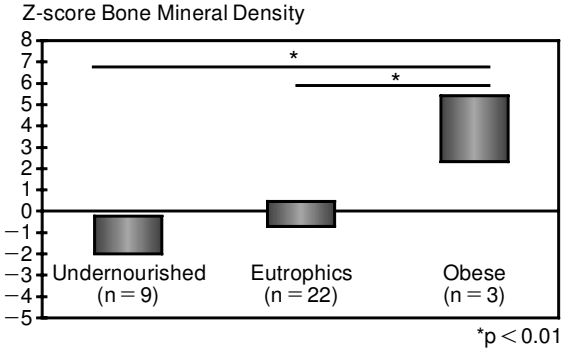

Figure 1.
Bony mineral density shown as the Z-score according to nutritional status (Z-score body mass index) for the 34 patients with tetralogy of Fallot. (Median and Confidence Intervals at 95%.)

undergone surgical repair of tetralogy of Fallot show a significantly better state of mineralization ($p < 0.01$) (Table 1). A significantly higher intake of calcium, however, was observed for the healthy control adolescents ($p < 0.01$) (Table 1). When the patients were divided according to their nutritional status, using the Z-score of the index of body mass, the obese adolescents had the greater mineral density of bone observed for the entire sample (Fig. 1).

The chronological age at the first surgical intervention, and also the number of surgical repairs required to produce definitive correction, showed no significant influence on either the nutritional status or on the acquisition of bone mass (Table 2). No significant differences where observed between the patients and their controls regarding bone density as assessed on Z-score, the gender, or the maturational status (Table 3).

Considering the mineral density of the bones as a dependent variable, multiple linear regression show that gender, nutritional status, and biological maturation as assessed on the Tanner stage are the only variables determining the value of the mineral density of the bones (Table 4).

Discussion

Osteoporosis is an irreversible disease, with a silent evolution in terms of signs and symptoms. Although clinical manifestation of the disease usually occurs at an adult age, the paediatrician must have always in mind the axiom "for osteoporosis: the only cure is prevention". From our overall sample of patients who had undergone surgical repair of tetralogy of Fallot, we chose a subsample of adolescents, since more than three-fifths of the accretion of bony mass occurs during this period of life. We chose the lumbar column as a representative site for assessing the accretion of minerals because of the precocity of acceleration on the bone mass increment observed for the spine.[26] The choice of dual-energy X-ray absorptiometry is based on the fact that it is a simple technique, and is recognised as the most reliable and reproducible method for studying the density of bone.

Table 2. The nutritional status according to body mass index, fat mass and bony mineral density assessed according to the time of the first and the number of surgical interventions in the 34 patients with tetralogy of Fallot (Median and Confidence Intervals at 95%).

	Time of first surgical intervention (months)		Number of surgical interventions	
	≤12	>12	1	≥2
Body mass index (Z-score)	−0.31 (0.57)	−0.33 (0.4)	−0.41 (0.48)	−0.26 (0.45)
Fat mass (%weight)	2.3 (0.4)	2.2 (0.3)	2.05 (0.35)	2.35 (0.35)
Bony mineral density (Z-score)	−0.08 (1.1)	−0.06 (0.8)	0.04 (0.95)	−0.14 (0.89)
		n.s.		n.s.

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It is now recognized that the human skeleton can be programmed by undernutrition.[27] Evidence from animal studies suggests that skeletal development might be programmed as a consequence of two mechanisms. First, the nutritional environment may permanently alter gene expression.[28] Second, early nutrition may permanently reduce cell numbers.[29] Nutritional status, therefore, is the greatest determinant of the acquisition of bony mass, not only during childhood and adolescence, but even during fetal and neonatal life. Our patients with tetralogy of Fallot were born at term, and with appropriate weight, presenting at the time an adequate state of nutrition and body composition (Table 1). We can conclude that the disease itself does not interfere with nutritional status and normal growth, even during the prenatal period.

Body mass is a major determinant of the accretion of bony mass during growth.[30,31] Our patients showed heterogeneity within their group regarding nutritional status. Considering the index of body mass, the obese patients had a significantly higher bony density ($p < 0.001$) (Fig. 1). It is this subgroup which is responsible for the significantly higher bony density observed between the patients with tetralogy of Fallot and their controls ($p < 0.01$) (Table 1). When overweight and obese, and undernourished, adolescents with repaired tetralogy of Fallot were excluded, no significant differences where observed regarding bony density between eutrophic patients and their controls. Our results suggest that there is no linkage between bony "programming" and the malformation of tetralogy of Fallot, as the values for the mineral density of the bones were within normal ranges at the time of our study.

Total energy, and also the intake of fat and protein, are also determinants for an appropriate nutritional status, and for the accretion of bony mass.[31–34] The population studied showed an appropriate total energy supply, but a globally unbalanced diet, with a high supply in protein and fat (Table 1). Although not clear, the relationship between bony mineral density and dietary fat supply can be justified by the change in the metabolism of oestrogens promoting the production of more active metabolites.[35] Concerning proteins, their pathway may be optimized due to essential amino acids and the connection of oestrogens to its receivers.[35] The intake of calcium also represents an important determinant of the formation of the bony mass, and besides the significant difference observed, all adolescents had an adequate intake of calcium (Table 1).

Neither the time of the first surgical correction, nor the number of surgical procedures until the definitive correction, had any significant influence on the value of the bony mass (Table 2). As previously discussed, tetralogy of Fallot is the most common cyanotic congenital cardiac malformation, and the cyanosis is the clinical expression of the hypoxic status, being dependent on the degree of pulmonary arterial obstruction. According to some authors, hypoxia itself induces metabolic changes, with repercussion on the markers of health, with variable reversibility.[13] Division of cells in the period of intrauterine and early postnatal growth, the "critical" periods,[14] differs in time for different tissues, with the long bones accelerating their rate of growth during the second trimester of gestation. The main adaptive response to a lack of nutrients and oxygen during this period of growth is

Table 3. The bony mineral density and bony mineral density to reference values (Z-score) by gender and maturational status according to the Tanner stage for the 34 patients with tetralogy of Fallot. (Median and Confidence Intervals at 95%.)

	Bone mineral density	Z-score bone mineral density
Tetralogy of Fallot		
Male (n = 18)	0.94 (0.87–1.02)*	0.039 (−0.84 to 0.92)
Female (n = 16)	1.09 (1.01–1.17)*	−0.17 (−1.11 to 0.77)
Control		
Male (n = 12)	0.86 (0.79–0.92)	−0.98 (−2.36 to −1.03)
Female (n = 13)	0.92 (0.85–0.99)	−1.69 (−2.36 to −1.03)
Tetralogy of Fallot		
Tanner stage		
<3 (n = 14)	0.92 (0.83–1.0)**	0.12 (−0.88 to 1.12)
≥3 (n = 20)	1.08 (1.0–1.15)**	−0.19 (−1.02 to 0.65)

*$p < 0.05$; **$p < 0.01$

Table 4. Multiple linear regression when bony mineral density is considered as a dependent variable for the 34 patients with tetralogy of Fallot.

	Dependent variable	Independent variable	T	r^2	f	p
Tetralogy of Fallot	Bony mineral density	Gender	−0.318	55.8	12.65	0.002
		Body mass index	3.99			
		Tanner	2.17			
Control	Bony mineral density	Gender	−4.86	65.4	20.76	0.001
		Body mass index	−0.5			
		Tanner	5.78			

T: t-value; r^2: coefficient of determination; f: f-test; p: p-value

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to slow the rate of cell division, especially in tissues that are undergoing critical changes at the time. This reduction in cell division is either direct, or mediated through altered concentrations of growth factors or hormones, in particular insulin, growth hormone, and cortisol.[36] The absence of cyanosis during fetal life, despite the degree of early postnatal cyanosis, might be one of the reasons for the appropriate mineral density of the bone observed in these adolescents.

According to the literature, the increase in the mass and mineral density of the bone between 11 and 18 years seems also to depend on the body mass, but to be strongly and directly dependent on gonadal hormones.[26] Although females show higher values of bony density, no significant differences for bony mineral density were observed between patients and their controls for either gender when assessed on the basis of Z-scores (Table 3). The greater value of bony mineral density observed for females is associated with a greater bony mass, depending on earlier biological maturation. The positive influence of maturative status on bone mineral accretion is showed on Table III. In fact, when bony mass expressed in bony mineral density is considered as a dependent variable, only nutritional status, gender, and biological maturity emerge as the variables accepted by a multiple linear regression model as determinants of the values of bony mineral density (Table 4).

Conclusions

Tetralogy of Fallot, independent of the age of the first surgical intervention, or the age of the definitive repair, has no significant repercussion on nutritional status, progression of puberty, and the accretion of bony minerals. Bony mass is directly dependent on the index of body mass, gender, and biological maturity. Our results suggest that there is no negative influence on bony programming produced by tetralogy of Fallot, independently of the duration of the postnatal cyanotic state.

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