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Myeloperoxidase as cardiovascular risk marker in pre-pubertal preterm children?

Denise O. Schoeps [a], Simone Holzer [a], Fabiola I. Suano-Souza [a,b,*], Sonia Hix [c], Fernando L.A. Fonseca [c], Roseli O.S. Sarni [a]

[a] Pediatric Department, ABC University Health Center/ABC Faculty of Medicine, Brazil
[b] Pediatric Department, Federal University of São Paulo – São Paulo Medical School, Brazil
[c] ABC University Health Center/ABC Faculty of Medicine, Brazil

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Abstract *Background and aims:* To evaluate the biomarkers related to cardiovascular risk in pre-pubertal preterm children with a birth weight of less than 1,500 g and relate them to current nutritional status, insulin resistance, and inflammation.
Methods & results: This is a cross-sectional, controlled study with pre-pubertal preterm children aged 5–9 years with a birth weight of less than 1500 g (Preterm group, n = 44) compared to full term children of adequate weight for gestational age (Control group, n = 30). Clinical evaluation: anthropometry and pubertal staging. Laboratory tests: total cholesterol and fractions, triglycerides, paraoxonase 1, apolipoproteins A-I and B, myeloperoxidase (MPO), high sensitivity C-reactive protein (hs-CRP), glycemia and insulin (to calculate HOMA-IR). In the preterm group, 19 (43.2%) were male, with mean birth weight and gestational age of 1157 ± 242 g and 30.0 ± 2.3 weeks, respectively. The preterm group showed lower concentrations of HDL-c (60.1 ± 10.1 vs. 69.0 ± 10.0 mg/dL; $p < 0.001$); higher concentrations of hs-CRP [0.55 mg/dL (0.30; 39.4) vs. 0.30 mg/dL (0.30; 10.80); $p = 0.043$], of MPO [21.1 ng/mL (5.7; 120.0) vs. 8.1 ng/mL (2.6; 29.6); $p < 0.001$] and of MPO/HDL-c ratio [0.39 (0.09; 2.07) ng/mg vs. 0.11 (0.05; 0.58)]. The MPO/HDL-c ratio was the variable that showed the best discriminatory power between the groups (AUC = 0.878; 95% CI; 0.795–0.961). MPO concentrations in the preterm group were correlated with those of hs-CRP ($r = 0.390$; $p = 0.009$), insulin ($r = 0.448$; $p = 0.002$) and HOMA-IR ($r = 0.462$; $p = 0.002$).
Conclusion: Prepubertal preterm children show high MPO concentrations and MPO/HDL-c ratio that are associated with inflammation and oxidative stress, which, in turn, may be associated with atherosclerosis.

Introduction

Prematurity occurs in 11.1% of the world's live births, corresponding to 14.9 million births before 37 weeks of gestation. Complications resulting from premature birth account for one million yearly deaths and are a risk factor in more than 50% of all neonatal deaths [1].

Short- and long-term complications in the preterm group include stunting, increased risk of infections, developmental impairment, and death in childhood [1,2]. The consequences of prematurity may, however, persist

* Corresponding author. Avenida Lauro Gomes 2000 – Santo André, São Paulo, 09060-000, Brazil.
E-mail address: fsuano@gmail.com (F.I. Suano-Souza).

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throughout adult life, increasing the likelihood of future cardiovascular, renal, and metabolic syndrome [2–4].

The early identification of cardiovascular risk markers in preterms may, therefore, prevent or reduce the likelihood of morbidity and mortality due to cardiovascular disease in adulthood. The use of lipid metabolism biomarkers in the identification of cardiovascular risk is well recognized. High-Density Lipoproteins (HDL) are considered anti-atherogenic particles as they have several protective functions against atherosclerosis, they stimulate efflux of cholesterol from macrophages present in atherosclerotic plaques, perform reverse cholesterol transport, as well as antioxidant and anti-inflammatory activities [5,6].

Although plasma levels of HDL cholesterol (HDL-c) are negatively related to cardiovascular risk in extensive population studies, Mendelian randomization studies indicate that most genetic variants that increase plasma HDL-c levels are not usually associated with reduced cardiovascular risk [7]. Indeed, U-shaped relation of HDL-c with mortality was described in some studies, including the prospective population-based studies [8]. Recent pharmacological, interventional studies with HDL-c elevating strategies also failed to reduce cardiovascular risk so far, despite raising HDL-c [9].

Besides classical lipid biomarkers, the measurements of apolipoproteins (Apo A-I and B), paraoxonases (PON), high-sensitivity C-reactive protein (hs-CRP) and myeloperoxidase (MPO) could help in evaluating HDL functionality and cardiovascular risk [10–12] indirectly. Apo A-I is the major protein component of HDL and is associated with reverse cholesterol transport and the antioxidant properties of HDL [13]. Apo B is essential for LDL removal from blood and the release of the transported cholesterol through receptor-mediated endocytosis, and is present as a single copy in all atherogenic lipoproteins reflecting the number of atherogenic particles [5,13].

MPO is an enzyme produced in neutrophils and monocytes involved in host defense. It produces oxidizing compounds such as hypochlorite from hydrogen peroxide. It has been associated with cardiovascular risk by several mechanisms, such as the release of reactive oxygen species, oxidation of LDL particles, conversion of HDL to dysfunctional particle, endothelial dysfunction, platelet aggregation and atheromatous plaque vulnerability [12,14].

Most of the available studies, including a meta-analysis, that assessed the effects of lifetime prematurity in the lipid metabolism, point to increased LDL-c and inflammatory markers, however with conflicting data regarding HDL-c [14–18].

The primary purpose of this study is to detect the presence of clinical or metabolic alterations in childhood by employing new biomarkers involved in cardiovascular risk, considering the literature findings of the relationship between prematurity, low birth weight and increased cardiometabolic risk in the adult life [16,19].

This study aimed to analyze the biomarkers related to cardiovascular risk in pre-pubertal preterm children with a birth weight of less than 1,500 g and relate them to current nutritional status, insulin resistance, and inflammation.

Methods

Study design

A cross-sectional and controlled study was carried out with pre-pubertal preterm children aged 5–10 years, with birth weight of less than 1500 g (preterm group, n = 44) who were compared to healthy term children with an adequate birth weight for gestational age (control group, n = 30); paired by age and gender with the study group.

The children of the preterm group were born at the *Municipal Hospital of São Bernardo Campo* (HMU-SBC) and were followed-up in an outpatient clinic by a multidisciplinary team from the same hospital. The control group consisted of healthy children voluntarily recruited from the Pediatrics Outpatient Clinic of the ABC Faculty of Medicine, ABC University Center, Santo André, Brazil.

The exclusion criteria of the preterm group were the presence of infectious or inflammatory processes at blood collection or presence of chronic diseases (cardiological, neurological, endocrinological and renal), except overweight; the use of corticosteroids in the three months prior to the collection of exams and those who required growth hormone replacement.

HMU-SBC is a Child-Friendly Hospital that adopts the Kangaroo Method and has a Milk Bank. It is the only public maternity in the municipality, and is a reference for high-risk pregnancies, performing about 350–400 monthly deliveries, representing 80% of the births coming from the Unified Health System of São Bernardo do Campo. The care protocols used are in line with the leading national and international scientific societies. The diet used in the neonatal unit for preterm newborns is exclusively breast milk, preferably mother's raw milk, and if not possible, pasteurized human milk.

We identified all the children enrolled in the outpatient clinic between 2004 and 2009, who were preterm and with a birth weight of less than 1,500 g, aged 5–10 years at the time of the study (2014 and 2015) to build the sample. We identified 130 children, of which 60 were selected and invited to participate in the study. We excluded four children whose parents/guardians refused to participate; four because they had pubertal development; seven patients with cerebral palsy and one child who used growth hormone at the time.

Therefore, the final sample consisted of 44 children. Parents/guardians and children in both groups agreed and signed the consent and assent form, respectively, to be included in the study. The Research Ethics Committee of FMABC approved the study under the Nº CAAE: 35173814.3.0000.0082.

Data collection

We used a standardized questionnaire and evaluated the medical records of the hospitalization time, collecting data on weight, length, head circumference at birth, gestational age, diseases developed in the neonatal period and nutritional therapy (parenteral and enteral). The reference

proposed by INTERGROWTH-21st [20] was used for the adequacy of birth weight for gestational age. Children were classified as small (SGA), adequate (AGA) and large (LGA) for gestational age. Outpatient follow-up provided information on total breastfeeding time and introduction of complementary feeding.

Clinical evaluation and collection of laboratory tests were performed at the follow-up ambulatory. The children were weighed and measured according to World Health Organization standards [21]. Current body weight and height (ZBMI) and height-for-age (ZHA) z scores were calculated as per the recommendations and cut-off points proposed by the World Health Organization [22].

The waist circumference measurement was obtained at the midpoint of the iliac crest and last fixed rib, from which the waist-to-height ratio was calculated. Increased waist was considered when this ratio was greater than 0.5 [23]. The evaluation of pubertal staging was performed by a pediatrician according to the criteria of Marshall & Tanner [24]. A 24-hour recall study was performed to evaluate food intake, and the calculation of energy intake and macronutrients was performed using Avanutri 4.0 ® software.

For laboratory tests, 10 mL of blood was collected by peripheral venipuncture after 12 h of fasting. The samples were transported to the Clinical Analysis Laboratory of the ABC Faculty of Medicine under refrigeration, centrifuged, and stored in a freezer at −20 °C.

Total cholesterol and fractions and triglycerides (TG) were determined by colorimetric enzymatic method. Apolipoprotein A (Apo A-I) and apolipoprotein B (Apo-B) were measured by turbidimetric immunoassay (In Vitro, Lion, France).

Paraoxonase (PON) and myeloperoxidase (MPO) were determined by immunosorbent assay, Elisa, (MyBioSource San Diego, CA, USA), and high-sensitivity C-reactive protein (hs-CRP) was determined by immunoturbidimetric method (Roche Basel, CA, Swiss).

Fasting glycemia was evaluated by enzymatic colorimetric method and insulin by chemiluminescence, used to calculate HOMA-IR [25]. For classification of the lipid profile, we used the cut-off points recommended by the American Academy of Pediatrics [26]. We also calculated the non-HDL-c and LDL/HDL, CT/HDL-c, Apo-B/Apo A-I, LDL/Apo-B PON/HDL-c, and MPO/HDL-c ratios.

Statistical analysis

The SPSS 25.0 program (IBM®) was used for statistical analysis. The qualitative variables were shown as total number and percentage, compared using the Chi-square test or Fisher's exact test. Continuous variables were tested for their normality employing the Kolmogorov–Smirnov test and compared by the t-Student test when parametric, and by the Mann–Whitney test when non-parametric. The Spearman coefficient was used for the correlation analysis. The discriminatory ability of the laboratory variables that showed a statistically significant difference between the preterm and control groups was evaluated in a combined manner by the calculation of the area under receiver operating curve (ROC curve). We adopted a significance level of 5% for the analyses.

Results

Table 1 shows the general characteristics, medical history, and nutritional assessment of the groups of preterm and control children. In the preterm group, 19 (43.2%) were male, and mean birth weight and gestational age were 1157 ± 242 g and 30.0 ± 2.3 weeks, respectively. There was

Table 1 General characteristics, medical history, and nutritional assessment of prepubertal children in the preterm and control group.

Variable		Preterm group (n = 44)	Control group (n = 30)	P-value
Age	Years	6.9 ± 1.5	7.1 ± 1.3	0.606[a]
Gender	Male	19 (43.2%)	13 (43.3%)	0.589[b]
Maternal age	Years	32.9 ± 8.2	34.4 ± 6.1	0.932[a]
Maternal schooling	Years	10.0 (8.0; 10.0)	10.0 (10.0; 15.0)	0.566[c]
Tobacco use	Yes	6 (13.6%)	1 (3.3%)	0.232[b]
Alcohol intake	Yes	4 (9.1%)	0 (0.0%)	0.142[b]
Gestations	Number	1.0 (1.0; 7.0)	1.0 (1.0; 3.0)	0.289[c]
Type of delivery	Cesarean	21 (47.7%)	11 (36.7%)	0.474[b]
Birth weight	Grams	1157 ± 242	3196 ± 348	<0.001[a]
Gestational age	Weeks	30.5 ± 2.3	39.0 ± 1.4	<0.001[a]
Height for age	z-score	−0.43 ± 1.11	0.17 ± 0.95	0.017[a]
	Short stature	4 (9.1%)	0 (0.0%)	0.142[b]
BMI for age	z-score	0.11 ± 1.34	−0.02 ± 0.96	0.317[a]
Classification	Obesity	5 (11.3%)	0 (0.0%)	0.221[b]
	Overweight	4 (9.0%)	5 (16.7%)	
	Eutrophy	35 (79.5%)	24 (80.0%)	
	Thinness	0 (0.0%)	1 (3.3%)	
Waist/height	cm/cm	0.47 ± 0.05	0.44 ± 0.03	0.868[a]
	>0.5	8 (18.2%)	1 (3.3%)	0.074[b]

[a] Student t-test.
[b] Chi-square test.
[c] Mann–Whitney test.

Table 2 Comparison of dietary intake between groups.

Variable		Preterm group (n = 44)	Control group (n = 30)	P-value[a]
Energy	Kcal	1530 (884; 2706)	1416 (782; 3438)	0.230
Protein	%	15.2 (2.0; 28.2)	14.5 (7.7; 24.0)	0.925
Carbohydrate	%	56.8 (27.0; 73.3)	57.7 (14.8; 74.3)	0.132
Fat	%	28.3 (15.3; 46.5)	23.7 (14.4; 76.6)	0.060
Cholesterol	mg	122.5 (26.4; 495.0)	110.5 (6.7; 494.0)	0.211

[a] Mann–Whitney test.

Table 3 Comparison of the proportion of inadequacy of the lipid profile between the preterm and control groups.

Variable		Preterm group (n = 44)	Control group (n = 30)	P-value[a]
Total Cholesterol	>170 mg/dL	20 (45.6%)	18 (60.0%)	0.245
LDL-c	>110 mg/dL	10 (22.7%)	5 (16.7%)	0.571
HDL-c	<45 mg/dL	3 (6.8%)	1 (3.3%)	0.642
Triglycerides	>75 mg/dL	17 (38.6%)	8 (29.6%)	0.609
Non HDL-c	>120 mg/dL	15 (34.1%)	10 (33.3%)	0.574
Apo A-I	<120 mg/dL	9 (20.5%)	2 (6.7%)	0.182
Apo B	>90 mg/dL	14 (31.8%)	14 (46.7%)	0.228

[a] Chi-square test.

no difference between the dietary intake of the preterm and control children (Table 2).

Twelve children in the preterm group (27.3%) were born with less than 1000 g, and 15 (34.1%) were SGA. In the preterm group, the median hospital stay was 51.0 days (41.1; 73.3), and median oxygen use was 18.1 days (3.5; 28.5). Regarding nutritional therapy, the onset of parenteral and enteral nutrition occurred with 3.0 days (2.0; 3.7) and 2.0 days (1.0, 3.0), respectively. Using chronological age, total breastfeeding time, and the introduction of complementary feeding of the preterm group was 9.7 ± 8.3 months and 6.9 ± 1.5 months, respectively.

Regarding the current anthropometric indicators, in the preterm group 5 (11.3%), 4 (9.1%) and 4 (9.1%) children were obese, overweight and stunted, respectively (Table 1). There was no statistically significant difference regarding the ZBMI and waist/height ratio between the groups. Mean ZHA in the preterm group was lower compared to the control group (−0.43 ± 1.11 vs. 0.17 ± 0.95, p = 0.017).

No statistically significant difference was observed when comparing the inadequacy of the lipid profile between the preterm and control groups (Table 3). However, when the continuous variables related to glucose metabolism, lipid profile and inflammatory tests were compared, the preterm group had lower concentrations of HDL-c (60.1 ± 10.1 vs. 69.0 ± 10.0 mg/dL, p < 0.001); higher levels of: hs-CRP [0.55 mg/dL (0.30; 9.4) vs.

Table 4 Comparison of laboratory variables related to glucose, lipid metabolisms, and inflammatory markers evaluated in preterm and control groups.

Variable		Preterm group (n = 44)	Control group (n = 30)	P-value
Glycemia	mg/dL	78.4 ± 5.9	80.8 ± 5.9	0.098[a]
Insulin	uU/mL	3.1 (2.0; 29.2)	4.6 (1.4; 15.1)	0.219[b]
HOMA-IR		0.61 (0.35; 5.76)	0.91 (0.24; 3.01)	0.265[b]
hs-CRP	mg/dL	0.55 (0.30; 9.4)	0.30 (0.30; 10.80)	0.043[b]
Total Cholesterol	mg/dL	164.4 ± 30.2	175.8 ± 25.6	0.096[a]
LDL-c	mg/dL	89.6 ± 28.4	91.2 ± 29.0	0.814[a]
HDL-c	mg/dL	60.1 ± 10.1	69.0 ± 10.0	<0.001[a]
VLDL-c	mg/dL	14.6 ± 6.8	13.1 ± 3.4	0.300[a]
Triglycerides	mg/dL	73.2 ± 34.4	65.7 ± 19.5	0.300[a]
Non HDL-c	mg/dL	104.3 ± 31.4	106.7 ± 27.8	0.732[a]
LDL-c/HDL-c	mg/dL	1.55 ± 0.58	1.37 ± 0.56	0.210[a]
CT/HDL-c	mg/dL	2.81 ± 0.71	2.60 ± 0.57	0.179[a]
Apo A-I	mg/dL	148.9 ± 37.1	162.4 ± 26.3	0.072[a]
Apo B	mg/dL	77.8 ± 32.9	85.1 ± 32.3	0.346[a]
Apo B/Apo A-I	mg/dL	0.57 ± 0.33	0.54 ± 0.22	0.686[a]
LDL-c/Apo-B	mg/dL	1.23 ± 0.31	1.16 ± 0.38	0.363[a]
Paraoxonase (PON)	ng/mL	3.34 ± 0.60	3.33 ± 0.62	0.919[a]
Myeloperoxidase	ng/mL	21.1 (5.7; 120.0)	8.1 (2.6; 29.6)	<0.001[b]
Myeloperoxidase/HDL-c	ratio	0.39 (0.09; 2.07)	0.11 (0.05; 0.58)	<0.001[b]

[a] Student t-test.
[b] Mann–Whitney test.

0.30 mg/dL (0.30; 10.80); p = 0.043], MPO levels [21.1 ng/mL (5.7; 120.0) vs. 8.1 ng/mL (2.6; 29.6); p < 0.001] and MPO/HDL-c ratio [0.39 (0.09; 2.07) ng/mg vs. 0.11 (0.05; 0.58) ng/mg; p < 0.01] (Table 4).

The MPO/HDL-c ratio was the variable with the best discriminatory power between preterm and control groups (AUC = 0.878, 95% CI, 0.795 to 0.961) (Fig. 1), suggesting a pro-inflammatory state associated with lower levels of HDL-c in the preterm group.

In the preterm group, the MPO/HDL-c ratio correlated directly with Apo-B/Apo A-I (r = 0.355; p = 0.018), TG/HDL (r = 0.451; p = 0.002), LDL/HDL (r = 0.336; p = 0.026), CT/HDL (r = 0.358; p = 0.017), triglycerides (r = 0.310; p = 0.040), hs-CRP (r = 0.390; p = 0.009), insulin (r = 0.448; p = 0.002), HOMA-IR (r = 0.462; p = 0.002) and inversely with Apo A-I (r = −0.332; p = 0.028), HDL-c (r = −0.399; p < 0.001) (Supplementary data).

SGA children of the preterm group, compared to those adequate for gestational age (AGA), had lower ZHA values (−1.13 ± 0.97 vs. −0.07 ± 1.00; p = 0.002). The other variables related to the nutritional status, body composition, inflammation, insulin resistance, and lipid profile did not show a statistically significant difference between SGA and AGA.

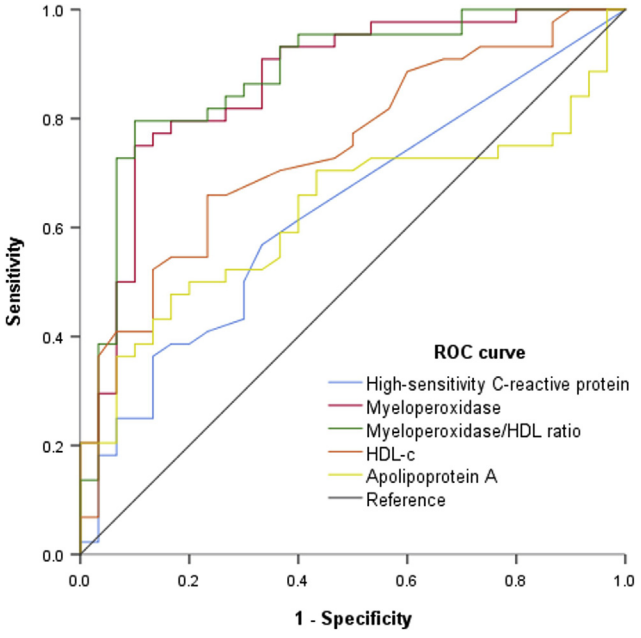

Figure 1 Receiver operating characteristic curve comparing the discriminatory power of the C-Reactive Protein, Myeloperoxidase, Myeloperoxidase/HDL-c ratio, HDL-c and Apolipoprotein A-I between the preterm and control groups.

Area under the curve (AUC) calculation

	AUC	95% Confidence Interval		p-value
Myeloperoxidase/HDL-c	0.878	0.795	0.961	0.000
Myeloperoxidase	0.866	0.779	0.953	0.000
HDL-c (1/HDL-c)	0.742	0.630	0.855	0.000
C-Reactive Protein	0.631	0.504	0.759	0.056
Apo A-I (1/Apo A-I)	0.629	0.501	0.756	0.061

Discussion

The data shown in this study found higher levels of MPO and of the MPO/HDL ratio in preterm children suggesting a possible link between inflammation and oxidative stress that may be associated with increased cardiovascular risk in the preterm group [14,17]. Two recent studies in prepubertal children and another in adolescents reported that MPO, a biomarker of cardiovascular risk, was significantly higher in the obese children [27,28].

To the best of authors' knowledge, there is no literature to date evaluating MPO and the MPO/HDL-c ratio in preterm children. MPO plays a crucial role in atherogenesis and is related to endothelial damage in incipient stages of the process [12,14]. It is known that atheroma plaques have high concentrations of this enzyme. MPO may favor early endothelial dysfunction by binding to the Cytokeratin-1-protein on its surface, reducing the release of bradykinin and thus interfering with vascular tone [29]. MPO also acts in the formation of the atheroma plaque by promoting LDL oxidation and making HDL dysfunctional [5]. Thus, it is believed that MPO is an early marker of damage, which may be useful in monitoring cardiovascular risk in prematurely born individuals.

A positive and significant correlation of MPO with markers of alteration of the lipid profile, hs-CRP, and HOMA-IR was found in this study. Garcia et al. also found a positive correlation of MPO with insulin resistance and inflammation in overweight subjects [30]. They proposed that the production of hypochlorous acid by MPO could trigger activation of metalloproteases leading to degradation of extracellular matrix proteins, damaging pancreatic β-cells resulting in insulin resistance. On the other hand, studies performed by Wang and collaborators [31], and discussed by Heinecke & Goldberg [32], proposed that MPO is a significant contributor to the development of inflammation-induced insulin resistance and metabolic disease. They showed that MPO deficient mice were resistant to diet-induced obesity and insulin resistance. The group also showed that hypochlorous acid, produced by MPO, inhibited insulin-stimulated phosphorylation of insulin receptor, insulin receptor substrate-1, and Akt thus affecting insulin signaling.

Insulin also plays a significant role in the genesis of atherosclerosis, since it is associated with the development of endothelial dysfunction related to the inadequate action of nitric oxide and its mitogenic effect promotes the thickening of the medial-intimal layers of the arteries by increasing the cells of the vascular smooth muscle and extracellular matrix [33].

Elevated MPO levels predict future risk of coronary artery disease in apparently healthy individuals. More recently, an American study on adults without cardiovascular diseases showed for the first time a significant association between the MPO/HDL-c, at the onset of the study, and the occurrence of future cardiovascular

outcomes, during a follow-up of 9.4 years [34]. They proposed that the MPO/HDL ratio could reflect more appropriately the oxidation status per HDL particle. Kimak and collaborators, 2018 showed that MPO levels and MPO/HDL-c ratio could differentiate patients at risk of acute coronary syndrome and stroke [35].

Some hypotheses may be conjured to explain the association between premature birth and short- and long-term inflammation, such as compromised organogenesis and function of cells/organs/tissues (e.g. hepatic and renal) in intrauterine life involved in synthesis; degradation and elimination of inflammatory mediators [36]; accelerated catch-up growth influencing adipocyte imprinting and cell hypertrophy [37]; maternal inflammation as the cause of prematurity and the dysregulation of inflammation in the concept by epigenetic mechanisms [38].

Regarding pregnant women, the presence of inflammatory, pro-inflammatory or oxidative phenotypes may predispose to preterm birth [39], possibly attributable to interactions between peripartum exposure to inflammatory cytokines, although the mechanisms are unknown [40]. Women who have experienced preterm birth show a higher risk of developing cardiovascular disease later in their lives [32]. The intrauterine environment and the neonatal period are relevant determinants of the risk of cardiovascular diseases. There is increasing evidence pointing to the negative impact of prematurity on future cardiovascular health in adolescents and adults [41,42].

Concerning lipid metabolism, a meta-analysis showed that preterm birth versus full term in adulthood is associated with higher concentrations of LDL-c without differences for triglycerides and HDL-c [16]. In our study, the HDL-c concentrations in the preterm group were significantly lower than in the control group, even though they were within the considered normal reference range. HDL concentrations are usually determined by their cholesterol content (HDL-c) as there are limitations in an unequivocal definition of what is considered an HDL particle and methods to isolate HDL currently available, but HDL-c does not reflect the functionality of the HDL particle. HDLs are a group of heterogeneous particles that differ quantitatively and qualitatively in apolipoprotein and lipid composition and consequently in its functional properties. The atheroprotective and anti-inflammatory properties of HDL depend on the presence and integrity of several associated proteins and other components and not by its cholesterol content [7].

Therefore, there is growing evidence that assessing the functional properties of HDL seems to be superior to measurement of HDL-c in evaluating cardiovascular risk, even though there is no agreement concerning methods of isolation of the HDL particles and methods to assess HDL function [7,43]. Higher levels of MPO could affect HDL functionality as it oxidizes HDL, which becomes dysfunctional [14,16].

The nutritional therapy given to preterm infants seems to permanently affect the profile of lipoproteins and inflammation with an evident protective role of breast milk compared to the use of formula in reducing the risk of atherosclerosis [44]. The children participating in this study were born in a maternity hospital registered in the Child-Friendly Hospital Initiative and received human milk in enteral nutritional therapy. The use of human milk as enteral nutrition in the preterm group could be the reason our group showed no differences in LDL-c levels compared to other studies [15,44]. Also, there are a few studies on lipid profile in young preterm. Most studies so far were performed in adults, which could account to differences in lipid profile.

Regarding the nutritional status and body composition, it is known that fat mass, especially central adiposity, are risk factors for cardiovascular disease. A study in preterm adults using dual emission x-ray absorptiometry showed increased fat mass and truncal fat compared to term adults [45]. Overweight and waist/height ratio >0.5 were observed in 20% and 18.2% of the preterm children, respectively.

Again, regarding the anthropometric evaluation, the preterm group had significantly lower height compared to the control group, which is in agreement with results of other studies. This slower growth of the very low birth weight preterm newborn can occur as early as 2 years of age and extend throughout childhood and adolescence, resulting in lower height in adulthood [46,47].

Advances in perinatal and neonatal medicine in recent decades have led to an increasingly higher number of surviving preterm newborns. Besides the neurodevelopment-related consequences, chronic non-communicable diseases in adolescents and young adults are emphasized, including cardiovascular, renal, and metabolic diseases [48]. Early nutrition and catch-up growth velocity may modify and influence this course. The identification and adequate monitoring of cardiovascular risk in prematurely born children can contribute to the planning of timely strategies to reduce the risk of the onset of these diseases throughout life.

This study showed for the first time that prepubertal preterm children evidence higher MPO concentrations and MPO/HDL-c ratios compared to term children. Further studies may establish whether the determination of these parameters may be useful in predicting cardiovascular risk in individuals born prematurely.

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Availability of data and material

The datasets used or analyzed in the current study are available from the corresponding author upon reasonable request.

Declaration of interest

The authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.08.012.

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