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Scientific Research

The Role of Asymmetric Dimethylarginine and Lipoprotein Associated Phospholipase A2 in Children and Adolescents with Dyslipidemia

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Abstract

Background: The pathophysiologic mechanisms which lead to cardiovascular (CV) events begin early in childhood. Atherosclerosis is recognized as a process of chronic and dynamic vascular inflammation induced primarily by endothelial dysfunction. Asymmetric dimethylarginine (ADMA) and lipoprotein associated phospholipase A2 (Lp-PLA2) are considered markers of early atherosclerosis and predictors of late complications in adults. Objectives: To establish the relationship between ADMA, Lp-PLA2 and traditional biochemically determined markers in children and adolescents with dyslipidemia. Material and Methods: The study population consisted of 102 children, 57 males/45 females, with a median age of 9.9 years. Seventy-one out of 102 had dyslipidemia (LDL-C levels ≥ 130 mg/dl). Lipid levels were estimated after an overnight fasting. LDL-C concentration was directly measured. ADMA and Lp-PLA2 levels were assessed by enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using STATA for Windows v8.5. Results: ADMA was significantly positively correlated with all TC, LDL-C and non-HDL-C. Even small changes of the ADMA concentration were found to be followed by corresponding alterations in lipid levels. A positive correlation of borderline significance between Lp-PLA2 and LDL-C or non-HDL-C was observed. In addition, ADMA and Lp-PLA2 were significantly correlated. A strong correlation between Lp-PLA2 and dyslipidemia or lipid levels could not be established, probably due

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to the size and heterogeneity of our sample. Conclusions: A relationship of ADMA and Lp-PLA2 levels with biochemical markers associated with long-term risk of atherosclerosis in children and adolescents is supported. The assessment of these two biomarkers combined may improve CV risk prediction and future management strategies in the pediatric population.

Keywords

Atherosclerosis, LDL-C, ADMA, Lp-PLA2, Childhood

1. Introduction

Cardiovascular diseases (CVD) are a major public health problem. Despite great advances in the field of prevention and clinical practice, CVD remain a leading cause of mortality and morbidity. Although adults are affected almost exclusively, it has been well documented that the pathophysiologic mechanisms which lead to cardiovascular (CV) events begin early in childhood [1]. Physicians and pediatricians should be aware of the importance of CV risk factors in childhood for the prediction of increased risk of CVD later in life [2] and take effective preventive measures of the modifiable ones [1].

Vascular dysfunction is considered as one of the hallmarks of atherosclerosis and its manifestations [3]. In particular, endothelial dysfunction precedes CV events and is considered a marker of early atherosclerosis and a predictor of late complications [4]. Asymmetric dimethylarginine (ADMA) is produced in human cells during proteolysis and reduces nitric oxide (NO) production by inhibiting the activity of nitric oxide synthase (NOS). Through the impairment of NO bioavailability, on which flow-mediated arterial vasodilatation depends, ADMA causes endothelial dysfunction, vasoconstriction and subclinical atherosclerosis. Although this naturally occurring amino acid has been thoroughly studied in adults as a strong risk and prediction marker for CV events [5]-[7], there is little research in pediatric conditions [8].

Atherosclerosis is recognized as a process of chronic and dynamic vascular inflammation induced primarily by endothelial dysfunction. Lipoprotein associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase or type VIIA PLA2, is considered to be a novel biomarker, highly specific for vascular inflammation and atherosclerosis [9]-[11]. Lp-PLA2 is released into the circulation from inflamed rupture-prone atherosclerotic plaques where it is densely concentrated. Secreted Lp-PLA2 mainly binds to Apolipoprotein B (ApoB) portion of low density lipoprotein (LDL-C) and hydrolyzes LDL-C into lysophosphotidylcholine (Lyso-PC) and arachidonic acid. In the atherosclerotic plaques Lp-PLA2 hydrolyzes oxidized LDL-C (oxLDL-C) into Lyso-PC and oxidized non-esterified fatty acids (oxNEFAs), both of which are lipid mediators of multiple inflammatory and atherogenic pathways [9]. Moreover, Lp-PLA2 has been currently recommended as an adjunct to traditional risk factors for CV risk evaluation [12] [13]. Simultaneous evaluation of risk factors is thought to be more effective in classification of CV risk [14] [15].

The aim of this study was to establish the relationship between ADMA, Lp-PLA2 and traditional biochemically determined markers in children and adolescents with dyslipidemia. To the best of our knowledge this is the first study that examines ADMA and Lp-PLA2 concurrently in the pediatric population.

2. Material and Methods

The study consisted of 102 children and adolescents (57 males/ 45 females, median age 9.9 years). All children were recruited from the Lipid Outpatient Clinic of the 2nd Department of Pediatrics of Athens University at "P. & A. Kyriakou" Children's Hospital. The study was approved by the local ethics committee. Written informed consent was obtained from parents or legal guardians.

Seventy one out of 102 children (40 males/31 females, median age 9.5 years) were classified as dyslipidemic and 31 (17 males/14 females) were stratified in the non-dyslipidemic group. Classification was based on LDL-C levels with a cut off level of 130mg/dl. At the time of enrollment, 13 children in the dyslipidemic group were being treated with lipid-lowering medication. None of the children in the non-dyslipidemic group received medications or vitamin supplementation. Exclusion criteria included other atherosclerotic risk factors, such as hypertension, diabetes mellitus, renal, liver and endocrine diseases.

Anthropometric data were obtained from all children according to a standardized protocol. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Venous blood samples were drawn in the morning after overnight fasting. All participants were well at the time of blood sampling. The lipid profile was analyzed on fresh serum samples. Concentrations of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) were assayed by enzymatic methods (Roche Diagnostics, Cobas Integra 800). LDL-C levels were directly measured by a homogenous assay (Roche Diagnostics, Cobas Integra 800). Non-HDL-C levels were calculated as the difference between concentrations of TC and HDL-C. All values are expressed in mg/dl. ADMA and Lp-PLA2 were analyzed in plasma. Samples were collected in EDTA tubes, placed in ice and immediately centrifugated at 1600 g at 4˚C for 10 minutes (Megafuge 16R, Thermo Scientific). Both ADMA and Lp-PLA2 were assessed by enzyme-linked immunosorbent assay (ELISA). The ELISA kit (Immundiagnostik, Bensheim, south-western Germany) for the quantitative determination of ADMA exhibited intra-assay coefficients of variation (CV) 5.8%, inter-assay CV 7.6% and detection limit 0.04 μmol/l. Similarly, intra-inter assay CV for Lp-PLA2 ELISA kit (USCN Life Science Inc., Houston, USA) was <10% and <12% respectively. The detection limit for Lp-PLA2 was 0.133 ng/ml. All samples were evaluated with the same assay.

3. Statistical Analysis

Frequency distributions were used for descriptive purposes. Median values along with 5th and 95th percentiles for baseline characteristics were computed for both dyslipidemic and non-dyslipidemic children. The association between TC, LDL-C, non-HDL-C, ADMA and Lp-PLA2, was estimated through Spearman rank correlation coefficients. Moreover, multivariate analysis using linear regression models was applied in order to estimate the relation of dyslipidemia with increasing levels of a) ADMA and b) Lp-PLA2. Linear regression was also used in order to assess the association of increased levels of 1) ADMA and 2) Lp-PLA2 with a) TC, b) LDL-C and c) non-HDL-C. Models were adjusted for potential confounders, *i.e.* for gender, age, BMI and presence of lipid-lowering treatment (Yes/No). Statistical analysis was performed using STATA for Windows v8.5. Statistical *tests were considered significant* when p-values were less than 5% (two-tailed).

4. Results

The baseline characteristics of the children investigated in the study are shown in **Table 1**. As expected, children with dyslipidemia exhibited significantly higher TC, LDL-C and non-HDL-C levels. At the time of sampling, 6 out of 13 children under medication had lipid levels within normal range. Correlations exhibited between ADMA, Lp-PLA2, TC, LDL-C and non-HDL-C levels are demonstrated in **Table 2**. ADMA was significantly positively correlated with TC, LDL-C and non-HDL-C ($p < 0.05$). ADMA and Lp-PLA2 also had significant relationship ($p < 0.001$). The positive correlation between Lp-PLA2 and LDL-C or non-HDL-C was of borderline significance. The association between Lp-PLA2 and TC did not reach statistical significance (data not shown).

The influence of dyslipidemia on ADMA and Lp-PLA2 levels is displayed in **Table 3**. Potentially confounding factors were taken into account. The presence of dyslipidemia resulted in increased levels for both molecules in question, but the impact was of borderline significance only for ADMA. Children younger than 11 years old exhibited more striking results ($p = 0.05$ & $p = 0.08$ for ADMA and Lp-PLA2 respectively, data not shown). **Table 4** displays the effect of ADMA and Lp-PLA2 increasing levels on TC, LDL-C and non-HDL-C. Potentially confounding factors were also taken into account. In fact, increment of ADMA was found to significantly increase TC, LDL-C and non-HDL-C levels ($p < 0.05$). As far as Lp-PLA2 is concerned, its increment also lead to increasing all variables levels, however the association found did not reach statistical significance.

5. Discussion

The present study supports that ADMA is independently associated with dyslipidemia in children and adolescents. Importantly, even small changes of the ADMA levels are found to be followed by corresponding alterations in TC, LDL-C and non-HDL-C levels. These observations are consistent with previously reported studies [16] [17].

Several studies have shown a relationship between ADMA and endothelial dysfunction, probably due to its role as an endogenous inhibitor of NO synthesis [18]-[22]. Degradation of NO synthesis is found to promote generalized atherosclerosis [23]. Elevated ADMA concentrations are found in adults suffering from conditions associated with atherosclerosis, including dyslipidemia. Moreover, increased ADMA levels were found to predict

Table 1. Frequency distributions for baseline characteristics.

	Overall (n = 102)			Non Dysplipidemic Group (n = 31)			Dyslipidemic Group (n = 71)		
	Median	**p5**	**p95**	**Median**	**p5**	**p95**	**Median**	**p5**	**p95**
Age	9.9	5.8	13.8	10.8	5.5	13.8	9.5	5.8	13.8
TC	221	148	344	178	126	212	243	164	356
LDL-C	145.5	85	263	98	68	126	171	105	298
HDL-C	57.5	39	90	59	39	99	57	39	85
TGs	53	30.5	116.5	56	30	101	51	31	128
Non-HDL-C	158.5	91	283	112	75	137	180	116	305
BMI	17.8	13.9	24.9	19.1	14.3	27.3	17.4	13.8	22.8
ADMA	0.60	0.47	0.77	0.57	0.42	0.73	0.62	0.49	0.78
Lp-PLA2	533.1	350.6	851.3	510.0	360.7	759.3	540.4	344.8	863.1

TC: Total Cholesterol, LDL-C: Low Density Lipoprotein-Cholesterol, HDL-C: High Density Lipoprotein-Cholesterol, TGs: Triglycerides, non-HDL-C: non High Density Lipoprotein-Cholesterol, BMI: Body Mass Index, ADMA: Asymmetric dimethylarginine, Lp-PLA2: Lipoprotein associated phospholipase A2. Age expressed in years, Lipid levels in mg/dl, BMI in kg/m^2, ADMA in μmol/l and Lp-PLA2 in ng/ml.

Table 2. Spearman correlation matrix between TC, LDL-C, non-HDL-C, ADMA and Lp-PLA2.

		TC	LDL-C	Non-HDL-C	ADMA	Lp-PLA2
TC	Rho	1				
	P					
LDL-C	Rho	0.965	1			
	P	0.000				
Non-HDL-C	Rho	0.959	0.983	1		
	P	0.071	0.000			
ADMA	Rho	0.225	0.261	0.264	1	
	P	0.000	0.008	0.007		
Lp-PLA2	Rho	0.151	0.174	0.180	0.368	1
	P	0.131	0.080	0.071	0.000	

Table 3. Beta coefficients (and confidence intervals) of dyslipidemia in linear regression model, using as dependent variable a) ADMA and b) Lp-PLA2, adjusting for sex, age, BMI and presence of treatment.

Dependent variable	b-coefficient	Se(b)	Confidence interval for b		p-value
ADMA	0.038	0.021	−0.004	0.079	0.076
Lp-PLA2	50.4	37.6	−24.2	125.1	0.183

Table 4. Association of 1) 0.1 μmol/l increment of ADMA and 2) 100 ng/ml increment of Lp-PLA2 with a) TC, b) LDL-C and c) non-HDL-C, through linear regression, adjusting for sex, age, BMI and presence of treatment.

Dependent variable		b-coefficient	Se(b)	Confidence interval for b		p-value
TC	ADMA	16.1	6.5	3.2	29.0	0.015
	Lp-PLA2	6.1	3.7	−1.2	13.5	0.102
LDL-C	ADMA	15.7	6.5	2.8	28.5	0.018
	Lp-PLA2	6.1	3.7	−1.3	13.4	0.105
Non-HDL-C	ADMA	16.3	6.6	3.2	29.4	0.015
	Lp-PLA2	6.4	3.8	−1.1	13.8	0.094

cardiovascular risk independently of other confounding variables [5]-[7] [24]-[26]. However, the role of ADMA in children and adolescents has been poorly investigated [8]. Independent association of ADMA with dyslipidemia in the pediatric population would be of potential significance in the evaluation and management of children with dyslipidemia.

In our sample, the increment of Lp-PLA2, led to an increase of TC, LDL-C and non-HDL-C levels, however the association did not reach statistical significance. In addition a positive correlation of borderline significance between Lp-PLA2 and LDL-C or non-HDL-C was observed. A strong correlation between Lp-PLA2 and dyslipidemia or lipid levels could not be established, probably due to the size and heterogeneity of our sample.

Lp-PLA2 was firstly introduced in the literature as a molecule with anti-inflammatory properties through the degradation of platelet-activating factor (PAF), a mediator of allergic and inflammatory reactions [27] [28]. Numerous studies followed which supported the notion that Lp-PLA2 is an agent involved in vascular inflammation participating in the atherosclerotic process and development [9] [11] [29]. Subsequently, international guidelines in adults propose the inclusion of Lp-PLA2 levels along with traditional factors for CV risk stratification [12] [13]. In addition, there is strong evidence that Lp-PLA2 reliably predicts CV events in adulthood [10] [30]. A study of Lp-PLA2 in children with heterozygous familial hypercholesterolemia and unaffected siblings demonstrated a significant correlation with lipid levels and a corresponding reduction with pravastatin therapy [31].

To the best of our knowledge this is the first study in children highlighting a significant relationship between ADMA and Lp-PLA2 levels. Simultaneous evaluation of multiple risk factors is thought to be more effective in classification of CV risk [14] [15]. The identification of measurable CV risk factors in childhood could be of paramount importance in primary and secondary prevention. Prevention in childhood has been shown to be much more effective and cost-saving than treating established CVD in adulthood. Given that vascular dysfunction and inflammation play a pivotal role in the atherosclerotic process and development, the investigation of biomarkers involved in the pathophysiologic mechanisms of subclinical vascular disease such as ADMA and Lp-PLA2 is of great importance [32].

6. Conclusion

In conclusion, the results of the present study support a relationship of ADMA and Lp-PLA2 levels with biochemical markers associated with long-term risk of atherosclerosis in children and adolescents. The inclusion of these two biomarkers combined may ameliorate our ability to assess CV risk prediction and future treatment strategies. Further studies exploring the exact role of ADMA and Lp-PLA2 in dyslipidemia, as well as in subclinical atherosclerosis are warranted, especially in the pediatric population.

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