ORIGINAL ARTICLE

Lipid profile of pediatric patients with chronic rheumatic diseases - a retrospective analysis

Wellington Douglas Rocha Rodrigues[1]
Roseli Oselka Saccardo Sarni[2]
Thais Tobaruela Ortiz Abad[1]
Simone Guerra Lopes da Silva[1]
Fabiola Isabel Suano de Souza[3]
Claudio Arnaldo Len[4]
Maria Teresa Terreri[4]

1. Nutricionista, Doutor, Departamento de Pediatria, Universidade Federal de São Paulo, São Paulo, SP, Brasil.
2. Médica assistente e pesquisadora associada, Universidade Federal de São Paulo, São Paulo, SP, Brasil.
3. Médica, Professora assistente, Departamento de Pediatria, Universidade Federal de São Paulo, São Paulo, SP, Brasil.
4. Médico, Professor associado, Departamento de Pediatria, Universidade Federal de São Paulo, São Paulo, SP, Brasil.

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SUMMARY

AIM: *To describe the prevalence of dyslipidemia in children and adolescents with autoimmune rheumatic diseases (ARDs), particularly juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus (jSLE), and juvenile dermatomyositis (JDM).*

METHODS: *Retrospective cross-sectional study conducted in the pediatric rheumatology outpatient clinic. We evaluated 186 children and adolescents between the ages of 5 and 19 years. The medical records were reviewed for the following data: demographic and clinical features, disease activity, and lipid profile (triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C) and very low density lipoprotein (VLDL-C)). In addition, non-HDL cholesterol was calculated as TC minus HDL-C. The cut-off points proposed by the American Academy of Pediatrics were used to classify the lipid profile.*

RESULTS: *Dyslipidemia was observed in 128 patients (68.8%), the most common being decreased HDL-C (74 patients, 39.8%). In the JIA group there was an association between the systemic subtype and altered LDL-C and NHDL-C, which demonstrated a more atherogenic profile in this subtype (p=0.027 and p=0.017, respectively). Among patients with jSLE, the cumulative corticosteroid dose was associated with an increase in LDL-C (p=0.013) and with a decrease in HDL-C (p=0.022).*

CONCLUSION: *Dyslipidemia is common in children and adolescents with ARDs, especially JIA, jSLE, and JDM, and the main alteration in the lipid profile of these patients was decreased HDL-C.*

KEYWORDS: *Juvenile idiopathic arthritis; Juvenile systemic lupus erythematosus; Juvenile dermatomyositis; Dyslipidemia*

INTRODUCTION

Cardiovascular diseases (CVDs) are highly prevalent and a serious public health problem in the general population.[1]

Evidence points to an association between autoimmune rheumatic diseases (ARDs) and increased risk of CVD.[1,2] The prevalence of acute myocardial infarction

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CORRESPONDING AUTHOR: Maria Teresa Terreri
Rua Borges Lagoa, 802, Vila Clementino, SP, Brasil – 04038-001
Tel: +55 11 5574-7627
E-mail: teterreri@terra.com.br

is approximately 50 times higher in women with systemic lupus erythematosus (SLE) than in those without the disease.[2] In relation to the pediatric population, a study evaluating the impact of juvenile SLE (jSLE) on cardiovascular risk demonstrated not only an incidence of infarction similar to that seen in adult onset SLE patients but also that the first event occurred much earlier (at 32 years of age on average).[3]

A recent study showed that adults with juvenile idiopathic arthritis (JIA) were five times more likely to have metabolic syndrome and consequent cardiovascular risk than healthy individuals.[4] A study evaluating adults with juvenile dermatomyositis (JDM) for 29 years showed changes in biomarkers and imaging exams associated with risk of CVD.[5]

Thus, with the increase in survival rates and the advancement in the treatment of ARDs, a new challenge arises: the identification of and early approach to risk factors for CVD.

In addition to the classic risk factors for the development of CVD, there are other triggers for ARD, such as chronic inflammatory processes and adverse events resulting from the therapy.

Our group has previously reported a high prevalence of dyslipidemia in children and adolescents with JIA and jSLE.[6-9] It is well established in the literature that dyslipidemia is a relevant factor for triggering the atherosclerotic process.[1] To our knowledge, this is the first study conducted in the pediatric population that describes the prevalence of dyslipidemia in individuals with JDM.

Therefore, the aim of this study was to describe the prevalence of dyslipidemia in children and adolescents with ARD, in particular JIA, jSLE and JDM.

METHODS

This was a retrospective cross-sectional study conducted in the pediatric rheumatology outpatient clinic. It involved 186 children and adolescents between five and 19 years of age with a diagnoses of JIA, jSLE, and JDM, according to the criteria of the International League of Association for Rheumatology (ILAR), the American College of Rheumatology (ACR), and the criteria of Bohan and Peter, respectively.[10-12]

Patients with any clinical manifestations and degree of disease activity, and having the disease for at least six months were included. Exclusion criteria were as follows: patients taking statins, pregnant women, patients with endocrine disorders, such as hypothyroidism, and with other autoimmune diseases or overlap syndrome. The medical records were reviewed for the following data: demographic and clinical features, disease activity, and lipid profile (triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), and very low density lipoprotein (VLDL-C)). Non-HDL cholesterol (NHDL-C) was also calculated as TC minus HDL-C. The cut-off points proposed by the American Academy of Pediatrics were used to classify the lipid profile.[13]

Wallace criteria were used to evaluate the activity of JIA.[14] The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[15] and the Systemic Lupus International Collaborating/ACR Damage Index (SLICC-ACR/DI)[16] were used to evaluate the activity of jSLE and irreversible cumulative damage. The activity of JDM was assessed considering the presence of skin alterations, muscle weakness, and increased levels of muscle enzymes.

SPSS software, version 20.0, was used to perform the statistical analysis. The categorical variables were expressed as frequencies and percentages and the continuous variables were presented as medians and interquartile intervals. The upper quartile (UQ) was used in the statistical analysis and was different for each disease: JIA: age ≥ 14.8 years, duration of progression ≥ 7.3 years, body mass index (BMI) ≥ 23.0, BMI-for-age Z-score (ZBMI) ≥ 1.6, height-for-age Z-score (ZHAZ) ≥ 0.47, erythrocyte sedimentation rate (ESR) ≥ 23.3, C-reactive protein (CRP ≥ 5.9); jSLE: age ≥ 18.6 years, duration of progression ≥ 6.6 years, BMI ≥ 24.3, ZBMI ≥ 1.08, ZHAZ ≥ -0.41, ESR ≥ 29, cumulative corticosteroid dose (CCD) ≥ 425.3 mg; and JDM: age ≥ 15.2 years, duration of progression ≥ 7.6 years, BMI ≥ 22.0, ZBMI ≥ 0.73, ZHAZ ≥ 0.29, and CCD ≥ 258.2 mg. Pearson's chi-square or Fisher's exact association tests were used for the qualitative variables, and logistic regression and Mann-Whitney test were used for the quantitative variables. The significance level was set at $p < 0.05$.

RESULTS

Table 1 shows the demographic, clinical, and laboratory data of children and adolescents with JIA, jSLE, and JDM, as well as their nutritional status. There was a predominance of patients with the oligoarticular subtype of JIA. According to the nutritional status classification, 63 patients (33.9%) were overweight/

TABLE 1. DEMOGRAPHIC, CLINICAL, AND LABORATORY FEATURES AND NUTRITIONAL STATUS OF CHILDREN AND ADOLESCENTS WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA), JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE), AND JUVENILE DERMATOMYOSITIS (JDM).

	JIA (N= 96)	jSLE (N= 62)	JDM (N=28)	Total (N=186)	*p*-value
Female	65 (67.7)	52 (83.9)	16 (57.1)	133 (71.5)	-
Age (years)	11.7 (5.1-19.0)	16.6 (5.2-19.0)	13.1 (5.2-19.0)	-	<0.001
Duration of progression (years)	4.4 (0.6-16.7)	4.6 (0.9-11.0)	5.0 (0.13-13.7)	-	0.691
Disease subtype					
Systemic N (%)	11 (11.4)	-	-	-	-
Polyarticular	38 (39.6)	-	-	-	-
Oligoarticular	47 (49)	-	-	-	-
BMI	19.3 (13.4-39.9)	21.3 (15.1-36.6)	18.2 (14.3-30.4)	-	0.136
≥ Upper quartile	24 (25.7)	16 (25.8)	7 (25)	47 (25.3)	-
ZBMI	0.57 (-3.4-+4.35)	0.28 (-2.48-+3.07)	0.3 (-1.79-+2.46)	-	0.365
ZHAZ	-0.23 (-3.56-+2.73)	-1.08 (-4.59-+1.05)	-0.91 (-2.39-+2.07)	-	0.001
Nutritional status					
Eutrophic	59 (61.5)	42 (67.7)	22 (78.6)	123 (67.2)	-
Overweight	22 (22.9)	11 (17.8)	4 (14.3)	37 (19.9)	-
Obese	15 (15.6)	9 (14.5)	2 (7.1)	26 (14)	-
Status of disease activity					
Active	32 (33.3)	-	8 (28.6)	40 (32.3)	-
SLEDAI ≥4	-	12 (19.4)	-	-	-
SLICC	-	5 (8.1)	-	-	-
us-CRP	1.8 (0.04-138.5)	2.67 (0.06-47.7)	-	-	-
≥ Upper quartile	22 (22.9)	-	-	-	-
ESR	12 (2-93)	14.7 (1-75)	-	-	1
≥ Upper quartile	22 (22.9)	16 (25.8)	-	38 (23.9)	-
Cumulative corticosteroid dose	-	267.8 (75-1212.8)	138.9 (32.3-572.6)	-	1
Glucocorticoids					
Yes	-	33 (53.2)	9 (32.1)	42 (46.7)	-
Biologics					
Yes	22 (22.9)	-	-	-	-
Non-biologics					
Yes	63 (65.6)	62 (100)	23 (82.1)	148 (79.6)	-

BMI: Body mass index; ZBMI: BMI-for-age Z-score; ZHAZ: height-for-age Z-score; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC: Systemic Lupus International Collaborating/ACR Damage Index; us-CRP: ultrasensitive C-reactive protein; ERS: erythrocyte sedimentation rate

TABLE 2. LIPID PROFILE OF CHILDREN AND ADOLESCENTS WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA), JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE), AND JUVENILE DERMATOMYOSITIS (JDM).

	JIA (N= 96)	jSLE (N=62)	JDM (N= 28)	Total (N=186)	*p*-value
TC	152.5 (101-313)	153.5 (105-259)	150 (90-277)	-	1
Borderline/High N (%)	27 (28.1)	20 (32.3)	6 (21.4)	53 (28.5)	-
LDL-C	90 (46-218)	85 (44-201)	85 (43.2-165)	-	0.285
Borderline/High N (%)	20 (20.8)	10 (16.1)	7 (25)	37 (19.9)	-
HDL-C	48.5 (17-82)	51 (27-93)	45 (25-90)	-	0.317
Borderline/Low N (%)	39 (40.6)	20 (32.3)	15 (56.3)	74 (39.8)	-
VLDL-C	15 (4.8-82)	17 (5-54)	19.5 (7-56)	-	0.223
NHDL-C	104 (61-243)	102 (57-220)	110 (51-199)	-	0.316
Borderline/High N (%)	28 (29.2)	12 (19.4)	11 (39.3)	51 (27.9)	-
TG	74 (31-271)	86 (45-270)	97 (35-279)	-	0.74
Borderline/High N (%)	33 (34.4)	24 (38.7)	14 (50)	71 (38.2)	-
Dyslipidemia N	65 (67.7)	42 (67.7)	21 (75)	128 (68.8)	-

TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; VLDL-C: Very-low-density lipoprotein cholesterol; NHDL-C: Non-high-density lipoprotein cholesterol; TG: Triglycerides

TABLE 3. DEMOGRAPHIC, CLINICAL, AND LABORATORY FEATURES AND LIPID PROFILE OF CHILDREN AND ADOLESCENTS WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA), JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE), AND JUVENILE DERMATOMYOSITIS (JDM).

	JIA										jSLE										JDM								
	TC	P	LDL	P	HDL	P	NHDL	P	TG	P	CT	P	LDL	P	HDL	P	NHDL	P	TG	P	CT	P	LDL	P	HDL	P	NHDL	P	TG	P
Women	19	0.727	13	0.767	24	0.304	19	0.83	24	0.446	18	0.365	9	0.531	17	0.836	11	0.38	21	0.529	5	0.196	4	1	6	0.047	7	1	8	1
Age ≥ UQ	9	1	4	0.186	8	0.003	10	0.346	11	0.74	0	0.053	0	0.176	3	0.702	0	0.13	3	1	3	0.634	2	0.678	5	0.706	4	1	7	0.218
Active disease	11	0.347	7	1	16	0.265	13	0.150	12	0.644	-	-	-	-	-	-	-	-	-	-	3	0.311	2	1	5	0.408	3	1	5	0.180
SLEDAI > 4	-	-	-	-	-	-	-	-	-	-	3	0.735	1	1	5	0.261	1	0.665	7	0.176	-	-	-	-	-	-	-	-	-	-
Duration of progression ≥ UQ	11	1	10	0.611	16	0.832	13	0.817	16	0.663	4	0.595	1	0.367	5	0.666	2	0.718	6	0.784	1	1	2	1	4	1	2	0.662	3	0.056
JIA subtype											-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Oligoarticular	14	0.06	11	0.027	17	0.379	16	0.017	15	0.052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Polyarticular	7		4		18		6		11		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Systemic	7		5		4		6		7		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ESR ≥ UQ	5	0.592	4	0.771	15	0.006	8	0.791	6	0.603	6	0.550	8	0.209	3	0.688	4	0.460	7	0.765	-	-	-	-	-	-	-	-	-	-
CRP ≥ UQ	5	0.434	3	0.378	12	0.204	6	0.602	7	1	7	0.211	2	1,00	5	0.503	3	0.693	8	0.232	-	-	-	-	-	-	-	-	-	-
ZBMI ≥ UQ	16	0.009	14	<0.001	17	0.259	18	<0.001	18	0.013	9	0.157	4	0.438	4	0.359	5	0.279	10	0.146	2	0.423	2	0.633	3	1	8	0.662	3	1
ZHAZ ≥ UQ	2	1	2	0.641	3	1	2	1	3	0.696	2	0.192	1	0.420	6	0.513	1	0.254	6	0.784	1	0.389	1	0.459	0	1	1	1	1	1
CCD ≥ UQ	-	-	-	-	-	-	-	-	-	-	7	0.211	6	0.013	9	0.022	6	0.057	7	0.551	2	0.622	3	0.328	3	0.662	4	0.391	4	0.661
Use of a biologic	7	0.788	5	0.768	9	1	6	1	7	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Use of a non-biologic	17	0.812	5	0.116	27	0.515	17	0.474	21	0.822	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

UQ: Upper quartile; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index 2000; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ZBMI: BMI-for-age Z-score; ZHAZ: height-for-age Z-score; CCD - Cumulative corticosteroid dose; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; NHDL-C: Non-high-density lipoprotein cholesterol; TG: Triglycerides

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obese. We observed that ZHAZ was lower among the patients with jSLE than among the other two groups of patients.

Table 2 shows the lipid profile of children and adolescents with JIA, jSLE, and JDM. Dyslipidemia was present in 128 patients (68.8%), the most common being decreased HDL-C (74 patients, 39.8%). TG elevation was the most prevalent dyslipidemia in patients with jSLE and decreased HDL-C in patients with JIA and JDM. We did not detect significant differences in lipid profile between the three diseases.

Table 3 shows the associations of demographic, clinical, and laboratory data with the lipid profile of children and adolescents with JIA, jSLE, and JDM. In the JIA group there was an association between the systemic subtype and LDL-C and NHDL-C abnormalities, which demonstrated a more atherogenic profile in this subtype (p=0.027 and 0.017, respectively). Logistic regression analysis showed that altered NHDL-C was associated with the JIA systemic subtype (p=0.002) (data not shown). High levels of ESR were associated with decreased HDL-C (p=0.006). With regard to the nutritional status, patients with JIA who had ZBMI ≥ 1.6 also had higher levels of TC (p=0.009), LDL-c (p<0.001), NHDL-c (p<0.001), and TG (p=0.013). Among the patients with jSLE, the CCD was associated with elevated LDL-C (p=0.013) and decreased HDL-C (p=0.022).

DISCUSSION

This study showed a high frequency of dyslipidemia in children and adolescents with JIA, jSLE, and JDM. The most prevalent dyslipidemia was decreased HDL-C.

Studies evaluating lipid metabolism-related biochemical markers in children and adolescents with ARD are of great relevance[6-9, 17] and have focused on patients with JIA and jSLE. To our knowledge, there are no studies assessing the frequency of dyslipidemia in the population with JDM, and this work is therefore the first on this topic.

The pathophysiological mechanisms involved in the origin of dyslipidemia and risk of CVD in ARD have not yet been fully elucidated. However, some studies[18-20] have shown that these diseases are associated with chronic inflammatory processes with elevated proinflammatory cytokines and also with adverse events related to drug therapy. In addition, classical risk factors for CVD such as unhealthy eating habits and poor lifestyle choices are involved.[6, 21, 22]

It has been previously reported that the prevalence of dyslipidemia in patients with ARD ranges from 46% to 85%.[23, 24] In our sample, the prevalence of dyslipidemia was 67.7% for JIA and jSLE and 75% for JDM.

Low HDL-C was the most frequently observed change among the cholesterol-carrying lipoproteins. Other studies that also evaluated the prevalence of dyslipidemia in childhood ARD have confirmed our findings.[8, 22]

Little is known about the causes of low HDL in ARD. However, it is worth noting that, in the presence of systemic inflammation, protective HDL can be converted into dysfunctional or pro-inflammatory HDL. This means that there is a modification in the protein content of the HDL molecules—a modification that favors the loss of its anti-inflammatory, anti-atherogenic, and anti-thrombotic effects, in addition to the loss of its function in the reverse transport of cholesterol.[25,26]

The most atherogenic lipid profile was observed in patients with the systemic subtype of JIA, with high levels of LDL-C and NHDL-C. Moreover, these patients had lower levels of HDL-C in association with increased ESR. It is known that the systemic subtype is associated with higher intensity of inflammation and manifestations such as anemia and thrombocytosis.

Our findings showed that JIA patients with a higher ZBMI had higher concentrations of TC, LDL-C, NHDL-C, and TG. In a study aiming to determine the prevalence of excess body mass and to investigate the influence of obesity on early subclinical changes in the cardiovascular system, Glowinska-Olszewska *et al.*[27] showed that patients with JIA and obesity had higher values of TC and TG than both non-obese JIA patients and healthy controls. Thus, these findings corroborate our results regarding these changes.

In relation to jSLE, we observed an association between CCD and high levels of LDL-C and low levels of HDL-C. Our findings are in line with those reported by other authors.[8, 28]

With regard to JDM, our results were similar to those obtained in patients with JIA and jSLE. There was a tendency for an association between the duration of disease progression and high concentrations of TG.

This study is the first to describe the prevalence of dyslipidemia in children and adolescents with JDM. However, it had some limitations, including its retrospective design and the absence of a control group.

CONCLUSION

We concluded that dyslipidemia is frequent in children and adolescents with ARD, especially JIA, jSLE, and JDM. The main change in the lipid profile of these patients was decreased HDL-C. Therefore, regular monitoring of lipid metabolism- related biomarkers is of paramount importance in the planning of interventions to reduce the risk of CVD in this population.

Declaration of conflict of interest

Nothing to declare

RESUMO

OBJETIVO: *Descrever a prevalência de dislipidemias em crianças e adolescentes com doenças reumáticas autoimunes (Drai), em particular artrite idiopática juvenil (AIJ), lúpus eritematoso sistêmico juvenil (Lesj) e dermatomiosite juvenil (DMJ).*

MÉTODOS: *Estudo transversal retrospectivo realizado no ambulatório de reumatologia pediátrica. Foram avaliados 186 crianças e adolescentes com idades entre 5 e 19 anos. Foram coletados dos prontuários dados demográficos, clínicos, atividade de doença e perfil lipídico (triglicérides (TG), colesterol total (CT) e frações LDL-c (low density lipoprotein); HDL-c (high density lipoprotein) e VLDL-c (very low density lipoprotein). Foi também calculada a fração não HDL do colesterol (CT-NHDL -c). Para classificação do perfil lipídico, foram adotados os pontos de corte propostos pela American Academy of Pediatrics.*

RESULTADOS: *A dislipidemia foi observada em 128 pacientes (68,8%), sendo a mais comum a diminuição do HDL-c em 74 (39,8%). No grupo AIJ houve uma associação entre o subtipo sistêmico com alteração de LDL-c e NHDL-c, mostrando um perfil mais aterogênico neste subtipo (p=0,027 e 0,017, respectivamente). Em relação aos pacientes com Lesj, podemos observar que a dose cumulativa de CTC teve associação com o aumento do LDL-c (p=0,013) e com a diminuição do HDL-c (p=0,022).*

CONCLUSÃO: *A dislipidemia é frequente em crianças e adolescentes com Drai, em especial, AIJ, Lesj e DMJ, e a principal alteração no perfil lipídico desses pacientes foi a diminuição do HDL-c.*

PALAVRAS-CHAVE: *Artrite idiopática juvenil. Lúpus eritematoso sistêmico juvenil. Dermatomiosite juvenil. Dislipidemia.*

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