CLINICAL SCIENCE

# Decreased high-density lipoprotein cholesterol levels in polyarticular juvenile idiopathic arthritis

**Roberta Gonçalves Marangoni, Andre L. Hayata, Eduardo F. Borba, Pedro M. Azevedo, Eloisa Bonfá, Claudia Goldenstein-Schainberg**

Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo/SP, Brazil.

**OBJECTIVES:** To investigate the prevalence of dyslipoproteinemia in a homogeneous cohort of polyarticular juvenile idiopathic arthritis patients.

**METHODS:** Based on the National Cholesterol Education Program, fasting lipoprotein levels and risk levels for coronary artery disease were determined in 28 patients with polyarticular juvenile idiopathic arthritis. The exclusion criteria included diabetes, thyroid dysfunction, smoking, proteinuria, lipid-lowering drugs, and hormone/diuretic therapy. Disease activity, disease duration, and therapy with corticosteroids and/or chloroquine were defined at the time of lipid measurements.

**RESULTS:** Dyslipoproteinemia was identified in 20 of the 28 (71%) patients with polyarticular juvenile idiopathic arthritis. The primary lipoprotein risk factor was decreased high-density lipoprotein cholesterol (57%), followed by elevated levels of low-density lipoprotein cholesterol (18%), triglycerides (14%), and total cholesterol (7%). The male patients had decreased high-density lipoprotein cholesterol levels than the female patients ($p<0.05$). The incidence of decreased high-density lipoprotein cholesterol levels did not seem to be affected by disease activity or therapy because the incidence was similar in patients with active or inactive disease, with or without corticosteroid use and with or without chloroquine use. In addition, the frequency of decreased high-density lipoprotein cholesterol levels was similar in patients with short ($\leq$5 years) *vs.* long (>5 years) disease duration.

**CONCLUSIONS:** Dyslipoproteinemia is highly prevalent in patients with polyarticular juvenile idiopathic arthritis and is primarily related to decreased high-density lipoprotein cholesterol levels; therefore, early intervention is essential.

**KEYWORDS:** Lipids; Atherosclerosis; Dyslipidemia; Rheumatic Disease; Juvenile.

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E-mail: cgs@usp.br

Tel.: 55 11 30617492

## INTRODUCTION

Overwhelming evidence indicates that abnormal lipoprotein levels play an important role in atherosclerotic processes that can be related to autoimmune disease. Indeed, the risk to develop atherosclerosis increases progressively with increasing low-density lipoprotein cholesterol (LDL) levels and declines with increasing levels of high-density lipoprotein cholesterol (HDL).[1] In adult patients with rheumatoid arthritis (RA), coronary artery disease (CAD) is the leading cause of shortened life expectancy relative to the general population,[2-4] and nearly half of these deaths can be attributed to CAD that is linked to inflammation and elevated C-reactive protein (CRP) levels.[5,6] Another important factor that certainly contributes to the development of atherosclerosis in rheumatological diseases is abnormal lipid levels. Of note, RA has its own pattern of dyslipoproteinemia (DL), and—though they are controversial—most studies have demonstrated decreased HDL levels in these patients.[7,8]

In juvenile idiopathic arthritis (JIA), the data regarding DL prevalence are scarce and do not conclusively define the role of JIA in this metabolic disturbance.[9-14] One study found altered lipid levels in both patients with active and inactive JIA,[9] whereas another study found that decreased HDL and elevated triglyceride (TG) levels were strongly correlated with the inflammatory state of the disease.[12] These contradictory findings may be explained by the broad spectrum of JIA subtypes because specific clinical and laboratory parameters can influence the lipid profile.[15] Furthermore, an altered lipid profile can occur in chronic inflammatory states that favor atherosclerosis.[16] Therefore, we evaluated the prevalence of DL in a homogeneous group of polyarticular JIA patients to define CAD lipoprotein risk in this patient population.

## METHODS

**Study population:** One hundred and eighty JIA patients who were regularly followed at the Rheumatology Division

of Hospital das Clínicas da Universidade de São Paulo were initially evaluated for this study. All of the patients fulfilled the International League of Associations for Rheumatology (ILAR) criteria for JIA.[17] Forty JIA patients were eligible for this study after excluding patients with diabetes mellitus, hypertension, renal disease, infection, thyroid or hepatic dysfunction, pregnancy, smoking, or the intake of drugs that could interfere with lipid metabolism (such as hormones, lipid-lowering agents, diuretics, and prednisone >10 mg/day). We then excluded JIA patients with systemic or oligoarticular JIA, enthesopathy-related arthritis (ERA), psoriatic arthritis, and inflammatory bowel disease to define a homogeneous group of 28 patients with polyarticular onset JIA. Corticosteroid and diphosphate chloroquine intake was calculated for each patient by analyzing the mean dosage over the previous three months and the stable dosage at least one month prior to inclusion in this study. The local ethics committee approved this study, and written, informed consent was obtained from each patient.

**JIA disease activity:** Clinical JIA disease activity was defined as the presence of clinically active synovitis in at least one joint together with an elevated erythrocyte sedimentation rate (ESR) (with normal defined as <12 mm/h) and/or elevated CRP levels (with normal defined as <5 mg/dl].

### Biochemical analysis

**Plasma lipid levels:** Each subject followed their own regular diet, and blood samples for lipoprotein evaluation were obtained after a 12-h overnight fast. Plasma total cholesterol (TC) and TG levels were measured enzymatically (Boehringer Mannheim, Buenos Aires, Argentina and Merck, Darmstadt, Germany, respectively) using an RA 1000 analyzer (Technicon Instruments Corp., Tarrytown, NY, USA).[18,19] HDL levels were obtained after precipitating very low-density lipoprotein cholesterol (VLDL) and LDL with phosphotungstic acid and magnesium chloride.[20] VLDL and LDL levels were estimated for samples with TG levels that were lower than 400 mg/dl.[21] VLDL levels were calculated by multiplying the TG level by 0.45, and LDL levels were estimated using the following equation: LDL = TC − (HDL+TG)/5.[21]

**Lipoprotein risk levels for CAD:** Lipoprotein risk levels for the JIA patients were determined based on the updated recommendations from the Brazilian consent guidelines for the detection and treatment of DL, which were established by the Brazilian Society of Cardiology and the Brazilian Society of Pediatrics.[22] These guidelines are in accordance with the National Cholesterol Education Program (NCEP) for subjects who are older than 20 years of age[23] and for children and adolescents (NCEP-Peds) ranging from 2 to 19 years of age.[24]

**Statistical analysis:** Values are expressed as the mean ± standard deviation (SD). Statistical comparisons were performed using the Mann-Whitney test, Kruskal-Wallis test, Student's *t*-test or $\chi 2$ test (Pearson Chi-square or Fisher's exact test), as appropriate. The relative risks for DL according to chloroquine and steroid intake and disease activity and duration were calculated by estimating the odds ratio (OR) and 95% confidence interval (95% CI) using unconditional binary logistic regression. Differences with a *p*-value <0.05 were considered to be significant. All of the analyses were performed using the Statistical Package of Social Sciences, version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

## RESULTS

We found a clear female predominance (75%) among the 28 polyarticular onset JIA patients. The mean age of all 28 patients was 19.9 ± 5.8 years, with 11 (39%) patients younger than 20 years and 17 (61%) patients older than 20 years. The mean weight and body mass index were 54 ± 10.2 kg and 21 ± 3.9 kg/m$^2$, respectively.

The mean disease duration was 9.4 ± 5.4 years. Upon joining the study, 17 of the patients (60.7%) had active JIA with a mean of four active joints (range 1-10 joints) and mean ESR and CRP levels of 26.4 ± 27.0 mm/h (range 1-110 mm/h) and 15.5 ± 23.2 mg/dl (range 0.26-76.9 mg/dl), respectively. At the time of their evaluation, 16 (57.1%) patients were taking diphosphate chloroquine at a mean dose of 227.2 ± 56 mg/day, range 50-250 mg/day (4 mg/kg/day), and nine (32.1%) patients were taking a low dose of prednisone with a mean dose of 5.8 ± 2.5 mg/day, range 2.5-10 mg/day (0.1 mg/kg/day). Additionally, 12 (42.8%) of the patients were on immunosuppressive therapy as follows: methotrexate at 18.7 ± 7.1 mg/day, range 10-30 mg/day (0.4 mg/kg/day), sulfasalazine at 2.2 ± 0.6mg/day, range 1.5-3.0 mg/day (0.04 mg/kg/day) and azathioprine at 75 ± 35.3 mg/day, range 50-100 mg/day (1.2 mg/kg/day). None of the patients were receiving biological therapy. All of the patients had a serum creatinine level below 1.3 mg/dl and a proteinuria level of less than 0.3 g (0.05 ± 0.01 g/24 h).

As shown in Table 1, the lipoprotein levels revealed a mean TC level of 150.3 ± 26.0 mg/dl, LDL level of 83.6 ± 23.1 mg/dl, HDL level of 50.6 ± 11.6 mg/dl, and TG level of 81.6 ± 49.4 mg/dl. According to the normal lipoprotein levels adjusted for the age range,[23,24] 57% of the subjects (16/28) had decreased HDL levels. In contrast, abnormal TC, LDL, and TG levels were observed in only 7 (2/28), 18 (5/28), and 14% (4/28) of the patients, respectively. Remarkably, the male patients had lower HDL levels than the female patients (42.6 ± 12.6 mg/dl vs. 53.3 ± 10.1 mg/dl, respectively; $p<0.05$) (Table 1).

Decreased HDL levels were not associated with disease activity ($p = 0.07$), corticosteroid ($p = 1.0$), or chloroquine therapy ($p = 0.4$). The frequency of patients with decreased HDL was similar in patients with a short (≤5 years) or long (>5 years) disease duration (50% *vs*. 50%, respectively; $p = 1.0$). A trend towards increased LDL levels was observed for the patients who were taking corticosteroid (OR: 9.0, 95% CI: 0.8 to 103.7, $p = 0.05$) but not for the patients were taking chloroquine or who had active JIA ($p>0.05$). Moreover, neither disease activity nor therapy influenced either the TC or TG levels ($p>0.05$).

An evaluation of the stratified lipoprotein risk factors for CAD revealed that 71% (20/28) of the patients had risk factors, with sixteen patients having one factor and four patients having two or more. Among the sixteen patients with a single lipoprotein risk factor, 81% (13/16) were attributed to decreased HDL levels.

## DISCUSSION

In this study, we found decreased HDL levels in polyarticular onset JIA patients, and this finding was not related to disease activity, disease duration, or therapy. Furthermore, we demonstrate here for the first time that male patients with polyarticular onset JIA have significantly lower HDL levels than female patients.

**Table 1 -** Characteristics and lipid profiles of 28 patients with polyarticular JIA.

| Variable | JIA patients (n = 28) | Female gender (n = 21) | Male gender (n = 7) | *p*-value† |
|---|---|---|---|---|
| Age, years | 19.86 ± 5.79 (5-29) | 20.00 ± 5.64 | 19.43 ± 6.68 | 0.826 |
| Age at diagnosis, years | 10.00 ± 5.03 (1-16) | 9.62 ± 4.96 | 11.14 ± 5.43 | 0.498 |
| Disease duration, years | 9.36 ± 5.41 (1-25) | 9.71 ± 5.12 | 8.29 ± 6.52 | 0.555 |
| Total cholesterol, mg/dl | 150.29 ± 26.04 (104-206) | 150.71 ± 26.44 | 149.00 ± 26.78 | 0.883 |
| Triglycerides, mg/dl | 81.61 ± 49.36 (33-255) | 72.62 ± 35.00 | 108.57 ± 75.82 | 0.265 |
| HDL, mg/dl | 50.61 ± 11.55 (30-74) | 53.29 ± 10.11 | 42.57 ± 12.62 | **0.031** |
| LDL, mg/dl | 83.61 ± 23.06 (41-138) | 83.29 ± 22.49 | 84.57 ± 26.58 | 0.901 |
| CV risk factor, number | 0.96 ± 0.92 (0-4) | 0.90 ± 0.89 | 1.14 ± 1.07 | 0.640 |

Except where indicated otherwise, data are expressed as mean ± standard deviation; the values in parentheses indicate the range. LDL – decreased-density lipoprotein cholesterol; HDL – high-density lipoprotein cholesterol; CV – cardiovascular. †*p*-values represent the correlation between female and male patients. The *p*-value in bold is statistically significant.

In contrast to previous studies, the lipid profile that we evaluated was focused on a homogeneous population of JIA patients with polyarticular onset.

JIA encompasses a broad spectrum of diseases, and a systemic onset has a pattern of inflammatory markers—with oligoarticular and polyarticular JIA subtypes having distinct markers—that can influence abnormal lipid levels.[15]

In this respect, there are differing reports of abnormal lipoprotein levels in JIA patients and a lack of a definitive prevalence of DL for this disease.[9-14] Ilowite and colleagues[9] were the first to describe an altered lipoprotein profile in both active and inactive JIA patients that was characterized by decreased HDL levels and increased TG and VLDL levels. Interestingly, these abnormalities were primarily observed in those patients with an active, systemic subtype of the disease.[9] In addition, an elevated TG level was the only finding that was observed in 99 Polish children with JIA (compared to age-matched healthy controls) when several subtypes of the disease were evaluated.[10] In contrast, no significant differences in TG, HDL, TC, or apolipoprotein B levels were detected between 37 Turkish JIA patients and 18 controls, although an inverse correlation between apolipoprotein A1 and inflammatory markers (ESR and CRP) was observed.[11] However, a study of 26 Greek children with JIA found decreased HDL and elevated TG levels that were strongly correlated with the inflammatory state of the disease.[12] Overall, ethnic differences, lifestyle, and environmental factors as well as genetic background may help explain these varied observations that are related to DL in patients with juvenile arthritis.[25,26]

Our results are in agreement with the majority of previous studies that have shown decreased HDL levels in patients with JIA. Decreased HDL levels have been described in patients with systemic lupus erythematosus (SLE); indeed, our group has previously reported decreased HDL levels in 88% of patients with juvenile SLE and a trend for an association of this reduced level with the active disease.[30]

In contrast to some studies that have demonstrated a correlation with active disease,[9,11,12] we found no association between decreased HDL cholesterol levels and disease activity; in this regard, abnormal lipid levels in active JIA may be related to the inflammatory state of the disease.[9,11,12] Considering the 15% probability of achieving disease remission within ten years of the initial diagnosis of polyarticular JIA,[31] most children will enter adulthood with ongoing active arthritis. In fact, more than 30% of our JIA patients still had active JIA five years after onset; thus, chronic inflammation seems to be a relevant issue of concern.

Although the relationship between physical activity and HDL was not addressed in this study, we can speculate that persistent active disease associated with physical incapacity due to functional impairment may play an important role in the dyslipidemic status that we observed in our JIA patients because a sedentary lifestyle is a contributing factor for decreased HDL. Moreover, decreased physical activity was recently associated with proinflammatory HDL in patients with SLE, which suggests that exercise can modulate the development of cardiovascular disease in this group of patients, possibly by decreasing inflammatory mediators.[32]

Alternatively, the role of drug intake may be a component of the abnormal lipid levels that we observed. Our findings cannot be explained by chloroquine treatment, which has a lipid-lowering effect that promotes an increase in HDL levels.[33] Moreover, decreased HDL levels cannot be related to steroid use, which enhances the levels of all lipid fractions.[34]

Furthermore, although diet intake was not specifically investigated, the majority of the children that we evaluated had a normal BMI, and we excluded children with diabetes or other factors that could have interfered with our evaluation of lipoprotein levels and CAD risk stratification.

In conclusion, we found a elevated prevalence of altered lipoprotein profiles in polyarticular onset JIA that was primarily related to decreased HDL levels and male gender, thereby emphasizing the need for early intervention in order to minimize this perturbation. Additional studies are needed to determine the role of diet, statins, and exercise in preventing cardiac events in JIA patients, with the aim of effectively assessing whether physical fitness and drug intake will have beneficial effects on future cardiovascular disease in these patients.

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