ORIGINAL ARTICLE

High frequency of lipoprotein risk levels for cardiovascular disease in Takayasu arteritis

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Abstract The objective of this study is to characterize the lipoprotein risk levels in Takayasu arteritis (TA) patients and its possible association with disease activity and glucocorticoid use. Twenty-five female TA patients were consecutively included and compared with 30 age-, gender-, and body mass index-matched healthy controls. Demographic features and the lipid profile were determined and cardiovascular risk levels were evaluated according to NCEP/ATPIII. Total cholesterol (TC), LDL-c, HDL-c, and triglycerides were determined after a 12-h overnight fast. Exclusion criteria were conditions that interfere in the lipid profile. The disease duration was 6.6 ± 7.4 years; 30% had clinical activity and 80% had laboratory activity. Regarding NCEP/ATPIII risk levels, TA patients presented higher frequency of lipid risk compared to controls: high TC (48% vs. 20%, $p=0.04$), low HDL-c (20% vs. 0%, $p=0.015$), and high triglycerides (36% vs. 10%, $p=0.026$). No difference was observed related to LDL-c risk levels between both groups (40% vs. 20%, $p=0.14$). Remarkably, 60% of the patients had at least one lipid risk factor for cardiovascular disease. No difference in the lipids was observed between patients with and without clinical activity; however, those with laboratory activity showed lower levels of HDL-c (1.37 ± 0.42 vs. 2.00 ± 0.63 mmol/L, $p=0.012$) than patients without this activity. A negative correlation was found between HDL-c and CRP levels ($r=-0.42$, $p=0.04$). Lipids were similar in patients under glucocorticoid compared to those without this therapy. This is the first study to identify that TA, an inflammatory disease, has a proatherogenic lipid profile which is associated to laboratory disease activity.

Keywords C-reactive protein · Dyslipidemia · Inflammatory markers · Lipid profile · Takayasu arteritis · Vasculitis

Introduction

Takayasu arteritis (TA) is a severe, chronic idiopathic inflammatory disease that primarily affects large vessels, thoracic, and abdominal aorta and its main branches [1]. Vessel inflammation and subsequent intimal proliferation of the involved arterial wall may lead to stenosis and occlusion while vessel dilatation or aneurysms may result from inflammatory process involving elastic lamina of arteries [2]. The usual serological finding in Takayasu arteritis is characterized by the presence of persistent high levels of inflammatory markers [3].

Over the last decade, atherosclerosis has also been recognized as an inflammatory vascular disease [4]. Moreover, one of the major risk factors for atherosclerosis is dyslipoproteinemia characterized by high plasma concentrations of cholesterol, in particular low-density lipoprotein (LDL) cholesterol, and low levels of high-density lipoprotein (HDL) cholesterol [5].

In this regard, autopsy studies have revealed atherosclerosis lesions in young patients with Takayasu arteritis [6–9]. Supporting these findings, image evaluation has confirmed early atherosclerosis in Takayasu arteritis [10–15].

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We therefore have undertaken the present study to determine the lipid profile in a homogeneous female young TA population in order to determine the cardiovascular lipid risk levels in this disease and its possible association with disease activity and glucocorticoid use.

Materials and methods

Patients

This study was conducted on 25 consecutive pre-menopausal women with TA, according to the American College of Rheumatology criteria [16], who were followed up at the Vasculitis Outpatient Clinic from the Rheumatology Division of São Paulo University Medical School. Thirty age-, sex-, and body mass index (BMI)-matched healthy pre-menopausal females served as controls.

The local ethics committees approved the study and written informed consent was obtained from patients and controls. Patients were clinically evaluated and medical records were extensively reviewed. Serum samples were obtained at the inclusion in the study.

Rigorous exclusion criteria of conditions that interfere in the lipid profile, such as diabetes mellitus, pregnancy, menopause, liver or thyroid disease, ingestion of lipid-raising drugs, or use of statins, were applied.

The following data were collected from all patients: identification, clinical manifestation, disease duration, risk factors for coronary disease, use of glucocorticoids, and clinical and laboratory disease activity. Clinical activity was defined based on the presence of new onset or worsening of fever or musculoskeletal problems, vascular ischaemia, or inflammation such as claudication, diminished or absent pulse, bruit, carotidynia, or asymmetric blood pressure (National Institute of Health (NIH) criteria) [17, 18]. High erythrocyte sedimentation rate (ESR) and/or ultrasensitive C-reactive protein (CRP) levels, in the absence of infection, characterized laboratory activity.

Lipid profiles

Cholesterol (total and fractions) and triglycerides (TG) in the serum were measured enzymatically (Boehringer Mannheim, Argentina, and Merck, Germany, respectively) on a RA 1000 analyser (Technicon Instruments Corp), as well as high-density lipoprotein cholesterol (HDL-c), after a 12-h overnight fast [19–21]. LDL-c was estimated since all samples had triglycerides less than 4.52 mmol/L [22]. Lipid parameters were considered to be altered when total cholesterol >5.18 mmol/L, low-density lipoprotein cholesterol >3.367 mmol/L, high-density lipoprotein cholesterol <1.036 mmol/L, and triglycerides >1.695 mmol/L. The risk levels of the lipid profile were evaluated according to the National Cholesterol Education Program—Adult Treatment Panel III (NCEP/ATPIII) [5].

Inflammatory markers

Ultrasensitive C-reactive protein serum levels were systematically determined in all patients by nephelometry. Erythrocyte sedimentation rate was measured using Westergren method. These parameters were considered to be altered when CRP >5 µg/mL and ESR >13 mm/first hour, according to the normal values from the laboratory of our hospital.

Statistical analysis

Data are reported as mean±SD, median, and percentage. Demographic and anthropometric variables were compared between patients and controls by the Student's t or Mann–Whitney tests. The frequency values of altered total and fraction cholesterol and triglycerides were compared

Table 1 Demographic, anthropometric, clinical, and laboratory features of Takayasu's arteritis patients and healthy controls

	Takayasu's arteritis patients ($n=25$)	Healthy controls ($n=30$)	p value
Age (years)	32.9±7.9	33.3±8.3	NS
BMI (kg/m^2)	24.9±4.8	24.3±3.9	0.59
White race (%)	70	70	NS
Disease duration (years)	6.6±7.4	NA	–
Clinical activity (%)	30	NA	–
Laboratorial activity (%)	80	ND	–
Current prednisone use (%)	56	NA	–
Current prednisone dose[a] (mg/day)	5.0 (0–15)	NA	–

Values are expressed in mean±SD, median (interquartile range), or percentage (%)

BMI body mass index, *NA* not applicable, *ND* not done, *NS* non-significant

[a] Median (interquartile range)

Table 2 Lipid profile and lipid risk levels according to NCEP/ATPIII risk levels in Takayasu's arteritis patients and healthy controls

	Takayasu's arteritis patients (n=25)	Healthy controls (n=30)	p value
Total cholesterol>5.18　mmol/L (%)	48	20	0.04
LDL-c>3.367　mmol/L (%)	40	20	0.14
HDL-c<1.036　mmol/L (%)	20	0	0.015
Triglycerides>1.695　mmol/L (%)	36	10	0.026

Values are expressed in percentage (%)

between patients and controls using chi-square or Fisher's exact tests. The P values <0.05 were considered to be significant.

Results

Patients and controls had a similar mean age, body mass index, and the frequency of white race. The mean disease duration was 6.6 years. Eighty percent of patients had systemic arterial hypertension. Thirty percent had clinical activity (NIH criteria) and 80% had laboratorial activity (high levels of erythrocyte sedimentation rate and/or C-reactive protein). More than half of the patients were in current use of prednisone (Table 1).

Significant higher levels of total cholesterol (5.18±0.87 vs. 4.65±0.78 mmol/L, p=0.02) and triglycerides (1.32± 0.70 vs. 0.89±0.48 mmol/L, p=0.01) were observed in patients compared to controls. HDL-c levels (1.49±0.52 vs. 1.54±0.31 mmol/L, p=0.69) and LDL-c levels (3.08±0.74 vs. 2.71±0.71 mmol/L, p=0.064) did not differ in both groups.

Regarding NCEP/ATPIII risk levels, TA patients present higher frequency of lipid risk compared to healthy controls: total cholesterol, low HDL-c, and high triglycerides. No difference was observed related to LDL-c risk levels between the two groups (Table 2). Remarkably, 60% of the patients had at least one lipid risk factor for coronary artery disease in spite of young age.

No difference in the lipid profile was observed between patients with and without clinical activity: total cholesterol (5.18±0.81 vs. 5.18±0.92 mmol/L, p=NS), HDL-c (1.32±

0.29 vs. 1.57±0.58 mmol/L, p=0.30), LDL-c (3.19±0.89 vs. 3.04±0.70 mmol/L, p=0.65), and triglycerides (1.47± 0.56 vs. 1.26±0.75 mmol/L, p=0.52). No significant difference in lipid profile was also found between patients in current use or not of prednisone: total cholesterol (5.25± 0.92 vs. 5.09±0.84 mmol/L, p=0.67), HDL-c (1.49±0.57 vs. 1.50±0.48 mmol/L, p=NS), LDL-c (3.09±0.82 vs. 3.07±0.66 mmol/L, p=NS), and triglycerides (1.46±0.57 vs. 1.14±0.82 mmol/L, p=0.26).

On the other hand, patients with laboratory activity showed lower levels of HDL-c than patients without this activity. No differences related to total cholesterol, LDL-c, and triglycerides were found between both groups (Table 3). In addition, a negative Spearman correlation was found between HDL-c and CRP levels (r=−0.42, p=0.04).

With regard to inflammatory markers, patients with Takayasu arteritis exhibited an increased mean level of CRP (8.7±9.3 mcg/mL) and ESR (21.7±12.2 mm/h). Importantly, 56% (n=14) of Takayasu patients had a high level of CRP and 68% (n=17) had high ESR levels.

Discussion

This is the first study to identify that Takayasu arteritis, an inflammatory disease, has a proatherogenic lipid profile, mainly characterized by low HDL levels during laboratory disease activity.

The accuracy of our data is supported by the study design with strict inclusion criteria. The selection of only pre-menopausal female patients was defined as an essential aspect to evaluate lipid profile in this disease since gender

Table 3 Lipid profile in Takayasu's arteritis patients with and without laboratory activity

	Takayasu's arteritis with laboratory activity (n=20)	Takayasu's arteritis without laboratory activity (n=5)	p value
Total cholesterol (mmol/L)	5.03±0.83	5.77±0.87	0.09
LDL-c (mmol/L)	3.05±0.77	3.19±0.70	NS
HDL-c (mmol/L)	1.37±0.42	2.00±0.63	0.012
Triglycerides (mmol/L)	1.33±0.72	1.27±0.67	NS

Values are expressed in mean±SD

is an important parameter that must be accounted for in dyslipidemia studies [23]. Concentrations of total cholesterol, LDL-c, and plasma triglycerides are lower, and HDL-c concentration is higher in pre-menopausal women compared with men, partially due to the effects of estrogen [24]. In addition, women normally have greater activity in lipoprotein transport and removal of VLDL-c from the plasma than men do [24]. Moreover, as patients are living longer, lipid abnormalities due to increasing age become relevant [25].

Importantly, all our patients were matched by BMI and also were within normal range for this parameter. Actually, being overweight and obesity are well known factors that modify the lipid profile [24].

Furthermore, the rigorous exclusion criteria used to select Takayasu patients without other conditions that could interfere with lipid metabolism such as diabetes, thyroid disease, renal and hepatic involvements, and use of lipid-lowering drugs provided a unique opportunity to define more accurately the lipid profile in this population [26–29].

Another important factor that could play a role in vascular atherogenesis, mainly in inflammatory disease, is the glucocorticoid treatment. This drug is the gold standard for TA treatment [30] and long-term treatment with these drugs is known to cause hyperlipidemia due to induced LDL hepatic synthesis and decreased LDL catabolism [31, 32]. In this study, LDL-c NCEP/ATPIII risk levels were comparable in TA patients and controls. Furthermore, our data did not show any association between use of glucocorticoids and lipid profile alterations; however, more studies in large cohorts are necessary to substantiate the role of corticosteroid in TA atherogenesis.

The main finding of the present study was to demonstrate that during laboratory activity TA patients display low levels of HDL-c, and this particle was negatively correlated with CRP. Low HDL-c is a well-established independent risk factor for atherosclerosis [33]. This lipid alteration is also observed during flares of systemic lupus erythematosus (SLE) and rheumatoid arthritis. In fact, the lipid profile of patients with active and untreated RA is primarily characterized by a decrease in serum levels of high-density lipoprotein cholesterol [34]. Similarly, our group studying female inactive SLE patients without corticosteroids has demonstrated that these patients have low levels of HDL-c and high triglyceride levels compared to healthy controls, and these abnormalities are enhanced by lupus disease activity. Moreover, these lipid alterations were particularly associated with vasculitis [35, 36]. Recently, Quéméneur et al. have demonstrated, in 33 patients with systemic vasculitis (including two patients with Takayasu arteritis), a negative association between CRP and HDL-c as observed in the present study [37]. These data suggest that the inflammatory process leading to vasculitis seems to be extremely relevant to induce an atherogenic lipid profile.

The remarkable association of low HDL-c with elevated CRP levels, demonstrated herein, reinforces the role of inflammation and disease activity in the atherosclerosis process in Takayasu patients.

This is the first study to identify that patients with Takayasu's arteritis have a proatherogenic lipid profile. Longitudinal studies are needed to evaluate if lipid preventive intervention could be therefore recommended for these patients.

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