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ORIGINAL ARTICLE

Link Between Traditional Cardiovascular Risk Factors and Inflammation in Patients With Early Arthritis: Results From a French Multicenter Cohort

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Objective. **To compare the characteristics of traditional cardiovascular risk factors for untreated patients with early arthritis (EA) and healthy subjects, and to look for a link between cardiovascular risk factors and inflammation in EA patients.**

Methods. **This multicenter case–control study enrolled 607 patients with EA (ESPOIR cohort) and 1,821 age- and sex-matched controls (World Health Organization MONICA survey). Lipid levels, blood pressure, glucose levels, and exposure to smoking were characterized in patients and controls. Systemic inflammation was quantified in EA patients. Traditional cardiovascular risk factor characteristics were compared between patients with EA and controls. The link between cardiovascular risk factors and inflammation was assessed in EA patients.**

Results. **Mean ± SEM total cholesterol (2.14 ± 0.022 versus 2.34 ± 0.017 gm/liter; $P < 0.001$), high-density lipoprotein (HDL) cholesterol (0.60 ± 0.011 versus 0.63 ± 0.007 gm/liter; $P = 0.020$), and low-density lipoprotein (LDL) cholesterol (1.28 ± 0.025 versus 1.51 ± 0.016 gm/liter; $P < 0.001$) were lower in EA patients than in controls. Triglycerides, triglycerides/HDL ratio, and pulse pressure were higher in patients with EA. Diastolic blood pressure and glucose levels were lower in EA patients. Former or current smokers were more frequent in patients with EA. Total and HDL cholesterol levels were negatively associated with C-reactive protein or serum interleukin-6 levels.**

Conclusion. **Total, HDL, and LDL cholesterol, triglycerides, diastolic blood pressure, pulse pressure, glucose, and triglycerides/HDL ratio differ between patients with EA and controls. Some of these risk factors appear to be linked to systemic inflammation. Such initial differences could modulate the risk of cardiovascular events later in the course of arthritis.**

INTRODUCTION

Rheumatoid arthritis (RA) is characterized by a significant increase in mortality rate, principally cardiovascular in origin. Higher mortality rates in patients with RA could be predicted by more severe clinical disease and comorbid cardiovascular disease (CVD) (1). A recent meta-analysis estimated a 60% increase in the risk of death from CVDs compared to the general population (2). This increase in cardiovascular mortality rate is the result of an increase in the risk of myocardial infarction, stroke, and heart failure (3,4). In general, patients with RA have a greater preva-

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Significance & Innovations

- We performed a large multicenter case–control study assessing traditional cardiovascular risk factors in a cohort of untreated patients with early arthritis (EA) and in a cohort of healthy age- and sex-matched controls.
- Total, high-density lipoprotein, and low-density lipoprotein cholesterol levels are lower in EA patients than in age- and sex-matched healthy controls.
- Serum interleukin-6 levels were negatively associated with cholesterol levels in patients with EA.
- Results were obtained in EA patients who had never taken corticosteroids and disease-modifying antirheumatic drugs.

lence of atheroma and an increase in the thickness of the intima-media of carotid arteries, established markers of atherosclerosis (5).

Recent epidemiologic data show that traditional cardiovascular risk factors and systemic inflammation, higher in severe forms of RA, contribute jointly to an increase in the risk of CVD (6). In addition, experimental data emphasize the key role of inflammation in the constitution and evolution of atheroma (7).

Among the traditional cardiovascular risk factors, most studies show an increase in the prevalence of smoking in RA (8–11). Smoking is involved in the triggering, the production of anticitrulline antibodies, and the severity of the disease (12). The prevalence of the other traditional cardiovascular risk factors is variable according to which study is looked at, with results that are sometimes contradictory with regard to hypertension (5,10–11,13) or diabetes mellitus (10,11,14). Numerous confounding factors can explain these differences, in particular how long RA has been in place and its severity, as well as the impact of certain types of treatment, either on blood pressure with nonsteroidal antiinflammatory drugs (15,16), on the metabolism of carbohydrates for corticosteroids (16), or more generally on morbidity or mortality from cardiovascular causes (17).

The prevalence of dyslipidemia during the course of RA also varies according to some studies, which may be due to disease duration or the impact of medications on lipid levels (18). The first study having reported a link between abnormalities in lipid profiles and level of activity of certain inflammatory rheumatic diseases suggested a decrease of 20–30% of total cholesterol and very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels in 69 patients with RA or spondylarthropathy in comparison to healthy subjects (19). This same study established a connection between these abnormalities in lipid profiles and the level of inflammatory activity (19). Later, several studies devoted to assessing the lipid profiles of patients with RA reported conflicting results (20–23).

Inflammation in general and interleukin-6 (IL-6) in particular may play a central role in the decrease in total cholesterol levels and fractions of cholesterol observed during acute or chronic inflammatory states (24,25). This action of IL-6 on the metabolism of lipids might explain the increase in total, LDL, and HDL cholesterol observed in RA patients treated with an anti–IL-6 receptor monoclonal antibody, tocilizumab (26).

In the present case–control observational study, we compared the prevalence and the mean level of traditional cardiovascular risk factors observed in a French multicenter cohort of patients with early arthritis (EA) who had never taken corticosteroids and disease-modifying antirheumatic drugs (DMARDs; ESPOIR cohort) (27) with those observed in controls from a multicenter survey that collected the traditional cardiovascular risk factors in a sample recruited from the French general population (World Health Organization [WHO] MONICA survey) (28). We then assessed, in the patients with EA, the link existing between traditional cardiovascular risk factors and the level of systemic inflammation, characterized by the concentration of C-reactive protein (CRP) or serum IL-6, in patients meeting the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 classification criteria for RA or not (29).

SUBJECTS AND METHODS

Constitution of the case sample. The cases were derived from a French cohort of 813 patients ages 18–70 years who had developed EA in the previous 6 months, characterized by the presence of at least 2 inflammatory joint sites for at least 6 weeks, who had never taken corticosteroids and DMARDs, and who were referred to 16 university hospital rheumatology departments (ESPOIR cohort) (27). Only patients between the ages of 35 and 64 years were included in the analysis so that there was a match with the age group of the control sample (28). Patients were classified into 2 subgroups according to whether they met the ACR/EULAR 2010 classification criteria for RA or not (29).

The ESPOIR cohort study protocol was approved in July 2002 by the Ethical Committee in Montpellier, France. All of the patients signed an informed consent form before inclusion (27).

Constitution of the control sample. Controls were recruited within the framework of the Third French WHO MONICA population survey on cardiovascular risk factor prevalence, conducted in 3 different parts of France: Lille

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Urban Community in Northern France, the Bas-Rhin metropolitan area in Eastern France, and the Haute-Garonne metropolitan area in Southern France. Subjects ages 35–64 years were selected randomly from electoral rolls after stratification by town size, sex, and age (28).

The WHO MONICA population survey protocol was approved by the appropriate independent ethics committees. All of the patients signed an informed consent form before inclusion (28).

Collection of clinical and biologic data of cases. Demographic data, medical history, and physical measurements of the cases were assessed as previously described (27). Blood pressure was measured after 10 minutes of rest by an experienced nurse. A fasting blood sample was drawn into a disodium EDTA tube (after the subjects had fasted for at least 10 hours), stored at room temperature, and centrifuged within 4 hours. Cholesterol, HDL cholesterol, triglyceride, and glucose concentrations were measured using standard methods in the biochemistry laboratory of each of the 16 university hospitals on the same day, without preliminary freezing. LDL cholesterol was determined by the Friedewald equation when triglycerides were lower than 4 gm/liter.

CRP level (normal value <10 mg/liter), IgM and IgA rheumatoid factors (enzyme-linked immunosorbent assay [ELISA], Menarini; positive at >9 IU/ml), and anti–cyclic citrullinated peptide 2 antibodies (ELISA, DiaSorin; positive at >50 units/ml) were quantified in a central laboratory (Bichat University Hospital, Paris, France) on serum samples collected at inclusion and immediately stored at −80°C until time of analysis (27).

The study protocol of the ESPOIR cohort did not plan to establish the interlaboratory variability for blood pressure or lipid and glucose measures. All of the measurements were performed in clinical research units and biochemistry laboratories of the university hospitals.

Collection of clinical and biologic data of controls. Demographic data, medical history, and physical measurements of the controls were assessed as previously described (28). Blood pressure was measured after 10 minutes of rest by an experienced nurse. A fasting blood sample was drawn into a disodium EDTA tube (after the subjects had fasted for at least 10 hours), stored at room temperature, and centrifuged within 4 hours. All of the measurements were performed in a central laboratory (Toulouse University Hospital, Toulouse, France) on briefly frozen samples. Cholesterol and triglyceride concentrations were measured using enzyme assays (Olympus). HDL cholesterol was measured after sodium/magnesium chloride precipitation (Olympus). Glucose was measured using the standard glucose hexokinase method (DuPont Dimension). LDL cholesterol was determined by the Friedewald equation when triglycerides were lower than 4 gm/liter (28).

Characterization of cardiovascular risk factors for the cases and controls. Hypercholesterolemia was established if the patient had treated hypercholesterolemia or if LDL cholesterol was ≥1.60 gm/liter as per the international guidelines (30). High blood pressure was established if the patient declared being hypertensive and under treatment or if blood pressure was ≥140/90 mm Hg, as per the international guidelines (30). Pulse pressure (the difference between systolic and diastolic blood pressure), which is known to be linked to vascular damage, was calculated (31). Diabetes mellitus was established if the patient had type 1 or 2 diabetes mellitus and was under treatment or had a blood glucose level ≥1.26 gm/liter, as per the international guidelines (30). The triglycerides/HDL ratio was used as a marker of insulin resistance (32). Subjects were categorized as never smokers, former smokers, and current smokers.

Quantification of serum IL-6 in cases. IL-6 (detection threshold 1.5 pg/ml) was quantified in patients at a central laboratory (Division of Immunology and Allergy, University Hospital of Geneva, Geneva, Switzerland) on serum samples collected at inclusion and stored at −80°C until analysis, using a commercially available multiplex bead immunoassay based on the Luminex platform (Fluorokine MAP Multiplex Human Cytokine Panel, R&D Systems), according to the supplier's instructions.

Statistical analysis. Matching of the cases and controls was done according to age, sex, and living area. Matching for living area was carried out because of the presence of a decreasing north–south gradient of incidence of ischemic coronary heart disease in France and of the prevalence of some associated risk factors (online at http://www.invs.sante.fr/beh/2006/08_09/beh_08_09_2006.pdf). Three controls were selected for each case (1 in each of the 3 French MONICA areas). When more than 3 controls were available for 1 case, a draw was carried out among all of the controls, corresponding to the criteria for matching.

Statistical analysis was performed on SAS statistical software. The distribution of all of the variables was described at inclusion in the 2 cohorts in terms of percentages for qualitative variables, means ± SDs for continuous variables with normal distribution, and medians (interquartile ranges) otherwise.

The chi-square test and Student's *t*-test were used to compare unadjusted percentages and means between patients from the ESPOIR cohort and subjects from the WHO MONICA survey. The SAS generalized linear model procedure was used to provide and compare adjusted means of lipids, blood pressure, and glucose between the controls and cases. Data related to lipids were adjusted for body mass index (BMI), hormone replacement therapy, and use of lipid-lowering and antihypertensive drug treatments, as these variables may play the role of confounders. Data related to blood pressure were adjusted for BMI, hormone replacement therapy, and use of antihypertensive drug treatments. Analyses regarding glucose were adjusted for BMI, hormone replacement therapy, and use of hypoglycemic drug treatments. For triglycerides, triglycerides/HDL ratio, and glucose, *P* values were computed on log-transformed data.

The ESPOIR population was first analyzed as a whole and then was split into 2 subgroups, depending on

Table 1. Main characteristics of patients with EA (ESPOIR cohort) and controls (WHO MONICA survey)*

	ESPOIR cohort (n = 607)	WHO MONICA survey (n = 1,821)	*P*
Age, mean ± SD years	51.1 ± 8.0	51.1 ± 8.1	0.962
Age groups, years			0.998
35–45	152 (25.0)	458 (25.1)	
45–55	237 (39.1)	711 (39.1)	
55–65	218 (35.9)	652 (35.8)	
Female sex	461 (75.9)	1,383 (75.9)	1.000
Menopausal women	246 (40.5)	715 (39.3)	0.582
Hormone replacement therapy	78 (12.8)	301 (16.5)	0.030
BMI, mean ± SD kg/m^2 (n = 605/n = 1,799)	25.4 ± 4.7	26.2 ± 5.0	0.002
Antihypertensive drug treatment	105 (17.3)	305 (16.7)	0.754
Hypertension (n = 595/n = 1,810)	231 (38.8)	728 (40.2)	0.546
Lipid-lowering drug treatment	69 (11.4)	203 (11.1)	0.882
Hypercholesterolemia (n = 343/n = 1,796)	106 (30.9)	719 (40.0)	0.001
Hypoglycemic drug treatment	23 (3.8)	53 (2.9)	0.282
Diabetes mellitus (n = 564/n = 1,821)	55 (9.7)	177 (9.7)	0.982
Smoking status			0.005
Never smoker	312 (51.4)	1,068 (58.6)	
Past smoker	168 (27.7)	449 (24.7)	
Current smoker	127 (20.9)	304 (16.7)	
Disease duration, mean ± SD months	3.4 ± 1.6	–	
ESR, median (IQR) mm/hour (n = 601)	21 (12–38)	–	
CRP level, median (IQR) mg/liter	8 (0–21)	–	
IL-6 serum concentration, median (IQR) pg/ml (n = 558)	3.4 (0–12.2)	–	
RF positive	290 (47.8)	–	
Anti–CCP-2 positive	242 (39.9)	–	
RA criteria positive†	442 (72.8)	–	

* Values are the number (percentage) unless otherwise indicated. EA = early arthritis; WHO = World Health Organization; BMI = body mass index; ESR = erythrocyte sedimentation rate; IQR = interquartile range; CRP = C-reactive protein; IL-6 = interleukin-6; RF = rheumatoid factor; anti–CCP-2 = anti–cyclic citrullinated peptide 2.
† 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (RA) (29).

whether the patients met the ACR/EULAR 2010 classification criteria for RA or not (29). Each time more than 2 groups were compared, Tukey's test was used to compute *P* values in order to take into account inflation of Type I error.

RESULTS

Main characteristics of EA patients (ESPOIR cohort) and controls (WHO MONICA survey). The main characteristics of the EA patients and controls and the main biologic and immunologic characteristics of the patients with EA are shown in Table 1.

The mean ± SD BMI was significantly lower in EA patients than in controls (25.4 ± 4.7 kg/m^2 versus 26.2 ± 5.0 kg/m^2; $P = 0.002$), and the percentage of women receiving hormone replacement therapy was lower in patients with EA than in controls (12.8% versus 16.5%; $P = 0.03$). The prevalence of hypercholesterolemia was lower in EA patients than in controls (30.9% versus 40.0%; $P = 0.001$), and the distribution of smoking status was significantly different between the cases and controls ($P = 0.005$).

Comparison of plasma lipids, blood pressure, and plasma glucose between EA patients (ESPOIR cohort) and controls (WHO MONICA survey). The results of the comparison of traditional cardiovascular risk factors between the patients and controls are shown in Table 2.

Total cholesterol, HDL cholesterol, LDL cholesterol, and total cholesterol/HDL ratio were significantly lower in patients with EA than in controls. Diastolic blood pressure was significantly lower in EA patients than in controls, whereas there was no significant difference in systolic blood pressure. Pulse pressure was significantly higher in patients with EA than in controls. Fasting glucose was significantly lower in EA patients than in controls. Triglycerides and triglycerides/HDL ratio, which is a marker of insulin resistance, were significantly higher in patients with EA than in controls. The prevalence of current or former smokers was significantly higher in EA patients than in controls (data not shown).

Table 2. Comparison of plasma lipids, blood pressure, and plasma glucose between patients with EA (ESPOIR cohort) and controls (WHO MONICA survey)*

	ESPOIR cohort (n = 607)	WHO MONICA survey (n = 1,821)	*P*
Total cholesterol, gm/liter (n = 577/n = 1,799)	2.14 ± 0.022	2.34 ± 0.017	< 0.001
HDL cholesterol, gm/liter (n = 316/n = 1,797)	0.60 ± 0.011	0.63 ± 0.007	0.020
LDL cholesterol, gm/liter (n = 315/n = 1,774)	1.28 ± 0.025	1.51 ± 0.016	< 0.001
Total cholesterol/HDL ratio (n = 316/n = 1,797)	3.84 ± 0.086	4.07 ± 0.055	0.005
Triglycerides, gm/liter (n = 580/n = 1,799)	0.99 ± 0.025	0.92 ± 0.019	0.001
Triglycerides/HDL ratio (n = 316/n = 1,797)	1.74 ± 0.042	1.54 ± 0.027	0.001
Systolic BP, mm Hg (n = 593/n = 1,788)	135.4 ± 0.814	136.7 ± 0.585	0.093
Diastolic BP, mm Hg (n = 593/n = 1,785)	79.5 ± 0.516	83.1 ± 0.371	< 0.001
Pulse pressure, mm Hg (n = 593/n = 1,785)	55.8 ± 0.617	53.6 ± 0.444	< 0.001
Glucose, gm/liter (n = 570/n = 1,799)	1.13 ± 0.013	1.20 ± 0.011	< 0.001

* Values are the adjusted mean ± SEM. For triglycerides, triglycerides/HDL ratio, and glucose, *P* values are computed on log-transformed data and the geometric mean is shown in the table. EA = early arthritis; WHO = World Health Organization; HDL = high-density lipoprotein; LDL = low-density lipoprotein; BP = blood pressure.

Comparison of plasma lipids, blood pressure, and plasma glucose between EA patients meeting the ACR/EULAR 2010 classification criteria for RA or not (ESPOIR cohort) and controls (WHO MONICA survey). The results of the comparison of plasma lipids, blood pressure, and plasma glucose between patients with EA meeting the ACR/EULAR 2010 classification criteria for RA or not (29) and controls are shown in Table 3.

The differences observed between EA patients meeting the ACR/EULAR 2010 classification criteria for RA and controls were similar to those previously observed in Table 2, except for HDL cholesterol and total cholesterol/HDL ratio, which did not reach statistical significance, probably because of the patient sample size.

The differences observed between patients with EA not meeting the ACR/EULAR 2010 classification for RA and controls remained statistically significant for total and LDL cholesterol, diastolic blood pressure, and glucose level, but were no longer significant for HDL cholesterol, total cholesterol/HDL ratio, triglycerides, triglycerides/HDL ratio, and pulse pressure, probably because of the patient sample size.

The distribution of smoking status significantly differed between patients positive for the RA criteria and WHO MONICA controls, with a lower prevalence of current and past smoking in controls. No difference was observed between patients negative for the RA criteria and controls (data not shown).

Link between the level of systemic inflammation and plasma lipids, blood pressure, and plasma glucose in patients with EA (ESPOIR cohort). The results of the search for a link between plasma lipids, blood pressure, and plasma glucose on the one hand, and systemic inflammation on the other hand, assessed on CRP and serum IL-6 levels in EA patients are shown in Tables 4 and 5, respectively.

With regard to the link with CRP levels, total, HDL, and

Table 3. Comparison of plasma lipids, blood pressure, and plasma glucose between patients with EA meeting the ACR/EULAR 2010 classification criteria for RA (29) or not (ESPOIR cohort) and controls (WHO MONICA survey)*

	RA criteria–positive patients (n = 442)	RA criteria–negative patients (n = 165)	WHO MONICA survey (n = 1,821)	RA criteria positive vs. controls, *P*	RA criteria negative vs. controls, *P*
Total cholesterol, gm/liter	2.15 ± 0.024	2.12 ± 0.035	2.34 ± 0.017	< 0.001	< 0.001
HDL cholesterol, gm/liter	0.60 ± 0.013	0.61 ± 0.019	0.63 ± 0.007	0.085	0.487
LDL cholesterol, gm/liter	1.28 ± 0.029	1.28 ± 0.042	1.51 ± 0.016	< 0.001	< 0.001
Total cholesterol/HDL ratio	3.85 ± 0.098	3.83 ± 0.142	4.07 ± 0.055	0.052	0.192
Triglycerides, gm/liter	0.99 ± 0.028	0.99 ± 0.040	0.92 ± 0.019	0.009	0.191
Triglycerides/HDL ratio	1.75 ± 0.048	1.73 ± 0.070	1.54 ± 0.027	0.012	0.214
Systolic BP, mm Hg	135.6 ± 0.909	134.7 ± 1.394	136.7 ± 0.585	0.454	0.301
Diastolic BP, mm Hg	79.7 ± 0.576	78.9 ± 0.884	83.1 ± 0.371	< 0.001	< 0.001
Pulse pressure, mm Hg	55.9 ± 0.690	55.7 ± 1.058	53.6 ± 0.444	0.002	0.088
Glucose, gm/liter	1.14 ± 0.014	1.10 ± 0.017	1.20 ± 0.011	< 0.001	< 0.001

* Values are the adjusted mean ± SEM. For triglycerides, triglycerides/HDL ratio, and glucose, *P* values are computed on log-transformed data and the geometric mean is shown in the table. *P* values are provided by Tukey's test to account for multiple comparisons. EA = early arthritis; ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; RA = rheumatoid arthritis; WHO = World Health Organization; HDL = high-density lipoprotein; LDL = low-density lipoprotein; BP = blood pressure.

Table 4. Link between CRP levels and plasma lipids, blood pressure, and plasma glucose in patients with EA (ESPOIR cohort)*

EA patients (n = 607)	CRP lower tertile (≤3 mg/liter)	CRP middle tertile (3–13 mg/liter)	CRP upper tertile (>13 mg/liter)	*P*
Total cholesterol, gm/liter (n = 577)	2.17 ± 0.040	2.14 ± 0.040	1.94 ± 0.040	< 0.001
HDL cholesterol, gm/liter (n = 316)	0.65 ± 0.026	0.57 ± 0.027	0.54 ± 0.025	< 0.001
LDL cholesterol, gm/liter (n = 315)	1.23 ± 0.048	1.26 ± 0.050	1.13 ± 0.047	0.021
Total cholesterol/HDL ratio (n = 316)	3.69 ± 0.182	4.09 ± 0.190	4.04 ± 0.179	0.061
Triglycerides, gm/liter (n = 580)	0.94 ± 0.047	1.07 ± 0.048	1.05 ± 0.047	0.015
Triglycerides/HDL ratio (n = 316)	1.67 ± 0.095	2.16 ± 0.100	2.18 ± 0.094	0.009
Systolic BP, mm Hg (n = 593)	133.2 ± 1.357	134.4 ± 1.364	136.4 ± 1.312	0.099
Diastolic BP, mm Hg (n = 593)	79.2 ± 0.958	79.7 ± 0.964	79.7 ± 0.926	0.890
Pulse pressure, mm Hg (n = 593)	54.0 ± 1.122	54.7 ± 1.129	56.7 ± 1.085	0.070
Glucose, gm/liter (n = 570)	1.08 ± 0.031	1.10 ± 0.032	1.10 ± 0.030	0.585

* Values are the adjusted mean ± SEM. For triglycerides, triglycerides/HDL ratio, and glucose, *P* values are computed on log-transformed data and the geometric mean is given in the table. CRP = C-reactive protein; EA = early arthritis; HDL = high-density lipoprotein; LDL = low-density lipoprotein; BP = blood pressure.

LDL cholesterol were significantly lower in patients whose CRP level was in the upper tertile in comparison with the middle and lower tertiles. Triglycerides and triglycerides/HDL ratio were significantly higher in the 2 higher tertiles of CRP level compared to the lower tertile. No significant link was shown for total cholesterol/HDL, fasting blood glucose, diastolic or systolic blood pressure, or pulse pressure (Table 4).

With regard to the link with IL-6 levels, similar trends were observed for total and HDL cholesterol, but did not reach statistical significance for LDL cholesterol. Total cholesterol/HDL ratio was higher in patients whose IL-6 was in the upper tertile in comparison with the middle and lower tertiles. We did not find any association between triglycerides or triglycerides/HDL ratio and IL-6 levels. Systolic blood pressure and pulse pressure were positively associated with serum IL-6 levels (Table 5).

DISCUSSION

This case–control study emphasizes a particular lipid profile, characterized by low cholesterol, LDL cholesterol, and HDL cholesterol levels and a high level of triglycerides in untreated patients with EA in comparison with healthy controls. In addition, decreases in diastolic blood pressure or fasting glucose, increases in pulse pressure or triglycerides/HDL ratio, and a higher prevalence of smoking appeared as additional characteristics of patients with EA. Similar trends were observed whether EA patients met the ACR/EULAR 2010 classification criteria for RA or not. In patients with EA, total cholesterol and HDL cholesterol levels were negatively associated with CRP or serum IL-6 levels. The triglycerides/HDL ratio was positively associated with CRP levels. Systolic blood pressure and pulse pressure were positively associated with serum IL-6.

Since the cases were derived from a cohort of patients with early RA who had never taken corticosteroids and DMARDs (ESPOIR cohort) (27), our results were not influenced by confounding factors such as the duration of the disease or medication, which might have an impact on the traditional cardiovascular risk factors such as total cholesterol and its fractions, blood pressure, or glucose levels (33,34). The controls were derived from a study of the traditional cardiovascular risk factors in the general pop-

Table 5. Link between IL-6 serum levels (n = 558) and plasma lipids, blood pressure, and plasma glucose in patients with EA (ESPOIR cohort)*

EA patients (n = 607)	IL-6 lower tertile (≤1.5 pg/ml)	IL-6 middle tertile (1.5–7.95 pg/ml)	IL-6 upper tertile (>7.95 pg/ml)	*P*
Total cholesterol, gm/liter (n = 530)	2.22 ± 0.042	2.10 ± 0.043	2.00 ± 0.041	< 0.001
HDL cholesterol, gm/liter (n = 296)	0.66 ± 0.028	0.60 ± 0.028	0.55 ± 0.027	< 0.001
LDL cholesterol, gm/liter (n = 295)	1.27 ± 0.051	1.22 ± 0.052	1.16 ± 0.050	0.085
Total cholesterol/HDL ratio (n = 296)	3.59 ± 0.196	3.88 ± 0.201	4.11 ± 0.192	0.021
Triglycerides, gm/liter (n = 533)	1.03 ± 0.050	0.99 ± 0.051	1.02 ± 0.050	0.761
Triglycerides/HDL ratio (n = 296)	1.70 ± 0.103	1.88 ± 0.105	2.05 ± 0.100	0.147
Systolic BP, mm Hg (n = 544)	132.1 ± 1.402	136.1 ± 1.455	135.7 ± 1.383	0.016
Diastolic BP, mm Hg (n = 544)	79.3 ± 0.999	80.1 ± 1.037	80.1 ± 0.986	0.690
Pulse pressure, mm Hg (n = 544)	52.8 ± 1.165	56.1 ± 1.209	55.6 ± 1.149	0.024
Glucose, gm/liter (n = 526)	1.10 ± 0.033	1.11 ± 0.034	1.13 ± 0.032	0.438

* Values are the adjusted mean ± SEM. For triglycerides, triglycerides/HDL ratio, and glucose, *P* values are computed on log-transformed data and the geometric mean is given in the table. IL-6 = interleukin-6; EA = early arthritis; HDL = high-density lipoprotein; LDL = low-density lipoprotein; BP = blood pressure.

ulation (WHO MONICA survey) and matched for age, sex, and region of origin, with a ratio of 3 controls to 1 patient, thus constituting a suitable control group (28). Since BMI influences the distribution of traditional cardiovascular risk factors, the comparison of these risk factors between the patients and the controls was adjusted for this parameter (35). Additional adjustments for hormone replacement therapy, lipid-lowering drugs, hypoglycemic treatment, and antihypertensive treatment were also performed to minimize confounding bias.

With regard to cholesterol levels, our results show a decrease in total, LDL, and HDL cholesterol and the total cholesterol/HDL ratio in patients with EA compared to healthy controls matched for age and sex, despite the adjustment for BMI, hormone replacement therapy, and lipid-lowering and antihypertensive drug use. These results confirm those of an earlier study involving a small number of patients with RA or spondylarthropathy (19), and of a recent study that did not take into account the other traditional cardiovascular risk factors or the impact of the level of inflammatory activity, corticosteroids, or DMARDs (23).

Although the difference in HDL cholesterol concentration between patients and controls appears quantitatively small (mean decrease of 0.03 gm/liter; $P = 0.007$), such a difference might be clinically significant since a meta-analysis showed that every increase in plasma HDL cholesterol levels of 0.01 gm/liter is associated with a 2–3% decrease in the risk of coronary artery disease (36). The difference in LDL cholesterol concentration between patients and controls was quantitatively more consequent (mean decrease of 0.23 gm/liter; $P < 0.001$). Such a difference might also be clinically significant since every 1% reduction in LDL cholesterol levels is associated with a 1% decrease in the risk of major cardiovascular events (37).

The decrease in total cholesterol and its fractions depends on the level of systemic inflammation, as shown by the inverse link existing between the levels of total, LDL, and HDL cholesterol and those of CRP or serum IL-6. These results concur with the data derived from clinical research. Therefore, clinical studies having assessed the efficacy and the tolerance of an anti–IL-6 receptor monoclonal antibody in RA demonstrated a significant increase in levels of total, LDL, and HDL cholesterol and of apolipoprotein A-I (Apo A-I) or Apo A-II during treatment with tocilizumab, with no significant variation in Apo B or the atherogenic index (26,38). It should be emphasized that this increase in total cholesterol and its fractions is not specific to this treatment, and it has been observed with penicillamine (39) and anti–tumor necrosis factor (anti-TNF) (18).

The inverse link between levels of total cholesterol and its fractions and the level of serum IL-6 observed in our clinical study also concurs with data from basic research. IL-6 facilitated lipolysis and the oxidation of fatty acids (24) and increased the expression of the receptors, enabling the capture of VLDL in coronary, hepatic, and fatty tissue, resulting in a decrease in the levels of circulating cholesterol (25).

The increase in pulse pressure observed in patients with EA in comparison with controls could be clinically significant since pulse pressure was shown to be associated with either microvascular damage in brain and kidney or coronary heart disease in the general population and in a large cohort of RA patients (40–42). In the present study, systolic blood pressure and pulse pressure were positively associated with serum IL-6 levels. These results are in accordance with those of previous epidemiologic or experimental studies that showed a link between serum IL-6 levels and systolic or diastolic blood pressure in healthy subjects or ventricular hypertrophy in rodents (43,44).

With regard to triglycerides, our results show an increase in triglyceride levels in patients with EA compared to healthy controls, despite the adjustment for BMI, hormone replacement therapy, and other drug treatments. Such an increase in triglycerides was previously reported in acute inflammatory states (18). It could involve modifications in expression and activity of lipid transfer proteins (e.g., phospholipid transfer protein and cholesteryl ester transfer protein), which was observed in inflammatory conditions (45).

The comparison between patients with EA and controls revealed an increase in the triglycerides/HDL ratio that was positively associated with CRP levels. These results are in accordance with those of previous studies that showed that the triglycerides/HDL ratio is associated with insulin resistance in subjects without diabetes mellitus (32,46), and that patients with RA are more susceptible to insulin resistance (47).

Finally, considerable data from both basic research and clinical research show that atherosclerosis is a chronic inflammatory disease (7). This is exemplified by the associations established in the general population between levels of CRP or serum IL-6 and the risk of cardiovascular events, the foremost of which is coronary heart disease (48,49).

Our case–control study shows that the prevalence of hypercholesterolemia and total, HDL, and LDL cholesterol levels are lower in untreated patients with EA than in age- and sex-matched healthy controls. A decrease in diastolic blood pressure and glucose level was observed in untreated EA patients in comparison with healthy controls. Furthermore, our results emphasize that IL-6 could impact traditional cardiovascular risk factors in patients with inflammatory rheumatic diseases, whereas serum IL-6 levels were negatively associated with cholesterol levels.

Even if the clinical significance of the particular lipid profile observed in patients with EA remains uncertain, decreasing cardiovascular risk in RA should be a major concern for rheumatologists. It involves the detection and management of traditional cardiovascular risk factors (50) and a strict monitoring of inflammation, aiming at best for remission of the disease (51,52). It must also take into account the potential impact of medication on the cardiovascular risk, whether involving corticosteroids, DMARDs, such as methotrexate, or biologic agents, such as anti-TNF or tocilizumab (16).

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Constantin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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