Prevalence of lipid phenotypes, serum lipid behaviour over follow-up and predictors of serum lipid levels in a cohort of Mexican Mestizo early rheumatoid arthritis patients treated with conventional disease-modifying anti-rheumatic drugs

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Abstract

Objective

Our aim was to describe the prevalence of dyslipidaemia, serum lipid behaviour and predictors of serum lipid levels in a cohort of early rheumatoid arthritis (RA) patients.

Methods

Charts from 146 patients who were lipid-lowering therapy (LLT) free at inclusion and had baseline complete serum fasting lipid profile and ≥1 lipid profile/patient/year of follow-up were reviewed. Patient's prevalence of dyslipidemia was compared to matched controls. Linear regression analysis was applied in 101 patients who achieved remission to define predictors of lipid levels according to disease activity status.

Results

At baseline, the 146 patients were most frequently female (89.7%), middle aged (37.6±12.5 years) and had high disease activity; 37 of them (25.3%) had normal lipid profile. When compared to controls, patients had lower prevalence of hypercholesterolaemia (19.8% vs. 33.5%) and raised LDL cholesterol (22.6% vs. 33.5%), and higher prevalence of hypoaphalipoproteinemia (54.8% vs. 18.4%) and of hypertriglycediremia (28.1% vs. 4.8%), p≤0.05.

During follow-up (45.6±26.3 months), 108 patients did not receive LLT; lipid levels increased up to last follow-up meanwhile DAS28, C-reactive protein and COL/HDL ratio decreased, especially during the first 2 years when RA treatment was intensive. Age, gender and body mass index predicted individual lipid levels in 101 patients who achieved remission. LLT was a strong predictor of triglycerides levels and of COL/HDL ratio only during remission.

Conclusion

The prevalence of dyslipidaemia in early RA patients differed from the matched controls. During follow-up and parallel to disease activity, the COL/HDL ratio decreased. Demographic and anthropometric variables and LLT predicted individual serum lipid levels.

Key words

rheumatoid arthritis, dyslipidaemia, lipids

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Introduction

Rheumatoid arthritis (RA) is associated with higher overall and cardiovascular (CV) mortality (1-3). CV disease is the leading cause of death. Besides a genetic component and chronic inflammation (4, 5), traditional CV risk factors are strong predictors of CV outcomes that contribute to the CV mortality in the general population, although their impact on CV mortality in RA patients is less clear (6-10). Disease and treatment related factors have been also proposed as responsible for the increased CV risk (11).

Dyslipidaemia is the most frequent cardiovascular risk factor in Mexican adults and it is caused by the interaction of genetic and environmental factors (12). In addition to hypoalphalipoproteinaemia, which has been found close to 60% of Mexican adults, several atherogenic lipid phenotypes have been described with isolated hypercholesterolaemia, mixed hyperlipidaemia and the combination of high triglycerides (TRG)/low high-density lipoprotein (HDL) being the most common (13).

Patients with active RA have altered lipid metabolism characterised by hypocholesterolemia with a global reduction of total cholesterol (COL), low-density lipoprotein (LDL), HDL, very-LDL, and TRG (14, 15). RA patients have shown low levels of HDL, and higher lipoprotein(a) and increase in the COL/HDL ratio; both are associated to an increased risk of CV disease (16, 17), although recent observations support the use of COL/HDL ratio as the most stable prognostic cardiovascular indicator in RA (18, 19). Higher inflammatory markers levels have been reported to correlate inversely with COL and HDL levels, but there is also evidence that controlling disease activity may improve lipid profiles (20, 21).

In the last years, it has been emphasised that Latin-American countries have distinctive epidemiological, serological and clinical characteristics of RA (22). Similarly, lipid phenotypes included in the concept of dyslipidaemia have distinctive characteristics in the Mexican population.

The objectives of the study were:

1. to describe the prevalence of lipid phenotype at first evaluation in a cohort of Mexican Mestizo early RA patients and to compare it with data from matched controls;
2. to describe longitudinal behaviour of serum lipid profile over follow-up in a real clinical setting of early RA patients treated with conventional DMARDs;
3. to identify individual predictors of serum lipid levels.

Material and methods

Setting and study population

The Early Arthritis Clinic of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán was established in February 2004. Patients with RA of less than a year of disease duration at first evaluation attend the Clinic. Patients receive "treat-to-target" oriented treatment (T2T). Traditional disease-modifying anti-rheumatic drugs (DMARDs) are used in 99% of our population.

At baseline, a complete medical history and sociodemographic characteristics are obtained. Laboratory includes a lipid profile with serum COL, LDL, HDL and TRG.

Standard baseline and consecutive rheumatic evaluations include extended joint counts, acute reactant phase determinations, physician and patient-reported outcomes (23, 24), the disease activity score (28 joints evaluated) (DAS28) (25), adverse events evaluations and comorbidity established by record review. Patients are evaluated every 2 months during the first two years of follow-up and thereafter, every 2, 4 or 6 (fixed and scheduled for all the patients) months. At fixed six month-intervals, serum lipid profiles are scheduled.

Treatment records include previous treatment (defined as prescribed during the month prior to the baseline evaluation) and current treatment (at baseline and consecutive evaluations), which includes names, doses, schedule, order start and stop dates of DMARDs, of corticosteroids and of any other drug.

All the information is recorded using standardised formats.

Up to September 2013, charts from 160 consecutive patients with early RA were reviewed. Inclusion criteria included patients with complete base-

line serum lipid profile (no patient was excluded); in order to describe lipid behaviour over follow-up, at least one complete serum lipid profile per year of follow-up was required (8 patients were excluded). Six additional patients were also discarded as they were taking lipid-lowering therapy before entering the cohort. There were completed data from 148 patients left (and were similar to data from patients excluded).

Control population

For each case, one control was randomly selected from a local database that included data from more than twelve thousands Mexican Mestizo adults without neither known medical condition nor treatment, in whom serum samples were obtained in order to investigate prevalence of the Metabolic Syndrome in Mexico. Controls were matched according to age (±5 years), gender, body mass index (±2), hypertension, mellitus diabetes and smoking habit. Two patients could not be matched and there were 146 pairs of patient/control left.

Variables and definitions

Remission was defined based on the DAS28 if scored ≤2.6 (26).

Fasting COL, LDL, HDL and TRG were measured in serum and reported in mg/dL.

Hypercholesterolaemia: ≥1 fasting serum level of COL ≥200 mg/dL.

Hypoalfalipoproteinaemia: ≥1 fasting serum level of HDL ≤40 mg/dL.

Raised LDL: ≥1 fasting serum level of LDL ≥130 mg/dL.

Hypertriglycediremia: ≥1 fasting serum level of TRG ≥150 mg/dL.

Statistical analysis

Prevalence of specific lipid phenotypes was determined based on serum lipid profile at baseline or within 2 months from baseline evaluation.

Distribution of each variable was analysed. Student *t*-test and χ^2 were used for normally distributed variables and Mann-Whitney U-test for non-normally distributed variables.

To summarise cumulative disease activity, the mean of consecutive values from corresponding evaluation was obtained. Linear regression analysis was applied in order to define which among the following variables predicted serum lipid levels and the COL/HDL ratio within each patient: age, gender, body mass index, corticosteroids use, number of DMARDs/patient and lipid-lowering therapy use. Models were applied during disease activity (defined as the length of months of follow-up with consecutive DAS28 score above 2.6) and during the first sustained remission period (if ever achieved, it was defined as the length of time with consecutive DAS28 ≤2.6 and maintained for at least one year).

All statistical tests were 2-sided and evaluated at the 0.05 significance level. Statistical analysis was performed using the SPSS/PC programme (v.17.0; Chicago, IL, USA).

Ethics

The study was approved by the internal review board. Written informed consent was obtained in order to have patient's charts reviewed and data presented in scientific forums or published.

Table I. Baseline characteristics of patients and controls.

Characteristics	Patients n=146	Controls n=146	*p*-value
Socio-demographic			
Female gender, n (%)	131 (89.7)	131 (89.7)	1
Age, mean±SD, years	37.6±12.5	37.8±12.2	1
Years of formal education, mean±SD	10.9±3.7	NA	
Current smokers, n (%)	14 (9.6)	14 (9.6)	1
Disease characteristics			
Disease duration, median (range), months	5.3 (3.5–7)		
Patients with RF, n (%)	119 (81.5)		
Patients with ACCP, n (%)	123 (84.2)		
DAS 28, median (range)	6.1 (5.1–7)		
ESR, median (range), mm/H	23 (16–42)		
CRP, median (range), mg/dL	0.77 (0.27–3.03)		
HAQ, median (range)	1.4 (0.9–2.1)		
Patients with erosions, n (%)	14 (9.6)		
Comorbid conditions			
Patients with ≥1 comorbid conditions, n (%)	69 (47.3)		
Comorbidity/patient, mean±SD	0.9±1.06		
Patients with diabetes, n (%)	4 (2.7)	4 (2.7)	1
Patients with hypertension, n (%)	6 (4.1)	6 (4.1)	1
Body mass index, median (range)	25.9 (22.8–29)	24.9 (23–29)	0.9
Treatment			
Patients with DMARDs, n (%)	78 (53.4)		
Patients with corticosteroids, n (%)	49 (33.6)		
Patients with antimalarials, n (%)	24 (16.4)		
Patients with other drugs, n (%)	75 (51.4)		

NA: not available; RF: rheumatoid factor; ACCP: antibodies to cyclic citrullinated peptides; DAS28: disease activity score, 28 joints evaluated; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; HAQ: health assessment questionnaire; DMARDs: disease-modifying anti-rheumatic drugs; n: number; H: hour.

Results

Baseline characteristics of the study population and of matched controls

The 146 patients included were most frequently females, middle aged, had 10.9±3.7 years of formal education and at least one comorbid condition. As expected at first evaluation, patients had very active disease and high disability. At baseline, 49 patients (33.6%) were receiving low doses of oral corticosteroids (equivalent to ≤10 mg/day of prednisone) and 78 patients (53.4%) DMARDs; among them, 24 were receiving antimalarials. Table I also shows the characteristics of the controls.

Prevalence of dyslipidaemia in the study population and comparison with matched controls

At baseline evaluation, 37 patients (25.3%) had normal serum lipid profiles, 54 (37%) had one distinct lipid phenotype, 39 (26.7%) had 2 concomitant lipid phenotypes, 13 (8.9%) had three and 3 patients (2.1%) had concomitantly four lipid phenotypes.

RA patients had lower prevalence of hypercholesterolaemia and raised LDL than controls. Conversely, they had higher prevalence of hypoalfalipoproteinaemia and hypertriglycediremia (Fig. 1).

Disease activity and serum lipid profile's behaviour over follow-up

We selected 108 RA patients who did not take lipid lowering therapy (LLT) during their follow-up. Their characteristics at baseline were similar to those who did.

Selected patients had (mean±SD) follow-up of 45.6±26.3 months, (mean) lipid panel result/patient/year of follow-up of 2 and (mean) disease activity evaluations/patient/year of follow-up of 7 (during the first 2 years) and of 5 (after the first 2 years of follow-up).

Figure 2A shows that serum COL, HDL and TRG increased over follow-up meanwhile serum LDL progressively decreased after it picked at the fourth year. Figure 2B shows that during the first 2 years of follow-up DAS28, CRP levels and COL/HDL ratio decreased. Thereafter, CRP levels appear to plateau, DAS28 showed a subtle increased up to last follow-up although always below remission value and, finally, COL/HDL ratio increased up to the 4th year and thereafter showed the lowers values up to last follow-up.

Number of DMARD/patient increased during the first 2 years up to 2.5, and there after appear to plateau up to 2/patient until last follow-up. The percentage of patients receiving corticosteroids increased during the first 3 years of follow-up and there after decreased up to last follow-up (Table II).

Predictors of serum lipid levels

During follow-up 101 patients achieved sustained remission.

Their paired data of serum COL, HDL, LDL, TRG and COL/HDL ratio measured during disease activity and during remission were compared. No differences were found but (mean±SD) HDL serum levels raised during remission (42.4±11.9 mg/dL *vs*. 44.7±11.1 mg/dL, p=0.03 meanwhile COL/HDL ratio decreased (4.2±1.1 *vs*. 4±1.2, p=0.004).

To determine predictors of serum lipid levels linear regression models were applied. Paired data regarding demography (age, gender), anthropometry (BMI), and treatment (corticosteroids use, antimalarials use, DMARDs/patient and lipid lowering therapy use) entered models. As shown in Table III, age, female gender and body mass index predicted serum lipid levels and the direction and magnitude of the relationship was similar during disease activity and during remission; gender had the greatest impact. Gender and body mass index predicted COL/HDL ratio during disease activity meanwhile during remission state, gender and the use of lipid lowering therapy were predictors. Also, during remission, lipid lowering therapy strongly impacted TRG serum levels.

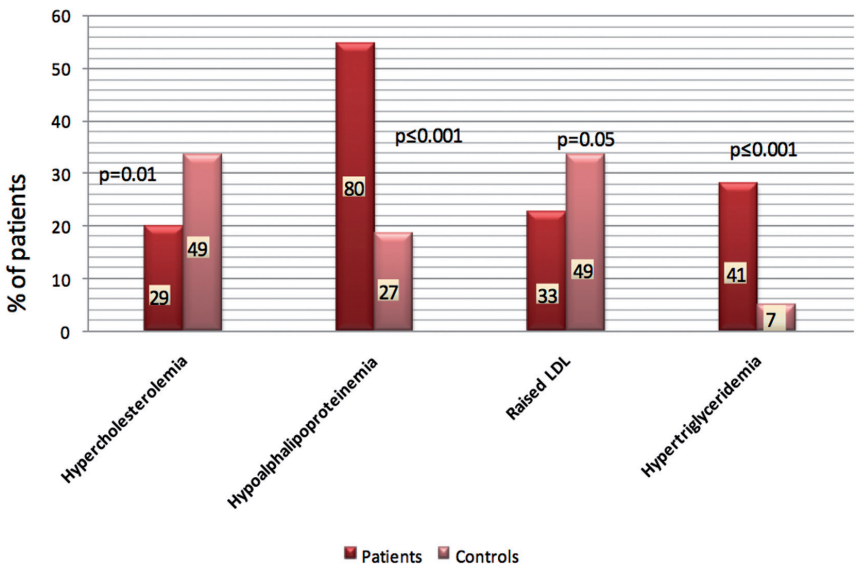

Fig. 1. Comparison of lipid phenotype's prevalence between patients and controls.
Prevalence of hypercholesterolaemia, hypoalphalipoproteinaemia, raised LDL and hypertriglyceridemia is defined at first evaluation in the early arthritis Clinic. Figure shows prevalence's comparison between patients (red boxes) and matched controls (pink boxes). Number inside the box represents number of patients and controls diagnosed in each lipid phenotype.

Discussion

Increasing evidence suggests that the treatment of atherogenic dyslipidaemia should be considered as part of cardiovascular management in RA (27-29) but practical questions are how to interpret an atherogenic lipid profile in a patient with active disease or when a specific intervention should be indicated.

Our study was performed in a real clinical setting and included patients with early disease, substantial comorbidity and receiving conventional DMARDs according to a T2T strategy. Standardised rheumatic assessments, comorbidity and treatment were routinely performed along with lipid serum determinations and for the present report data from up to 7 years of follow-up are presented. Accordingly, we consider that our results are of practical relevance as they reflect daily patient's conditions.

At baseline, the vast majority of (active) patients presented an abnormal lipid profile and the frequency and distribution of dyslipidaemia significantly differed from that of matched controls, in accordance to previous descriptions (1, 11, 30). Dyslipidaemia (alterations of individual lipid components and their ratios as defined by specific criteria) was detected in 75% of our patients meanwhile it has been described to affect up to half of all patients with RA in a hospital setting (31). Our higher prevalence could be explained by the distinctive genetic background of our population of Mexican Mestizos patients in whom a high (and undetected) prevalence of atherogenic lipid phenotypes has been described (13).

We found that serum COL, HDL and TRG levels increased up to last follow-up, meanwhile serum LDL picked and then decreased. Nonetheless, the COL/

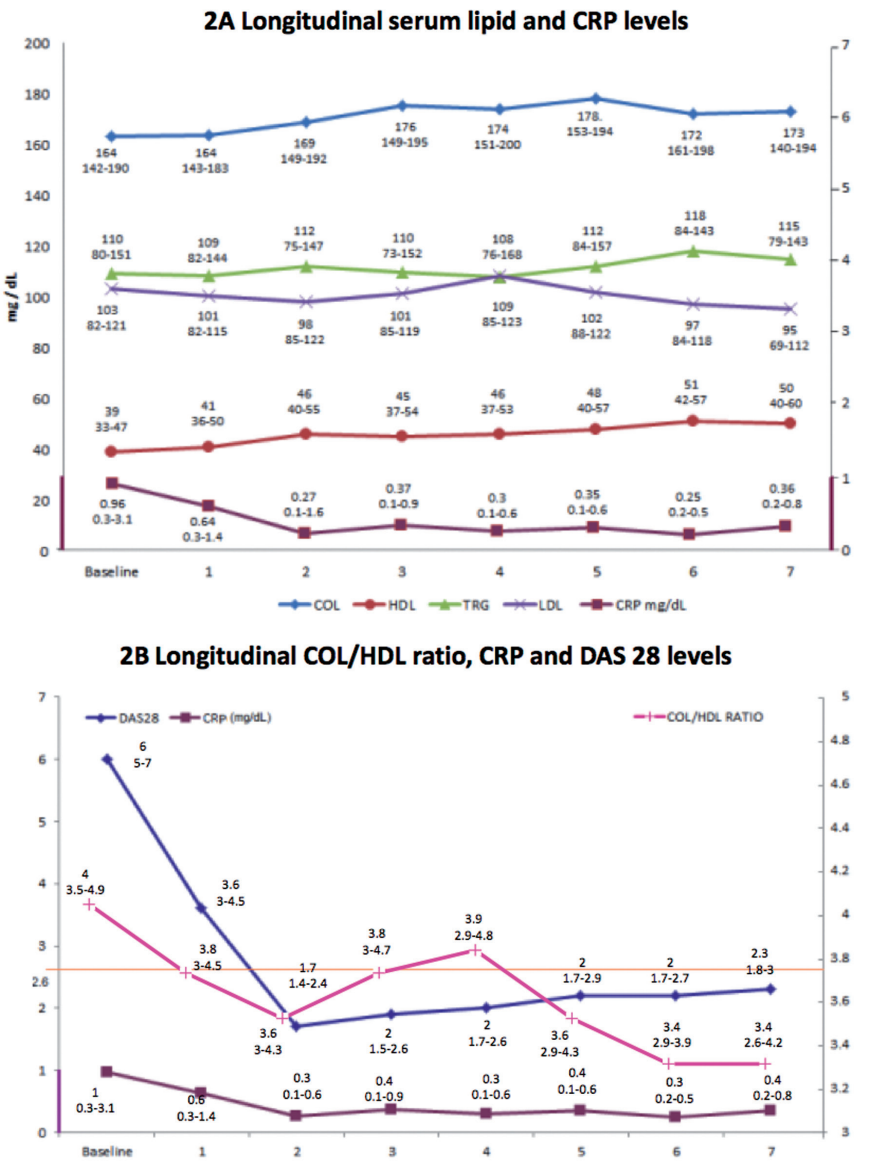

Fig. 2. Longitudinal serum lipid and CRP levels (Fig. 2A), and longitudinal COL/HDL ratio, DAS28 and CRP (Fig. 2B) during follow-up.
2A. Median (range) of serum mg/dL of COL, HDL, LDL, TRG and CRP at follow-up are represented. The X axis represents scale for years of follow-up and the Y axis scale in mg/dL of serum lipid levels (left side) and of CRP (right side).
2B. Median (range) of COL/HDL, DAS 28 and CRP ratio during 7 years of follow-up are represented. The X axis represents scale for years of follow-up. Right Y axis represents scale for COL/HDL ratio and left Y axis scales for DAS28 and for CRP (in mg/dL).
The continuous orange line represents the DAS28 score below which value remission is defined.

HDL ratio which has been suggested as the most stable prognostic cardiovascular indicator in RA (18, 19) decreased and paralleled disease activity control. Our study corroborates that dampening of inflammation in RA patients reduces the risk of CV disease. Nonetheless, it may also be possible that DMARDs (isolated or in specific combination with/without corticosteroids [32]) may directly affect serum lipid levels and lipoprotein(a) by a mechanism independent of (and/or added to) the abrogation of inflammation as it has been suggested in previous studies (33-39). Furthermore, the impact of the mechanisms described on each specific lipid level may vary and could explain why serum LDL levels had a different behaviour over follow-up than that of HDL, COL and TRG levels. Additionally, multiple other factors are involved in lipid regulation and function, including physical activity, adiposity, diet, alcohol intake, and smoking and their effect may be distinct according to specific lipid phenotypes. Recently, a single-center prospective study has reported that RA patients with persistently higher LDL cholesterol levels were more likely to have chronic inflammation (40). This observation suggests that remission of inflammation may have contrasting consequences on the lipid profile. Thus, it is likely that LDL had a small decrement in our cohort due to the attainment of lower disease activity levels/remission in most of the patients.

Similar to it has been described in non-RA Mexican Mestizos, demographic and anthropometric variables predicted individual serum lipid levels and the COL/HDL ratio irrespective of the patient disease activity status. Interestingly, LLT was found a strong predictor of serum TRG levels (in addition to gender) and on the COL/HDL ratio only during remission state which suggests that this therapy may have a greater impact when inflammation has been abrogated. In the most recent Mexican National Health and Nutrition Survey it was shown that the prevalence of the simultaneous elevation of cholesterol and triglycerides concentrations increased in direct proportion with age (13); also, the prevalence of hypertriglycediremia/hypoalphalipoproteinaemia was significantly higher in men compared to woman; finally, the same study showed that higher BMI was associated with a higher prevalence of several atherogenic lipid profiles (13).

Limitations of our study need to be addressed. Our cohort of patient with early RA is limited to a population of Mexican Mestizos which has a particular genetic background that affects both the disease itself and dyslipidemia syndromes; accordingly, our results may not be generalised although the present study is of value for the understanding of worldwide RA epidemiology.

The study addresses the potential impact of disease activity on serum lipid behaviour although it is well known that besides inflammation, multiple other factors are involved in lipid regulation and function but their effects were not

Table II. Follow-up treatment in 108 patients who were lipid lowering therapy-free: corticosteroids and DMARDs.

Years of follow-up	Baseline	1	2	3	4	5	6	7
Patients, n	108	108	95	86	73	68	55	42
DMARDs/patient, n Median (range)	1 (0–1)	2 (1.7–2.7)	2.5 (2–3)	2 (1.5–3)	2 (1.5–3)	2 (1–2.5)	2 (1–2)	2 (1–2)
Patients on corticosteroids, n (%)	43 (40)	52 (48)	46 (48)	42 (49)	34 (46)	31 (46)	25 (46)	16 (37)

DMARDs: disease-modifying anti-rheumatic drugs.

Table III. Significant predictors of serum lipids levels and of COL/HDL ratio during disease activity and *during sustained remission*.

	COL*	HDL*	LDL*	TRG*	COL/HDL ratio*
Age	0.2, (0.4–1.2), 0.000 *1.1, (0.7–1.5), 0.000*	0.2, (0.1–0.4), 0.002	0.7, (0.3–1), 0.000 *0.9, (0.6–1.2), 0.000*		
Female gender		10.7, (5–16.5), 0.000 *11.4, (5.3–17.4), 0.000*		-50.6, (-80 to -1.3), 0.001	-1, (-1.5 to -0.5), 0.000 *-1.3, (-2 to -0.6,) 0.001*
Body mass index		-0.4, (-0.8 to -0.1), 0.01		2.8, (1.1–4.4), 0.001 *0.03 (0.01–0.06), 0.05*	3.1, (0.9–5.3), 0.005
Lipid lowering therapy				*-39, (-66 to -12), 0.005*	*-0.6, (-1.1 to -0.2), 0.01*

*Serum levels expressed as mg/dL. Data are presented as B coefficient (95% CI), *p*-value. COL: total cholesterol; HDL: high density cholesterol; LDL: low density cholesterol; TRG: triglycerides.

assessed. It should also be emphasised that the interplay between inflammation and lipid components is far more complex than just the alteration of the serum lipid levels (41) and that inflammation-induced alterations of structure and function affect LDL and TRG in addition to HDL (42).

CV outcomes were not assessed; we were limited by the length of the patient's follow-up, up to 7 years, which is considerable for the study but insufficient for evaluating cardiovascular outcomes.

A crude description of the prevalence of isolated lipid abnormalities is considered a gross estimation of the lipid-related cardiovascular risk of a population meanwhile a more precise description is addressed when the lipid abnormalities are grouped and combined as lipid phenotypes.

Finally, the study was retrospective and the number of patients which data were analysed were limited, including those taking LLT. Accordingly, some potential predictors may have been missed.

Conclusions

In conclusion, the vast majority of early and active RA Mexican Mestizos patients had unrecognised atherogenic lipid phenotypes when first referred to a rheumatologist. A higher prevalence of hypoalphalipoproteinaemia and hypertriglycediremia was found in patients compared to matched controls. This particular prevalence and distribution of lipid phenotypes may be influenced by 2 main factors in our population, a distinctive genetic background and inflammation burden. Following intensive treatment with DMARDs according to a treat-to target-strategy, most of the patients achieved and maintained a state of remission. Control of disease activity paralleled serum decreases in the COL/HDL ratio. Individual patient's serum lipid levels were influenced by age, gender and body mass index no matter the disease activity status and in the same direction as it has been described in non-RA populations. Nonetheless, during remission state, lipid lowering therapy (specifically fibrates) use was also a strong predictor of serum TRG levels and of the COL/HDL ratio.

Evidence-based EULAR recommendations for cardiovascular risk management in patients with RA have been recently published (43). We reinforce the recommendation that RA patient's evaluations should include periodic assessment of CV risk factors, including of serum lipid levels. Specific clinical situations where disease activity is detected and treatment is intensified should be targeted and appropriated follow-up of serum lipid levels performed. To date, there are no specific guidelines for dyslipidemia management in RA patients and rheumatologists are prone to adopt those designed to treat non rheumatic patients. Nonetheless, we should be aware that in addition to genetics and factors related to lifestyle, other potential mechanisms unique to the RA population such as inflammation and treatment strategies influence lipids levels over follow-up. We proposed that strategies to improve atherogenic lipid phenotypes, specifically fibrates should be individually considered and customised according to disease activity status. Special attention should be given to serum lipid levels when remission is achieved (and maintained) and LLT accordingly modified. It remains to be determined if there is a critical level of serum lipid above which LLT should be indicated and the potential impact of lipid-lowering therapy on CV outcomes. A special matter of concern should be the increasing costs derived from the implementation of such strategies.

References

1. SOLOMON DH, CURHAN GC, RIMM EB, CANNUSCIO CC, KARLSON EW: Cardiovascular risk factors in women with and without rheumatoid arthritis. *Arthritis Rheum* 2004; 50: 3444-9.
2. WOLFE F, MITCHELL DM, SIBLEY JT *et al*.:

The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 481-94.
3. WALLBERG-JONSSON S, OHMAN ML, DAHLQVIST SR: Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. *J Rheumatol* 1997; 24: 445-51.
4. RODRÍGUEZ-RODRÍGUEZ L, GONZÁLEZ-JUANATEY C, PALOMINO-MORALES R *et al*.: TNFA- 308 (RS1800629) polymorphism is associated with a higher risk of cardiovascular disease in patients with rheumatoid arthritis. *Atherosclerosis* 2011; 216: 125-30.
5. GONZÁLEZ-GAY MA, GONZÁLEZ-JUANATEY C, LÓPEZ-DÍAZ MJ *et al*.: HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 57: 125-32.
6. HAHN BH, GROSSMAN J, CHEN W, MCMAHON M: The pathogenesis of atherosclerosis in autoimmune rheumatic diseases: roles of inflammation and dyslipidemia. *J Autoimm* 2007; 28: 69-75.
7. WOLFE F, MICHAUD K: The risk of myocardial infarction and pharmacologic and nonpharmacological myocardial infarction predictors in rheumatoid arthritis: a cohort and nested case-control analysis. *Arthritis Rheum* 2008; 58: 2612-21.
8. ERB N, PACE AV, DOUGLAS KM, BANKS MJ, KITAS GD: Risk assessment for coronary heart disease in rheumatoid arthritis and osteoarthritis. *Scan J Rheumatol* 2004; 33: 293-9.
9. ESCALANTE A, HAAS RW, DEL RINCÓN I: Paradoxical effect of body mass index on survival in rheumatoid arthritis: role of comorbidity and systemic inflammation. *Arch Intern Med* 2005; 165: 1624-9.
10. GABRIEL SE: Heart disease and rheumatoid arthritis: understanding the risks. *Ann Rheum Dis* 2012; 69: 161-4.
11. GONZÁLEZ A, MARADIT KREMERS H, CROWSON CS *et al*.: Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? *Ann Rheum Dis* 2008; 67: 64-9.
12. AGUILAR-SALINAS CA, CANIZALES-QUINTEROS S, ROJAS-MARTÍNEZ R *et al*.: Hypoalphalipoproteinemia in populations of Native American ancestry: an opportunity to assess the interaction of genes and the environment. *Curr Opin Lipidol* 2009; 20: 92-7.
13. AGUILAR-SALINAS CA, GÓMEZ-PÉREZ FJ, RULL J, VILLAPLANDO S, BARQUERA S, ROJAS R: Prevalence of dyslipidemias in the Mexican National Health and Nutrition Survey 2006. *Salud Publica Mex* 2010, Suppl. 52: S44-53.
14. SVENSON KL, LITHELL H, HALLGREN R, SELINUS I, VESSBY B: Serum lipoprotein in active rheumatoid arthritis and other chronic inflammatory arthritides. Relativity to inflammatory activity. *Arch Inter Med* 1987; 147: 1912-6.
15. PARK YB, LEE SK, LEE WK *et al*.: Lipid profile in untreated patients with rheumatoid arthritis. *J Rheumatol* 1999; 26: 1701-4.
16. RANTAPÄÄ DAHLQVIST S, WÅLLBERG-JONSSON S, DAHLEN G: Lipoproteins (a), lipids and lipoproteins in patients with rheumatoid arthritis. *Ann Rheum Dis* 1991; 50: 366-8.
17. STAMPFER MJ, SACKS FM, SALVINI S WILLETT WC, HENNEKENS CH: A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med* 1991; 325: 373-81.
18. SOLOMON DH, PETERS MJL, NURMOHAMED MT, DIXON W: Motion for debate: The data support evidence-based management recommendations for cardiovascular disease in rheumatoid arthritis. *Arthritis Rheum* 2013; 65: 1675-83.
19. PETERS MJ, VOSKUYL AD, SATTAR N, DIJKMANS DA, SMULDERS YM, NUSMOHAMED MT: The interplay between inflammation, lipids and cardiovascular risk in rheumatoid arthritis: why ratios may be better. *Int J Clin Pract* 2010; 64: 1440-3.
20. CHO JY, PARK JS, BAIK KU *et al*.: Differential effect of phosphodiesterase IV inhibitor RP73401 on various inflammatory and immune responses relevant to rheumatoid arthritis. *Pharmacol Res* 2004; 49: 423-31.
21. PARK YB, CHOI HK, KIM MY *et al*.: Effects of anti-rheumatic therapy on serum lipid levels in patients with rheumatoid arthritis: a prospective study. *Am J Med* 2002; 113: 188-93.
22. MODY GM, CARDIEL MH: Challenges in the management of rheumatoid arthritis in developing countries. *Best Pract Res Clin Rheumatol* 2008; 22: 621-41.
23. RAMEY DR, RAYNAULD JP, FRIES JF: The health assessment questionnaire 1992; status and review. *Arthritis Care Res* 1992; 5: 119-29.
24. KOSINSKI M, KELLER SD, WARE JE JR, HATOUM HT, KONG SX: The SF-36 Health Survey as a generic outcome measure in clinical trials of patients with osteoarthritis and rheumatoid arthritis: Relative validity of scales in relation to clinical measures of arthritis severity. *Med Care* 1999; 37 (5 Suppl.): MS23-29.
25. PREVOO ML, VAN'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LB, VAN RIEL PL: Modified disease activity score that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
26. MAKINEN H, KAUTIAINEN H, HANNONEN P, SOKKA T: Is DAS28 an appropriated tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2005; 64: 1410-3.
27. GEORGIADIS AN, PAPAVASILIOU EC, LOURIDA ES *et al*.: Atherogenic lipid profile is a feature of patients with early rheumatoid arthritis: effect of early treatment -- a prospective controlled study. *Arthritis Res Ther* 2006; 8: R82.
28. RIZZO M, SPINAS GA, CESUR M, OZBALKAN Z, RINI GB, BERNEIS K: Atherogenic lipoprotein phenotype and LDL size and subclasses in drug-naïve patients with early rheumatoid arthritis. *Atherosclerosis* 2009; 207: 502-6.
29. NURMOHAMED MT: Atherogenic lipid profiles and its management in patients with rheumatoid arthritis. *Vasc Health Risk Manag* 2007; 3: 845-52.
30. KITAS GD, GABRIEL SE: Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. *Ann Rheum Dis* 2011; 70: 8-14.
31. TOMS TE, PANOULAS VE, DOUGLAS KM *et al*.: Statin use in rheumatoid arthritis in relation to actual cardiovascular risk: evidence of substantial undertreatment of lipid-associated cardiovascular risk? *Ann Rheum Dis* 2010; 69: 683-8.
32. CAPORALI R, SCIRÈ CA, TODOERTI M, MONTECUCCO C: The role of low-dose glucocorticoids for rheumatoid arthritis in the biologic era. *Clin Exp Rheumatol* 2013; 31 (Suppl.): S9-13.
33. CHOEY E, SATTAR N: Interpreting lipid levels in the context of high-grade inflammatory states, with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risks actions. *Ann Rheum Dis* 2009; 68: 460-9.
34. MUNRO R, MORRISON E, MC DONALD AG. HUNTER JA, MADHOK R, CAPELL HA: Effects of disease modifying agents on the lipid profiles of patients with rheumatoid arthritis. *Ann Rheum Dis* 1997; 56: 374-7.
35. BOERS M, NURMOHAMED MT, DOELMAN CJ *et al*.: Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 842-5.
36. POPA C, NETEA MG, RADSTAKE T *et al*.: Influence of anti-tumour necrosis factor therapy on cardiovascular risk factors in patients with active rheumatic arthritis. *Ann Rheum Dis* 2005; 64: 303-5.
37. ALETAHA D, WARD MM, MACHOLD KP, NELL VP, STAMM T, SMOLEN JS: Remission and active disease in rheumatoid arthritis. Defining criteria for disease activity states. *Arthritis Rheum* 2005; 52: 2625-36.
38. ALAMANOS Y, VOULGARI PV, DROSOS AA: Incidence and prevalence of rheumatoid arthritis, base on the 1987 American College of Rheumatology criteria: A systematic review. *Sem Arthritis Rheum* 2006; 36: 182-8.
39. HJELTNES G, HOLLAN I, FØRRE O *et al*.: Serum levels of lipoprotein(a) and E selectin are reduced in rheumatoid arthritis patients treated with metotrexate or methotrexate in combination with TNF-alpha-inhibitor. *Clin Exp Rheumatol* 2013; 31: 415-21.
40. PARK YJ, CHO CS, EMERY P, KIM WU: LDL cholesterolemia as a novel risk factor for radiographic progression of rheumatoid arthritis: a single-center prospective study. *PLoS ONE* 2013; 8: e68975.
41. CHARLES-SCHOEMAN C, WATANABE J, YINN LEE Y *et al*.: Abnormal function of high-density lipoprotein is associated with poor disease control and altered protein cargo in rheumatoid arthritis. *Arthritis Rheum* 2009; 60: 2870-9.
42. TOMS TE, SYMMONS DP, KITAS GD: Dyslipidimiaemia in rheumatoid arthritis: the role of inflammations, drugs, lifestyle and genetic factors. *Curr Vasc Pharmacol* 2010; 8: 301-26.
43. PETERS MJL, SYMMONS D PM, MCCAREY D *et al*.: EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010; 69: 325-31.