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Lipid and lipoprotein levels and trends in rheumatoid arthritis compared to the general population

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Abstract

Objectives—Differences in lipid levels associated with cardiovascular (CV) risk between rheumatoid arthritis (RA) and the general population remain unclear. Determining these differences is important in understanding the role of lipids in CV risk in RA.

Methods—We studied 2,005 RA subjects from two large academic medical centers. We extracted electronic medical record (EMR) data on the first low density lipoprotein (LDL), total cholesterol (TChol) and high density lipoprotein (HDL) within 1 year of the LDL. Subjects with an electronic statin prescription prior to the first LDL were excluded.

We compared lipid levels in RA to levels from the general United States population (Carroll, et al., *JAMA* 2012), using the t-test and stratifying by published parameters, i.e. 2007–2010, women. We determined lipid trends using separate linear regression models for TChol, LDL and HDL, testing the association between year of measurement (1989–2010) and lipid level, adjusted by age and gender. Lipid trends were qualitatively compared to those reported in Carroll, et al.

Results—Women with RA had a significantly lower Tchol (186 vs 200mg/dL, p=0.002) and LDL (105 vs 118mg/dL, p=0.001) compared to the general population (2007–2010). HDL was not significantly different in the two groups. In the RA cohort, Tchol and LDL significantly decreased

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each year, while HDL increased (all with p<0.0001), consistent with overall trends observed in Carroll, et al.

Conclusion—RA patients appear to have an overall lower Tchol and LDL than the general population, despite the general overall risk of CVD in RA from observational studies.

Introduction

Excess risk of cardiovascular disease (CVD) is a large contributor to a widening mortality gap observed between rheumatoid arthritis (RA) and the general population, whereby the survival rate of RA patients is not improving at the same rate the general population(1). Although lipids are a major risk factor for CVD and are routinely measured for CVD risk stratification, differences in the levels of total cholesterol (Tchol), low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterols, between RA and the general population remain unclear. Some studies observed that dyslipidemia has a higher prevalence in RA(2, 3) while others did not(4, 5). In most cases, relative lipid levels were reported as a covariate in the study of CVD risk but were not the primary variable of interest. Establishing the relative levels of lipids in RA compared to the general population is critical for understanding the role of lipids in CVD risk among RA patients.

Recently, Carroll and colleagues reported lipid and lipoprotein levels in the general United States population using data from the National Health and Nutrition Examination Surveys (NHANES)(6) from 1988–2010. They also observed significant declines in cross-sectional levels of Tchol and LDL, and increasing levels of HDL in the general population over this time interval. Whether these favorable secular trends in lipids are also occurring among RA patients is unknown.

The objectives of this study were to: (1) directly compare lipid levels in a large RA cohort to the general US population (using published data from NHANES), and (2) compare trends in lipid and lipoprotein levels in an RA cohort over time to trends in the general population.

METHODS

We studied a validated RA(7, 8) cohort identified through the electronic medical record (EMR) data of Brigham and Women's Hospital and Massachusetts General Hospital (Boston, MA). RA subjects were identified using a published RA EMR phenotype algorithm with a positive predictive value (PPV) of 94% trained on a gold standard set of subjects classified either as RA or not RA cases by 3 board certified rheumatologists (KPL, EWK, RMP) using the 1987 American College of Rheumatology Classification Criteria for RA(9) as the benchmark. Please refer to Liao, et al., 2010 for details on development, training, and validation of this RA phenotype algorithm(8).

We extracted EMR data on the first LDL, and Tchol and HDL (within 1 year of the first LDL) measured from 1989–2010, age at lipid measurement, self-reported race and anti-citrullinated protein antibody (ACPA) status for each subject. All subjects had prevalent RA, defined as subjects in the RA cohort with ≥1 RA ICD9 code (714.x) or mention of 'rheumatoid arthritis' in the text note prior to the 1st LDL measurement. Mentions of

'rheumatoid arthritis' were extracted using natural language programming as described in Liao, et al., Arthritis Care & Research 2010(8). All RA cases with an electronic statin prescription prior to the first LDL measurement were excluded.

We calculated mean Tchol, LDL and HDL levels in the RA cohort annually, stratifying by published parameters corresponding to Tables 4 and 5 in Carroll et al(6), replicable in our dataset: age ≥20 years, not on statins prior to first lipid measurement (NHANES patient self-report), women (majority of RA subjects), time periods 1999–2002 and 2007–2010; we further limited the analysis to non-Hispanic whites (majority of RA subjects) as a sensitivity analysis to control for racial heterogeneity between the two groups. We calculated the age adjusted mean measurements for Tchol, LDL and HDL using projected 2000 Census population estimates for each stratum as described in Carroll, et al(6). We conducted unpaired t-tests to determine differences in mean lipid levels between the RA cohort and NHANES stratifying by the parameters and time intervals published in Carroll, et al(6), 1999–2002 and 2007–2010.

To determine cross-sectional changes in lipid levels in the RA cohort with each passing year, we constructed separate linear regression models for mean Tchol, LDL and HDL. We tested the cross-sectional association between year of lipid measurement (1989–2010) and lipid level, adjusted by age and gender among all RA cases with available lipid levels. For this analysis, we comment only on whether the trend was qualitatively similar to NHANES, as we could not exactly replicate the time interval for their study which started in 1988 one year before the EMR data were widely available.

This study was approved by the Partners' Institutional Review Board. Statistical analyses were conducted using the SAS and R 2.10 software packages.

RESULTS

Our cohort included 2,005 RA subjects, not on statins prior to their first LDL measurement. Characteristics of RA subjects included a mean age of 52.9 years, 80.2% women, 76% non-Hispanic white, and 62.4% were ACPA positive (among 914 RA subjects with available ACPA data). Female RA patients had significantly lower mean Tchol and LDL levels compared to women in the general population both in the period from 1999–2002 and 2007–2010 (Table 1). HDL levels were not statistically different between the two groups. We observed the same differences when the analysis was stratified by non-Hispanic white women.

Favorable trends in lipid levels were observed in the RA cohort from 1989–2010, qualitatively similar to the trends observed in NHANES from 1988–2010. For all RA subjects (men and women, all races), a significant linear decrease was observed in Tchol levels in the RA cohort (2.3mg/dL per year), and LDL (2.0mg/dL per year, both, $p<0.0001$). A significant increase was observed in HDL over time (0.27mg/dL per year, $p<0.0001$) (Table 2). All models were adjusted by age and gender.

DISCUSSION

Female RA patients in our study had a significantly lower mean Tchol and LDL levels than women in the general population. Specifically, the levels of Tchol and LDL were consistently lower in RA patients in the two time intervals studied, 1999–2002 and 2007–2010. Establishing significant differences in lipid levels between RA and the general population addresses a gap in knowledge in relative lipid levels between the two groups and provides a foundation for continued studies investigating why these differences exist.

Our observation of lower Tchol and LDL in prevalent RA extends findings from a previous study demonstrating significant decreases in Tchol and LDL in the years prior to the development of RA(10). Our study demonstrates that the decreases in Tchol and LDL result in sustained lower levels after diagnosis of RA compared to the general population. These lower levels, in conjunction with known elevated CVD risk in RA compared to the general population from observational studies(11, 12), also support the concept of a lipid paradox in RA(13). In the lipid paradox, lower Tchol was associated with an elevated risk of CVD in RA than higher levels. Potential causes for this paradox include inflammation, which may lower Tchol and LDL levels while simultaneously elevating CVD risk.

The favorable trends in lipid profiles observed in the RA cohort, decreasing Tchol, LDL and increasing HDL, are qualitatively similar to trends observed in the general population(6). The forces influencing these trends are unclear for both RA and the general population. However, these findings suggest that clinically measured lipid profiles are not likely to explain the mortality gap(1) between RA and the general population.

In this study, we did not account for other important RA clinical factors that may influence lipid levels, such as RA treatments and disease activity(10, 14) by design. The goal of this study was to determine the overall relative levels in a large RA cohort and the general population to provide a baseline for future studies of lipids. However, notably, despite secular trends in management of RA, i.e. new biologic agents, Tchol and LDL remained consistently lower in RA than the general population over the past decade.

A unique aspect of our study is the use of EMR data which afforded the opportunity to perform a direct comparison on lipid levels in a large cohort of RA patients with clinical data, to a decade of data from NHANES. Few alternative clinical datasets have sufficient available data for this type of analysis.

Limitations to this study include potential incomplete capture of statin use in the EMR which can bias towards lower Tchol and LDL levels. To estimate the extent of statin use misclassification, we compared the EMR statin prescription data to Medicare statin prescription data in a subset of RA subjects for which we have available Medicare data (2006–2010). Forty RA subjects had their 1st LDL checked between 2006 and 2010 and were not on statins prior to LDL per EMR data. Out of these 40 subjects, two (5%) had billing codes for statins in Medicare dated prior to the first LDL, not captured in the EMR. Statin use in the NHANES study was obtained using data from self-report. We also had incomplete information on fasting status, which can have the opposite effect of incomplete statin capture, biasing towards higher Tchol and LDL levels. However, a recent study

demonstrated that in general there was no significant variation between fasting and non-fasting levels for Tchol and LDL(15).

In summary, RA subjects were observed to have significantly lower Tchol and LDL levels than the general population and non-significant differences in HDL levels. Thus, current routinely measured lipid profiles in RA may be unreliable predictors of CVD risk. Fortunately, the overall trends of lipid levels appear to be favorable for both RA patients as it is for the general population. Further studies are needed to integrate how inflammation and RA treatments may contribute to differences in lipid levels in RA compared to the general population, and the role of these combined factors for CVD risk in RA.

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Significance and Innovation

- The relative differences in clinically measured lipids associated with cardiovascular (CV) risk have not been directly compared between a large RA cohort and a comprehensive sample of the general population. To address this gap in knowledge, this study takes advantage of two data sources that allow for this comparison: (1) a recent United States population based study on lipid levels and trends between 1988–2010 (Carroll, et al., *JAMA* 2012), and (2) a large RA cohort with clinical and laboratory data on routinely measured lipids in the electronic medical record data from 1989–2010.
- We observed that total cholesterol (Tchol) and low density lipoprotein (LDL) were significantly lower in RA patients compared to the general population and were consistently lower over the past decade. These findings suggest that clinically measured lipid levels may not be as informative for CV risk in RA as the general population.
- We demonstrate for the first time, secular trends in favorable lipid profiles (decreasing Tchol, LDL and increasing HDL) among RA patients (from 1989–2010) similar to those observed in the general population (from 1988–2010).

Table 1

Comparison of mean total cholesterol, LDL and HDL in RA cases compared to fasting lipid levels in NHANES*, among women aged 20 years or older, not on statins, 1999–2010.

		RA cases		NHANES*		
	Time periods (Tchol)	**n**	**Mean (SD), mg/dL**	**n**	**Mean (SD), mg/dL**	**p-value**
Total cholesterol						
All race/ethnicity groups	1999–2002	363	196.75 (20.90)	4645	204 (69.54)	0.048
	2007–2010	290	185.76 (20.1)	4486	200 (64.17)	0.0002
Non-Hispanic white	1999–2002	264	197.62 (20.95)	1918	206 (44.67)	0.0027
	2007–2010	222	186.38 (20.34)	2073	202 (46.46)	<0.0001
Low density lipoprotein (LDL) cholesterol						
All race/ethnicity groups	1999–2002	369	111.12 (17.05)	1797	122 (64.88)	0.0014
	2007–2010	297	104.75 (17.50)	2027	118 (68.91)	0.0010
Non-Hispanic white	1999–2002	267	111.41 (16.94)	871	123 (45.17)	<0.0001
	2007–2010	228	104.38 (17.72)	923	118 (46.50)	<0.0001
High density lipoprotein (HDL) cholesterol						
All race/ethnicity groups	1999–2002	366	59.56 (9.60)	4645	56.6 (38.25)	0.14
	2007–2010	295	58.41 (9.70)	4486	58.3 (30.76)	0.11
Non-Hispanic white	1999–2002	266	59.61 (8.89)	1918	57.1 (33.52)	0.22
	2007–2010	226	60.38 (9.67)	2073	58.9 (30.20)	0.40

*National Health and Nutrition Examination Survey (NHANES) corresponds to data published in Carroll, et al, *JAMA*, 2012, Tables 4 & 5, age-adjusted mean, not on lipid-lowering medications, 'All race/ethnicity groups' and 'non-Hispanic white', women, 1999–2002 and 2007–2010(6)

Table 2

Qualitative comparison of cross-sectional trends in LDL, HDL, and total cholesterol (mg/dL) per year among the RA cohort, 1989–2007 (not on statins, adjusted by age and gender, all races) compared to the general population**.

Lipid/lipoprotein	RA cohort			NHANES**
	n	Δ*, mg/dL per year (SE)	p-value for linear trend (1989–2010)	P-value for linear trend (1988 to 2010)
Total cholesterol	802	−2.4 (0.29)	<0.0001	Decrease, <0.001
LDL	804	−2.3 (0.24)	<0.0001	Decrease, <0.001
HDL	801	0.54 (0.12)	<0.0001	Increase, <0.001

* Association between “year of lipid measurement” and lipid levels, in a multivariate linear regression model adjusted by age and gender (all races included).

** National Health and Nutrition Examination Survey (NHANES) corresponds to data published in Carroll, et al, *JAMA*, 2012, Tables 4 & 5, ‘All race/ethnicity groups’, ‘both sexes’.