HDL Cholesterol Efflux Capacity and Concentration in Patients With Rheumatoid Arthritis: a Systematic Review and Meta-Analysis

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Research

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Abstract

Background: HDL cholesterol efflux capacity has been proposed as an independent risk factor of cardiovascular diseases. However, the presented data has been less than convincing in RA. This meta-analysis aimed to identify whether CEC was impaired in RA or altered by drug therapy.

Methods: PubMed, Embase, and Cochrane library databases were searched to identify studies for CEC in RA patients. The primary outcomes were CEC, high-density lipoprotein cholesterol and C-reactive protein.

Results: A total of 11 eligible articles including 6 observational and 5 intervention studies. Pooled results showed there was no significantly decrease in the CEC of RA patients comparing with the healthy controls (SMD: -0.22, 95% CI: -0.65 to 0.20), whereas the plasma HDL-C levels was decreased in RA patients (WMD: -5.21, 95% CI: -7.69 to -2.72). Furthermore, in the before-after studies, CEC of RA patients (SMD: 0.20, 95% CI: 0.03 to 0.38) was increased but the plasma HDL-C levels (WMD: 3.26, 95% CI: -0.17 to 6.69) was similar after anti-rheumatic treatment comparing to the baseline. In addition, stratified analysis suggested that DAS28 could be potential sources of heterogeneity for CEC. The funnel plot was relatively symmetric and was not suggestive of presence of publication bias.

Conclusion The current meta-analysis demonstrated a slight, nonsignificant, decrease in the CEC among RA patients as compared with healthy individuals, but it can be improved substantially following anti-rheumatic treatment. More large population studies evaluating the predictive role of CEC on cardiovascular risk in RA are needed.

Introduction

Rheumatoid arthritis (RA), a chronic polyarthritis autoimmune disease, causing arthrosis impairment and even leading to disability[1], affects approximately 0.3%-1.0% people around the world[2]. In addition to a heavy burden for both patient and society, those living with RA have a significantly reduced life expectancy. High risk of cardiovascular diseases (CVD) has been found in patients with RA compared with the general population[3]. RA inflammation increases arterial stiffness, changes lipid profile, and destabilizes plaque. Moreover, 60% excess mortality in RA is attributed to CVD[4], which is one of the most severe complications of RA and cannot be fully explained by traditional cardiovascular risk factors.

The high-density lipoprotein cholesterol (HDL-C) is known as the “good cholesterol” owing to its protective effects against CVD[5]. Numerous studies suggested that the plasma HDL-C levels were reduced in patients with RA compared to general individuals[6-8]. For example, a study noted that an average of 9% drop in the plasma HDL-C level has been observed before the onset of symptoms among RA patients[9]. In addition, paradoxical associations among lowering lipid levels (i.e., total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and HDL-C) and the ongoing risk of CVD were observed in patients with poorly controlled RA[10], while the initial reductions in these parameters have increased with anti-inflammatory treatment in patients with RA. So the European League Against Rheumatism (EULAR) indicated that the TC to HDL-C ratio would seem more appropriate to predict the CVD risk in RA[11]. However, recent clinical trials with HDL-C-raising therapies has shown rather than being protective, which still associated with high cardiovascular events risk[12-14]. Therefore, whether the concentrations of circulating HDL-C in patients with RA were altered even after anti-inflammatory treatment merits further investigation.

HDL exerts several key atheroprotective functions, including its capacity of reverse cholesterol transport, maintenance endothelial function, anti-inflammatory and inhibition of platelet aggregation[15]. Of these functions, reverse cholesterol transport (RCT) is a overriding process that promote excess plasma cholesterol from cell to the liver for catabolism⁶. Macrophages cholesterol efflux as the first critical step of RCT which is considered a key atheroprotective property[16]. The impaired HDL cholesterol efflux capacity (CEC) has been proven to increase the risk of CVD, which is independent of the plasma HDL-C levels[17,18]. However, the epidemiological data that have been performed to explore the association between CEC and RA was less convincing. Some of them have shown that the CEC was significantly reduced in RA patients compared to healthy controls, but others failed to reach the conclusions[19-28]. In 2012, Charles-schoeman et al. first reported that there was no significant difference in CEC among RA patients comparing to control groups, but which was inversely associated with high disease activity in RA patients[21]. Subsequently, another cross-sectional study published in 2014, which analyzed different CEC efflux pathways, demonstrated that ABCG1-mediated CEC was markedly impaired in RA group[19]. Furthermore, in 2015, another study also conducted by Ronda et al. found that CEC can be modified by methotrexate (MTX), but not MTX + adalimumab (ADA) in RA patients[25].

Therefore, to assess the conflicting results, we systematically reviewed and meta-analyzed the epidemiological evidence on the changes in CEC as well as HDL-C levels of RA patients.

Methods

Literature Search and Selection Criteria

We conduct this meta-analysis and written the manuscript according to the PRISMA guidelines. EMBASE, MEDLINE and Cochrane Library databases were searched for records reporting CEC in patients with RA. Searches were focused on human subjects with no restriction on language and published before 10 June 2020. To avoid missing any relevant studies, we also searched manually the bibliographies of identified studies and review papers. The following medical subject headings terms and keywords were used alone or in combination: “high density lipoprotein” or “HDL” or “HDL-C”, “rheumatoid arthritis” or “RA”, “high density lipoprotein function” or “cholesterol efflux capacity” or “CEC” or “HDL-mediated cholesterol efflux”.

Study selection

Studies were initially assessed according to the following inclusion criteria: 1) we included all intervention trials and observational studies; 2) all subjects were older than 18 years of age; 3) RA patients who fulfilled 1987 or 2011 ACR criteria (fulfilling the American College of Rheumatology criteria) regardless of

whether or not combination cardiovascular disease; 4) healthy control subjects without inflammatory conditions; 5) the outcomes of interest were CEC and HDL-C levels. Two researchers independently deleted duplicate records, screened the titles and abstracts to identify potentially relevant articles. We further performed a full-text screening to identify additional eligible studies. If data were duplicated in more than one study, we gave priority to include the articles with the largest datasets and populations.

Data extraction and outcome measures

Two reviewers independently extracted data on each eligible articles by using a standardized data collection form, including first author's name, publication year, study design, country, patient characteristics, sample size, gender proportion, CEC assay methods, plasma HDL-C levels, CEC, Disease Activity Score for 28 joints (DAS28), C-reactive protein (CRP), records of all medicines taken, length of follow-up and study outcome. For data reported as medians and ranges, which were converted to means and standard deviations using Hozo's approach[29]. Although some participants were followed-up for varying durations, data were extracted from the greatest time. If necessary, we contacted authors for additional data. Disagreements between reviewers were resolved by discussion among third author.

We firstly retrieved 2270 articles from the various databases. After deleting duplication and screening title and abstract, 2235 articles were further excluded. The remaining 35 articles were reviewed with full text according to inclusion criterion. Eventually, only 11 articles were included. 26 papers were excluded due to the following reasons: 6 studies did not assess the outcome of CEC; 3 were reviews; 10 were abstracts without published full-text; 6 were animal experimentation. For the rest listed of studies, there were totally 6 observational studies and 5 intervention studies. The whole screening flow chart was posted in Fig 1.

Quality and risk Assessment

Two quality ratings scales assessed the methodological quality of studies. First, the quality of observational study was evaluated by the Newcastle-Ottawa Scale (NOS). According to the guidelines, three aspects were assessed: selection, comparability and exposure. The score of 1-4 were defined as low quality, and 5-9 as high quality respectively. Second, the Downs and Black scale (D&B) was adopted to analyze the bias risk of non-randomized and randomized studies from a list of 27 criteria. The last question about power was replaced by modification version, that was published in previous systematic reviews[30]. The score of 1-14 were defined as low quality, and 15-32 as high quality respectively.

Statistical Analysis

Data from observational studies and intervention studies were analyzed respectively. Mean and SD were commonly used to evaluate the changes of CEC and plasma HDL-C levels in RA patients. For continuous variables, the standardized and weighted mean differences (SMD & WMD) as well as corresponding 95% confidence intervals (CI₉₅) were calculated. For the intervention studies, baseline data was collected as the control group and data from the end of the treatment phase as the experimental group. Heterogeneity across eligible studies were obtained by using the Cochran's Q test. We further performed subgroup analysis to explore the sources of heterogeneity. By comparing the random and fixed effects models, we subsequently conducted a sensitivity analysis, and the influence of each individual study on the overall outcome was accessed by excluding one study at a time. The risk of publication bias was observed by visual graph of funnel plots and further quantified using Egger's test, where $P < 0.1$ indicates potential publication bias[31,32]. All analyses were performed using STATA version 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) and Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Literature search results and study characteristics

Table 1 and Table 2 showed the main characteristic of the included studies. These 11 articles were published during 2012 to 2019. Of which 7 studies were conducted in the USA, 3 in UK, and 1 in Spain. The sample size of those studies ranged from 36 to 401, several of them with sample sizes range 50 to 100 were considered modest, and 3 other studies with a large sample size (> 100). The average age of participants ranged from 42 to 65 years. Cases and controls were matched by gender, age and body mass index (BMI) in case-control study. According to the NOS and D&B standard criteria, the quality scores of the 6 observational studies were 5 to 8, which were all considered as moderate and high-quality. Moreover, the quality scores of the intervention studies ranged from 11 to 17, and 2 studies were considered as high-quality and 3 as low-quality studies. Most observational studies did not report the non-response rate, and the D&B scores showed weak external validity of intervention studies.

The main outcome: changes in CEC and HDL-C levels among RA patients

Observational studies: 5 observational studies reported the CEC in both case and control groups with a total of 809 participants. Pooled results showed that the CEC of RA patients didn't decrease significantly comparing with the healthy controls (SMD: -0.22, 95% CI: -0.65 to 0.20; $I^2 = 86\%$, P for heterogeneity < 0.001). In addition, 6 studies with 845 subjects measuring the plasma HDL-C levels showed the patients with RA had a lower HDL-C levels (WMD: -5.21, 95% CI: -7.69 to -2.72), with a nonsignificant heterogeneity ($I^2 = 54\%$, P for heterogeneity = 0.050) (Fig 2). Besides, the plasma levels of TC (total cholesterol) and LDL were both significantly altered in two groups, except for TG (triglycerides) (see Additional file 1).

Before-after studies: 5 studies that include 8 trials revealed a statistically significant elevation of CEC in RA patients who had taken anti-rheumatic medications comparing to the baseline (SMD: 0.20, 95% CI: 0.03 to 0.38; $I^2 = 0\%$, P for heterogeneity = 0.650). In addition, only 4 studies were suitable to analyze the change of HDL-C levels in the intervention studies. In contrast, the plasma HDL-C levels were slightly higher in RA patients after anti-rheumatic drug treatment comparing to the baseline, but the difference did not reach the level of significance. (WMD: 3.26, 95% CI: -0.17 to 6.69). The heterogeneity was

quite high ($I^2 = 0\%$, P for heterogeneity = 0.640) (Fig 3). Other lipid parameters such as LDL, TC and TG were not significantly different between baseline and follow-up (see Additional file 2). 5 studies reported CRP levels as a continuous variable. Accordingly, in observational studies, the pooled analysis data showed that the CRP levels increased in RA patients compared to the healthy controls (SMD: 1.25, 95% CI: 0.33 to 2.16; $I^2 = 96\%$, P for heterogeneity < 0.001). However, the CRP levels were significantly reduced after anti-rheumatic drug therapy among the intervention studies (SMD: -0.46, 95% CI: -0.71 to -0.21; $I^2 = 0\%$, P for heterogeneity = 0.830).

Subgroups and sensitivity analysis

Our results found that DAS28 had a significant impact on the heterogeneity of CEC ($I^2 = 22.6\%$). In addition, subgroup analysis stratified by BMI and age showed that the heterogeneity of HDL-C levels was significantly decreased ($I^2 = 36.8\%$; $I^2 = 19.6\%$, respectively) (see Additional file 3). The sensitivity analysis showed that the overall effect size of CEC and CRP obtained using fixed-effect and random-effects models were identical and no individual study significantly affected the pooled results. The results in the random effects and fixed effects models as well as the subgroup analysis were similar. After further excluding a signal article[18], low heterogeneity was found after remerging ($I^2 = 36.8\%$), and the results of random effects models were consistent with the results of fixed effects model (fixed effects model: WMD: -6.07, 95% CI: -8.67 to -3.64; random effects model: WMD: -5.45, 95% CI: -9.40 to -1.51) (see Additional file 4).

Publication bias

We performed funnel plots for CEC, HDL and CRP to assess publication bias (Fig 4). The presence of publication bias was also evaluated by using the Begg and Egger tests. Currently, the publication bias of CEC, HDL-C and CRP were calculated ($P_{\text{CEC}} = 0.106$; $P_{\text{HDL-C}} = 0.342$; $P_{\text{CRP}} = 0.721$) according to funnel plot and Egger's test. However, statistical power of publication bias was low due to a small number of studies.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to simultaneously evaluate whether the CEC and plasma HDL-C levels were decreased in RA or altered by drug therapy. The results did not show any significant change in the HDL-mediated CEC, while the plasma HDL-C levels decreased significantly in patients with RA compared to the healthy subjects. In addition, stratified analysis did not influence the tendency of CEC and HDL-C levels in RA. However, it is interesting that in the intervention study, the elevated CEC was seen in RA patients taking their medications, followed by reduction of the CRP levels compared to the baselines. These findings suggested that inhibition of inflammation might improve HDL-mediated CEC. Although the plasma HDL-C levels were slightly increased after RA treatment, the difference did not reach the level of significance, which indirectly indicated that CEC is more sensitive than HDL-C. Several potential mechanisms can thus be proposed to explain the changes of CEC, plasma HDL-C and CRP levels in patients with RA.

RA is an autoimmunity disease associated with chronic inflammation, which might lead to multiple changes in HDL structure and alterations in HDL function[33]. First, most patients with RA have elevated levels of certain proinflammatory cytokines, including CRP, interleukin-6 in their blood. Many studies have indicated that HDL-C levels were dramatically reduced during inflammation, and one possible mechanism underlying these changes associated with the live phospholipid transfer protein (PLTP) expression. For example, Audo et al. showed that PLTP is highly expressed in the joints of RA patients and may directly trigger inflammation[34]. Furthermore, Jiang et al. demonstrated that the reduced plasma PLTP activity results in markedly decreased plasma HDL lipid and apolipoproteins, indicating the importance of the transfer of triglyceride-rich lipoproteins surface components in maintaining HDL levels[35]. In our meta-analysis, we found that the plasma HDL-C levels were significantly decreased in the RA patients compared to the healthy groups, which suggested that the inflammatory status and severity of patients with RA was inversely related to the plasma HDL-C levels. However, the plasma HDL-C levels did not change significantly after RA treatment.

Second, substantial evidence has now accumulated, suggesting that a high inflammation status would limit capacity for HDL to promote cholesterol efflux from of macrophages[36]. McGillicuddy et al. conducted a study in mice found that acute inflammation has a broad and integrated impact on RCT in vivo, attenuating several steps including macrophage cholesterol efflux, HDL acceptor function, and hepatic to bile/fecal cholesterol elimination[37]. Thus, which suggested that the inflammatory status in patients with RA not only affect the rate of cholesterol efflux but also other steps in RCT. Surprisingly, in our meta-analysis we found that the CEC was not significantly decreased different between the RA patients and control groups. Possibly, routinely measured baseline CEC in RA patients may not accurate due to the fluctuations of inflammatory status. Meanwhile, despite several studies used a few different approaches to measure CEC, and even some of them might under estimate the actual cholesterol efflux. However, large quantity of population-based evidences demonstrated that CEC was a sensitive predictor of the risk of CVD, independent of circulating HDL-C concentrations[38,39]. In addition, we found that the CEC was significantly increased in patients with RA after medicine care, followed by reduction of the CRP levels compared to the baselines, while the HDL-C levels did not significantly alter after anti-rheumatoid treatment. These findings indirectly indicated that CEC might serve as more sensitive indicator than HDL-C levels in prevention of CVD in RA. Generally, effectively control inflammation in RA might help to improve the function of HDL. Some possible mechanisms have been proposed to determine the specific role of increasing CEC for prevention of CVD in patients with RA in present evidences. Further larger-scale population-based studies and experimental researches are needed to confirm the fundamental roles and mechanisms.

Heterogeneity poses an important challenge in conducting and interpreting the results of meta-analyses[40]. We conducted subgroup analysis to evaluate the heterogeneity of CEC and HDL-C. The analysis results have found that DAS 28 is the source of statistic heterogeneity. For the HDL levels, BMI and age, not DAS28, were the sources of heterogeneity. Sensitivity analysis were performed to enhance the robustness and reliability of results. The effect size of HDL-C levels was not significantly different in random model, when we included a study conducted by Ronda et al[25], which may due to the younger age and prohibition of taking statins in RA patients, both could leading to markedly raise of the plasma HDL-C levels. Furthermore, nearly half of the included studies were case-control studies, which have comparatively low quality. Given that the possible recall bias and selection bias in case-control studies, more large-scale

prospective cohort studies with full adjustment for potential confounding factors are urgently needed to confirm the inverse association between CEC and CRP levels.

Several potential limitations should be taken into consideration. First, the quality of meta and pooled analysis largely depended on the quality of the original studies. Among the studies included, there were six observational studies, which were susceptible to selection and recall bias. Second, a substantial heterogeneity have reported in this meta analysis. Therefore, sensitivity analyses were conducted to confirm the stability of the results. Third, currently there was no established gold-standard for ex-vivo CEC assays. Besides, the rate of cholesterol efflux was expressed in various form, leading to slight difference between CEC values. Thus, to minimize the variation, we calculated standardized effect sizes. Fourth, the small number of included studies could limit the ability to interpret the funnel plot.

Conclusion

In summary, our meta-analysis observed a slight, nonsignificant, decrease in the CEC among RA patients as compared with healthy individuals but it can be improved substantially following anti-rheumatic treatment. In contrast, the plasma HDL-C levels were not associated with risk of RA. Overall, the CEC of RA patients could be improved through earlier control of inflammation and anti-rheumatic treatment. Future large population-based and long-term studies should further elucidate the changes in CEC of RA patients and assess the function in preventing CVD.

Abbreviations

RA Rheumatoid arthritis

CVD Cardiovascular diseases

HDL-C High-density lipoprotein cholesterol

TC Total cholesterol

LDL-C Low-density lipoprotein cholesterol

TG Triglycerides

EULAR The European League Against Rheumatism

RCT Reverse cholesterol transport

MTX Methotrexate

ADA Adalimumab

PLTP Phospholipid transfer protein

DAS28 Disease Activity Score for 28 joints

CRP C-reactive protein

D&B Downs and Black scale

NOS Newcastle-Ottawa Scale

SMD Standardized mean differences

WMD Weighted mean differences

CIs 95% 95% Confidence intervals

BMI Body mass index

Declarations

Availability of data and materials

Not applicable.

Authors' contribution

Study concept and design: CQ-L and JH. Data extraction and analysis: B-BX, YL and TL. Manuscript drafting: B-BX and CQ-L. All authors were involved in data analysis, drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no competing interest.

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Tables

Table 1. Characteristics of observational studies in this systematic review and meta-analysis

Authors	Country	Study type	Subjects (female, %)	Duration ^a (month)	Assay method of CEC	Labeled-cholesterol	Quality score	Outcome summary
Ronda et al., 2013 ^[18]	USA	Case-control	52 (86.7)	N/A ^c	J774, Fu5AH, CHO-k1 to ApoB-depleted serum	³ H-cholesterol	5	CEC ^b is impaired in RA
Vivekanandan-Giri et al., 2013 ^[19]	USA	Case-control	34 (58.6)	4.0	J774 to ApoB-depleted serum	³ H-cholesterol	5	CEC was diminished in RA patients
Charles-Schoeman et al., 2015 ^[20]	USA	Case-control	66 (82.0)	12.8	RAW264.7 to isolated HDL	³ H-cholesterol	9	no difference of CEC between RA patients and controls
O'Neill et al., 2016 ^[21]	UK	Case-control	22 (73.0)	5.0	J774 to ApoB-depleted serum	³ H-cholesterol	7	-
Ormseth et al., 2016 ^[22]	USA	Case-control	144 (68.6)	3.9	THP-1 to ApoB-depleted serum	³ H-cholesterol	6	CEC is not significantly altered in RA patients
Tejera-Segura et al., 2017 ^[23]	Spain	Cross-sectional	295 (73.6)	7.0	J774 to ApoB-depleted serum	BODIPY-cholesterol	7	CEC is not significantly altered in RA patients

Data are presented as median (interquartile range) or mean ± SD unless otherwise indicated; ^a duration of RA; ^b cholesterol efflux capacity; ^c not available.

Table 2. Characteristics of interventional studies in this systematic review and meta-analysis

Authors	Country	Treatment	Dose of drugs	Study design	N/female (%)		Mean (age)	Duration ^a (year)	Length of follow-up (m)	Quality score	Outcome summary
Ronda et al., 2015 ^[24]	USA	MTX ^c , ADA ^d , MTX	MTX: 3-5 mg ADA: 40 mg	One-arm study	56 (N/A)		57.0	2.0	6	11	CEC ^b was not significantly altered after RA treatment
P.Liao et al., 2015 ^[25]	USA	MTX, INF ^e , MTX + INF	NA ⁱ	One-arm study	80 (88.9)		57.0	16.5	12	13	CEC was improved after therapy
O'Neill et al., 2016 ^[21]	UK	MTX+INF, MTX+PLA ^f	M+I: 5 mg/kg M+p: 2.5-25 mg/kg	Two-arm study	18 (66.7)		58.6	5.0	12	16	CEC was not significantly altered after RA treatment
Ormseth et al., 2016 ^[26]	USA	MTX, TCZ ^g , ADA ^h	NA	Three-arm study	59 (84.0)	53.0	9.0	6	17		CEC was not significantly altered after RA treatment
Ferraz-Amaro et al., 2019 ^[27]	UK	TCZ	8 mg/kg	One-arm study	24 (88)	52.0	8.0	12	12		CEC was significantly increased after RA treatment

Data are presented as median (interquartile range) or mean $\pm$ SD unless otherwise indicated; ^a duration of RA; ^b cholesterol efflux capacity; ^c methotrexate; ^d adalimumab; ^e infliximab; ^f placebo; ^g tocilizumab; ^h adalimumab; ⁱ not available.

Figures

Figure 1

Flow diagram of selection process in the meta-analysis.

Figure 2

Forest plot of the plasma levels of CEC (a), high-density lipoprotein (b) and C-reactive protein (c) for patients with RA versus control group in observational study.

Figure 3

Forest plot of the plasma levels of CEC (a), high-density lipoprotein (b) and C-reaction protein (c) for patients with RA and control group in before-after studies

Figure 4

Funnel plots evaluating the pooled estimates for the plasma levels of CEC (a), high-density lipoprotein (b) and C-reaction protein (c) among patients with RA.

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