Type of the Paper (Systematic Review)

Meta-Analysis of High-Density Lipoprotein Levels in Leprosy

Amel R. H. Abd El Aziz[1], Rania H. M. Salem[2], Samaa H. M. Soror[1]*, Noha E. M. Abdel Gawad[1]

[1] Dermatology & Venereology Department, Faculty of Medicine, Fayoum University, Fayoum, 63514 Egypt.

[2] Medical Biochemistry Department, Faculty of Medicine, Fayoum University, Fayoum, 63514 Egypt.

*Correspondence: Samaa H. M. Soror, sh1169@fayoum.edu.eg, Tel: (002) 01148162677.

Received: 2 November, 2024 Reviewed: 1 February, 2025
Accepted: 4 May, 2025 Published online: 26 June 2025

Abstract:

Introduction: The relationship between High-Density Lipoprotein (HDL) and leprosy is a relatively underexplored area of research, but emerging studies suggest that HDL may play a role in the management of the disease.

Aim of the study: To assess the relation between the levels of High-density lipoprotein (HDL) and leprosy.

Methods: We searched the Cochrane Library, Web of Science, PubMed, and Scopus for relevant articles. We utilized a strategy for our search by combining these keywords: (‘’ High-density lipoprotein’’ OR ‘’ HDL’’) AND (‘’ Leprosy ‘’ OR ‘’ Mycobacterium leprae ‘’ OR ‘’ Lepromatous leprosy ‘’ OR ‘’ Tuberculoid leprosy ‘’). The quality evaluation of the involved studies was assessed using Cochrane’s risk of bias tool (ROB).

Results: Our meta-analysis included four articles. We found that leprosy patients had lower levels of HDL. Additionally, the HDL and TC levels were similar in both cohorts (paucibacillary and Multibacillary) without any substantial variations (MD = 8.57 [-12.70, 29.85], *P* = 0.43) and (MD = -7.43 [-24.07, 9.22], *P* = 0.38), respectively.

Conclusions: Leprosy is accompanied by decreased levels of HDL in the patients, and the treatment of leprosy may help in the elevation of HDL levels slightly. That’s why HDL plays a crucial role in the follow-up of leprosy progression and assessing the effectiveness of MDT for the management of leprosy.

Keywords: High-density lipoprotein; Mycobacterium leprae; Leprosy; Lepromatous leprosy; Tuberculoid leprosy.

1. Introduction

Leprosy, also called Hansen's disease, is a chronic infectious condition resulting from Mycobacterium leprae. It primarily impacts the nerves, skin, respiratory tract, and eyes, leading to disfigurement, disability, and social stigma if left untreated [1]. Leprosy spreads through prolonged close contact with an infected person, mainly via droplets from the nose and mouth. The disease has a long incubation period, often taking years before symptoms appear, which include skin lesions, numbness, and muscle weakness [2].

Historically, leprosy has been associated with significant social stigma and isolation due to its disfiguring effects and misconceptions about its contagiousness [3]. However, with the advent of modern medicine, effective multi-drug therapy (MDT) has made the disease curable, and early diagnosis and treatment can prevent most of its complications. Global efforts have significantly reduced the prevalence of leprosy, but it is still a concern for public health in some regions, especially in parts of South America, Africa, and Asia [4].

High-density lipoprotein (HDL), commonly referred to as "good cholesterol," plays a vital role in the metabolism of lipids and cardiovascular health by moving cholesterol from the arteries to the liver for excretion [5]. HDL is more than a mere cholesterol transporter; it is a complex particle with a range of functions, including anti-inflammatory, antioxidant, and immunomodulatory properties. Given these properties, researchers have begun to investigate HDL levels in the context of various diseases beyond cardiovascular health. In infectious diseases, including bacterial infections, viral infections, and chronic inflammatory conditions, HDL levels have been observed to fluctuate, potentially reflecting the body’s immune response and overall metabolic state during infection. In the context of leprosy, the role of HDL has gained attention due to the disease's impact on lipid metabolism and immune function [6].

Leprosy induces a chronic inflammatory response in the body, which can alter lipid profiles, including HDL levels. Research has shown that individuals with leprosy often exhibit altered lipid profiles, characterized by changes in HDL levels [7]. Typically, patients with leprosy might have reduced HDL levels, which is

concerning because low HDL levels are associated with an increased risk of cardiovascular diseases. This reduction in HDL may be due to the infection's chronic inflammatory state, which can influence lipid metabolism and the body's immune response [8]. Moreover, HDL has anti-inflammatory and immunomodulatory properties, which are significant in the context of leprosy. HDL is known to bind and neutralize bacterial lipopolysaccharides, which are components of the outer membrane of certain bacteria, thereby playing a role in the body's defense mechanisms [8]. In leprosy, the interaction between HDL and *Mycobacterium leprae* could potentially influence the course of the disease and the body's ability to manage the infection [9].

Understanding the relationship between HDL and leprosy is crucial because it may offer insights into managing lipid abnormalities and reducing cardiovascular risks in leprosy patients. Additionally, this understanding could help in developing therapeutic strategies that modulate lipid profiles to improve disease outcomes and overall health in affected individuals. In this meta-analysis, we aim to assess the correlation between HDL and leprosy.

2. Methods

We performed this study based on the PRISMA guidelines and recommendations [10].

2.1. Information Sources and Search Strategy

We utilized a strategy for our search by combining these keywords: (‘’ High-density lipoprotein’’ OR ‘’ HDL’’) AND (‘’ Leprosy ‘’ OR ‘’ Mycobacterium leprae ‘’ OR ‘’ Lepromatous leprosy ‘’ OR ‘’ Tuberculoid leprosy ‘’). Regarding the sources of data, we utilized Cochrane Library, Google Scholar, Web of Science, PubMed, and SCOPUS databases in the process of searching. We searched these databases till August 2024.

2.2. Study selection

We started by screening the titles and abstracts. We then carried out a full-text screening. Finally, we choose the qualifying articles by the following eligibility requirements: Case cohort: Adult individuals suffering from paucibacillary (PB) leprosy or untreated patients, Control cohort: Adult

individuals suffering from Multibacillary (MB) leprosy or treated patients, Intervention: Assessing the levels of HDL and total cholesterol (TC), and Outcome: levels of HDL and TC.

Inclusion criteria

We included papers that met our eligibility criteria, which were recent studies above 2010, studies that included both males and females, studies that evaluated the levels of TC and HDL, double-arm studies that had case and control cohorts, and articles in English. We chose observational studies and blind or non-blind, and non-randomized or randomized controlled clinical trials (RCTs)

Exclusion criteria

We excluded reviews, surveys, abstracts, and meta-analyses. Also, we excluded single-arm studies that assessed only one group and studies in languages other than English.

2.3. Quality assessment

Since observational studies were involved, the Cochrane risk of bias (ROB) evaluation was employed, which assesses 14 categories in each clinical study [11]. Each study got a score from 1 to 14, and the overall average score will be calculated.

2.4. Data extraction

Two different categories of data were taken from the involved papers. The first type includes the demographic information about the patients involved and the baseline data for our results. Data extraction for the following outcomes was the second category for analysis: levels of TC and HDL. The third category was data on quality assessment. Microsoft Excel was used to carry out the data collection process [12].

2.5. Statistical analysis

Review Manager Software was employed to conduct this meta-analysis (13). Our study involved continuous outcomes. For the analysis of continuous data, we used a 95% confidence interval (CI) and mean difference (MD). The fixed-effects model was applied to consistent data, and the random-effects model was applied to inconsistent data. The degree of consistency between the data was evaluated using the p-value and I2 of the Chi-square tests [14]. Heterogeneity was significantly suggested by values of I2 > 50% or $P < 0.1$.

3. Results

3.1. Summary of the involved articles

The results of our database search are demonstrated in the PRISMA flow chart **(Figure 1)**.

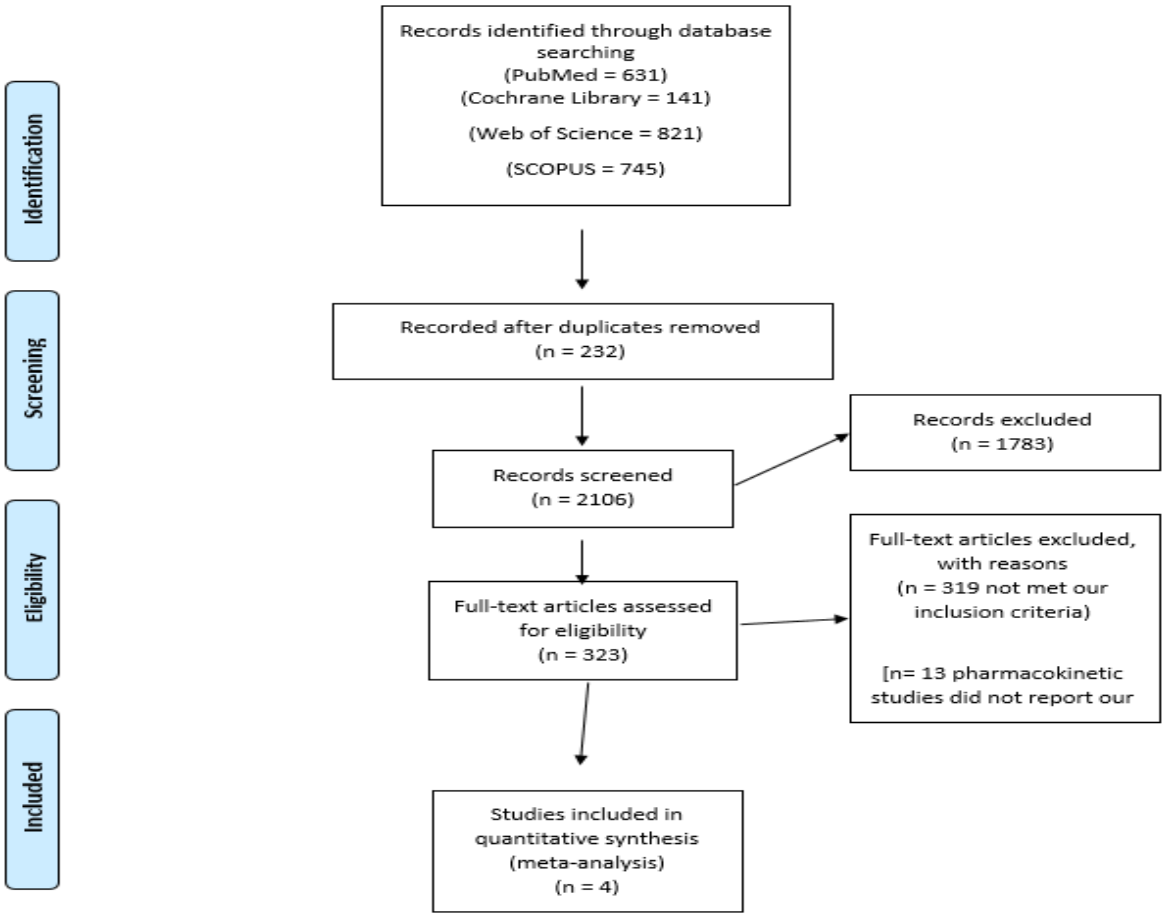

Figure 1: Literature search's PRISMA flow diagram.

We involved four studies [15-18] that met the inclusion criteria of our meta-analysis. Our study involved 218 individuals divided into two cohorts: the case cohort, which included 82 patients and the control cohort, which included 136 individuals. The

case cohort included 29 females and 68 males, while the control cohort included 32 females and 78 males. The average age of the included individuals in the case cohort was 39.75 years, while that of the control cohort was 41 years. **Table 1** illustrates the features of the involved studies and individuals. **Table 2** shows the disease characteristics, including type of leprosy, treatment duration, history of lepra reactions, and macroscopic index.

Table 1: The baseline features of the involved individuals and articles.

Study ID	Year	Country	Sample size		Age, years		Male, N (%)		Female, N (%)	
			Case	Control	Case	Control	Case	Control	Case	Control
Bassey et al. [15]	2020	Nigeria	30	30	38.4	49.8	19	22	11	8
Negara et al. [16]	2018	London	30	30	27.5	25	20	22	10	8
Lemes et al. [17]	2020	Brazil	6	8	44	40	2	7	4	1
Silva et al. [18]	2017	China	16	68	50-60		55		29	

Table 2: The disease characteristics, including type of leprosy, treatment duration, history of lepra reactions, and macroscopic index.

Study ID	Treatment duration		Type of leprosy (%)		Bacilloscopic index (median)		History of Lepra Reactions (%)	
	Leprosy	Control	Paucibacillary	Multibacillary	Leprosy	Control	Leprosy	Control
Bassey et al. [15]	23	-	0	30 (100%)	-	-	24 (40%)	-
Negara et al. [16]	-	-	6 (43%)	8 (57%)	4,87	-	-	-
Lemes et al. [17]	-	-	16 (19%)	68 (81%)	-	-	-	-
Silva et al. [18]	24	-	-	-	Above 2	-	30 (50%)	-

3.2. *Results of quality assessment*

Since we included four observational studies, we assessed their quality using Cochrane's tool. Cochrane's tool indicated that the observational studies' mean score was 10.75 out of 14. The quality evaluation of the observational articles is shown in detail in **Table 2.**

Table 1: The quality assessment of the included articles.

	Bassey 2020	**Lemes 2020**	**Negera 2018**	**Silva 2017**
1. Was the paper's goal or research question made clear??	1	1	1	1
2. Was the target population for the study well-defined and specified?	1	1	1	1
3. Was at least 50% of the eligible individuals participating?	1	1	1	1
4. Did all the participants come from the same or comparable populations, and did they all participate over the same period?	0	1	1	1
5. Was there a power description, an explanation for sample size, or estimates of effect and variance?	0	0	0	0
6. Were the exposure(s) wanted to be measured before the outcome(s) were determined for the analysis in this paper?	1	1	1	1
7. Was the duration such that, if a relationship between outcome and exposure existed, one could fairly anticipate seeing it?	1	1	1	1
8. Was the relationship between different exposure levels and outcomes for exposures that can change in quantity or degree (such as exposure categories or exposure measured as a continuous variable) examined in the study?	1	1	1	1
9. Were the exposure measures, or independent variables, well-defined, legitimate, dependable, and applied similarly to every study participant?	1	1	1	1
10. Was there a repeated evaluation of the exposure(s) throughout time?	0	0	1	0
11. Were the dependent variables, or outcome measurements, properly defined, dependable, valid, and applied similarly to every study participant?	1	1	1	1
12. Were the people evaluating the results blinded to the participants' exposure status?	*	*	*	*
13. Was the follow-up loss 20% or less of the baseline?	1	1	1	1
14. Has the impact of important potential confounding variables on the link between outcome(s) and exposure(s) been quantified and statistically adjusted?	1	0	1	1
Total score (out of 14)	11/14	10/14	12/14	10/14

*0 = No, Key: 1 = Yes, N/A = Not applicable, * = Not reported.*

3.3. Analysis of outcomes

High-density lipoproteins (HDL)

As shown in **Figure 2**, the HDL level was assessed by two included articles that involved 98 patients. The analysis proved that leprosy patients had lower levels of HDL. Additionally, the HDL level was similar in both cohorts (paucibacillary and Multibacillary) without any substantial variations (MD = 8.57 [-12.70, 29.85], *P* = 0.43). There was some sort of inconsistency between the pooled data (*P* = 0.004, I^2 = 88%).

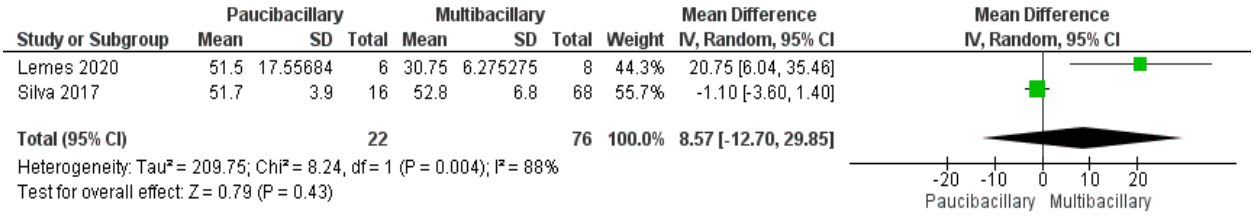

Figure 2: HDL levels in paucibacillary and Multibacillary patients.

Total cholesterol (TC)

Leprosy patients showed borderline levels of cholesterol. Also, the TC level was the same in both cohorts (paucibacillary and Multibacillary) without any remarkable differences (MD = -7.43 [-24.07, 9.22], *P* = 0.38). There was consistency between the pooled data (*P* = 0.41, I^2 = 0%) **(Figure 3).**

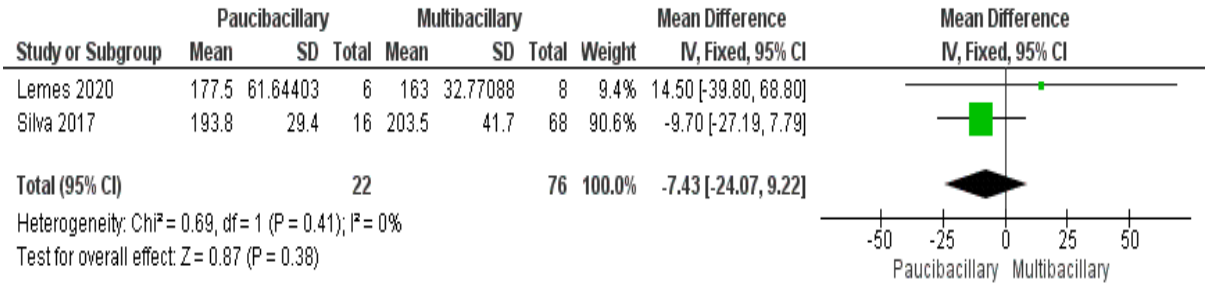

Figure 3: TC levels in paucibacillary and Multibacillary patients.

3.4. Untreated leprosy patients versus treated leprosy patients

High-density lipoproteins (HDL)

HDL levels were assessed in 120 leprosy patients, and the analysis revealed that HDL levels increased with treatment. However, the elevation of HDL levels was not statistically remarkable (MD = -2.39 [-6.55, 1.76], *P* = 0.26). There was consistency between the pooled data (*P* = 0.77, I^2 = 0%) **(Figure 4).**

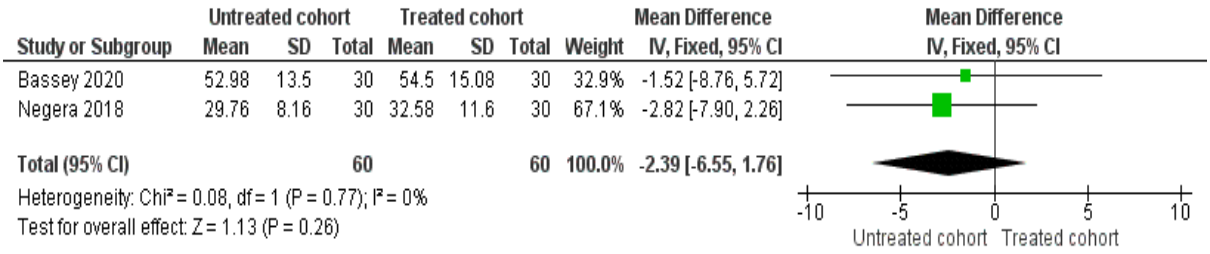

Figure 4: HDL levels in untreated and treated patients.

Total cholesterol (TC)

The results of the analysis prove that there was a slightly significant elevation of the levels of TC in the treatment group more to without its group (MD = -35.51 [-72.01, 1.00], *P* = 0.06). There was heterogeneity between the pooled data (*P* = 0.004, I^2 = 88%) **(Figure 5).**

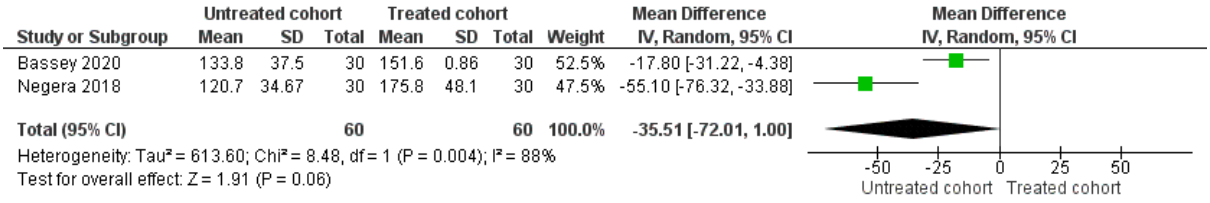

Figure 5: A Forest plot illustrates the analysis of TC levels in untreated and treated patients.

4. Discussion

The interplay between HDL and leprosy is a complex and multifaceted area of study. HDL is known for its protective roles in cardiovascular health, primarily

through cholesterol transport, reversion, antioxidant, and anti-inflammatory functions. Regarding leprosy, the connection between the disease's pathophysiology and HDL provides insights into how chronic infections can influence lipid metabolism and potentially affect overall health. Leprosy patients often exhibit dyslipidemia, including changes in HDL levels [4].

Research indicates that individuals with leprosy may have reduced HDL cholesterol levels, especially those with the lepromatous form of the disease, which is characterized by widespread skin lesions and a high bacterial load. The reduction in HDL levels could be attributed to the chronic inflammation induced by M. leprae infection. Inflammation can alter the activity of enzymes involved in lipid metabolism, such as lecithin-cholesterol acyltransferase (LCAT), which is crucial for HDL synthesis and maturation [8].

Reduced HDL levels in leprosy patients are of particular concern due to the connection between low HDL and increased cardiovascular disease (CVD) risk. Chronic inflammatory diseases like leprosy can exacerbate CVD risk factors, including dyslipidemia, insulin resistance, and hypertension. Therefore, monitoring lipid profiles, including HDL levels, in leprosy patients is essential for the early identification of cardiovascular risks and the implementation of preventive measures [3].

While existing studies highlight the altered lipid profiles in leprosy patients, more research is needed to understand the molecular mechanisms underlying HDL changes and their clinical implications. Longitudinal studies can help elucidate the connection between HDL levels, disease progression, and cardiovascular outcomes. Investigating the impact of MDT, the standard treatment for leprosy, on lipid metabolism and HDL function could provide insights into how treatment affects cardiovascular health in these patients [5].

The treatment of leprosy may cause slight elevations of the HDL level. These outcomes support those of Moschella, who noted that HDL levels in PB and MB patients increased following the MDT; yet, these increases fell within the normal range [19]. In line with earlier authors' findings [20], Bansal et al. also discovered a significant rise in HDL levels in patients with MB and PB forms when compared to the control group [21]. Gupta et al., on the other hand, found that individuals with the lepromatous form of leprosy had

considerably lower HDL-c levels than the controls [22].

Lower levels of HDL were also seen in Mb patients in other research on serum lipids in leprosy. However, earlier research found greater HDL-cholesterol levels in Mb patients; this was likely because the demographics and analytical techniques used were different [7]. Low plasma HDL levels are thought to be a risk factor for disorders like atherosclerosis, which are characterized by lipid buildup in tissues as a result of ineffective lipid export activity [23]. While one study found a low frequency of atherosclerosis in leprosy cases, other studies documenting autopsy results in leprosy (both PB and MB) found that plaque calcification and atherosclerosis were present in every case. Atherosclerosis was found in 193 out of 209 leprosy autopsies, according to a Brazilian study [22].

Our meta-analysis has several limitations, such as the presence of heterogeneity between the included articles, the small sample size, and the inclusion of only observational studies, as our study did not include any randomized clinical trials.

5. Conclusion

Leprosy is associated with decreased HDL levels in patients, and the treatment of leprosy may help in the elevation of HDL levels slightly. That's why HDL plays a crucial role in the follow-up of leprosy progression and in assessing the effectiveness of MDT for the management of leprosy.

Ethical committee approval: not applicable

Competing interests: All authors declare no conflict of interest.

Funding: This research is not funded.

AI declaration statement: None declared.

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