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ASSOCIATION BETWEEN TOTAL BILIRUBIN LEVELS WITH INCIDENCE OF ATHEROSCLEROSIS: SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background. Bilirubin is a byproduct of the breakdown of erythrocytes. Bilirubin levels can potentially serve as a biomarker for cardiovascular risk assessment. In this study, we would be investigating most recent manuscripts, published in the last 5 years, that studied association of serum bilirubin level to atherosclerosis progression to elicit how strongly low level of total bilirubin can prognose the disease progression.

Methods. Using Pubmed search engine, all articles that included keywords "bilirubin" and "atherosclerosis" were retrieved. In total 67 search results emerged for the 2019-2023 timeline, the last 5 years.6 population-based studies that studied association between total bilirubin concentration and atherosclerosis development were used for the meta-analysis.

Results. Increasing blood total bilirubin level seems to decrease the odds of developing atherosclerosis, meaning that there is an inverse correlation between total bilirubin level and arterial plaque formation or stenosis. Pooled odds ratio was found to be 0.86 (95% CI 0.83-0.9), suggesting that there is 14% decreased chance of developing atherosclerosis for each mmol/L increase in bilirubin levels. Overall, higher total serum bilirubin levels were associated with a significantly decreased risk of progression to atherosclerosis.

Conclusion. The meta-analysis indicates a significant inverse association between low total bilirubin levels and the risk of developing atherosclerosis, suggesting that higher bilirubin levels may be protective against the progression of this disease.

Жалпы билирубин деңгейі мен атеросклероздың даму жиілігі арасындағы байланыс: жүйелі шолу және мета-талдау

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Тұжырым

Өзектілігі. Билирубин-эритроциттердің ыдырауының жанама өнімі. Билирубин деңгейі жүрек-қан тамырлары қаупін бағалау үшін биомаркер бола алады. Бұл зерттеуде біз сарысулық билирубин деңгейінің атеросклероздың прогрессиясымен байланысын зерттеген соңғы 5 жылда жарияланған ең соңғы қолжазбаларды зерттеп, жалпы билирубин деңгейінің аурудың дамуын қаншалықты төмен болжай алатынын анықтаймыз.

Әдістері. PubMed іздеу жүйесінің көмегімен "билирубин" және "атеросклероз"- кілттік сөздері бар барлық мақалалар табылды. 2019-2023 жылдар кезеңінде, соңғы 5 жылда барлығы 67 іздеу нәтижелері пайда болды. Мета-талдау үшін жалпы билирубин концентрациясы мен атеросклероздың дамуы арасындағы байланысты зерттейтін 6 популяциялық зерттеу қолданылды.

Нәтижелер. қандағы жалпы билирубин деңгейінің жоғарылауы атеросклероздың даму ықтималдығын төмендетеді, яғни жалпы билирубин деңгейі мен артериялық бляшкалардың пайда болуы немесе стеноз арасында кері байланыс бар. Біріктірілген коэффициент 0.86 (95% СИ 0.83–0.9) болды, бұл ммоль/л үшін билирубин деңгейінің әрбір жоғарылауымен атеросклероздың даму ықтималдығы 14% төмендейтінін көрсетеді. Жалпы, сарысудағы жалпы билирубиннің жоғары деңгейі атеросклероздың даму қаупінің айтарлықтай төмендеуімен байланысты болды.

Қорытынды. Мета-талдау жалпы билирубиннің төмен деңгейі мен атеросклероздың даму қаупі арасындағы айтарлықтай кері байланысты көрсетеді, бұл билирубиннің жоғары деңгейі аурудың дамуынан қорғай алады деп болжайды.

Связь между уровнем общего билирубина и частотой развития атеросклероза: систематический обзор и мета-анализ

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Абстракт

Введение. Билирубин является побочным продуктом распада эритроцитов. Уровни билирубина потенциально могут служить биомаркером для оценки сердечно-сосудистого риска. В этом исследовании мы будем исследовать самые последние рукописи, опубликованные за последние 5 лет, в которых изучалась связь уровня сывороточного билирубина с прогрессированием атеросклероза, чтобы выяснить, насколько сильно низкий уровень общего билирубина может прогнозировать прогрессирование заболевания.

Материалы и методы. С помощью поисковой системы Pubmed были найдены все статьи, содержащие ключевые слова «билирубин» и «атеросклероз». Всего появилось 67 результатов поиска за период 2019–2023 гг., за последние 5 лет. Для мета-анализа были использованы 6 популяционных исследований, изучавших связь между концентрацией общего билирубина и развитием атеросклероза.

Результаты. Повышение уровня общего билирубина в крови, по-видимому, снижает вероятность развития атеросклероза, а это означает, что существует обратная корреляция между уровня общего билирубина и образованием артериальных бляшек или стенозом. Было обнаружено, что объединенное отношение шансов составило 0.86 (95% ДИ 0.83–0.9), что позволяет предположить, что вероятность развития атеросклероза снижается на 14% при каждом увеличении уровня билирубина на ммоль/л. В целом, более высокие уровни общего билирубина в сыворотке были связаны со значительно сниженным риском прогрессирования атеросклероза.

Заключение. Мета-анализ указывает на значительную обратную связь между низким уровнем общего билирубина и риском развития атеросклероза, предполагая, что более высокие уровни билирубина могут защищать от прогрессирования этого заболевания.

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Introduction

Bilirubin is a byproduct of the breakdown of erythrocytes. It is generally recognized as a marker of liver function, however antioxidant and anti-inflammatory effects of bilirubin were extensively described in modern scientific literature. Naturally, bilirubin has been investigated for its role in different pathologic states. It was not until 1994, when the first clinical data showed that low bilirubin level can be an independent risk factor for atherosclerotic disease.

The relationship between bilirubin levels and atherosclerosis is complex and may involve different mechanisms. It has been widely described how total bilirubin (Tbil) level effect progression of atherosclerosis in patients with certain comorbidities. For instance, *Duman et al.* showed that low total bilirubin level and elevated high-sensitive C-reactive protein is associated with subclinical atherosclerosis. *Lee et al.* and *Hamur et al.* described that high total bilirubin level is associated with atherosclerosis in T2DM and prediabetes, respectively.[1-3]

Bilirubin levels can potentially serve as a biomarker for cardiovascular risk assessment. Protective role of total bilirubin was analyzed in meta-analysis by *L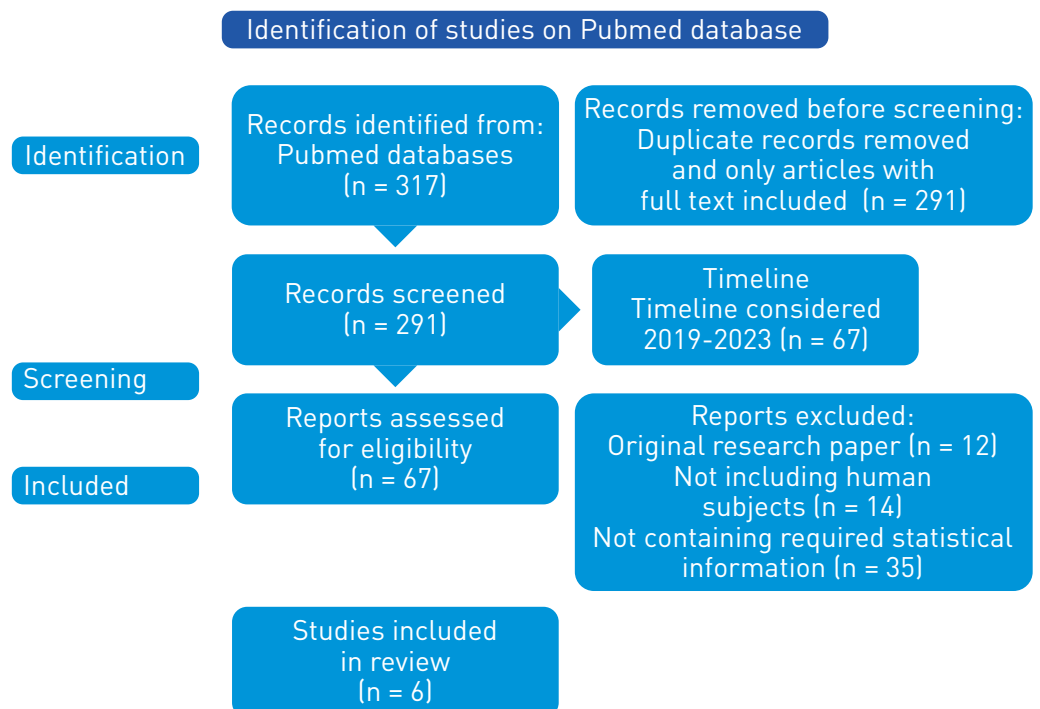an et al.,* higher total bilirubin was significantly negatively correlated with cardiovascular disease, pooled HR=0.83 (95% CI 0.73–0.94, P=.003). However, there is a lack of reviews that cover the research past 2019.[4,5]

In this study, we would be investigating most recent manuscripts, published in the last 5 years, that studied association of serum bilirubin level to atherosclerosis progression to elicit how strongly low level of Tbil can prognose the disease progression.

Methods

Using Pubmed search engine, all articles that included keywords "bilirubin" and "atherosclerosis" were retrieved. In total 67 search results emerged for the 2019-2023 timeline, the last 5 years (Figure 1). Inclusion criteria were: original studies on the adult population of patients that studied the effect of bilirubin level on atherosclerosis. Exclusion criteria were studies that did not report on association between bilirubin and atherosclerosis development; studies that did not include human subjects (animal studies); review articles, meta-analysis, letters, abstracts, and articles that did report statistical results on effect estimate of OR and 95%CI. Among the eligible studies, only the category of subjects with atherosclerotic disease was used for calculations.

Figure 1.
Flow chart showing selection of studies for meta-analysis.

Identification of studies on Pubmed database

Identification

Records identified from: Pubmed databases (n = 317)

Records removed before screening: Duplicate records removed and only articles with full text included (n = 291)

Records screened (n = 291)

Timeline Timeline considered 2019-2023 (n = 67)

Screening

Included

Reports assessed for eligibility (n = 67)

Reports excluded: Original research paper (n = 12) Not including human subjects (n = 14) Not containing required statistical information (n = 35)

Studies included in review (n = 6)

Furthermore, forest plot was calculated along with the pooled odds ratio for the extracted odds ratio and 95% CI intervals. All data were analyzed using the Excel and STATA 18.0 program. P < 0.05 was considered statistically significant.

Results

6 population-based studies that studied association between total bilirubin concentration and atherosclerosis development were used for the meta-analysis (Table 1). All odds ratios were found to be less than 1, and 95% confidence interval did not include 1, except for the *Su et al.* study, depicting no statistical difference.[6] (Figure 1) Increasing blood total bilirubin (Tbil) level seems to decrease the odds of developing atherosclerosis, meaning that there is an inverse correlation between Tbil and arterial plaque formation or stenosis. Pooled odds ratio was found to be 0.86 (95% CI 0.83-0.9), suggesting that there is 14% decreased chance of developing atherosclerosis for each mmol/L increase in bilirubin levels. Overall, higher total serum bilirubin levels were associated with a significantly decreased risk of progression to atherosclerosis.

Authors (et al.)	Publication year	Sample size	Sex (M)	Median age	Study design	Events
Zhong et al.[7]	2020	NA	NA	57.59	Population-based study	Intracranial atherosclerosis
Lan et al.[5]	2020	78/543	287/543	NA	Retrospective	Peripheral arterial disease
Lee et al.[2]	2020	599/1381	277/599	59.6±9.2	Retrospective	Carotid atherosclerosis
Vitek et al.[8]	2022	69/466	35/69	62	Retrospective	Peripheral arterial disease
Su et al.[6]	2023	171/1274	NA	65	Cross sectional	Femoral and carotid atherosclerosis
Zhao et al.[7]	2023	5281/7284	3726/5281	60.2±12	Cross sectional	Lower limb plaque

Table 1.
Characteristics of studies included to meta-analysis
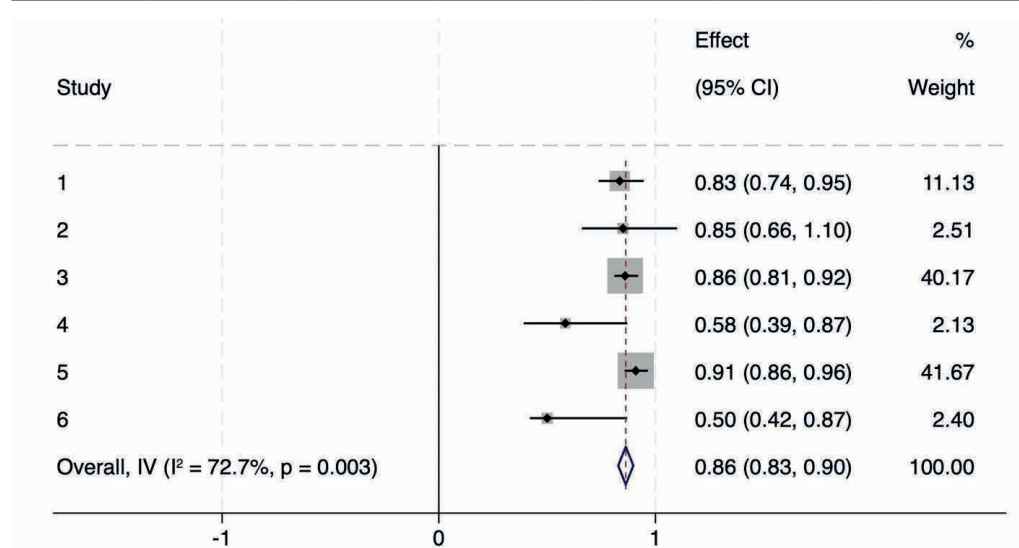
Figure 2.
Forest plot showing association between total bilirubin level and atherosclerosis

1 - Zhao et al.7, 2 - Su et al.6, 3 - Vitek et al.8, 4 - Lee et al.2, 5 - Lan et al.5, 6 - Zhong et al.7

Table 2.
Total bilirubin concentration values for patients with and without atherosclerosis

	With atherosclerosis			No atherosclerosis		
	Total bilirubin (mmol/L)	95%CI low	95% CI high	Total bilirubin (mmol/L)	95%CI low	95% CI high
Zhao et al.[9]	10.1	8.3	13.0	11.1	9.0	13.9
Su et al.[6]	15.6	12.4	19.9	15.7	12.5	19.8
Vitek et al.[8]	8.5	6.3	11,2	12.2	9.0	17.5
Lee et al.[2]	13.68±6.84	13.1	14.3	14.88±6.84	14.5	15.2
Lan et al.[5]	10.4±3.8	9.5	11.2	12.7±4.8	12.2	13.1

Total bilirubin level is lower in those patients that have atherosclerosis in comparison with patients that do not have (Table 2).

Discussion

In this meta-analysis, we tried to elicit the strength of inverse association between total bilirubin and atherosclerosis development. Our results align with previously described findings on this topic.

There are many proposed mechanisms of bilirubin's protective action in atherosclerotic patients. One of the possible mechanisms to target for reducing incidence of cardiovascular disease in patients with Gilbert's syndrome according to *Boon et al.* could be the facts that unconjugated bilirubin at physiologically normal level protects from protein and lipid induced MPO-generated hypochlorous acid, HOCL oxidation.[10] Bilirubin has been implicated in improving lipid profiles. Higher bilirubin levels were associated with lower values of total and LDL cholesterol, which are major risk factors for atherosclerosis.[11] Moreover, bilirubin seems to improve endothelial function by enhancing nitric oxide (NO) availability. Thus, it helps maintain vascular tone, reducing the risk of stenosis and atherosclerotic changes,[12] showed that bilirubin inhibits the proliferation of vascular smooth muscle cells, thus stabilizing the plaque. Most recently, showed that knockout of Bvra gene resulting in low bilirubin levels leads to proatherogenic changes in mice. Bilirubin deficient mice had increased systemic oxidative stress, endothelial dysfunction, thinning fibrous cap which led to plaque destabilization.[13]

A recent study in mouse animal models has revealed another possible mechanism of action of bilirubin on the development of atherosclerosis. *Wen et al.,* found that bilirubin can inhibit cholesterol synthesis by interfering with the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase, which is involved in endogenous synthesis of cholesterol, further contributing to the reduction of atherosclerosis. They also found that bilirubin can influence the number of immune cells such as myeloid-derived suppressor cells, natural killer cells and dendritic cells, which are associated with the formation of plaque, thereby improving atherosclerosis.[14]

Strength of the study is that it gives a glimpse on the association between bilirubin level and atherosclerosis development risk based on the past 5-year studies. It could be useful for making clinical decisions to increase the upper limit for total bilirubin, since mildly elevated bilirubin levels in the absence of underlying liver disease have a protective effect on the cardiovascular system. Limitation of the study is that there was a relatively small number of studies (six) for the meta-analysis. Small sample size may restrict the generalizability of the findings and increase the potential for bias. Moreover, the heterogeneity among the included studies in terms of population characteristics, study design, and measurement of bilirubin levels could introduce variability that impacts the robustness of the pooled results. Future research with a larger number of studies and more standardized methodologies would be beneficial to confirm and extend these findings.

What's known? The relationship between bilirubin levels and athero-

sclerosis is complex and may involve different mechanisms. Total bilirubin level effect progression of atherosclerosis in patients with certain comorbidities. Non-alcoholic fatty liver disease increases the risk of developing type 2 diabetes. Bilirubin levels can potentially serve as a biomarker for cardiovascular risk assessment.

What's new? Significant inverse association between low total bilirubin levels and the risk of developing atherosclerosis, suggesting that higher bilirubin levels may be protective against the progression of this disease.

Conclusion

The meta-analysis indicates a significant inverse association between low total bilirubin levels and the risk of developing atherosclerosis, suggesting that higher bilirubin levels may be protective against the progression of this disease.

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