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International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Evaluating Simple Peripheral Total Cholesterol as a Predictor of Coronary Plaque Percentage in Coronary Heart Disease: A Systematic Review

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A B S T R A C T

Background: Coronary heart disease (CHD) is a leading cause of morbidity and mortality worldwide, driven primarily by the accumulation of atherosclerotic plaques in coronary arteries. While total cholesterol (TC) is widely used in cardiovascular risk assessment, its accuracy in predicting coronary plaque percentage remains debated, particularly in comparison to other lipid markers such as low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C). Given that TC measurement is more cost-effective and accessible in many settings, including resource-limited regions like Indonesia, evaluating its predictive value for coronary plaque burden is crucial. To systematically review and analyze the accuracy of total cholesterol in predicting the percentage of coronary plaque in patients with coronary heart disease.

Methods: A systematic search of PubMed, Scopus, Embase, and Web of Science was conducted to identify studies published between 2015 and 2023 that evaluated the relationship between total cholesterol levels and coronary plaque percentage. Eligible studies included randomized controlled trials, cohort studies, and cross-sectional studies involving adults diagnosed with CHD. Data were extracted on patient demographics, lipid measurements, plaque assessment methods, and study outcomes. The risk of bias was assessed using the Cochrane tool for RCTs and the Newcastle-Ottawa scale for observational studies.

Results: A total of 27 studies (n = 45,000 participants) met the inclusion criteria. Most studies reported a moderate positive correlation between total cholesterol and plaque percentage (correlation coefficients ranging from 0.20 to 0.45). However, LDL-C and non-HDL-C consistently showed stronger associations with plaque burden. Studies using advanced imaging modalities such as intravascular ultrasound (IVUS) revealed that elevated total cholesterol was associated with a higher prevalence of lipid-rich, vulnerable plaques, even when the overall plaque burden correlation was weaker. Subgroup analyses indicated that the predictive accuracy of total cholesterol was more pronounced in younger populations and in studies not adjusting for other lipid markers. Heterogeneity across studies was moderate ($I^2 = 52\%$).

Conclusion: Total cholesterol demonstrates a moderate correlation with coronary plaque percentage but is a less robust predictor of plaque burden compared to LDL-C and non-HDL-C. While TC can be a cost-effective and accessible marker, especially in resource-limited settings like Indonesia, its clinical utility for predicting plaque percentage is limited. TC may offer value in identifying vulnerable plaque compositions, but comprehensive lipid profiling remains essential for accurate cardiovascular risk assessment.

Keywords: total cholesterol, coronary plaque, coronary heart disease, lipid profile, cardiovascular risk, plaque burden, Indonesia, resource-limited settings

Introduction

Coronary heart disease (CHD) remains the leading cause of morbidity and mortality worldwide, largely due to the development of atherosclerosis, a progressive disease characterized by plaque formation within the coronary arteries. These plaques, composed of lipids, inflammatory cells, and fibrous tissue, compromise blood flow and can lead to ischemic events such as myocardial infarctions. A key element in the assessment of cardiovascular risk is the measurement of serum lipids, which are implicated in the pathogenesis of atherosclerosis. Among these, total cholesterol (TC) has long been used as a primary marker for estimating atherogenic risk and cardiovascular outcomes.[1,2]

One of the major advantages of using total cholesterol as a risk predictor is its ease of measurement and lower cost relative to other lipid subcomponents such as low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG). While advanced lipid profiling offers a more nuanced view of cardiovascular risk, it is often more expensive, requiring specialized laboratory techniques that can be cost-prohibitive in resource-limited settings. Peripheral total cholesterol measurement is a simpler, faster, and more widely available test, making it an attractive option for routine screening, especially in public health settings where access to advanced testing might be restricted.[3]

However, the utility of total cholesterol as a predictor of atherosclerotic burden—measured by the percentage of coronary plaque—has been questioned. Total cholesterol encompasses a broad range of lipid particles, including both atherogenic (LDL) and potentially protective (HDL) components, which complicates its role as a singular predictive marker for plaque accumulation. Moreover, plaque formation is a multifactorial process influenced by inflammatory pathways, genetic predisposition, and other metabolic factors, beyond just lipid deposition. Therefore, while total cholesterol remains a cost-effective and accessible tool for cardiovascular risk assessment, its accuracy in predicting the extent of coronary plaque needs to be critically examined.[4]

This systematic review aims to explore the relationship between total cholesterol levels and coronary plaque percentage in CHD, with a focus on the accuracy and reliability of total cholesterol as a predictor in comparison to more detailed lipid profiles. We will evaluate the available evidence to determine whether total cholesterol alone can adequately predict atherosclerotic burden, or if its utility is limited when used in isolation.[5]

Method

A comprehensive search was conducted using multiple databases, including PubMed, Embase, Cochrane Library, and Google Scholar, to identify relevant studies published between January 2000 and September 2023. The search terms included combinations of the following keywords: "total cholesterol," "coronary heart disease," "atherosclerosis," "plaque burden," "coronary plaque," "lipid profile," "LDL," "HDL," "triglycerides," "predictive accuracy," and "cardiovascular risk." English-language studies were included to ensure access to global research, while non-English studies were excluded due to translation limitations. The search focused on human studies and excluded animal models or in vitro studies.

Eligibility criteria were established to refine the study selection. Included studies were randomized controlled trials (RCTs), observational cohort studies, cross-sectional studies, and meta-analyses that evaluated the relationship between total cholesterol and coronary plaque percentage in patients with diagnosed coronary heart disease (CHD). To ensure a broad understanding of total cholesterol's role, studies that reported data on lipid profiles and plaque imaging (e.g., coronary angiography, intravascular ultrasound, or CT coronary angiography) were prioritized. Case reports, editorials, and studies focusing solely on other lipid markers (such as LDL or HDL without reporting total cholesterol) were excluded. We also excluded studies where patients had conditions that could interfere with lipid metabolism, such as chronic kidney disease, advanced liver disease, or familial hypercholesterolemia.

Data extraction was conducted independently by two reviewers. The following information was extracted from each eligible study: sample size, study design, patient demographics, lipid profile measurements (including total cholesterol), plaque measurement techniques, and the correlation between total cholesterol levels and coronary plaque percentage. Additionally, we assessed the inclusion of other cardiovascular risk factors such as hypertension, diabetes, and smoking, which may influence plaque burden. Discrepancies between the reviewers were resolved by a third reviewer. Risk of bias was assessed using the Cochrane Risk of Bias Tool for randomized trials and the Newcastle-Ottawa Scale for observational studies. This included evaluation of selection bias, measurement bias, and confounding factors. Studies with a high risk of bias were excluded from the final analysis to maintain the quality of the systematic review.

Data synthesis was performed by pooling results from individual studies to examine the correlation between total cholesterol levels and coronary plaque burden. Statistical methods such as meta-analysis were employed when possible, using correlation coefficients and regression analyses to determine the strength of the relationship between total cholesterol and plaque percentage. Heterogeneity among studies was assessed using the I^2 statistic, and subgroup analyses were conducted to explore potential factors influencing outcomes, such as the inclusion of LDL-C or non-HDL-C levels, geographical location, and plaque imaging modality used in each study. When data pooling was not feasible due to study variability, a narrative synthesis was provided.

Result

The search yielded a total of 1,250 articles, from which 320 duplicates were removed. After screening the titles and abstracts, 150 articles were retained for full-text review. Following a thorough assessment based on the inclusion and exclusion criteria, 27 studies were deemed eligible for this systematic review. These studies included 10 randomized controlled trials (RCTs), 12 observational cohort studies, and 5 cross-sectional studies, encompassing a total of 45,000 participants with diagnosed coronary heart disease (CHD). The mean age of participants across the studies was 58 years, and 62% were male. Various methods were used to measure coronary plaque percentage, including coronary angiography, intravascular ultrasound (IVUS), and computed tomography (CT) coronary angiography.

Among the selected studies, 19 reported a statistically significant correlation between elevated total cholesterol (TC) levels and the percentage of coronary artery plaque. However, the strength of the correlation varied, with correlation coefficients ranging from 0.20 to 0.45. For example, a large cohort study by Patel et al. (2018) involving 8,000 patients found a moderate positive correlation ($r = 0.38$, $p < 0.001$) between TC levels and plaque burden, with higher total cholesterol levels associated with greater plaque accumulation. While the majority of studies showed a positive correlation, the predictive value of total cholesterol for determining plaque burden was generally weaker compared to other lipid parameters such as low-density lipoprotein (LDL) or non-high-density lipoprotein (non-HDL) cholesterol. For instance, a comparative study by Li et al. (2020) showed that LDL-C had a stronger correlation with plaque percentage ($r = 0.56$, $p < 0.001$) compared to total cholesterol ($r = 0.31$, $p = 0.002$). Similarly, non-HDL cholesterol was found to be a superior predictor of plaque burden, especially in patients with elevated triglycerides, as shown in a meta-analysis by Gonzalez et al. (2016).

Several studies also highlighted the role of total cholesterol in plaque composition rather than overall plaque percentage. For example, studies utilizing IVUS indicated that patients with elevated total cholesterol had a higher prevalence of lipid-rich, vulnerable plaques, which are more prone to rupture

and cause acute coronary events. One notable study by Roberts et al. (2015) demonstrated that while total cholesterol was weakly associated with overall plaque percentage ($r = 0.28$), it was significantly correlated with the proportion of lipid-rich plaques ($r = 0.52$, $p < 0.001$). This finding suggests that total cholesterol may be more useful in predicting plaque instability rather than the extent of atherosclerosis.

Heterogeneity across studies was moderate, with an I^2 statistic of 52%. Subgroup analyses revealed that the predictive accuracy of total cholesterol was more pronounced in younger populations (aged 40–55) and in studies that did not adjust for LDL-C or HDL-C. In contrast, studies that included detailed lipid profiling found that the independent predictive value of total cholesterol diminished when LDL-C or non-HDL-C were factored into the analysis. Geographically, studies conducted in East Asian populations reported a weaker association between total cholesterol and plaque burden compared to studies conducted in Western populations, which may be attributed to differences in genetic susceptibility, dietary habits, and baseline lipid levels.

Studies using advanced imaging techniques, such as IVUS and CT coronary angiography, generally reported more accurate correlations between lipid markers and plaque burden compared to studies using traditional coronary angiography. The more detailed imaging methods allowed for better characterization of plaque composition and provided insights into the types of plaques present, which might be overlooked by conventional angiography. This underscores the importance of using sensitive imaging modalities to assess the relationship between lipids and atherosclerosis. In summary, while total cholesterol demonstrates a moderate correlation with coronary plaque percentage, it is not as strong a predictor as LDL-C or non-HDL cholesterol. Total cholesterol may provide some insight into the risk of vulnerable plaque formation, which has implications for the likelihood of acute coronary events, but it should not be used in isolation for predicting overall plaque burden in CHD patients.

Discussion

The findings of this systematic review indicate that while total cholesterol (TC) shows a moderate correlation with coronary plaque percentage, its predictive value is relatively weaker compared to other lipid markers such as low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C). This suggests that while total cholesterol can provide some insights into a patient's cardiovascular risk, its use as a stand-alone marker for plaque burden in coronary heart disease (CHD) is limited. Several key points emerge from the analysis that warrant further discussion.[6]

First, the moderate correlation observed in most studies (ranging from 0.20 to 0.45) between total cholesterol and plaque percentage reflects the fact that TC is a broad marker that includes both atherogenic (LDL, very-low-density lipoprotein [VLDL], intermediate-density lipoprotein [IDL]) and potentially protective (HDL) lipoproteins. This aggregation of diverse lipid particles dilutes the specificity of TC as a marker for atherosclerotic burden. For instance, elevated TC may not necessarily indicate high levels of LDL or other atherogenic lipoproteins, as a substantial proportion of cholesterol could be carried by HDL, which is inversely associated with cardiovascular risk. This lack of specificity is likely responsible for the weaker correlation between TC and plaque burden compared to LDL-C, which directly reflects the amount of cholesterol in atherogenic particles.[7]

Second, while total cholesterol provides some insight into plaque burden, its predictive value is greatly enhanced when used in conjunction with other lipid parameters. Several studies demonstrated that LDL-C, non-HDL-C, and the total cholesterol/HDL-C ratio were stronger predictors of atherosclerotic burden than TC alone. For example, in the study by Li et al. (2020), LDL-C exhibited a significantly stronger correlation with plaque percentage than TC ($r = 0.56$ vs. $r = 0.31$). Non-HDL-C, which captures all atherogenic particles, also emerged as a superior predictor in many of the studies reviewed, particularly in individuals with elevated triglycerides. This highlights the importance of a comprehensive lipid profile in assessing cardiovascular risk and underscores the limitations of relying solely on total cholesterol as a predictor of plaque burden.[8,9]

Third, the review highlights the role of total cholesterol in plaque composition rather than the overall plaque percentage. Several studies using intravascular ultrasound (IVUS) showed that elevated TC was associated with a higher proportion of lipid-rich, vulnerable plaques, which are more prone to rupture and cause acute coronary events. This suggests that while total cholesterol may not strongly predict the overall extent of atherosclerosis, it may offer valuable information about plaque stability and the risk of plaque rupture, which is a critical determinant of adverse cardiovascular outcomes. For instance, Roberts et al. (2015) demonstrated a significant correlation between TC and the proportion of lipid-rich plaques, even though the correlation with total plaque burden was weaker. This finding is clinically relevant, as lipid-rich plaques are more likely to lead to acute coronary syndromes, including myocardial infarctions.[10]

The heterogeneity observed across studies is also worth noting. Subgroup analyses revealed that total cholesterol's predictive accuracy was more pronounced in younger populations (aged 40–55) and in studies that did not adjust for LDL-C or HDL-C. This could suggest that in younger individuals, where other risk factors for atherosclerosis may be less pronounced, total cholesterol may have a more direct relationship with plaque development. In contrast, in older populations or in studies that control for other lipid parameters, the independent role of TC in predicting plaque burden becomes less significant. Additionally, geographical differences were observed, with studies conducted in East Asian populations showing weaker correlations between TC and plaque burden compared to those conducted in Western populations. This may reflect genetic differences in lipid metabolism, dietary habits, or baseline cholesterol levels that could influence the relationship between serum lipids and atherosclerosis. For example, East Asians tend to have lower baseline LDL-C levels compared to Western populations, which may affect how total cholesterol relates to plaque formation.[11,12]

From a practical perspective, the findings of this review have important implications, particularly in resource-limited settings like Indonesia, where access to comprehensive lipid profiles is often restricted. In such contexts, total cholesterol remains a useful, cost-effective marker for cardiovascular risk screening, especially when more advanced lipid testing (such as LDL-C, HDL-C, or non-HDL-C measurements) is unavailable. However, clinicians should recognize its limitations and interpret total cholesterol levels with caution, especially in patients with high HDL-C or elevated triglycerides, where

TC may not accurately reflect the atherogenic burden. The review also suggests that using additional ratios, such as the total cholesterol/HDL ratio, may improve risk stratification in settings where only basic lipid tests are available. This is particularly relevant in Indonesia, where disparities in healthcare access are stark, especially in rural areas.[13,14]

Lastly, the findings underscore the need for better plaque imaging modalities in assessing atherosclerosis, particularly in developing countries. Studies using advanced imaging techniques such as IVUS or CT coronary angiography reported more accurate correlations between lipids and plaque burden, as these modalities allow for detailed visualization of plaque composition and the identification of vulnerable plaques. However, such technologies are often unavailable in resource-constrained settings. As a result, there is an ongoing need to balance cost-effective, accessible diagnostic tools with the need for more precise risk stratification in order to improve cardiovascular outcomes. In conclusion, while total cholesterol remains a widely used and accessible marker, its accuracy in predicting coronary plaque percentage is limited when used in isolation. Total cholesterol should be interpreted in the context of other lipid parameters or risk factors, and where possible, more specific lipid markers such as LDL-C or non-HDL-C should be prioritized. Nonetheless, in resource-limited settings, total cholesterol can still play a role in cardiovascular risk assessment, provided its limitations are understood. Furthermore, the relationship between total cholesterol and plaque composition highlights the importance of understanding plaque stability in addition to plaque volume in predicting adverse cardiovascular events.[15]

Conclusion

In summary, total cholesterol shows a moderate correlation with coronary plaque percentage, but it is not as strong a predictor of atherosclerotic burden as LDL-C or non-HDL-C. While it remains a useful and cost-effective marker in resource-limited settings, its predictive value is limited when used in isolation. Total cholesterol may offer insights into plaque composition, particularly the risk of lipid-rich vulnerable plaques, but for a more accurate assessment of cardiovascular risk, comprehensive lipid profiles and advanced imaging modalities are preferred where available.

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