PREGLED LITERATURE – REVIEW ARTICLE

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Overview of the lipid abnormalities in the heart failure

Pregled abnormalnosti lipidnih parametara kod srčane insuficijencije

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Summary A complicated clinical disease known as heart failure (HF) comes on by anatomical or functional anomalies in the heart that compromise blood flow. This review article presents a comprehensive examination of the role of lipid profiles in the HF. It specifically focuses on the serum levels of traditional lipid parameters, such as total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) in the development and progression of the HF. To conduct this review, several databases such as Google Scholar, PubMed, and Science Direct were utilized. Specific keywords used in the search include “heart failure”, “lipid profile”, “triglycerides”, “total cholesterol”, “high-density lipoprotein cholesterol”, and “low-density lipoprotein cholesterol”. The language for clinical investigations included in this review were limited to those set to English. The findings suggest that lower levels of TG may be associated with elevated pulmonary artery pressure, tricuspid regurgitation, and increased dimensions of the right side of the heart. These associations indicate impaired liver function due to right-sided HF in the chronic HF patients. Dysfunctional HDL-C is believed to contribute to the occurrence and advancement of HF. Additionally, serum TC levels have been identified as a potential prognostic factor in individuals with advanced HF. On the other hand, lower LDL-C levels seem to indicate worse prognosis for HF patients. However, further research is required to determine the precise mechanisms by which these lipid profiles influence the development and progression of the HF.

Key words: heart failure, lipid profile, atherosclerosis

Sažetak Srčana insuficijencija je složeno kliničko stanje uzrokovano funkcionalnim ili strukturnim abnormalnostima u srcu koji dovode do poremećenog protoka krvi. Ovaj pregledni članak predstavlja sveobuhvatno ispitivanje uloge lipidnih parametara u srčanoj insuficijenciji, sa posebnim akcentom na serumske nivoe tradicionalnih lipidnih parametara, tj. ukupnog holesterola (TC), triglicerida (TG), koncentracije holesterola u lipoproteinima velike gustine (HDL-C) i koncentracije holesterola u lipoproteinima male gustine (LDL-C), u razvoju i napredovanju srčane insuficijencije. Pretraživano je nekoliko baza podataka, kao što su Google Scholar, PubMed i Science Direct. Nekoliko ključnih reči je korišteno, kao što su: “heart failure”, “lipid profile”, “triglycerides”, “total cholesterol”, “high-density lipoprotein cholesterol”, and “low-density lipoprotein cholesterol”. Za pretraživanje i prikupljanje podataka korišten je engleski jezik . Rezultati studija sugerišu da niži nivoi TG mogu biti povezani sa povišenim pritiskom u plućnoj arteriji, trikuspidalnom regurgitacijom i povećanim dimenzijama desne strane srca. Ove korelacije ukazuju na oštećenu funkciju jetre usled desnostrane srčane insuficijencije. Veruje se da disfunkcionalni HDL-C doprinosi pojavi i napredovanju srčane insuficijencije. Pored toga, nivo TC u serumu je prepoznat kao potencijalni prognostički faktor kod osoba sa uznapredovalom srčanom insuficijencijom. Nasuprot tome, čini se da niži nivoi LDL-C predviđaju lošije ishode kod pacijenata sa srčanom insuficijencijom. Potrebna su dalja istraživanja kako bi se utvrdili precizni mehanizmi pomoću kojih nepovoljan lipidni status utiče na razvoj i napredovanje srčane insuficijencije.

Ključne reči: srčana insuficijencija, lipidni status, ateroskleroza

Introduction

An underlying anatomical or functional defect in the heart causes heart failure (HF), a difficult clinical illness that impairs the heart's ability to fill or expel blood into the systemic circulation. It is characterized by the heart's inability to adequately meet the circulatory demands of the body. The HF continues to be a widespread disorder globally, associated with significant morbidity and mortality rates. It is supposed that approximately 64.3 million people worldwide are affected by HF, resulting in substantial healthcare expenses on a global scale (1). Multiple research studies have provided evidence regarding the significance of lipid profiles in the advancement of cardiovascular disease (CVD). Higher levels of triglycerides (TG) and total cholesterol (TC) have been shown to have an impact on the

narrowing and blockage of heart vessels, and are strongly associated with the risk of developing CVD (2-4). Furthermore, elevated levels of low-density lipoprotein cholesterol (LDL-C) can lead to the development of atherosclerosis due to the accumulation of LDL-C in the inner layers of the artery wall (intima-media), which can subsequently promote the production of blood platelets (5). Conversely, individuals with increased levels of high-density lipoprotein cholesterol (HDL-C) may experience a reduced risk of CVD and may be better protected against the risk of developing CVD (6, 7).

Changes in lipid metabolism have been associated with the development of HF, but there is a lack of prospective studies investigating comprehensive lipidomics data and its subsequent correlation with the HF risk. Wittenbecher et al. (8) successfully identified and confirmed two lipid metabolites, along with several lipidomics patterns, that have the potential to serve as novel biomarkers for predicting the risk of HF. By analyzing lipid profiles, it was possible to detect molecular changes in the preclinical stage that might contribute to the predisposition for developing the HF in the future (8).

Methodology

This review presents the current understanding of lipid abnormalities in the HF. It focuses on the examination of serum levels of traditional lipid parameters, such as TG, TC, HDL-C, and LDL-C in HF. To conduct this review, several databases such as Google Scholar, PubMed, and Science Direct were utilized. Specific keywords used in the search include “heart failure”, “lipid profile”, “triglycerides”, “total cholesterol”, “high-density lipoprotein cholesterol”, and “low-density lipoprotein cholesterol”. The language for clinical investigations included in this review were limited to those set to English.

While more recent studies were prioritized, no specific time limit was imposed. In addition to the identified articles, relevant references were examined, and similar articles were included for comprehensive analysis.

Role of Lipid Profile in Heart Failure

A lipid profile test in routine clinical practice measures the levels of four distinct types of cholesterol and TG. Excess calories in the body are converted into TG and stored as body fat. Higher TG levels pose risks to the heart, liver, and pancreas. HDL-C is often referred to as "good cholesterol" because it aids in the removal of harmful LDL-C from the body, preventing its accumulation. TC denotes the combined measurement of all cholesterol types in the body, including LDL, VLDL, and HDL. LDL-C is commonly known as "bad cholesterol" since it contributes to the formation of artery-clogging plaques, thereby negatively impacting heart health. Hence, it is crucial to maintain LDL-C levels within a lower range.

The purpose of conducting a lipid profile test is to assess the risk factors associated with cardiovascular health. Increased levels of cholesterol detected through this test can serve as an indication of a heightened likelihood of experiencing heart-related problems like atherosclerosis, hypertension, heart attack (i.e., myocardial infarction (MI)), or stroke. There are numerous types of lipids but this review article only focuses on the role of serum levels of traditional lipid parameters in the HF.

TG are a type of neutral lipid composed of a glycerol backbone and three long-chain fatty acids. They serve as a significant source of stored energy in various tissues, including adipose tissue and skeletal muscle. Additionally, they are crucial components of lipoprotein particles produced by the liver and small intestine (9). High levels of TG in the bloodstream, rather than TC, among women aged 50, are linked to a higher probability of experiencing the HF at a later stage and hence can be seen as an indicator of the risk for developing the HF in the future (10).

One possible explanation is that lower levels of serum TG and TC may indicate a more advanced stage of the HF or a malnourished patient, such as those with cardiac cachexia, who typically have a worse prognosis than healthier individuals. Additionally, it has been suggested that higher cholesterol levels in chronic heart failure (CHF) may be beneficial because circulating cholesterol-rich lipoproteins can bind and neutralize endotoxin, a potent stimulator of inflammatory cytokine release from immune cells. Without this binding, endotoxin may cause significant immune activation in HF patients (11). A group of outpatients with symptomatic heart failure of varying causes were studied, and it was shown that having higher levels of HDL-C and TG in the bloodstream was linked to a reduced risk of mortality (12).

Kozdag et al. (13) showed that lower levels of TG are associated with higher pulmonary artery pressure, tricuspid regurgitation, and right-sided heart dimensions, indicating impaired liver function due to right-sided HF in CHF. Repeated episodes of hepatic congestion during CHF exacerbations may negatively affect the liver's ability to synthesize molecules. As CHF advances, the liver may lose its ability to synthesize, leading to a liver condition called "cardiac cirrhosis" caused by chronic venous congestion due to right-sided heart failure, which is a signal for end-stage CHF (13,14). The decreased levels of TG may be a consequence of associated factors during CHF, such as advanced gastrointestinal and liver congestion, decreased food intake, increased cachexia, and inflammation. While decreased serum TG levels have been linked to an increased risk of cardiovascular death in HF patients, the underlying reasons for this association remain unclear and require further exploration (13).

Low levels of TG observed in advanced HF may be a consequence of the disease itself. In a study by Kato and colleagues (15), rats with CHF had lower levels of glucose and insulin in the fed condition, and decreased levels of glycogen in the liver, but increased levels of TG. The examination of the metabolome also showed that some metabolites related to glycolysis rose, whereas metabolites related to the Krebs cycle, such citrate and acetyl-CoA, fell. These findings imply that acetyl-CoA is used in the production of TG and cholesterol and that hepatic lipogenesis is elevated. In a different research, plasma levels of TG and cholesterol were up while those of free fatty acids (FFAs) were lowered in Dahl salt-sensitive rats with CHF. Despite the rats' decreased food intake and lower glucose and insulin levels suggesting starvation, the decreased level of FFAs and increased level of TG are not consistent with a starved condition (15).

High levels of cholesterol are commonly associated with a greater risk of death and health problems related to coronary heart disease (CHD). However, lower levels of serum cholesterol have been linked to a worse outcome in CHF, which seems contradictory. The marker pre-albumin is used to indicate undernutrition in chronic diseases. The patients with stable mild to moderate CHF and TC levels were associated with nutritional status regardless of statin therapy (16).

Another research found a correlation between an increased risk of heart failure and lower levels of HDL-C and greater levels of non-HDL-C by closely monitoring the lipid levels of a sample of healthy adults over time. It's significant to remember that low HDL-C levels contributed to 15% of HF cases. It seems that the relationship between dyslipidemia and the risk of heart failure is not entirely reliant on how lipids affect the risk of myocardial infarction. These findings offer a molecular interpretation for earlier findings that lipid treatment can lower the risk of heart failure. Given the high incidence of dyslipidemia in the general population, these findings are significant. It highlights the possibility of reducing HF burden by targeting abnormal lipid concentrations for the treatment (17). In patients with HF, low levels of HDL-C and apolipoprotein A-I (apo A-I), the primary apolipoprotein found in HDL, are associated with an unfavourable prognosis, regardless of the underlying cause of the condition (18,19).

Abnormal TG-rich lipoprotein metabolism, insulin resistance, and persistent tissue inflammation are just a few of the unfavorable metabolic processes for which low HDL-C levels may act as indicators. The onset and progression of heart failure may be influenced by HDL impairment. This is partially due to the intimate relationship between inflammation and heart failure, and the fact that systemic insulin resistance frequently coexists with HF. A pattern of cyclic causation may arise from the mutual contribution of insulin resistance and inflammation to HDL malfunction, which may exacerbate HF. Strong evidence has been shown by recent mouse research suggesting that HDL may influence the myocardium directly, apart from its effects on the epicardial coronary arteries (20,21).

Another study investigated the connection between TC levels and survival in individuals diagnosed with CHF. High levels of lipoproteins are known to increase the risk of CVD. However, it is not entirely clear what role endogenous lipoproteins play in predicting outcomes for patients with CHF. The patients with CHF, lower levels of TC in the bloodstream were independently linked to a poorer prognosis (22).

One potentially effective treatment option for people with HF is to target HDL apolipoproteins [19]. Recent developments in lipidomic and proteomic technology have allowed for the identification of different HDL constituents and the investigation of their effects on the pathophysiology of HF, mostly in preclinical models. Among these, apoA-I and apo-M exhibit the most promise because of their many cardioprotective qualities, which have been shown in mouse studies (23). In order to treat patients with HF, more study is needed to better understand the functional characteristics of HDL proteomic and lipidomic components and investigate potential therapeutic targets (23).

Another study revealed a strong correlation between low levels of HDL-C and increased risk of death or hospitalization due to HF in patients. In a subsequent follow-up study, it was suggested that the composition of HDL proteome may partly explain this association. However, the role of HDL function in predicting the prognosis of HF patients remains unexplored. Regardless of their HDL-C levels, the patients who had higher HDL-C efflux at baseline also had reduced follow-up death rates. Furthermore, in HF patients, HDL's ability to lower inflammation deteriorated with time. These results suggest that measures of HDL function may provide valuable clinical information beyond HDL-C levels for patients with HF (24).

Advanced HF is a condition characterized by high levels of catabolism and is often accompanied by cardiac cachexia, elevated inflammatory markers, and low levels of TC, which are all indicative of a poor prognosis (25). Despite this, observational and experimental studies suggest that statin therapy may have several potential benefits for individuals with HF. The results of ongoing randomized controlled trials will soon provide a definitive answer regarding the role of statins in managing HF (25).

Multiple research studies have suggested that apolipoproteins may be a more precise alternative to LDL-C as a risk indicator for CVD. According to a recent study, after adjusting for age, TC, and TG, the apoB/apoA-I ratio was a potent independent marker of fatal MI (26).
This may be because the apoB/apoA-I ratio provides information on other lipoproteins that contribute to atherosclerosis, including TG-rich VLDL containing apoB and HDL-containing apoA-I. Therefore, the ratio provides a comprehensive view of the traditional risk factor of LDL-C,

as well as other crucial components of the metabolic syndrome. While the direct impact of this ratio on cardiac performance independent of MI was unknown, recent research indicates a close relationship between apolipoproteins and endothelial function, which is a determinant of cardiac afterload (27).

As increased afterload can affect both left ventricular systolic and diastolic function, the mechanism by which the apoB/apoA-I ratio raises the risk for HF may be through its effects on the vasculature rather than a direct action on the heart. The authors discovered new indicators of insulin resistance, including a high apoB/A-I ratio and low levels of the antioxidant beta-carotene, which increase the risk of HF, independent of MI and other commonly recognized risk factors for HF (28).

The earlier research indicates that low TC levels, rather than high levels, are linked to unfavourable clinical outcomes in CHF patients (29). This association is not dependent on the underlying cause of HF and suggests that traditional risk factors are no longer relevant once HF has been established. The relatively unknown ability of all lipoprotein fractions to bind endotoxin and act as natural buffer substances may explain the relationship between lower lipoprotein levels, elevated cytokine levels, and poor prognosis (29).

Statins are shown to lower LDL-C levels and have other positive effects. Using statins could potentially help patients with HF, which is linked to lipoproteins. A recent study showed that low HDL-C levels are the biggest predictor of worsening HF. TC levels are also a factor in predicting the prognosis of HF. Although the different lipoproteins have varying associations with HF and prognosis, it is unclear which one is most important. HDL-C, however, is known to protect against heart disease by promoting the reverse transport of cholesterol and also has other beneficial properties like anti-oxidant, anti-inflammatory, and anti-thrombotic effects. Increasing HDL-C or apoA-I, which is the main apolipoprotein of HDL, could be a potential treatment for HF. Thus, controlling lipoprotein metabolism and using statins may help avoid heart failure (30).

Numerous theories and clinical studies have examined the impact of reducing LDL-C levels in patients with congestive CHF. Current evidence report that there is no obligate reason to introduce statins to patients with nonischemic CHF, since these medications do not decrease the mortality rate but may still lower LDL-C levels and enable some advantages to individuals with ischemic CHF. However, some clinicians believe that statin therapy could worsen outcomes in CHF patients, particularly if it leads to excessive reduction in LDL-C levels. This review explores theories that attempt to link the negative effects of statin-induced LDL reduction in CHF to increased endotoxin levels or decreased coenzyme Q10 levels. It also explores the two largest double-blind, randomized, placebo-controlled clinical trials (CORONA and GISSI-HF). Because of this, HF may be prevented by the advantages of taking statins and controlling lipoprotein metabolism (31).

Statins are frequently used to prevent cardiac events by reducing LDL-C, as the prevalence of HF is increasing in Western nations. Regarding whether LDL-C is a bad prognostic indicator in individuals with advanced heart failure, there are differing data. An analysis was conducted on the relationship between LDL-C levels and clinical outcomes in 297 patients with severe HF (average New York Heart Association class 2.8). A third of the patients passed away during the follow-up period, which had a median length of 3.7 years (with a range of 8 months to 11.5 years). The findings demonstrated that individuals with the greatest LDL-C levels had superior results, whereas the highest mortality was observed in those with the lowest LDL-C values. Additionally, the research showed that only HF patients receiving statin treatment had a negative correlation between LDL-C levels and death. The implication is that, irrespective of the underlying cause of their heart failure, individuals with heart failure may benefit more from aggressive LDL-C-lowering techniques as lower LDL-C levels may be associated with poorer outcomes in these patients, especially those on statin treatment (32).

Although there is proof that hypercholesterolemia increases the risk of morbidity and death from coronary artery disease, little study has been done on the connection between cholesterol and heart failure. However, recent studies have found that serum TC is a new prognostic indicator for patients with advanced HF. Further research is needed to explore the possibility of low TC and lipoproteins contributing to the pathophysiology of HF progression (33).

Another study explained a correlation between higher TC levels and increased survival in patients with CHF, regardless of their age, the cause of their CHF, their left ventricular function, and exercise capacity. This has important implications for CHF treatment. Despite the exclusion of CHF patients from clinical trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, many clinicians have applied the results of these studies to CHF patients. However, it was suggested that caution is necessary. While reducing TC may have negative consequences for CHF, the potential benefits of HMG-CoA reductase inhibitors may outweigh this risk. To determine the effectiveness and safety of statin therapy in CHF patients, controlled trials are required (34).
The significant link between reduced serum TC levels and higher mortality rates in advanced HF was also explained. Additionally, low levels of LDL-C were also linked to an unfavourable prognosis in HF (35).

Conclusion

In this review, it is concluded that traditional lipid panel comprising TC, TG, HDL-C, and LDL-C have a notable impact on the development of HF. However, it should be

noted that this article does not specifically address the involvement of other lipid types. The analysis of lipid profile has the potential to introduce innovative approaches in predicting and stratifying the risk of HF, thereby supporting personalized prevention strategies. Overall, an early detection of lipid profile abnormalities plays a crucial role in preventing CVD, thus allowing the timely interventions and lifestyle modifications to reduce the risk of developing these conditions, guiding treatment plans, monitoring progress, identifying underlying conditions, and promoting patient engagement in maintaining heart health.

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