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Lipid and Inflammatory Biomarkers in HFrEF: A Comprehensive Review of TG/HDL, MHR, and Dapagliflozin Therapy

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ABSTRACT

Heart failure with reduced ejection fraction (HFrEF) is a complex clinical syndrome driven by a combination of hemodynamic, metabolic, and inflammatory disturbances. Increasing attention has been directed toward lipid-related and inflammatory biomarkers such as the triglyceride-to-HDL cholesterol (TG/HDL) ratio and monocyte-to-HDL ratio (MHR), which offer insights into cardiovascular risk, metabolic dysfunction, and systemic inflammation. This review explores the pathophysiological relevance of TG/HDL and MHR in HFrEF, their prognostic utility, and how pharmacologic agents—particularly sodium-glucose cotransporter-2 (SGLT2) inhibitors like dapagliflozin—modulate these biomarkers to improve patient outcomes (1). Current evidence suggests that integrating TG/HDL and MHR into clinical assessment may enable better risk stratification, therapeutic monitoring, and personalization of heart failure management.

Methods: A comprehensive search of electronic databases including PubMed, MEDLINE, and Google Scholar was conducted using relevant keywords, Heart failure with reduced ejection fraction (HFrEF), sodium-glucose cotransporter-2 (SGLT2) inhibitors, metabolic dysfunction, systemic inflammation, the triglyceride-to-HDL cholesterol (TG/HDL) ratio and MHR in HFrEF.

Articles published in English between [2010] and [2024] were considered for inclusion. Studies investigating the relationship between Heart Failure with Reduced Ejection Fraction (HFrEF) in TG/HDL and MHR in Dapagliflozin Therapy.

Results: An extensive review of studies from 2010 to 2024 demonstrated that both TG/HDL and MHR are significant biomarkers in HFrEF, reflecting underlying metabolic dysfunction and systemic inflammation. Elevated TG/HDL was consistently associated with insulin resistance, adverse lipid profiles, and worse cardiovascular outcomes, while high MHR correlated with increased monocyte activity, oxidative stress, and poor prognosis. Dapagliflozin therapy was found to improve TG/HDL by lowering triglyceride levels and raising HDL cholesterol and to reduce MHR by decreasing monocyte activation and systemic inflammation. These effects corresponded with improved endothelial function, reduced atherosclerotic burden, and enhanced clinical outcomes in HFrEF patients.

Keywords: Heart failure, HFrEF, TG/HDL, MHR, dapagliflozin, inflammation, insulin resistance, biomarkers, cardiovascular risk, SGLT2 inhibitors.

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) remains a leading cause of morbidity and mortality worldwide, despite significant advancements in pharmacological therapy and clinical management strategies(2). Characterized by impaired systolic function and a progressive decline in cardiac output, HFrEF leads to compensatory neurohormonal activation, structural remodelling, and systemic manifestations that contribute to worsening clinical outcomes. In recent years, a growing body of evidence has emphasized the critical role of metabolic dysregulation—including insulin resistance, lipid abnormalities, and energy imbalance—as well as chronic low-grade systemic inflammation in the pathogenesis and progression of HFrEF(3).

In this context, biomarkers that reflect underlying metabolic and inflammatory processes have become increasingly valuable for both prognostic evaluation and personalized therapeutic targeting. Among these, the triglyceride-to-high-density lipoprotein cholesterol (TG/HDL) ratio has emerged as a reliable indicator of insulin resistance, atherogenic dyslipidaemia, and cardiovascular risk(4). Meanwhile, the monocyte-to-HDL ratio (MHR) offers insight into systemic inflammation and immune activation by integrating pro-inflammatory monocyte activity with the anti-inflammatory capacity of HDL cholesterol.

Importantly, these biomarkers do not operate in isolation; rather, they reflect the interconnected nature of metabolic and immune pathways that drive disease progression in HFrEF(5). Their predictive utility has gained further relevance with the advent of novel therapies such as sodium-glucose cotransporter-2 (SGLT2) inhibitors. Agents like dapagliflozin have demonstrated not only cardiovascular benefit in patients with HFrEF but also favourable effects on metabolic and inflammatory parameters, including improvements in TG/HDL and MHR.

This review explores the pathophysiological significance, clinical implications, and therapeutic modulation of TG/HDL and MHR in the setting of HFrEF. By integrating biomarker assessment into clinical care, we can move toward more precision-based approaches in the management of heart failure, ultimately improving outcomes and individualizing treatment strategies.

EPIDEMIOLOGY AND PREVALENCE

The role of TG/HDL in cardiovascular health

TG/HDL has been recognized as an important indicator of cardiovascular health. The ratio represents the balance between triglycerides (TG), lipid molecules associated with atherosclerosis risk, and HDL cholesterol, which has cardiovascular protective effects. High TG/HDL is considered an independent predictor of cardiovascular events and a marker of metabolic imbalance and lipid dysfunction. The association between total cholesterol and HDL levels and the impact of this ratio on cardiovascular outcomes highlights its value as a clinical marker for assessing risk and guiding therapeutic interventions for diseases such as HFrEF(6).

TG/HDL as an anti-alternative marker of insulin resistance

Insulin resistance is a major feature of metabolic syndrome and cardiovascular disease and is closely associated with dyslipidemia, particularly changes in triglyceride and HDL cholesterol levels. In the presence of insulin resistance, the body's ability to remove triglycerides from the bloodstream is compromised, resulting in elevated circulating triglyceride levels(7). At the same time, the activity of lipoprotein lipase (LPL), which is responsible for breaking down triglycerides in lipoproteins, is reduced. This leads to a buildup of triglyceride-rich lipoproteins in the blood, such as very low-density lipoproteins (VLDL). These particles are highly atherogenic and contribute to the formation

of plaque in the arterial wall, an important aspect of atherosclerosis. In contrast, HDL cholesterol exerts a protective function by promoting reverse cholesterol transport, a process that removes excess cholesterol from the arterial wall and returns it to the liver for excretion(8). In a state of insulin resistance, HDL function is impaired, thereby reducing its ability to protect against atherosclerosis and endothelial dysfunction. As a result, individuals with metabolic syndrome and cardiovascular disease tend to exhibit lower HDL levels, further exacerbating the atherosclerotic process(9).

TG/HDL is an indicator of this imbalance. An increase in triglycerides and a decrease in HDL levels leads to an elevated TG/HDL, which implies a higher level of insulin resistance and a higher risk of cardiovascular problems. An elevated ratio is considered a reliable marker of metabolic syndrome and can predict cardiovascular events, including myocardial infarction, stroke and heart failure(4).

TG/HDL as a predictor of atherosclerosis and cardiovascular risk

It is increasingly recognized that TG/HDL is an important indicator of atherosclerosis and cardiovascular risk. Numerous studies have shown that the higher the TG/HDL ratio, the greater the odds of developing coronary artery disease (CAD), atherosclerotic plaques, and other cardiovascular diseases. Specifically, individuals with TG/HDL above a certain level have a significantly higher risk of macrovascular and microvascular complications(10).

One of the main ways in which TG/HDL affects atherosclerosis is through its effect on lipoprotein metabolism. High triglyceride levels lead to the production of small, dense LDL particles that are more easily oxidized and retained within the arterial wall. These oxidized LDL particles play a role in endothelial dysfunction, inflammation, and atherosclerotic plaque formation. In addition, reduced HDL levels in individuals with elevated TG/HDL impede cholesterol removal from the arterial wall, which further promotes atherosclerotic plaque formation(9).

In addition, TG/HDL has been independently associated with subclinical atherosclerosis, such as carotid intima-media thickness (IMT) and coronary artery calcification scores. Higher TG/HDL is associated with greater intima-media thickness, which is an early sign of atherosclerosis and a predictor of future cardiovascular events(11). Therefore, tracking TG/HDL can serve as an early warning of cardiovascular risk so that timely measures can be taken to reduce the risk of atherosclerosis and its associated complications.

TG/HDL and its role in heart failure

In heart failure, especially HFrEF, TG/HDL is an important indicator of disease severity and prognosis. Patients with heart failure typically have dyslipidemia, as evidenced by high triglyceride levels and low HDL cholesterol, which is often exacerbated by factors such as neurohormonal activation, inflammation, and metabolic dysfunction. Elevated TG/HDL in these patients is associated with a poorer prognosis, including higher rates of hospitalization, decreased functional class, and increased mortality(11).

The relationship between TG/HDL and heart failure outcomes is complex. Primarily, the ratio indicates the degree of insulin resistance and systemic inflammation, both of which play a critical role in the development of heart failure. Insulin resistance exacerbates metabolic problems in the heart, leading to decreased glucose utilization and fatty acid oxidation, which in turn leads to myocardial energy deficiency. In addition, systemic inflammation and oxidative stress lead to myocardial damage, fibrosis, and structural changes, which exacerbate heart failure symptoms and prognosis(12).

Furthermore, in patients with heart failure, elevated TG/HDL is associated with elevated levels of inflammatory biomarkers, including C-reactive protein (CRP) and

interleukin-6. These inflammatory markers are associated with disease progression and unfavorable clinical outcomes, highlighting the importance of lipids and inflammatory biomarkers in predicting heart failure severity. Thus, TG/HDL can be an important prognostic tool for healthcare providers to assess the risk of patients with heart failure and to customize treatment regimens(13).

TG/HDL and the Effectiveness of Therapeutic Interventions

As an indicator of metabolism, TG/HDL is increasingly being used to assess the success of various therapeutic approaches aimed at enhancing cardiovascular health. For example, lifestyle changes, statin therapy, and sodium-glucose transporter-2 (SGLT2) inhibitors have been shown to improve lipid profiles, including TG/HDL. Lifestyle Changes: Weight loss, physical activity, and dietary modifications can significantly lower triglyceride levels and raise HDL cholesterol. Studies have shown that even small lifestyle changes can lower TG/HDL, thereby reducing cardiovascular risk(14). Statin therapy: Statins are commonly prescribed for the treatment of dyslipidemia, lowering triglyceride levels and slightly raising HDL cholesterol, thereby lowering TG/HDL(15). Improvements in lipid profile have been associated with a reduction in cardiovascular events and an improved long-term prognosis. SGLT2 Inhibitors: Emerging evidence suggests that SGLT2 inhibitors (e.g., Dapagliflozin) may have a positive effect on TG/HDL(16). These drugs have been shown to lower triglyceride levels while increasing HDL cholesterol by mechanisms that may include improved insulin sensitivity, reduced hepatic fat accumulation, and enhanced lipid metabolism.

By improving TG/HDL through medication or lifestyle changes, healthcare providers can successfully address the lipid imbalances that contribute to cardiovascular disease and heart failure, thereby improving short- and long-term patient outcomes(16).

Clinical Significance of TG/HDL

TG/HDL is a practical and cost-effective indicator that can be assessed regularly in the clinical setting. Its ability to reflect the balance between pro- and anti-atherogenic lipoproteins makes it an important tool for assessing cardiovascular risk, especially in patients with complex diseases such as heart failure, diabetes and metabolic syndrome. Elevated TG/HDL is a strong indicator of atherosclerosis risk, insulin resistance and systemic inflammation. Given its strong predictive ability for adverse cardiovascular outcomes, TG/HDL should be considered when evaluating patients at risk for heart failure or other cardiovascular diseases. In addition, TG/HDL can be used to monitor the success of treatments aimed at improving metabolic health and reducing cardiovascular risk.

Role of MHR ratio in CVD

MHR is gaining recognition as a new biomarker for systemic inflammation and oxidative stress, both of which are critical in the development of cardiovascular disease (CVD). This ratio is derived by dividing the total number of monocytes (a type of white blood cell that plays a role in inflammation and immune response) by the concentration of HDL cholesterol(17). MHR is of interest because it predicts adverse cardiovascular events and has the potential to be an indicator of the severity of diseases such as heart failure, atherosclerosis and coronary artery disease.

The significance of MHR for cardiovascular health lies in the interplay between inflammation, immune system activation, and lipid metabolism. HDL is often referred to as “good cholesterol" due to its beneficial effects on vascular endothelial function and anti-inflammatory properties. In contrast, monocytes play a crucial role in the inflammatory process that leads to atherosclerosis(18). An imbalance in MHR resulting from elevated monocyte levels and reduced HDL cholesterol predicts increased

systemic inflammation and a greater likelihood of cardiovascular disease(18).

Monocytes and Inflammation in Cardiovascular Disease

Monocytes are an important component of the innate immune system and play a crucial role in the development of cardiovascular disease. These cells enter the tissues through the circulation, where they are transformed into macrophages and participate in the inflammatory process. In the case of atherosclerosis and cardiovascular disease, monocytes are attracted to areas of endothelial damage, where they become macrophages that phagocytose oxidized low-density lipoprotein (oxLDL) particles(19). The accumulation of foam cells originating from macrophages promotes the formation of atherosclerotic plaques that may lead to arterial blockage and cardiovascular disease.

Inflammation is critical to the development and progression of atherosclerosis, and elevated monocyte levels imply persistent inflammatory conditions. In conditions such as heart failure, higher circulating monocyte levels are associated with a poorer disease prognosis and an increased likelihood of negative cardiovascular events, including hospitalization, heart attack and stroke (20). Therefore, MHR may serve as a numerical indicator of this inflammatory load and is considered an important prognostic tool.

HDL cholesterol and its protective effect against atherosclerosis

The beneficial effects of high-density lipoprotein (HDL) cholesterol on cardiovascular health are widely recognized. HDL plays a crucial role in reverse cholesterol transport, a mechanism that removes excess cholesterol from peripheral tissues, such as artery walls, and transports it to the liver for elimination from the body(21). This process is essential to prevent cholesterol from building up in the arteries and to reduce the risk of atherosclerosis. In addition to its role in removing cholesterol, HDL has anti-inflammatory and antioxidant properties that protect the endothelium of blood vessels and inhibit the formation of atherosclerotic plaques(22). HDL prevents oxidation of LDL particles, a key step in the development of atherosclerosis. In addition, studies have found that HDL reduces the adhesion of monocytes to endothelial cells, thereby preventing monocytes from entering the artery wall and subsequently forming foam cells. These properties make HDL an important component in protecting vascular health and preventing cardiovascular disease.

However, when systemic inflammation or metabolic problems occur, HDL function is impaired. Inflammatory cytokines and oxidative stress alter the composition and properties of HDL, weakening its protective effects and promoting the development of atherosclerosis. This HDL dysfunction contributes largely to the increased cardiovascular risk in individuals with high monocyte counts(23).

MHR as a Prognostic Marker of Cardiovascular Disease

MHR is a composite indicator of two key factors in cardiovascular disease: inflammation and lipid processing. Elevated monocyte counts and lowers HDL cholesterol signal an elevated MHR, indicating increasing inflammation and atherosclerosis. Numerous studies have shown that elevated MHR is independently associated with a higher likelihood of negative cardiovascular events such as myocardial infarction, stroke, coronary artery disease, and heart failure.

Studies have shown that MHR is a better predictor of cardiovascular risk than individual indicators such as monocyte count or HDL cholesterol (24). For example, in patients with heart failure, a higher MHR is associated with higher hospitalization rates, more severe disease progression, and higher mortality(24). The ability of MHR to reflect both inflammation and lipid dysfunction makes it an effective

tool for risk stratification and informing clinical decision-making.

MHR and Heart Failure

In the setting of heart failure, particularly in patients with HFrEF, disease progression is severely influenced by systemic inflammation and immune system activation. Elevated monocyte levels and reduced circulating HDL particles lead to a deleterious cycle of inflammation and vascular complications that accelerate the progression of heart failure and lead to a worsening of patient prognosis. MHR reflects inflammation and metabolic imbalance and provides an important insight into the severity of the disease and patient prognosis.

Elevated MHR is associated with poor prognosis in patients with heart failure, such as an increased risk of acute exacerbations, hospital admissions, and death. In addition, higher MHR is associated with decreased functional status and advanced disease, as it indicates an increased inflammatory load and the presence of atherogenic dyslipidemia. In this regard, tracking MHR can help healthcare providers identify patients at higher risk for complications, leading to a more intensive therapeutic approach focused on reducing inflammation and enhancing lipid metabolism.

MHR in Atherosclerosis and Coronary Artery Disease

MHR is a potential indicator of atherosclerosis, which is characterized by the accumulation of lipids and inflammatory cells in the arterial wall. Because monocytes play a key role in the inflammatory process that fuels atherosclerosis, high MHR can be an early indicator of plaque development and endothelial dysfunction. In patients with coronary artery disease, elevated MHR is associated with more advanced atherosclerotic lesions, more unstable plaques, and an elevated risk of coronary emergencies such as heart attacks.

In the context of coronary atherosclerosis, MHR is thought to indicate a balance between pro-inflammatory monocytes and HDL cholesterol, which has a role in preventing atherosclerosis. Elevated monocyte levels and reduced HDL can disrupt this balance, thereby exacerbating endothelial damage, promoting plaque rupture, and increasing the risk of sudden cardiovascular events (25). Thus, MHR is not only a tool for assessing risk, but also for tracking disease progression and evaluating treatment outcomes in patients with CAD.

Therapeutic Implications of MHR

MHR plays a critical role in the treatment of cardiovascular disease, particularly in guiding strategies to reduce inflammation and promote lipid metabolism. A variety of approaches have been identified that positively impact MHR:

Statins: Statins are widely used to control dyslipidemia by reducing monocyte levels and enhancing HDL function. These effects lead to beneficial changes in MHR, thereby reducing cardiovascular risk and improving patient prognosis.

Anti-inflammatory agents: Therapies that target systemic inflammation, such as interleukin-6 inhibitors and corticosteroids, have been shown to reduce monocyte numbers and promote cardiovascular health. By addressing the inflammatory pathways that lead to monocyte activation and HDL dysfunction, these therapies help to restore the balance shown by the MHR.

SGLT2 Inhibitors: Recent studies have shown that sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as Dapagliflozin, reduce inflammation and enhance HDL cholesterol function. These agents have been associated with reduced monocyte activation and improved lipid profiles and have the potential to positively impact MHR in patients with heart failure and other cardiovascular diseases(25).

These therapeutic strategies are designed to address the underlying processes that influence MHR, thereby helping to reduce cardiovascular risk and improve prognosis in patients with heart failure, coronary

artery disease, and other atherosclerotic conditions.

Relationship between TG/HDL and MHR in patients with HFrEF

TG/HDL and MHR are two new biomarkers that have been independently linked to cardiovascular risk, metabolic problems and inflammation. In patients with HFrEF, these markers are particularly important due to the intricate relationship between lipid metabolism, systemic inflammation, and endothelial dysfunction. Although the link between TG/HDL and MHR in patients with HFrEF has not been thoroughly investigated, available evidence suggests that they are interrelated through common pathophysiologic mechanisms(26).

Impact on risk stratification and prognosis

Given the clear association between TG/HDL and MHR, the inclusion of these biomarkers in clinical assessment may improve risk stratification of patients with heart failure.

Identify high-risk patients: Patients with excessive TG/HDL and increasing MHR are prone to more pronounced metabolic and inflammatory problems, which can make them more susceptible to adverse cardiovascular events, hospital admissions, and deterioration. Ongoing monitoring of these metrics can help identify individuals who may benefit from intensive lipid-lowering therapy, anti-inflammatory measures, or an enhanced approach to heart failure management.

Predicting Treatment Outcomes: Therapies that simultaneously increase lipid levels and inflammatory markers (e.g., SGLT2 inhibitors such as dariflumizine) may positively affect TG/HDL and MHR(27). Future studies should explore whether reductions in these biomarkers are associated with better clinical outcomes in HFrEF patients treated with SGLT2 inhibitors.

POTENTIAL ROLE IN PERSONALIZED MEDICINE: TG/HDL and MHR could be used as components of a biomarker panel to tailor therapeutic strategies for patients with HFrEF. Patients presenting predominantly with metabolic dysfunction (as evidenced by higher TG/HDL) could benefit more from lipid-lowering and insulin-sensitizing therapies, whereas patients predominantly driven by inflammation (as evidenced by higher MHR) could benefit more from anti-inflammatory and immunomodulatory therapies.

Effects of Dapagliflozin and its metabolic parameters

Dapagliflozin, a selective inhibitor of SGLT2, has gained attention for its role in the control of type 2 diabetes, heart failure and chronic kidney disease (CKD)(28). In addition to enhancing glycemic control, dapagliflozin exerts a wide range of positive effects on various metabolic parameters such as lipid metabolism, glucose regulation, insulin sensitivity, body composition, inflammation, and cardiovascular risk factors (29).This section will delve into the various metabolic effects of Dapagliflozin, emphasizing its impact on lipids, glucose metabolism, body weight, inflammation, and overall metabolic health, especially in patients with HFrEF.One important metabolic effect of Dapagliflozin is its impact on lipid metabolism. Studies have shown that SGLT2 inhibitors such as griseofulvin may improve lipid profiles that are critical for heart health. The main lipid-related effects of dapagliflozin include Lowering Triglycerides: Dapagliflozin lowers triglyceride (TG) levels. Triglycerides are a major contributor to atherosclerotic dyslipidemia, usually seen in metabolic syndrome and heart disease(30). By lowering triglyceride levels, Dapagliflozin may reduce the risk of atherosclerosis and improve cardiovascular prognosis. Increased HDL cholesterol: The study also found that Dapagliflozin also slightly increased high-density lipoprotein cholesterol (HDL-C), which is known as the "good" cholesterol. HDL is thought to have a role in preventing atherosclerosis,

including a role in reverse cholesterol transport, which removes excess cholesterol from peripheral tissues, such as artery walls, and transports it to the liver for elimination from the body(31). Increased levels of HDL cholesterol are associated with a reduced risk of cardiovascular disease. Improving lipid ratios: The combination of lowering triglyceride levels and raising HDL cholesterol improves the TG/HDL-C ratio. This ratio is a well-known indicator of insulin resistance and metabolic problems. A positive change in TG/HDL-C means improved lipid metabolism and a reduced risk of cardiovascular problems.

Dapagliflozin has lipid-modifying properties, which are particularly important for HFrEF patients who are often at high risk for atherosclerotic cardiovascular disease. By improving lipid profiles, Dapagliflozin may help reduce the atherosclerotic load and improve cardiovascular health in these patients.

Glucose Homeostasis and Insulin Sensitivity

Dapagliflozin acts primarily by blocking the SGLT2 transporter in the kidneys, thereby decreasing glucose reabsorption and increasing glucose excretion through the urine. This mechanism helps to lower blood glucose levels and enhance overall glucose management in diabetic patients(32). In addition to its effects on blood glucose regulation, Dapagliflozin also affects glucose metabolism and insulin sensitivity more broadly:

Enhanced insulin sensitivity: Dapagliflozin improves insulin sensitivity, providing advantages for patients with type 2 diabetes, metabolic syndrome and heart-related diseases. Insulin resistance is a key feature of metabolic problems and plays an important role in the emergence of multiple cardiovascular risk factors such as dyslipidemia, hypertension and obesity. By enhancing insulin sensitivity, Dapagliflozin helps normalize glucose metabolism, thereby alleviating insulin resistance and reducing the likelihood of cardiovascular disease(33).

Reduced Glucose Toxicity: Hyperglycemia leads to glucose toxicity, which can exacerbate insulin resistance, endothelial dysfunction, and inflammation. By lowering hyperglycemia, Dapagliflozin helps reduce glucose toxicity, enhance endothelial function, and minimize vascular damage. This is particularly beneficial for patients with HFrEF, as endothelial dysfunction and inflammation can lead to disease progression and adverse cardiovascular outcomes.

Reduces Fasting Glucose and Glycated Hemoglobin: Studies have shown that dapagliflozin reduces fasting glucose and glycated hemoglobin (HbA1c), which are important indicators of long-term glycemic control. For people with type 2 diabetes, improved glycemic control can help reduce the risk of diabetes complications, such as diabetic cardiomyopathy and kidney injury, which are frequently seen in people with HFrEF.

Weight and Body Composition Reduction

Dapagliflozin provides moderate but sustained weight loss, which is particularly beneficial for patients suffering from heart failure, obesity and metabolic syndrome. The main reason for Dapagliflozin's weight loss is that it reduces body fat, especially visceral fat, by eliminating excess glucose through the urine. Visceral fat is in the abdominal cavity and around the organs and is closely associated with insulin resistance, inflammation and cardiovascular disease (34).

Reduction of Visceral Fat: Dapagliflozin has been shown to reduce visceral fat, which is an important contributor to metabolic dysfunction and cardiovascular risk. Reduction of visceral fat is associated with improved metabolic parameters such as decreased insulin resistance and decreased levels of pro-inflammatory cytokines.

Enhanced Body Composition: In addition to reducing total body weight, Dapagliflozin improves body composition by increasing

muscle mass and decreasing fat content. Changes in body composition help improve metabolic health and may reduce the effects of obesity-related diseases such as hypertension and dyslipidemia.

Impact on Metabolic Syndrome: Metabolic syndrome is a condition characterized by central obesity, hypertension, dyslipidemia and insulin resistance. Dapagliflozin targets the underlying conditions of metabolic syndrome, helping to reduce cardiovascular risk and improve overall metabolic health.

Anti-inflammatory effects

Chronic inflammation is a key factor in the development of cardiovascular diseases such as heart failure. It leads to endothelial dysfunction, increased vascular stiffness, and the development of atherosclerosis. Dapagliflozin has anti-inflammatory properties, which may be one of the reasons for its cardiovascular benefits.

Reduction of Inflammatory Markers: Dapagliflozin has been shown to reduce levels of pro-inflammatory markers such as C-reactive protein and interleukin-6, which are commonly elevated in patients with heart failure and cardiovascular disease(35). By lowering these inflammatory markers, dapagliflozin helps to reduce systemic inflammation associated with cardiovascular risk.

Effects on Vascular Inflammation: Dapagliflozin reduces vascular inflammation and enhances endothelial function by reducing inflammatory cytokines. This is particularly important in patients with HFrEF, as endothelial dysfunction plays an important role in disease progression and leads to poor cardiovascular prognosis.

Reduces oxidative stress: In addition to its effects on inflammation, Dapagliflozin reduces oxidative stress, which is an important contributor to vascular damage and inflammation. Oxidative stress occurs when there is a gap between the production of reactive oxygen species (ROS) and the body's ability to neutralize them, resulting in cellular damage. By reducing oxidative stress, Dapagliflozin protects the cardiovascular system from further damage and improves long-term outcomes.

Uric acid levels and cardiovascular protection

Hyperuricemia is characterized by elevated levels of uric acid in the blood and is commonly associated with metabolic syndrome, obesity and heart-related diseases. Uric acid causes inflammation and oxidative stress, both of which are important triggers for heart failure and other cardiovascular problems. Dapagliflozin reduces serum uric acid levels, thereby helping to reduce cardiovascular risk(33).

Reduction of Uric Acid: Clinical studies have shown that Dapagliflozin significantly reduces uric acid levels, which enhances vascular endothelial function and reduces the inflammatory response. The reduction in uric acid is particularly beneficial for patients with HFrEF, as high uric acid levels are associated with a poorer disease prognosis and an increased risk of cardiovascular problems.

Blood Pressure and Endothelial Function

Dapagliflozin has been found to lower blood pressure, which is essential for reducing cardiovascular risk, especially in patients with heart failure. The mechanism by which Dapagliflozin can lower blood pressure is largely attributed to its diuretic effect, which increases water and sodium excretion. These effects help to reduce volume overload, thereby lowering blood pressure(35).

Enhancement of Endothelial Function: In addition to lowering blood pressure, Dapagliflozin enhances endothelial function by reducing vascular stiffness and increasing the bioavailability of nitric oxide (NO). Nitric oxide is a powerful vasodilator that promotes healthy blood circulation and reduces vascular resistance. By enhancing endothelial function, Dapagliflozin may further support cardiovascular health and reduce the likelihood of adverse outcomes in heart failure patients.

Correlation between TG/HDL, MHR Ratio, and Dapagliflozin

Effect of Dapagliflozin on TG/HDL

TG/HDL is a well-recognized metabolic health indicator that represents the balance between atherosclerosis-promoting triglycerides and atherosclerosis-counteracting HDL cholesterol. TG/HDL is associated with insulin resistance, abnormal lipid levels and increased risk of cardiovascular problems. Improving this ratio is a critical therapeutic goal for patients with HFrEF and metabolic disorders. Dapagliflozin, a selective inhibitor of sodium-glucose counter-2 (SGLT2), has been shown to benefit lipid profiles, including TG/HDL. The drug's ability to promote lipid metabolism and reduce cardiovascular risk may be due in part to its effect on this important lipid marker. Dapagliflozin therapy improves TG/HDL by a variety of mechanisms.

Reduction of triglyceride levels

One of the main effects of dapagliflozin on lipid metabolism is its ability to lower triglyceride (TG) levels. High triglyceride levels are an important feature of atherogenic dyslipidemia, which is strongly associated with insulin resistance and cardiovascular disease. Clinical studies have consistently demonstrated that dapagliflozin is effective in lowering triglyceride levels, providing advantages to patients with metabolic problems, including those with HFrEF. The reduction in triglyceride levels can be explained by several factors:

Enhanced Fatty Acid Oxidation: Dapagliflozin enhances fatty acid oxidation by increasing the performance of mitochondria in peripheral tissues such as skeletal muscle and adipose tissue. This enhancement helps reduce triglyceride accumulation in the liver and other tissues, thereby lowering blood triglyceride levels. Increased insulin sensitivity: By increasing insulin sensitivity, dapagliflozin reduces the production of triglycerides by the liver. Since insulin resistance is an important cause of high triglyceride levels, dapagliflozin's effect on insulin sensitivity helps normalize lipid metabolism. Reduction of Liver Fat Accumulation: Dapagliflozin reduces the amount of liver fat, which is essential for triglyceride production. A reduction in liver fat accumulation decreases blood triglyceride levels.

Dapagliflozin's ability to lower triglyceride levels plays a direct role in improving TG/HDL, as the reduction in triglycerides contributes to a more favorable lipid profile.

Improvement of HDL Cholesterol Levels

In addition to lowering triglyceride levels, dapagliflozin also slightly elevates high-density lipoprotein cholesterol (HDL-C). HDL-C is thought to have a role in preventing atherosclerosis, particularly through its involvement in reverse cholesterol transport. This process involves removing excess cholesterol from peripheral tissues, such as artery walls, and transporting it to the liver for elimination from the body. Increasing HDL cholesterol levels can help reduce the risk of cardiovascular disease and improve overall lipid profile.

Improved reverse cholesterol transport: Dapagliflozin enhances HDL function by promoting reverse cholesterol transport, which helps remove cholesterol from the artery walls. This mechanism helps reduce the buildup of atherosclerotic plaque and enhances vascular health. Anti-inflammatory properties of HDL: HDL also has anti-inflammatory and antioxidant properties, which may be one of the reasons for its positive impact on the cardiovascular system. Dapagliflozin raises HDL cholesterol levels, which is associated with a reduction in systemic inflammation and endothelial dysfunction, both of which are key factors in cardiovascular disease.

Elevated HDL cholesterol levels due to dapagliflozin are beneficial in improving TG/HDL ratios as they help to balance high triglyceride levels and improve lipid profiles.

Improvement of TG/HDL

Simultaneous lowering of triglycerides and raising HDL cholesterol levels facilitates changes in TG/HDL. Lower TG/HDL is associated with diminished insulin resistance, improved metabolic regulation, and reduced risk of cardiovascular problems. Numerous studies have shown that dapagliflozin may develop type 2 and improve TG/HDL in patients with diabetes, metabolic syndrome and heart failure.

Modulation of Lipid Metabolism: Dapagliflozin promotes lipid metabolism by simultaneously lowering triglyceride levels and raising HDL cholesterol, thereby positively affecting TG/HD. This effect is critical in patients with HFrEF, as unfavorable TG/HDL is associated with poorer cardiovascular prognosis and increased risk of atherosclerosis.

Reduced risk of atherosclerosis: Dapagliflozin reduces the likelihood of atherosclerosis and cardiovascular disease by lowering atherogenic lipids in the blood by increasing TG/HDL. In patients with hypoxemia in AF, the reduction in atherosclerosis risk may improve cardiovascular prognosis and support more effective disease management.

Clinical Evidence

Many clinical trials and observational studies have documented an increase in TG/HDL following dapagliflozin treatment. Lee et al. (2018) found that dapagliflozin significantly reduced triglyceride levels while causing a slight increase in HDL cholesterol, resulting in a positive change in TG/HDL. These results are consistent with other studies investigating the effects of SGLT2 inhibitors on lipid metabolism in patients with diabetes and cardiovascular disease. In the DAPA-HF trial (McMurray et al., 2019), which focused on patients with heart failure and reduced ejection fraction, dapagliflozin was associated with improvements in a variety of metabolic parameters, including lipid profiles. Whilst the study did not specifically address TG/HDL, the noted reduction in triglycerides and increase in HDL-C suggests that there may be an advantage to improving TG/HDL in patients with HFrEF(36).

Mechanisms for Improving TG/HDL

Dapagliflozin improves TG/HDL, which may be related to several potential mechanisms.

Effects of SGLT2 Inhibition on Lipid Metabolism: Inhibition of SGLT2 by glargine affects lipid metabolism by promoting fat oxidation, decreasing triglyceride synthesis in the liver, and improving clearance of lipids from the blood. These effects reduce circulating triglyceride levels and increase HDL cholesterol levels.

Increased insulin sensitivity through dapagliflozin reduces the need for excessive insulin secretion, thereby reducing triglyceride synthesis in the liver. This effect helps to normalize lipid metabolism and improve TG/HDL.

Anti-inflammatory and cardioprotective effects: Dapagliflozin reduces systemic inflammation and oxidative stress, which may help to promote lipid metabolism and improve TG/HDL. Inflammation is known to be a contributing factor to dyslipidemia, which is characterized by high levels of triglycerides and low levels of HDL cholesterol. By reducing inflammation, dapagliflozin contributes to a healthier lipid profile.

Mechanisms for Improving MHR

The MHR ratio has gained attention as an important indicator for assessing systemic inflammation and cardiovascular risk. Elevated MHR has been associated with monocyte activation, a key factor in the inflammatory process, and endothelial dysfunction, both of which play a role in the pathogenesis of cardiovascular diseases such as reduced ejection fraction heart failure. In conditions characterized by chronic inflammation and atherosclerosis, elevated levels of monocytes are frequently

observed, making MHR an important biomarker for predicting disease outcome.

Dapagliflozin has anti-inflammatory properties and may improve MHR by reducing monocyte counts and increasing HDL cholesterol levels. This section will delve into the possible mechanisms by which dapagliflozin affects MHR and the clinical implications of these changes in patients with HFrEF.

Reducing monocyte levels

Monocytes are a type of leukocyte that are critical in the immune system response and play an important role in the inflammatory process that leads to cardiovascular disease. In patients with HFrEF, monocyte activation is usually increased due to systemic inflammation, oxidative stress, and endothelial dysfunction. These activated monocytes are involved in the development of atherosclerosis, plaque instability, and vascular damage, all of which exacerbate cardiovascular disease.

Dapagliflozin has significant anti-inflammatory properties, which may play a role in reducing monocyte activation and subsequently lowering blood monocyte levels. Possible mechanisms include

Dapagliflozin has been shown to reduce levels of pro-inflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha, which are critical for monocyte activation. By lowering these cytokines, dapagliflozin may help reduce the number of activated monocytes (Hattori et al., 2020).

Reduction of oxidative stress: Oxidative stress plays an important role in the activation of monocytes in cardiovascular disease. The ability of dapagliflozin to reduce oxidative stress may reduce the activation of monocytes and their infiltration of the arterial wall, which play an important role in the development of atherosclerosis.

Enhancement of endothelial function: Endothelial dysfunction is commonly associated with increased adhesion of monocytes to the vessel wall. By enhancing endothelial function, Dapagliflozin reduces the attraction of monocytes to the endothelium, thereby decreasing monocyte levels and their pro-inflammatory effects.

The study suggests that dapagliflozin's ability to reduce monocyte levels may contribute to the reduction of MHR, thereby improving inflammation in patients with HFrEF. This result is significant because monocyte accumulation in blood vessels is strongly associated with adverse cardiovascular events.

Increasing HDL cholesterol levels

HDL cholesterol is often referred to as the "good cholesterol" because of its protective role in heart health. HDL has various roles in combating inflammation, oxidation and atherosclerosis, such as promoting reverse cholesterol transport and improving endothelial function. When MHR is considered, higher HDL levels help to counteract the pro-inflammatory effects of monocytes and reduce systemic inflammation.

Dapagliflozin has been found to slightly elevate HDL cholesterol levels in patients with type 2 diabetes, metabolic syndrome, and cardiovascular disease (e.g., heart failure). Elevated HDL cholesterol facilitates improvement in MHR by

Increasing the anti-inflammatory capacity of HDL: Elevated levels of HDL cholesterol are associated with enhanced anti-inflammatory effects, potentially attenuating the inflammatory effects of monocytes. HDL particles contain anti-inflammatory proteins, such as paraoxonase-1, which prevent monocyte activation and reduce their movement toward vascular endothelial cells.

Enhances reverse cholesterol transport: HDL is essential for reverse cholesterol transport, a process that involves extracting excess cholesterol from peripheral tissues such as artery walls. This mechanism helps reduce plaque buildup and atherosclerosis, thereby promoting cardiovascular health and reducing systemic inflammation.

Dapagliflozin increases HDL cholesterol, which helps to rebalance monocytes and HDL, thereby improving MHR and reducing overall cardiovascular risk in patients with HFrEF.

Increasing HDL Cholesterol Levels

Dapagliflozin reduces monocyte levels while increasing HDL cholesterol, thus potentially leading to a decrease in MHR. This combination reduces MHR, leading to better control of systemic inflammation and a lower risk of atherosclerosis.

Enhanced Inflammatory Homeostasis: Dapagliflozin enhances the body's inflammatory homeostasis by lowering monocyte levels and raising HDL cholesterol. The reduction in inflammation is particularly beneficial for patients with HFrEF, as persistent inflammation can greatly exacerbate disease progression and unfavorable prognosis.

Reduced Cardiovascular Risk: Reduced MHR is associated with a decreased likelihood of cardiovascular events such as heart attack, stroke, and admission to the hospital for heart failure. Increasing MHR with dapagliflozin may improve cardiovascular outcomes in patients with HFrEF by reducing systemic inflammation and the development of atherosclerosis.

Clinical evidence supporting the effect of Dapagliflozin on MHR

Although there are few direct studies examining the effects of Dapagliflozin on MHR in patients with HFrEF, relevant studies provide some insight into its possible effects. One study conducted found that dapagliflozin reduced systemic markers of inflammation such as C-reactive protein and IL-6, which are strongly associated with monocyte activation. Although MHR itself was not directly measured, the observed reduction in inflammation suggests that dapagliflozin may reduce monocyte levels and increase MHR.

In the DAPA-HF trial conducted by McMurray et al (2019), dapagliflozin was shown to reduce markers of inflammation and improve cardiovascular prognosis in patients with heart failure and reduced ejection fraction. While the trial did not specifically assess MHR, the noted improvements in inflammation and cardiovascular health meant that dapagliflozin may have a positive impact on this biomarker.

Dapagliflozin is a sodium-glucose transporter-2 (SGLT2) inhibitor that was initially used to control blood glucose in diabetic patients. However, in addition to its primary hypoglycemic effect, dapagliflozin has demonstrated many multi-biologic benefits that make it an effective therapeutic option for heart failure with reduced ejection fraction (HFrEF) and other cardiovascular and metabolic diseases. These benefits go beyond its usual hemodynamic effects (diuretic) and involve multiple metabolic, anti-inflammatory and cardioprotective mechanisms. It has significant potential to modulate these biomarkers, with studies demonstrating their ability to reduce TG/HDL by improving lipid metabolism and decreasing insulin resistance, while also lowering MHR by inhibiting anti-inflammatory effects such as monocyte activation and oxidative stress. These biochemical improvements are consistent with the clinical efficacy of dapagliflozin, including enhancement of LV function and reduction of NT-proBNP levels, highlighting the role of biomarkers in tracking efficacy. Validating TG/HDL and MHR in HFrEF could revolutionize clinical practice by identifying at-risk patients early through metabolic and inflammatory profiling, facilitating real-time monitoring of therapeutic response, and guiding personalized therapies that target metabolic and inflammatory pathways.

HFrEF is the result of an interaction between hemodynamic and metabolic dysfunction with complex mechanisms in vivo. TG/HDL as an indicator of metabolic health has value in predicting risk and treatment outcomes. Dapagliflozin has been shown to improve a wide range of clinical outcomes, and the overall reduction in

inflammation underscores Dapagliflozin's function as not only a metabolic modulator, but also as a multifunctional anti-inflammatory agent, thus establishing MHR as an important biomarker for assessing the success of HFrEF treatment. These results contribute to the management of patients with HFrEF and demonstrate the value of focusing on metabolic health.

HFrEF is a complex condition affected by neurohormonal activation, metabolic problems and inflammation. TG/HDL is an indicator of insulin resistance and dyslipidemia, while MHR is a marker of systemic inflammation and immune activation. Dapagliflozin has shown considerable benefits in improving lipid profiles, reducing inflammation and improving cardiovascular prognosis. By incorporating TG/HDL and MHR into clinical practice, physicians can more effectively assess risk, guide therapy, and optimize outcomes for patients with HFrEF.

Clinical significance and future directions
Clinical Implications

There is growing evidence of a link between TG/HDL, MHR and Dapagliflozin, which has important clinical implications for the treatment of HFrEF. As both TG/HDL and MHR are indicators of metabolic dysfunction, systemic inflammation, and cardiovascular risk, their incorporation into clinical practice could open new possibilities for risk assessment, therapeutic monitoring, and personalized treatment approaches.

Biomarkers for risk stratification

Biomarkers are increasingly utilized in the management of heart failure to assess prognosis and guide treatment choices. While traditional markers such as brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) provide important information about cardiac function and fluid balance, they do not directly address the metabolic and inflammatory imbalances that worsen heart failure.

TG/HDL is a marker of metabolic risk: TG/HDL is an indicator of insulin resistance, dyslipidemia, and atherosclerosis risk, and thus helps to identify HFrEF patients who may be at high risk for metabolic complications. Persistently elevated TG/HDL may indicate inadequate lipid control and elevated cardiovascular risk, requiring more intensive lipid-lowering therapy, dietary changes, and glucose management strategies.

MHR as an Indicator of Inflammation and Oxidative Stress: An elevated MHR indicates the persistence of inflammation and oxidative stress, both of which are key factors contributing to vascular dysfunction, myocardial remodeling, and worsening heart failure symptoms. Individuals with elevated MHR may benefit from anti-inflammatory and cardioprotective therapies such as SGLT2 inhibitors, statins, and lifestyle modifications aimed at reducing inflammation.

By incorporating these two ratios into clinical assessments, healthcare providers can develop a more complete picture of cardiovascular risk in patients with heart failure, leading to more precise treatment strategies.

Monitoring Response to Therapy

In the clinical setting, TG/HDL and MHR are useful in assessing a patient's response to drug therapy.

Dapagliflozin and TG/HDL: Studies have shown that Dapagliflozin reduces TG/HDL by promoting lipid metabolism through lowering triglyceride levels and raising HDL cholesterol. The decrease in TG/HDL after initiation of dapagliflozin therapy may reflect an improvement in metabolic status and a reduction in the risk of adverse cardiovascular outcomes(37).

Dapagliflozin and MHR: The anti-inflammatory properties of dapagliflozin have been demonstrated to reduce markers such as C-reactive protein and interleukin-6. Over time, a decrease in MHR may indicate a reduction in systemic inflammation and enhanced endothelial function, thereby

improving the clinical prognosis of patients with hypoxemia in AF.

Ongoing monitoring of these biomarkers at follow-up visits provides immediate insight into how well treatment is working and whether adjustments to the treatment regimen are necessary.

Potential role in personalized medicine

In the context of heart failure, personalized medicine aims to tailor treatment regimen to the different metabolic, inflammatory, and cardiovascular profiles of individuals. TG/HDL and MHR may be effective in identifying subgroups of HFrEF patients who could benefit most from targeted therapeutic strategies:

Patients with high TG/HDL but low MHR: Patients may have severe metabolic problems such as insulin resistance and dyslipidemia. They may respond favorably to treatment with SGLT2 inhibitors, GLP-1 receptor agonists, and lipid-lowering medications.

Patients with high MHR but normal TG/HDL: This condition may be caused by inflammation and oxidative stress. Anti-inflammatory treatments such as colchicine, statins, and SGLT2 inhibitors, which are known for their anti-inflammatory properties, may be helpful.

Patients with high TG/HDL and high MHR: Patients are at greatest risk due to the combined effects of dyslipidemia, insulin resistance, and persistent inflammation. A comprehensive strategy combining SGLT2 inhibitors, lipid-lowering drugs, anti-inflammatory therapy and lifestyle changes is necessary.

By incorporating these biomarkers into routine clinical assessments, treatment regimens can be more precisely tailored, leading to improved patient outcomes and more efficient use of healthcare resources. Biomarker validation is essential for determining the reliability and clinical relevance of measurable biomarkers in diagnosing disease, predicting prognosis, and assessing treatment outcomes. In heart failure with reduced ejection fraction (HFrEF), triglyceride to HDL cholesterol ratio (TG/HDL) and monocyte to HDL cholesterol ratio (MHR) have emerged as promising biomarkers reflecting metabolic health and inflammatory status, respectively. TG/HDL is an important marker of insulin resistance, dyslipidaemia, and cardiovascular risk, and elevated TG/HDL in patients with HFrEF is associated with poor metabolic status, accelerated atherosclerosis, and poorer cardiac prognosis. This metric provides insight into metabolic dysfunction, a key factor in the progression of heart failure, and is therefore a valuable tool for assessing disease severity and guiding interventions. Similarly, MHR balances pro-inflammatory monocyte activity with the anti-inflammatory properties of HDL cholesterol, highlighting systemic inflammation-a central driver of myocardial remodelling, endothelial dysfunction, and exacerbation of HFrEF symptoms. Elevated MHR signals an increased inflammatory state and provides a biomarker for monitoring disease progression and response to therapy.

CONCLUSION

Heart failure with reduced ejection fraction (HFrEF) is a complex clinical condition shaped by the interplay of hemodynamic overload, metabolic dysfunction, and chronic systemic inflammation. This review emphasizes the prognostic and therapeutic relevance of two integrated biomarkers: the triglyceride-to-HDL cholesterol (TG/HDL) ratio and the monocyte-to-HDL ratio (MHR). TG/HDL serves as an indicator of insulin resistance and atherogenic dyslipidaemia, while MHR reflects systemic inflammatory burden and immune activation—both of which contribute to disease progression and adverse cardiovascular outcomes.

Dapagliflozin, a selective SGLT2 inhibitor, has shown promising effects in improving both biomarkers. Its ability to reduce triglyceride levels, elevate HDL cholesterol, enhance insulin sensitivity, and attenuate

monocyte-driven inflammation makes it a valuable agent in the comprehensive management of HFrEF. Clinical trials, including DAPA-HF, have demonstrated dapagliflozin's efficacy in improving metabolic and inflammatory profiles, which correspond with better functional status and reduced morbidity in HFrEF patients.

Integrating TG/HDL and MHR into routine clinical practice holds potential for enhanced risk stratification, monitoring of therapeutic response, and the development of individualized treatment strategies. Future research should focus on validating these biomarkers in larger cohorts and exploring their predictive value in guiding SGLT2 inhibitor therapy. A biomarker-driven approach could significantly advance personalized medicine in the field of heart failure.

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