Chapter

Biomarkers of Metabolic Syndrome in Cardiomyopathy: A Leading Cause of Heart Failure

Saima Sharif, Saira Rafaqat and Shagufta Naz

Abstract

Cardiomyopathy is a disease of the heart muscle, which makes the muscles harder to pump blood to the rest of the body leading to heart failure. The main types of cardiomyopathies include dilated cardiomyopathy, hypertrophic cardiomyopathy, ischemic cardiomyopathy, arrhythmogenic right ventricular dysplasia, restrictive cardiomyopathy, and Takotsubo cardiomyopathy. On the other hand, Metabolic syndrome (MetS) is the clustering of different medical conditions, which requires at least three of the five following diseases. These diseases are high blood sugar, high blood pressure, high serum triglycerides, low serum high-density lipoprotein, and central obesity. The risk of developing type 2 diabetes and cardiovascular disease associated with metabolic syndrome. In MetS, many different biomarkers are used in the early detection and risk stratification of MetS patients. It includes adiponectin, leptin, interleukin 6, tumor necrosis factor-alpha, uric acid, interleukin 10, ghrelin, adiponectin, paraoxonase, oxidized low-density lipoprotein, and plasminogen activator inhibitor-1. This chapter provides an overview and focuses on the basic role of major biomarkers of metabolic syndrome in the pathogenesis of different types of cardiomyopathies, which mainly highlights recent pathophysiological aspects in the development and progress of cardiomyopathy which is the leading cause of heart failure. In conclusion, biomarkers of metabolic syndrome play a significant role in the development and progress of cardiomyopathy which is the leading cause of heart failure.

Keywords: cardiomyopathy, types of cardiomyopathies, metabolic syndrome, biomarkers, heart failure

1. Introduction

Metabolic syndrome (MetS) is known by other names such as dysmetabolic syndrome, syndrome X, insulin resistance syndrome, and deadly quartet. It is a fast-growing health problem worldwide [1]. Metabolic syndrome is the clustering of different medical conditions, which requires at least three of the five following diseases. These diseases are high blood sugar, high blood pressure, high serum triglycerides, low serum high-density lipoprotein, and central obesity. The risk of developing type 2 diabetes and cardiovascular disease associated with metabolic syndrome [2].

A biomarker is a quantifiable sign of a certain biological state or condition. It is used to evaluate or measure the normal biological process, pharmacologic response, and pathogenic processes of a therapeutic intervention. In MetS, many different biomarkers are used in the early detection and risk stratification of MetS patients. It includes adiponectin, leptin, interleukin 6, tumor necrosis factor-alpha, uric acid, interleukin 10, ghrelin, adiponectin, paraoxonase, oxidized low-density lipoprotein (Ox-LDL), and plasminogen activator inhibitor-1 [3].

Cardiomyopathy is a disease of the heart muscle which makes the muscles harder to pump blood to the rest of the body leading to heart failure. The main types of cardiomyopathies include restricted cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, ischemic cardiomyopathy, arrhythmogenic right ventricular dysplasia, and Takotsubo cardiomyopathy. The pathogenesis of dilated cardiomyopathy is complicated and includes myocardial fibrosis as well as myocyte injury induced by abnormal immune responses after viral infection are considered to be critical factors in the progress of dilated cardiomyopathy [4, 5]. Viral myocarditis-triggered dilated cardiomyopathy is a common cause of heart failure and is characterized by systolic dysfunction as well as left ventricular dilation [6]. Heart failure is a complex progressive pathology in which phenotype is reflective of end-organ damage as a result of insulin/injuries such as post-partum cardiomyopathy, dyslipidemia, congenital disorders, hypertension, ischemic heart disease, and diabetes [7–10].

This chapter will give the recent development of major biomarkers of metabolic syndrome (adiponectin, leptin, uric acid, TNF-α, interleukin-6) in the development and progress of cardiomyopathy which includes the different types of cardiomyopathies such as dilated cardiomyopathy, ischemic cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, and so on, and also emphasized their contribution in the heart failure patients.

2. Major biomarkers of metabolic syndrome in cardiomyopathy which is the leading cause of heart failure

According to the literature, there are many biomarkers of metabolic syndrome. However, this chapter has discussed only major biomarkers of metabolic syndrome such as adiponectin, leptin, uric acid, TNF-α, and interleukin-6 in the development and progress of cardiomyopathy which includes the different types of cardiomyopathies such as dilated cardiomyopathy, ischemic cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, and so on, and also emphasized their contribution in the heart failure patients as explained in **Figure 1** and **Table 1**.

2.1 Adiponectin

Adiponectin is an adipokine that adipocytes manufacture and release. Adiponectin's biological activities are mediated by interactions with receptor subtypes: adiponectin receptor 1 (AdipoR1), adiponectin receptor 2 (AdipoR2), and T-cadherin. Adiponectin has a variety of protective effects on different cell types, including insulin sensitization, anti-inflammation, anti-proliferation, anti-atherosclerosis, and carcinogenesis suppression. In humans, Adiponectin is a relatively prevalent serum protein. Insulin resistance, type 2 diabetes mellitus, obesity, metabolic syndrome, and cardiovascular diseases all cause a reduction in their levels.

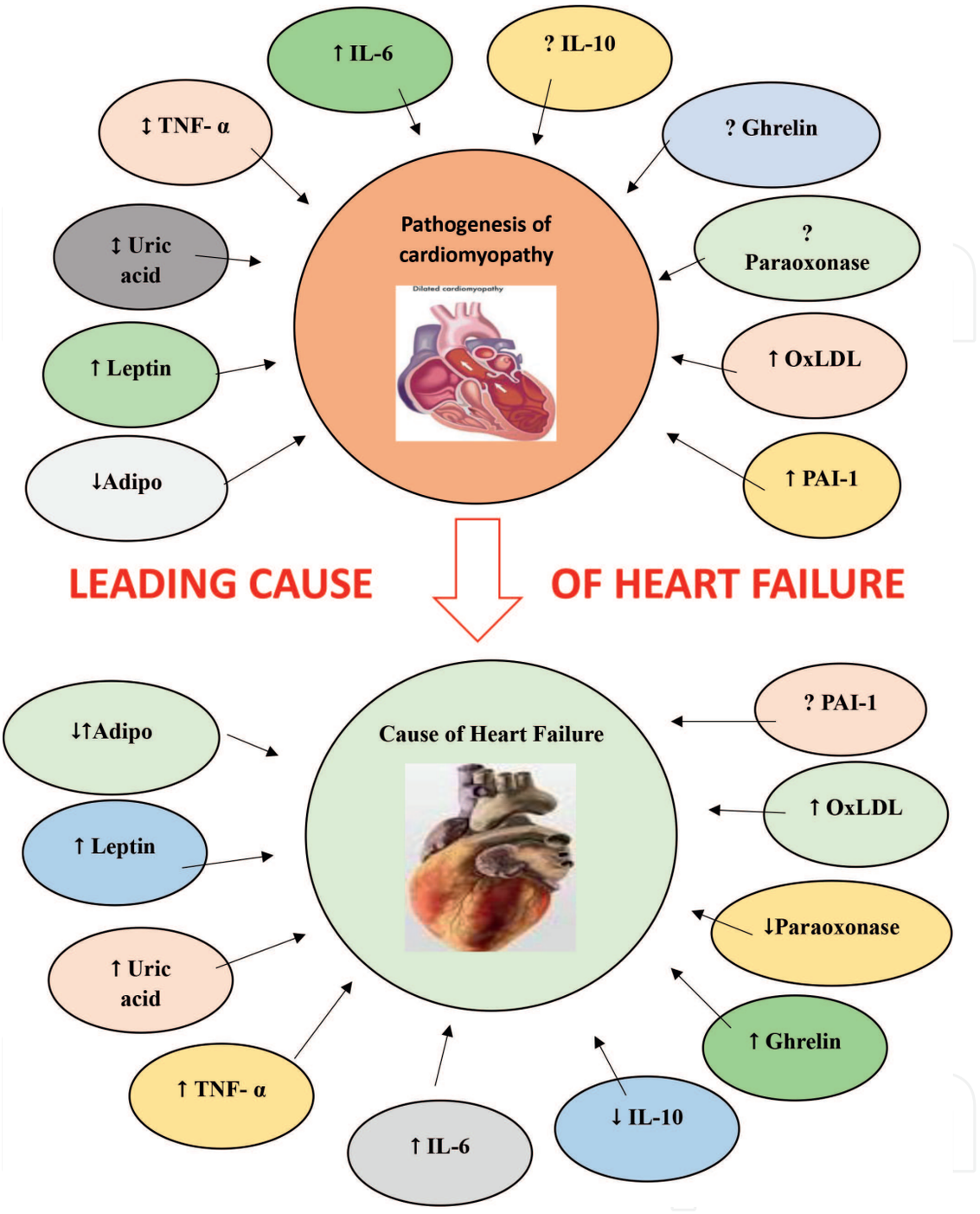

Figure 1.
Overview presentation of major biomarkers of metabolic syndrome in the pathogenesis of cardiomyopathy which is also a leading cause of heart failure. Source: Designed by the authors with the help of articles. Signs show further information, for example, ↑ (increased levels), ↓ (decreased levels), ? (No study still reported), ↕ (not sure if increased or decreased levels).

Adiponectin's preventive impact on obesity-related diseases and cancer has been demonstrated in numerous research. To carry out its physiological and defensive roles, adiponectin regulates many signaling pathways [39].

The pathogenesis of cardiovascular disease is closely linked with obesity-associated disorders. Adiponectin is a circulating adipose tissue-derived hormone that is down-regulated in obese patients. The independent risk of hypertension, type 2 diabetes, and coronary artery disease are linked with hypoadiponectinemia. In the

First author	Year of publication	Biomarkers of metabolic syndrome	The main finding of major biomarkers of metabolic syndrome in the development of heart failure and the prognostic implications of each biomarker	References
George et al.	2006	Adiponectin	Reported the elevated concentration of adiponectin in chronic heart failure patients and predicts mortality and morbidity	[11]
Won et al.	2012	Adiponectin	Decreased concentration of adiponectin in heart failure subjects with metabolic syndrome	[12]
Baldasseroni et al.	2012	Adiponectin	In the presence of diabetes, the progressive increase of adiponectin in the severity of left ventricular dysfunction was hampered and becomes evident only in overt heart failure	[13]
Bobbert et al.	2012	Leptin	Elevated expression of leptin and resistin in non-ischemic dilated patients and inflammatory cardiomyopathy was connected with chronic heart failure progression including independent of immune responses as well as severe cardiac dysfunction	[14]
Toth et al.	1997	Leptin	Leptin could contribute to the regulation of body energy stores as well as energy expenditure in heart failure subjects	[15]
Barbosa-Ferreira et al.	2013	Leptin	Leptin was important as a diagnostic and prognostic marker for heart failure patients and should be included in the routine investigation of heart failure patients	[16]
Wannamethee et al.	2014	Leptin	Decreased mortality risk linked with excess weight in men with CHD without heart failure could be due to elevated muscle mass, leptin (possibly reflecting cachexia) represents the inverse linked in men with heart failure	[17]
Wannamethee et al.	2011	Leptin	The link between obesity and heart failure may be mediated by plasma leptin in the absence of established coronary heart disease. Obesity seems to raise the risk of heart failure in those with coronary heart disease independently of leptin	[18]
Filippatos et al.	2000	Leptin	More prospective studies clarify the contribution of leptin in the pathophysiology of heart failure cachexia	[19]

First author	Year of publication	Biomarkers of metabolic syndrome	The main finding of major biomarkers of metabolic syndrome in the development of heart failure and the prognostic implications of each biomarker	References
Schulze et al.	2003	Leptin	Indicated that the participation of leptin in the catabolic state leads to the progress of cardiac cachexia in the context of CHF	[20]
Murdoch et al.	1999	Leptin	Leptin did not contribute to the cachexia of CHF	[21]
Lieb et al.	2009	Leptin	Elevated risk of chronic heart failure as well as cardiovascular disease was linked with elevated circulating levels of leptin, therefore, leptin did not give incremental prognostic information beyond body mass index	[22]
Anker et al.	2003	Uric acid	Elevated serum uric acid concentrations were strong as well as an independent marker of impaired prognosis in moderate to severe chronic heart failure patients	[23]
Cicoira et al.	2002	Uric acid	In chronic heart failure, elevated uric acid levels are linked to diastolic dysfunction. Theoretically, the diastolic function could be improved in patients with chronic heart failure by inhibiting xanthine oxydase	[24]
Wannamethee et al.	2018	Uric acid	The serum uric acid as a marker of increased xanthine oxidase activity may be a useful prognostic marker for heart failure risk in older men on antihypertensive treatment	[25]
Hamaguchi et al.	2011	Uric acid	In heart failure patients, hyperuricemia was common in clinical practice and elevated uric acid was independently linked with long-term adverse outcomes	[26]
Krishnan et al.	2009	Uric acid	The elevated uric acid level was a novel as well as an independent risk factor for heart failure in a group of young general community residents. This has implications for the development of preventive strategies for heart failure	[27]
Huang et al.	2014	Uric acid	Elevated serum uric acid was related to an increased risk of incident heart failure and adverse outcomes in heart failure patients	[28]
Doehner et al. Xu et al.	2002 2008	Uric acid	Individuals with heart failure have shown therapeutic benefits from serum uric acid-lowering medication with xanthine oxidase inhibitors such as allopurinol or febuxostat	[29, 30]

First author	Year of publication	Biomarkers of metabolic syndrome	The main finding of major biomarkers of metabolic syndrome in the development of heart failure and the prognostic implications of each biomarker	References
Dunlay et al.	2008	Tumor necrosis factor-alpha	Heart failure had elevated tumor necrosis factor-alpha, which was also associated with a significant decline in survival and provided a significant incremental increase in risk assessment over baseline signs. When determining risk in patients with heart failure with both preserved and lowered ejection fractions, tumor necrosis factor-alpha was helpful	[31]
Chia et al.	2021	Interleukin-6	The authors suggested whether interleukin-6 could be a novel treatment target to prevent heart failure with preserved ejection fraction	[32]
Markousis-Mavrogenis et al.	2019	Interleukin-6	Further studies were required to identify interleukin-6 as a potential therapeutic target in specific heart failure subpopulations	[33]
Deokar et al.	2018	Interleukin-6	Increased levels of interleukin-6 in heart failure patients played an important role as a pro-inflammatory marker in the development of cardiovascular disease including heart failure	[34]
Hudzik et al.	2011	Interleukin-6	The elevated level of interleukin-6 might be in the earlier manifestation of heart failure symptoms	[35]
MacGowan et al.	1997	Interleukin-6, TNF-α	Elevated concentrations of TNF-α and IL-6 could be present even in the absence of cachexia in heart failure patients	[36]
Meléndez et al. Rauchhaus et al.	2010 2000	Interleukin-6	Elevated IL-6 could be used as a predictive biomarker in HF and be considered a significant independent predictor for HF	[37, 38]

Table 1.
Summary of major biomarkers of metabolic syndrome in the pathogenesis of heart failure.

same way, adiponectin has a protective role in the development of inflammation, insulin resistance as well as atherosclerosis. The regulation of acute cardiac injury, as well as myocardial remodeling, is due to the role of adiponectin [40].

The presence of a local cardiac adiponectin system which is regulated independently of adiponectin as well as tumor necrosis factor-α serum concentrations also disturbed the cardiac pathology. Moreover, endomyocardial biopsies by immunohistological analysis revealed significant downregulation of cardiac adiponectin protein expression independent of serum tumor necrosis factor-α levels or serum

adiponectin levels. Neither adiponectin receptor 1 nor adiponectin receptor 2 was deregulated in early dilated cardiomyopathy. Adiponectin mRNA and protein down-regulation were confirmed in the explanted hearts of patients with advanced dilated cardiomyopathy (LVEF <25%, n = 8). Neonatal rat ventricular myocytes incubated with adiponectin activated the pro-survival protein kinase B or PKB/Akt, enhanced eNOS-phosphorylation, and inhibited stress-induced cardiomyocyte apoptosis in an Akt-dependent manner in vitro. Additionally, the expression of the cytokine and its receptors increased along with the suppression of adiponectin release. The scientists also speculated that adiponectin may have a role in the pathophysiology of dilated cardiomyopathy (DCM) and identified adipocytokines as a potential new treatment target for dilated cardiomyopathy [41].

Oppositely, other studies reported that adiponectin expression in dilated cardiomyopathy subjects has been inconclusive partly because of the survival benefit of a high body mass index which was inversely correlated with adiponectin expression [42, 43].

New insights in variants of adiponectin receptor 1 are the risk factor for hypertrophic cardiomyopathy (HCM) in which adiponectin receptor 1 variant dysregulate lipid as well glucose metabolism which causes cardiac hypertrophy through the extracellular signal-regulated kinase pathways as well as the p38/mammalian target of rapamycin. In the same way, a transgenic mouse model representing an adiponectin receptor 1 variant displayed cardiomyopathy which recapitulated the cellular discoveries and these features were rescued by rapamycin [44]. These results collectively imply that the adiponectin-AMP-activated protein kinase (AMPK) regulatory axis controls intracellular signaling and metabolic alterations that were connected to the development of cardiac hypertrophy [40].

According to recent investigations, Adiponectin impacts heart remodeling in pathologic situations. Pressure overload causes increased concentric cardiac hypertrophy and worse mortality in adiponectin knockout (APN-KO) mice [45, 46]. On the other hand, in APN-KO, wild-type, and diabetic db/db mice, adenovirus-mediated administration of adiponectin reduces ventricular hypertrophy in response to pressure overload. Additionally, adiponectin overexpression reduces angiotensin II-induced cardiac hypertrophy, indicating that adiponectin has a broader role in suppressing pathological cardiac development. These results imply that in obese people, decreased adiponectin levels may play a role in the development of hypertrophic cardiomyopathy [40].

In the same way, Tamariz et al. reported the prevalence of the metabolic syndrome was elevated in indigent heart failure and also increased the risk of death. Moreover, physicians treating heart failure patients need to address the current metabolic syndrome epidemic in heart failure [47]. In contrast, Frankel et al. demonstrated that heart failure was not linked with concentrations of adiponectin [48].

Moreover, George et al. stated the elevated concentration of adiponectin in chronic heart failure patients predicts mortality and morbidity [11]. In contrast, decreased concentration of adiponectin in heart failure subjects with metabolic syndrome, and that relationship between adiponectin, abnormal diastolic function, and inflammation possibly leads to the progression of heart failure [12]. Additionally, adiponectin levels were raised throughout the stages of chronic heart failure; however, type 2 diabetic individuals show less of this tendency. Diabetes hinders the gradual rise in adiponectin, which revealed the extent of left ventricular dysfunction (LVD), and it only becomes visible in overt heart failure [13].

2.2 Leptin

The white adipocytes produced most abundantly leptin hormone which is act in the hypothalamus of the brain to lower the appetite and elevate energy expenditure. In the early 1990s, leptin was discovered after genetic mapping of the mutation in the gene which was observed in a specific strain of obese mice, the *ob/ob* mouse, which was originally represented in the 1950s [49, 50].

Additionally, leptin was linked with cardiovascular complications resulting from obesity including heart disease as well as hypertension. Obese patients have elevated concentrations of circulating leptin due to increased fat mass. Various clinical, as well as population studies, reported the elevated concentration of leptin with the development of cardiac hypertrophy in obesity. Increased growth of cultured cardiomyocytes was due to leptin. It also regulates cardiac metabolism which helps the oxidation of fatty acids as well as glucose [51]. Leptin could contribute to vascular stiffness as well as endothelial dysfunction which might also contribute to cardiac hypertrophy [52].

Bobbert et al., the study reported for the first time, In the incidence of chronic heart failure, the expression of leptin as well as resistin were positively correlated which was also implicated in cardiac remodeling and immunomodulation. Furthermore, elevated expression of leptin and resistin in non-ischaemic dilated patients and inflammatory cardiomyopathy was connected with chronic heart failure progression including independent of immune responses as well as severe cardiac dysfunction [14]. In the same context, Toth et al. concluded the relationship between energy expenditure and plasma leptin levels in heart failure patients, but not in healthy controls. Therefore, leptin could contribute to the regulation of body energy stores as well as energy expenditure in heart failure subjects [15]. Another study reported the finding which explains that leptin is important as a diagnostic and prognostic marker for heart failure patients and should be included in the routine investigation of heart failure patients [16]. Furthermore, Wannamethee's study concluded the decreased mortality risk linked with excess weight in men with coronary heart disease (CHD) without heart failure could be due to elevated muscle mass, leptin (possibly reflecting cachexia) represents the inverse linked in men with heart failure [17].

The relationship between heart failure and obesity could be mediated by plasma leptin concentration in the absence of established CHD. On the other side, for those with CHD, obesity appears to elevate the risk of heart failure independently of leptin levels [18]. Oppositely, Filippatos' study indicated a need for more prospective studies which clarify the contribution of leptin in the pathophysiology of heart failure cachexia [19]. Also, elevated serum concentration of leptin in advance CHF and its soluble receptor. Moreover, the authors indicated that the participation of leptin in the catabolic state leads to the progress of cardiac cachexia in the context of CHF [20]. In contrast, another study reported that leptin does not contribute to the cachexia of CHF [21].

Lieb et al., reported in the moderate-sized community-based elderly sample, elevated risk of chronic heart failure as well as a cardiovascular disease were linked with elevated circulating levels of leptin, therefore, leptin did not give incremental prognostic information beyond body mass index. So, the authors required more investigation which elucidates the U-shaped link of leptin to mortality [22].

2.3 Uric acid

The uric acid is the end product of an external purine pool and endogenous purine metabolism. Animal proteins contribute significantly to the exogenous purine pool, which varies significantly with diet. The liver, intestines, and other tissues such as muscles, kidneys, and the vascular endothelium are the main sources of endogenous uric acid synthesis. Uric acid synthesis and metabolism are complicated processes involving several variables that control the hepatic, renal, and gastrointestinal excretion of this molecule [53]. The association between uric acid and metabolic syndrome was explored, and it was discovered that increasing uric acid causes a gradual increase in the prevalence of metabolic syndrome in both sexes, although there were differences in levels between males and females [54].

Various clinical and experimental studies explain the numerous mechanisms through which elevated uric acid levels exert deleterious effects on cardiovascular health such as insulin resistance, reduced availability of nitric oxide, elevated oxidative stress, promotion of local and systemic inflammation as well as vasoconstriction, reduced endothelial dysfunction, the proliferation of vascular smooth muscle cells, and metabolic dysregulation [55].

Elevated serum uric acid concentrations were strong as well as an independent marker of impaired prognosis in moderate to severe chronic heart failure patients. The authors graded the relationship between serum uric acid and survival in chronic heart failure. The metabolic, hemodynamic, and functional staging of patients with chronic heart failure was feasible [23].

Another study investigated the potential relationship between left ventricular systolic, diastolic dysfunction, and serum uric acid, a marker of altered oxidative metabolism, in chronic heart failure. In chronic heart failure, elevated uric acid levels were linked to diastolic dysfunction. Theoretically, the diastolic function could be improved in patients with chronic heart failure by inhibiting xanthine oxidase [24].

The serum uric acid as a marker of increased xanthine oxidase activity may be a useful prognostic marker for heart failure risk in older men on antihypertensive treatment [25]. In heart failure patients, hyperuricemia was common in clinical practice and elevated uric acid was independently linked with long-term adverse outcomes in these patients [26]. Krishnan et al. described that elevated uric acid level was a novel as well as an independent risk factor for heart failure in a group of young general community residents. This has implications for the development of preventive strategies for heart failure [27]. Huang et al. also demonstrated that Elevated serum uric acid was related to an increased risk of incident heart failure and adverse outcomes in heart failure patients [28].

Based on these presumptions, individuals with heart failure have shown therapeutic benefits from serum uric acid-lowering medication with xanthine oxidase inhibitors such as allopurinol or febuxostat [29, 30]. Further research was required because some trials have not found any notable advantages of uric acid-lowering therapy with xanthine oxidase inhibitors in heart failure patients with hyperuricemia [56, 57].

2.4 TNF-α

Tumor necrosis factor-α (TNFα) is an inflammatory cytokine produced by macrophages/monocytes during acute inflammation. It is responsible for a variety of signaling events within cells, including necrosis and apoptosis. The protein is also necessary for infection resistance and cancer resistance [58]. The early identification

of a patient's inflammatory status, including TNF-α and IL-6, could be effective in metabolic syndrome and its comorbidities monitoring and early intervention [59].

The overwhelming inflammatory reactions caused by viral myocarditis, which are mediated by CD4+ T lymphocytes, cause myocardial fibrosis in people with dilated cardiomyopathy. Recently, a small number of researchers found that B cells also possess an aberrant pro-inflammatory potential in addition to producing autoantibodies. First, the authors proposed that TNF-secreting B cells were involved in cardiac fibrosis, revealing a novel pathogenic mechanism of B cells in dilated cardiomyopathy and suggesting potential therapeutic options against these cells [60].

A considerable number of patients with community-acquired heart failure elevated tumor necrosis factor-α which was also associated with a significant decline in survival and provided a significant incremental increase in risk assessment over baseline signs. When determining risk in patients with heart failure with both preserved and lowered ejection fractions, Tumor necrosis factor-α was helpful [31]. Tumor necrosis factor-α contributes to adverse left ventricular remodeling during pressure overload through regulation of cardiac repair as well as remodeling which leads to ventricular dysfunction [61]. Numerous studies have found a persistent relationship between circulating TNFα and soluble TNF receptors and mortality in patients with heart failure [62]. Schumacher et al. explained the understanding of how tumor necrosis factor-α, as well as interleukin-6, contribute to cardiac failure and cardiac dysfunction [63].

2.5 Interleukin-6

IL-6 is a soluble mediator that affects inflammation, immunological response, and hematopoiesis in a pleiotropic manner. The human IL-6 gene has been localized to chromosome 7p21 and has 212 amino acids, including a 28-amino-acid signal peptide. Although the core protein is only about 20 kDa, glycosylation accounts for the size of natural IL-6, which is between 21 and 26 kDa [64].

The initiation as well as the development of heart failure contributes to immune activation and inflammation. Interleukin-6 was not only a sign of inflammatory activation but also could induce ventricular dilatation, apoptosis, systolic dysfunction, and cardiomyocyte hypertrophy through various mechanisms that directly act on the pathological process of heart failure, assisting the progression and deterioration, which is the primary pathophysiological mechanism of heart failure. Interleukin-6, a potent inflammatory cytokine inducer, alters heart failure patients' hemodynamic and oxidative stress status [65].

Elevated serum levels of IL-6 were linked with lower ejection fraction, elevated incidence of functional class III to IV and worse prognosis in idiopathic dilated cardiomyopathy [66]. In the same way, Santoro et al. hypothesized that systemic inflammation is the possible mechanism of Takotsubo cardiomyopathy (TTC) in which authors aimed to assess the role of interleukin-6 and interleukin-10 in subjects with an episode of Takotsubo cardiomyopathy. The authors concluded that serum interleukin-6 as well as interleukin-10 admission levels related to an elevated risk of adverse events during follow-up [67].

The interleukin-6 was linked with a new onset of heart failure with preserved ejection fraction (HFrEF) individuals, independent of potential confounders. Moreover, the authors suggested whether interleukin-6 could be a novel treatment target to prevent heart failure with preserved ejection fraction [32].

Similarly, a higher level of interleukin-6 was determined in more than 50% of heart failure patients. Interleukin-6 was linked with reduced left ventricular ejection fraction, iron deficiency, atrial fibrillation, and poor clinical outcomes. Additionally, the authors investigated those further studies that were required to identify interleukin-6 as a potential therapeutic target in specific heart failure subpopulations [33].

The significantly increased serum interleukin-6 (median [IQR] 14.3[26.2] pg/mL) in heart failure patients as compared to age and sex-matched controls (median [IQR] 0[2.4] pg/mL). The authors showed an increased level of interleukin-6 in heart failure patients played an important role as a pro-inflammatory marker in the development of cardiovascular disease including heart failure [34].

In the severity of chronic heart failure, interleukin-6 spillover was increased in the peripheral circulation and mainly linked with the activation of the sympathetic nervous system. Elevation levels of interleukin-6 could provide prognostic information in chronic heart failure patients which was independent of left ventricular ejection fraction as well as plasma norepinephrine (NE) which was suggesting an important contribution to the interleukin-6 in the pathophysiology of chronic heart failure [68]. In the same context, the elevated level of interleukin-6 might be in the earlier manifestation of heart failure symptoms [35]. Additionally, elevated concentrations of TNF-α and IL-6 could be present even in the absence of cachexia in heart failure patients [36].

The data was overwhelming in demonstrating that individuals with HF had higher levels of IL-6 in their blood circulation as well as myocardium and these levels were correlated with the progression of their condition. A key factor in the development and progression of HF is ventricular remodeling, which was mediated by inflammation. IL-6 controls the entire inflammatory process and encourages the development of ventricular remodeling [28].

The IL-6 induced cardiac interstitial fibrosis, which in turn produced ventricular wall sclerosis and HF, by encouraging cardiac fibroblasts to produce collagen. IL-6 can also make cardiomyocytes stiffer by decreasing actin phosphorylation. In conclusion, elevated IL-6 could be used as a predictive biomarker in HF and be considered a significant independent predictor for HF [37, 38].

3. Conclusion

In conclusion, biomarkers of metabolic syndrome play a significant role in the development and progress of cardiomyopathy which is the leading cause of heart failure. Also, major biomarkers of metabolic syndrome such as adiponectin, leptin, uric acid, TNF-α, and interleukin-6 played their pathophysiological role in different types of cardiomyopathies as well as in heart failure. However, future studies are also required to control metabolic diseases in cardiomyopathy patients which ultimately prevents heart failure which in turn does not increase the prevalence of cardiovascular diseases.

Conflict of interest

The authors declare that they have no competing interests.

List of abbreviations.

AdipoR1	adiponectin receptor 1
AdipoR2	adiponectin receptor 2
CHD	coronary heart disease
DCM	dilated cardiomyopathy
IL-10	interleukin 10
IL-6	interleukin 6
MetS	metabolic syndrome
Ox-LDL	oxidized low-density lipoprotein or oxidized LDL
TNF alpha or TNF-α	tumor necrosis factor-alpha

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