

## Challenging Role of Myokines In Heart Failure

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### Abstract

The aim of the narrative mini review is depicted the role of the myokines in patients with heart failure (HF). The myokines (irisin, myostatin, myonectin, brain-derived neurotrophic factor, interleukins [IL]-6, IL-8, IL-15, tumor necrosis factor-alpha, fibroblast growth factor 21, growth differential factor-11) are produced predominantly by skeletal muscle cells in response to physical activity and regulate metabolic homeostasis, proliferation, angiogenesis, neovascularization, reparation and neurogenesis in skeletal muscle tissue. HF is strongly associated with decrease in physical endurance and led to myopathy having established negative impact on the clinical outcomes and quality of life. Impaired myokine profile has been found in patients with HF regardless of phenotypes of cardiac dysfunction and, so important, prior to sarcopenia. It has been postulated that altered profile of the myokines can improve a stratification of HF patients at higher risk of poor clinical outcomes independently left ventricular ejection fraction and metabolic disease presentation.

**Keywords:** Heart failure; Myokines; Outcomes; Sarcopenia; Risk stratification; Prognosis

**Abbreviations:** AKT: RAC-Alpha Serine/Threonine-Protein Kinase; CAD: Coronary Artery Disease; CV – Cardiovascular; ECVs: Extracellular Vesicles; ERK: Extracellular Signal Regulated Kinase; GDF: Growth-Differentiation Factor; HF: Heart Failure; HfrEF: Heart Failure with Reduced Ejection Fraction; IL: Interleukin; MAP: Mitogen Activated Protein Kinase; T2DM: Type 2 Diabetes Mellitus; TGF: Transforming Growth Factor; TNF: Tumor Necrosis Factor

### Editorial

Skeletal muscle cells are involved in the pathogenesis of heart failure (HF) and are not merely effectors mediating physical activity, endocrine organ that secrete wide spectrum of cytokines, namely myokines [1]. Conventionally, myokines' family consist of irisin, myostatin, myonectin, brain-derived neurotrophic factor (BDNF), and some interleukins (IL), such as IL-8, and IL-15, whereas later it has been observed certain cytokines (fibroblast growth factor 21 [FGF-21], growth differential factor-11) that were produced both adipocytes and skeletal muscle myocytes having powerful ability to regulate myocyte tissue homeostasis [2,3]. In addition, some adipocytokines (leptin, adiponectin, resistin, chemerin, visfatin, IL-6), and tumor necrosis factor [TNF]-alpha), which are predominantly released by adipose tissue, were found to be produced by skeletal muscle cells and consequently

they were named adipomyokines [4]. In physiological condition myokines produced by skeletal muscle cells regulate myofibril tube formation, proliferation of skeletal muscle progenitor cells, neovascularization, neoangiogenesis, neurogenesis, and cell-to-cell communication including skeletal muscle cell-to-adipocyte crosstalk. There is large body evidence of the protective ability of myokines in insulin resistance among patients with abdominal obesity, metabolic syndrome, and type 2 diabetes mellitus, whereas the role of myokines in the myopathy occurrence in HF is known much less [5-7]. The aim of the narrative mini review is to summarize the knowledge with respect to clinical perspectives to use of myokines in HF patients.

### The Vicious Cycle of Myopathy and HF

The secretory potency of the skeletal muscle is well known,

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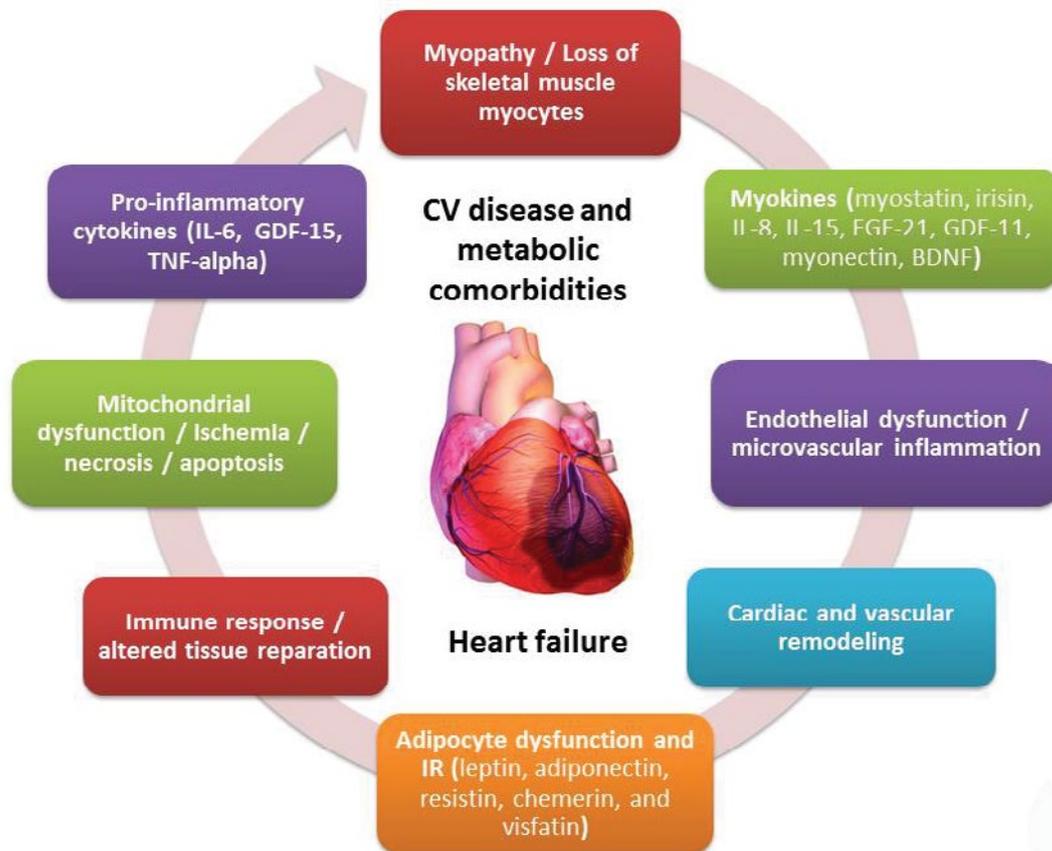
although during long time HF-related myopathy has been considered as secondary muscle injury that was associated with low capillary perfusion due to HF progression [8]. Over last two decades it has been found that skeletal muscle myopathy can be related to altered age-dependent mechanisms including impaired profile of myokines including growth differential factor-11 and myostatin [9]. Because the specific skeletal muscle myopathy has been previously defined as one of the leading causes of physical exercise intolerance in patients with HF with reduced ejection fraction (HFrEF), the lack of strong relation of HF-induced myopathy to left ventricular ejection fraction has been required to be explained [10,11]. In this context, primary impairment of the skeletal muscle homeostasis has been speculated as a crucial mechanism in the occurrence and the development of the HF in patients with metabolic diseases predominantly diabetes mellitus beyond adverse cardiac remodeling due to ischemia causes [12,13]. In fact, there is vicious circle that corresponds to aberrant skeletal muscle impairments and pathophysiological mechanisms of HF development (Figure 1).

The wide spectrum of myokines provides controversial actions on skeletal muscle cells and mediate pleiotropic effects (Table 1). Most of myokines are controlled by muscle contractory function and activity and consequently closely regulates exercise tolerance

via intracellular signal pathways including Janus 1 and 2 kinases/3 and 5 signal transducer and activator of transcription proteins/ Nuclear Factor Kappa B, PI3 kinase/MAP kinase pathways. It is interesting that some potentially pro-inflammatory myokines, such as TNF-alpha, simultaneously provide provide angiopoetic effects and support pro-apoptotic impact on myoblasts. It has been found interrelationship between NO-mediated cellular signaling and production of the myokines in skeletal muscle cells [9]. However, hyperemia in skeletal muscle over physical exercise was strong associated with myokines release [10]. In addition, occurrence of cardiac cachexia accompanies with cross over changes in the spectrum of the myokines, for instance, there were found elevated serum concentrations of myostatin and IL-8, whereas isirin, FGF-21 and myonectin demonstrated significant decrease in their circulating levels. The serum levels of BDNF and growth differential factor-11 were variable and exhibited strong relation to age of the HF patients rather than severity of contractility dysfunction and sarcopenia [8-22].

## Myokines and HF-Related Clinical Outcomes

Development of HF is associated with up-regulation of myostatin, IL-6, IL-8, TNF-alpha, and down-regulation of irisin, myonectin,



**Figure 1** The interrelation between heart failure, skeletal muscle myopathy and myokines dysfunction. The vicious cycle in heart failure. **Abbreviations:** IR: Insulin Resistance; IL: Interleukins; TNF: Tumor Necrosis Factor; FGF: Fibroblast Growth Factor; GDF: Growth Differential Factor; BDNF: Brain-Derived Neurotrophic Factor.

**Table 1:** Biological role and function of myokines in HF.

Name of myokine	Affiliation	Biological action	HF-related actions	References
Irisin	Muscle tissue-secreted peptide FND5	↑ expenditure, ↑ oxidative metabolism, ↑ myoblast differentiation, ↑ glucose uptake,	<b>Down-regulated in HF</b> ↓ Tolerance to physical exercise, ↑ skeletal muscle hypotrophy	14
Myonectin	CTRP15	↑ Oxidation of free fatty acid, ↑ oxidative metabolism, ↑ myoblast differentiation, ↑ glucose uptake	<b>Down-regulated in HF</b> ↑ Skeletal muscle hypotrophy	15
FGF-21	FGF super-family	↑ Glucose uptake and protein synthesis in skeletal muscle, ↓ lipolysis in WAT, ↑ browning of WAT	<b>Down-regulated in HF</b> ↑ Skeletal muscle mass, ↓ IR, ↑ exercise tolerance	16
Myostatin	TGF-β superfamily	↑ Skeletal muscle fiber-type switches, ↓ fast myosin heavy-chain expression, ↓ differentiation of myoblasts, ↑ ubiquitin-proteasomal activity in myocytes and ILGF-PKB pathway	<b>Up-regulated in HF</b> ↑ Skeletal muscle hypotrophy, ↑IR, ↑ autophagy, ↑ muscle weakness, ↓ exercise tolerance	17
BDNF	Neurotrophin family	↑ Myoblast proliferation, ↑ neurogenesis, ↑ angiogenesis, ↑ vascular reparation	<b>Down-regulated in HF</b> ↑ Tolerance to physical exercise	3, 18
IL-8	Cysteine-X-cysteine family of chemokines	↓ Glucose disposal, ↑ IR	<b>Up-regulated in HF</b> ↓ Skeletal muscle energy metabolism	19
IL-15	Pleiotropic cytokine with structural similarity with IL-2	Anabolic effect, ↓ oxidative stress	<b>Down-regulated in HF</b> ↑ Tolerance to physical exercise, ↑ skeletal muscle mass, ↓ WAT, ↓ apoptosis of cardiac myocytes and myoblasts	20
IL-6	Member of the IL-6 family	↓ Glucose disposal, ↑ IR, ↓ oxidation of free fatty acids, ↑ angiogenesis, ↑ cell proliferation	<b>Up-regulated in HF</b> ↑ Skeletal muscle hypotrophy and weakness	21
TNF-alpha	Member of the cell signaling protein family	↓ Myoblast differentiation, ↑ oxidative stress and transcription of IL-6, ↓ oxidation of free fatty acids, ↑ lactate production, ↑ lipolysis, ↓ F-actin microfilament assembly, ↑ angiogenesis / neovascularization	<b>Up-regulated in HF</b> ↑ Skeletal muscle hypotrophy and weakness, ↓ physical endurance	22
GDF-11	TGF-β super family	↓ Differentiation of myoblasts, angiogenesis and neovascularization	<b>Down-regulated in HF</b> ↓ Physical endurance, ↑ skeletal muscle hypotrophy and weakness	23

**Abbreviation:** FGF-21: Fibroblast Growth Factor-21; TGF-β: Transforming Growth Factor-beta; IR: Insulin Resistance; ILGF-PKB: Insulin-Like Growth Factor-Protein Kinase B; WAT: White Adipose Tissue; TNF: Tumor Necrosis Factor; GDF-11: Growth Differentiation Factor-11

FGF-21, BDNF, and IL-15 [4]. There is a large body of conflicted evidence that indicates that lowered concentrations of several myokines (predominantly irisin, BDNF, GDF-11, TNF-alpha, IL-6) were related to impaired physical exercise tolerance, decreased quality of life and adverse clinical outcomes in HF and rarely among patients with HF with preserved ejection fraction (HFpEF) regardless of sarcopenia [23-28]. In contrast, there were established excess risks of cardiovascular mortality, stroke, HF occurrence, and revascularization in individuals with the highest concentrations of irisin in comparison with those who had low levels of the biomarker, BDNF and myostatin [29,30]. The discovery of exact molecular pathways that correspond to the link between myokines and HF outcomes remains uncertain and requires to be clear elucidated in the future. However, the idea

regarding that the myokines could be new biological target to point-of-care therapy in HF with various phenotypes is promising especially among HF patients with metabolic comorbidities.

## Conclusion

Whether myokines could be predictive biological markers that independently were associated with an increased risk of HF-related mortality and clinical outcomes is not fully understood and require to be thoroughly investigated in the large clinical trials. However, these cytokines are involved in skeletal muscle myopathy and the evaluation of their circulating levels could provide new insights to the course of HF and stratify patients at higher risk of poor outcomes prior to sarcopenic stage.

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### Authorship declaration

This article had not been submitted to another journal before and it is not currently under consideration to be published elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

### Authorship contributions

All authors contributed equally in literature search, review design, data collection and analysis, finding interpretation, figure design, and writing of the paper.

### Compliance with ethics guidelines

The narrative review does not require ethical declaration, because it is based on previously conducted studies and does not contain any studies with human participants or animals.

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### Disclosures

Authors have no conflict of interests.

### Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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