Transylvanian Review

Vol XXVII, No. 50, 2020

Transylvanian Review
Centrul de Studii Transilvane| str. Mihail Kogalniceanu nr. 12-14, et.5, Cluj-Napoca
Email: transylvanianreview@gmail.com
Online Submission System: http://transylvanianreviewjournal.org/

Altered Profile of Circulating Myokines as a Predictor of Poor Prognosis in Heart Failure

Alexander E. Berezin[1*], Alexander A. Berezin[2] and Sergii Myrnyi[3]

[1]Internal Medicine Department, State Medical University of Zaporozhye, Ministry of Health of Ukraine, Zaporozhye, 69035, Ukraine

[2]Internal Medicine Department, Medical Academy of Post-Graduate Education, Ministry of Health of Ukraine, Zaporozhye, 69096, Ukraine

[3]Department of Medical Catastrophes, Military Medicine and Neurosurgery, State Medical University of Zaporozhye, 69035, Ukraine

ABSTRACT

Background: The myokines 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. The aim of the narrative mini review is depicted the role of the myokines in patients with heart failure (HF). Methods: Search in the data bases including SCOPUS, Web of Science, PubMed, Copernicus. Result: Impaired myokine (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) 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. Conclusion: Myokines 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. The large clinical trials are needed whether myokines are predictive biomarkers that are independently associated with an increased risk of HF-related mortality and clinical outcomes.

Keywords: Heart failure, Myokines, Outcomes, Sarcopenia, Risk stratification, Prognosis.

Introduction

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 (Li et al., 2017). 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 (Chung & Choi, 2018; Nakano et al., 2020). 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 (Di Raimondo et al., 2016). 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 (Berezin & Berezin, 2019; Silva et al., 2019; Berezin, 2017). The aim of the narrative mini

* Corresponding: aeberezin@gmail.com

review is to summarize the knowledge with respect to clinical perspectives to use of myokines in HF patients.

Methodology of the Review

Search of English written articles has been executed using key words [heart failure], [cardiac dysfunction], [myokines], [cachexia], [inflammation], [heart failure-related outcomes], and [prognosis of heart failure] by the authors in the data bases including SCOPUS, Web of Science, PubMed and Copernicus.

The Vicious Cycle of Myopathy and HF

The secretory potency of the skeletal muscle is well known, 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 (Paneroni et al., 2018). 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 (Tzanis et al., 2017). 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 (Poole et al., 2012; Brown et al., 2017). 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 (Brum et al., 2014; Lavine & Sierra, 2017). In fact, there is vicious circle that corresponds to aberrant skeletal muscle impairments and pathophysiological mechanisms of HF development (Figure 1).

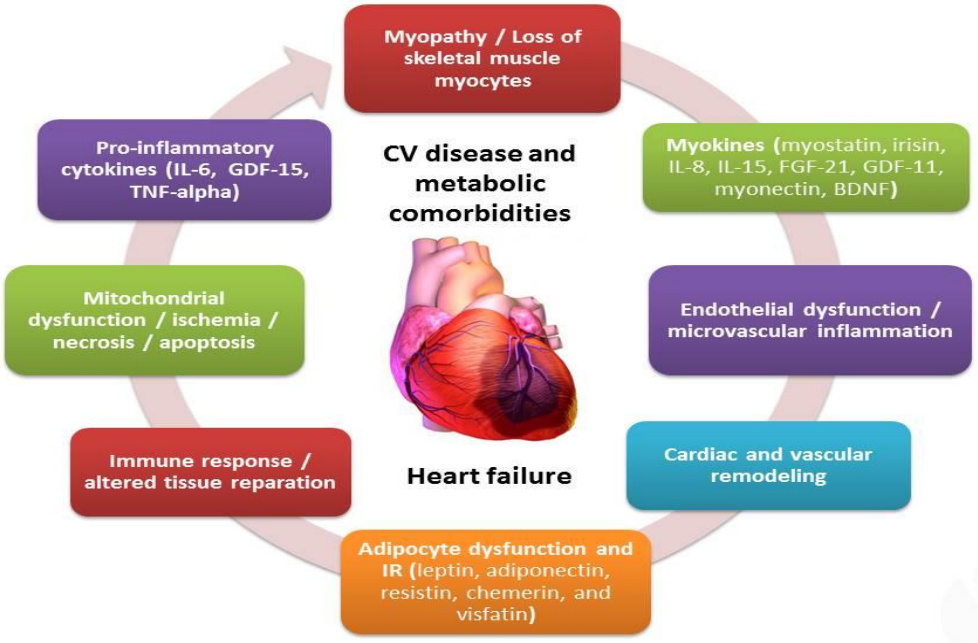

Fig.1 The interrelation between heart failure, skeletal muscle myopathy and myokines dysfunction

Abbreviations: IR, insulin resistance; IL, interleukins; TNF, tumor necrosis factor; FGF, fibroblast growth factor; GDF, growth differential factor; BDNF, brain-derived neurotrophic factor.

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 (Tzanis et al., 2017). However, hyperemia in skeletal muscle over physical exercise was strong associated with myokines release (Poole et al., 2012).

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 (Poole et al., 2012; Lavine & Sierra, 2017).

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 FNDC5	↑ expenditure, ↑ oxidative metabolism, ↑ myoblast differentiation, ↑ glucose uptake,	**Down-regulated in HF** ↓ tolerance to physical exercise, ↑ skeletal muscle hypotrophy	Abd El-Mottaleb et al., 2019
Myonectin	CTRP15	↑ oxidation of free fatty acid, ↑ oxidative metabolism, ↑ myoblast differentiation, ↑ glucose uptake	**Down-regulated in HF** ↑ skeletal muscle hypotrophy	Otaka et al., 2018
FGF-21	FGF super-family	↑ glucose uptake and protein synthesis in skeletal muscle, ↓ lipolysis in WAT, ↑ browning of WAT	**Down-regulated in HF** ↑ skeletal muscle mass, ↓ IR, ↑ exercise tolerance	Olsen et al., 2020
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	**Up-regulated in HF** ↑ skeletal muscle hypotrophy, ↑IR, ↑ autophagy, ↑ muscle weakness, ↓ exercise tolerance	Ishida et al., 2017
BDNF	Neurotrophin family	↑ myoblast proliferation, ↑ neurogenesis, ↑ angiogenesis, ↑ vascular reparation	**Down-regulated in HF** ↑ tolerance to physical exercise	Binder & Scharfman, 2004
IL-8	cysteine-X-cysteine family of chemokines	↓ glucose disposal, ↑ IR	**Up-regulated in HF** ↓ skeletal muscle energy metabolism	Segiet et al., 2019
IL-15	pleiotropic cytokine with structural similarity with IL-2	Anabolic effect, ↓ oxidative stress	**Down-regulated in HF** ↑ tolerance to physical exercise, ↑ skeletal muscle mass, ↓ WAT, ↓ apoptosis of cardiac myocytes and myoblasts	Budagian, et al., 2006
IL-6	member of the IL-6 family	↓ glucose disposal, ↑ IR, ↓ oxidation of free fatty acids, ↑ angiogenesis, ↑ cell proliferation	**Up-regulated in HF** ↑ skeletal muscle hypotrophy and weakness	Sente, et al., 2016
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	**Up-regulated in HF** ↑ skeletal muscle hypotrophy and weakness, ↓ physical endurance	Batista et al., 2010
GDF-11	TGF-β super family	↓ differentiation of myoblasts, angiogenesis and neovascularization	**Down-regulated in HF** ↓ physical endurance, ↑ skeletal muscle hypotrophy and weakness	Goletti & Gruson, 2015

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

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, FGF-21, BDNF, and IL-15 (Di Raimondo et al., 2016). 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 HFrEF and rarely among patients with HF with preserved ejection fraction (HFpEF) regardless of sarcopenia (Goletti & Gruson, 2015; Silvestrini et al., 2019; Fukushima et al., 2015; Lopez et al., 2019; Matsuo et al., 2015; Duan et al., 2019). 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 (Hsieh et al., Takada et al., 2020). 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 were independently 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.

Acknowledgments

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.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

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

List of 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

References

1. Li F, Li Y, Duan Y, Hu CA, Tang Y, Yin Y. Myokines and adipokines: Involvement in the crosstalk between skeletal muscle and adipose tissue. Cytokine Growth Factor Rev. 2017; 33:73-82. doi: 10.1016/j.cytogfr.2016.10.003.
2. Chung HS, Choi KM. Adipokines and Myokines: A Pivotal Role in Metabolic and Cardiovascular Disorders. Curr Med Chem. 2018; 25(20):2401-2415. doi:10.2174/0929867325666171205144627
3. Nakano I, Kinugawa S, Hori H, Fukushima A, Yokota T, Takada S, et al. Serum Brain-Derived Neurotrophic Factor Levels Are Associated with

Skeletal Muscle Function but Not with Muscle Mass in Patients with Heart Failure. Int Heart J. 2020; 61(1):96-102. doi: 10.1536/ihj.19-400.
4. Di Raimondo D, Tuttolomondo A, Musiari G, Schimmenti C, D'Angelo A, Pinto A. Are the Myokines the Mediators of Physical Activity-Induced Health Benefits?. Curr Pharm Des. 2016; 22(24):3622-3647. doi:10.2174/1381612822666160429121934
5. Berezin AE, Berezin AA. Impaired function of fibroblast growth factor 23 / Klotho protein axis in prediabetes and diabetes mellitus: Promising predictor of cardiovascular risk. Diabetes Metab Syndr. 2019; 13(4):2549-2556. doi:10.1016/j.dsx.2019.07.018
6. Silva AP, Mendes F, Carias E, Gonçalves RB, Fragoso A, Dias C, et al. Plasmatic Klotho and FGF23 Levels as Biomarkers of CKD-Associated Cardiac Disease in Type 2 Diabetic Patients. Int J Mol Sci. 2019; 20(7):1536. doi: 10.3390/ijms20071536.
7. Berezin AE. Cardiac biomarkers in diabetes mellitus: New dawn for risk stratification?. Diabetes Metab Syndr. 2017; 11 Suppl 1:S201-S208. doi:10.1016/j.dsx.2016.12.032
8. Paneroni M, Pasini E, Comini L, Vitacca M, Schena F, Scalvini S, Venturelli M. Skeletal Muscle Myopathy in Heart Failure: the Role of Ejection Fraction. Curr Cardiol Rep. 2018; 20(11):116. doi: 10.1007/s11886-018-1056-x. PMID: 30259199.
9. Tzanis G, Philippou A, Karatzanos E, Dimopoulos S, Kaldara E, Nana E, et al. Effects of High-Intensity Interval Exercise Training on Skeletal Myopathy of Chronic Heart Failure. J Card Fail. 2017; 23(1):36-46. doi: 10.1016/j.cardfail.2016.06.007..
10. Poole DC, Hirai DM, Copp SW, Musch TI. Muscle oxygen transport and utilization in heart failure: implications for exercise (in)tolerance. Am J Physiol Heart Circ Physiol. 2012; 302(5):H1050-H1063. doi:10.1152/ajpheart.00943.2011.
11. Brown DA, Perry JB, Allen ME, Sabbah HN, Stauffer BL, Shaikh SR, Cleland JG, Colucci WS, Butler J, Voors AA, Anker SD, Pitt B, Pieske B, Filippatos G, Greene SJ, Gheorghiade M. Expert consensus document: Mitochondrial function as a therapeutic target in heart failure. Nat Rev Cardiol. 2017;14(4):238-250. doi: 10.1038/nrcardio.2016.203.
12. Brum PC, Bacurau AV, Cunha TF, Bechara LR, Moreira JB. Skeletal myopathy in heart failure: effects of aerobic exercise training. Exp Physiol. 2014; 99(4):616-620. doi:10.1113/expphysiol.2013.076844
13. Lavine KJ, Sierra OL. Skeletal muscle inflammation and atrophy in heart failure. Heart Fail Rev. 2017; 22(2):179-189. doi:10.1007/s10741-016-9593-0
14. Abd El-Mottaleb NA, Galal HM, El Maghraby KM, Gadallah AI. Serum irisin level in myocardial infarction patients with or without heart failure. Can J Physiol Pharmacol. 2019; 97(10):932-938. doi:10.1139/cjpp-2018-0736
15. Otaka N, Shibata R, Ohashi K, Uemura Y, Kambara T, Enomoto T, et al. Myonectin Is an Exercise-Induced Myokine That Protects the Heart From Ischemia-Reperfusion Injury. Circ Res. 2018;123(12):1326-1338. doi: 10.1161/CIRCRESAHA.118.313777.
16. Olsen T, Øvrebø B, Haj-Yasein N, Lee S, Svendsen K, Hjorth M, et al. Effects of dietary methionine and cysteine restriction on plasma biomarkers, serum fibroblast growth factor 21, and adipose tissue gene expression in women with overweight or obesity: a double-blind randomized controlled pilot study. J Transl Med. 2020; 18(1):122. doi: 10.1186/s12967-020-02288-x.
17. Ishida J, Konishi M, Saitoh M, Anker M, Anker SD, Springer J. Myostatin signaling is up-regulated in female patients with advanced heart failure. Int J Cardiol. 2017; 238:37-42. doi:10.1016/j.ijcard.2017.03.153
18. Binder DK, Scharfman HE. Brain-derived neurotrophic factor. Growth Factors. 2004; 22(3):123-131. doi:10.1080/08977190410001723308
19. Segiet OA, Piecuch A, Mielanczyk L, Michalski M, Nowalany-Kozielska E. Role of interleukins in heart failure with reduced ejection fraction. Anatol J Cardiol. 2019; 22(6):287-299. doi:10.14744/AnatolJCardiol.2019.32748
20. Budagian V, Bulanova E, Paus R, Bulfone-Paus S. IL-15/IL-15 receptor biology: a guided tour through an expanding universe. Cytokine Growth Factor Rev. 2006; 17(4):259-280. doi:10.1016/j.cytogfr.2006.05.001
21. Sente T, Van Berendoncks AM, Jonckheere AI, Rodenburg RJ, Lauwers P, Van Hoof V, et al. Primary skeletal muscle myoblasts from chronic heart failure patients exhibit loss of anti-inflammatory and proliferative activity. BMC Cardiovasc Disord. 2016;16:107. doi: 10.1186/s12872-016-0278-3.
22. Batista ML Jr, Rosa JC, Lopes RD, Lira FS, Martins E Jr, Yamashita AS, et al. Exercise training changes IL-10/TNF-alpha ratio in the skeletal muscle of post-MI rats. Cytokine. 2010; 49(1):102-8. doi: 10.1016/j.cyto.2009.10.007.
23. Goletti S, Gruson D. Personalized risk assessment of heart failure patients: more perspectives from

transforming growth factor super-family members. Clin Chim Acta. 2015; 443:94-99. doi:10.1016/j.cca.2014.09.014

24. Silvestrini A, Bruno C, Vergani E, Venuti A, Favuzzi AMR, Guidi F, et al. Circulating irisin levels in heart failure with preserved or reduced ejection fraction: A pilot study. PLoS One. 2019; 14(1):e0210320. doi: 10.1371/journal.pone.0210320.
25. Fukushima A, Kinugawa S, Homma T, Masaki Y, Furihata T, Yokota T, et al. Serum brain-derived neurotropic factor level predicts adverse clinical outcomes in patients with heart failure. J Card Fail. 2015; 21(4):300-6. doi: 10.1016/j.cardfail.2015.01.003.
26. Lopez PD, Nepal P, Akinlonu A, Nekkalapudi D, Kim K, Cativo EH, et al. Low Skeletal Muscle Mass Independently Predicts Mortality in Patients with Chronic Heart Failure after an Acute Hospitalization. Cardiology. 2019; 142(1):28-36. doi: 10.1159/000496460.
27. Matsuo Y, Gleitsmann K, Mangner N, Werner S, Fischer T, Bowen TS, et al. Fibronectin type III domain containing 5 expression in skeletal muscle in chronic heart failure-relevance of inflammatory cytokines. J Cachexia Sarcopenia Muscle. 2015;6(1):62-72. doi: 10.1002/jcsm.12006
28. Duan J, Zhu B, Wu Y, Chen Z, Yang L. Myokines: An Available Biomarker to Evaluate Cardiac Functions?. Cardiology. 2019; 142(4):211-212. doi:10.1159/000500320
29. Hsieh IC, Ho MY, Wen MS, Chen CC, Hsieh MJ, Lin CP, et al. Serum irisin levels are associated with adverse cardiovascular outcomes in patients with acute myocardial infarction. Int J Cardiol. 2018; 261:12-17. doi: 10.1016/j.ijcard.2017.11.072.
30. Takada S, Sabe H, Kinugawa S. Abnormalities of Skeletal Muscle, Adipocyte Tissue, and Lipid Metabolism in Heart Failure: Practical Therapeutic Targets. Front Cardiovasc Med. 2020; 7:79. doi:10.3389/fcvm.2020.00079