Canadian Science Publishing | Canadian Journal of Physiology and Pharmacology

SERUM IRISIN LEVEL IN MYOCARDIAL INFARCTION PATIENTS WITH OR WITHOUT HEART FAILURE

Journal:	*Canadian Journal of Physiology and Pharmacology*
Manuscript ID	cjpp-2018-0736.R1
Manuscript Type:	Article
Date Submitted by the Author:	03-Mar-2019
Complete List of Authors:	Abd El-Mottaleb, Nashwa; Assiut University, Medical Physiology Galal, Heba; Assiut University El Maghraby, Khaled; Assiut University Faculty of Medicine, Cardiology Gadallah, Aml; Assiut University Faculty of Medicine, Medical Physiology
Is the invited manuscript for consideration in a Special Issue:	Not applicable (regular submission)
Keyword:	Irisin, myocardial infarction, heart failure, tumor necrosis factor-α, lipid profile

SCHOLARONE™
Manuscripts

SERUM IRISIN LEVEL IN MYOCARDIAL INFARCTION PATIENTS WITH OR WITHOUT HEART FAILURE

Nashwa A. Abd El-Mottaleb[1], Heba M. Galal[1, 2], Khaled M. El maghraby[3], Aml I. Gadallah[1]

Department of Medical Physiology, Faculty of Medicine, Assiut University, Egypt[1]

Department of Medical Physiology, Faculty of Medicine, Jouf University, Saudi Arabia [2]

Department of Cardiology, Faculty of Medicine, Assiut University, Egypt[3]

Draft

Aml I. Gadallah (Corresponding author):

Faculty of Medicine,
Assiut University,
Assiut, Egypt
amlgadallah2@gmail.com
Telephone: 01095411194

Abstract

This study aimed to assess serum irisin level in myocardial infarction (MI) with or without heart failure (HF) and the possible relation between irisin and cardiac markers, TNF-α and lipid profile. 86 subjects were included (33 patients had MI, 33 patients had MI with HF and 20 controls). Body Mass Index (BMI), waist/hip ratio (WHR), systolic and diastolic blood pressure (SBP and DBP), heart rate, left ventricular ejection fraction (LVEF) were measured. Blood samples were withdrawn on admission for measuring irisin, cardiac markers, TNF-α, total cholesterol (TC), triglycerides (TGs), low density lipoprotein-cholesterol concentration (LDL-C) and high-density lipoprotein-cholesterol concentration (HDL-C). Patients with MI and HF had reduced serum irisin, LVEF and HDL-C and higher levels of BMI, WHR, SBP, DBP, troponin-I, CK-MB, TNF-α, TC, TGs and LDL-C compared to control. Negative correlations were observed between irisin and BMI, WHR, SBP, DBP, troponin-I, CK-MB, TNF-α, TC, TGs and LDL- C. However, positive association was noticed between irisin and LVEF and HDL-C. Irisin might be a useful biomarker in diagnosis of MI with or without HF. It could have anti-inflammatory and hypolipidemic effects. Further studies are needed to elucidate the role of irisin as a promising prophylactic or therapeutic agent in cardiovascular diseases.

Keywords: Irisin, myocardial infarction, heart failure, tumor necrosis factor-α, lipid profile.

Draft

Introduction

Myocardial infarction (MI) is defined pathologically as myocardial cell death caused by prolonged ischemia (Thygesen et al. 2012). It is the major cause of morbidity and mortality worldwide with a steady increase in incidence (Ahmed et al. 2014). According to Heart Disease and Stroke Statistics 2017 update, about 790,000 people in the US experience an attack of acute MI each year (Benjamin et al. 2017). It may lead to serious complications like heart failure, myocardial rupture and arrhythmias (Piccini et al. 2008). In spite of recent advances in the management of MI, these patients are still at high risk for development of ischemic heart failure (HF) (Matsumoto et al. 2012).

Myocardial infarction is associated with up-regulation and production of cytokines such as tumor necrosis factor-α (TNF-α) that are rapidly released in the ischemic zone from the unstable atheromatous plaque in MI patients (Valgimigli et al. 2005). The causal link between lipid abnormalities and cardiovascular disease (CVD) is well established (Kumar et al. 2009).

Irisin is a myokine that was discovered in 2012 by Boström et al. to be increased in the skeletal muscle after exercise. It is a peptide hormone, containing 112 amino acids, cleaved from a plasma membrane protein fibronectin type III domain containing protein 5 (FNDC-5) (Tsuchiya et al. 2014). The principal role of irisin is to convert white adipose tissue into brown adipose tissue (Timmons et al. 2012) and regulates energy metabolism & ATP production as it increases the expression of uncoupling protein (UCP-1), a mitochondrial protein that uncouples the electron transport chain from energy production so reduce ATP synthesis and release energy as heat (Boström et al. 2012).

Draft

In addition to skeletal muscle, it is highly expressed in the cardiac muscles, brain and spinal cord, whereas lung, liver, spleen and kidney show a relatively very low expression of irisin (Wrann et al. 2013). It was reported that the cardiac muscle produces more irisin than skeletal muscle considering the cardiac muscle is the best source of irisin and affects the irisin level (Boström et al. 2012). There are few studies about irisin level in cardiovascular diseases in both human and experimental animals (Aydin & Aydin 2016).

It was considered that irisin can affect metabolism and modify cytokine production, but the relation between it and TNF-α is unknown (Pedersen & Febbraio 2012 ;Olesen et al. 2012). In addition, the interactions between it and lipid profile are still controversial and need to be clarified (Buscemi et al. 2017). Therefore, the aim of the present study is to assess the level of serum irisin in MI patients with or without HF and to evaluate the possible relation between irisin and cardiac markers, inflammatory cytokine TNF-α and lipid profile.

Draft

Subjects and methods

This study was carried out on 86 subjects (33 patients had MI, 33 patients had MI with HF and 20 controls of matched age and sex). The patients were admitted to Coronary Care Unit (CCU) of Assiut University hospital, Assiut, Egypt during the period of October 2015 until April 2017. The Age of patients was between 40-70 years old.

Myocardial infarction was diagnosed according to the European Society of Cardiology and the American College of Cardiology, which requires at least 2 of the 3 following characteristics to be satisfied (Alpert et al. 2000): (1) Typical symptoms. (2) Characteristic rise-and-fall pattern of a cardiac marker (e.g., MB isoenzymes of creatine

kinase) or, preferably, serum troponins (I). (3) Typical ECG pattern involving the development of Q waves.

Patients with ejection fraction ≤ 40% (confirmed by echocardiography) were included in HF group.

Patients who had known cardiomyopathy, known congestive heart failure, symptoms of muscle disease as muscular weakness, rigidity or muscular dystrophy, acute or chronic inflammatory disease, abnormal liver function, renal insufficiency, diabetes mellitus, regular intense exercise (>15 min of aerobic exercise 3 times per week), severe valvular disease in patients with HF were excluded.

All participants were subjected to: Clinical and anthropometric measurements including measurement of body mass index (BMI)= weight in kg / (height in meter)^2, waist circumference, hip circumference, waist/ hip ratio (WHR), heart rate, blood pressure, ECG, Echocardiography: left ventricular ejection fraction (LVEF).

Draft

The study protocol was approved by the Ethical Committee at Faculty of Medicine, Assiut University. Written consent was obtained from all participants.

Sample collection:

Fasting blood samples (as possible) were obtained from all participants. Patient's samples were taken from patients on admission before receiving thrombolytic therapy or undergoing percutaneous coronary intervention. The blood samples were divided into two parts. One part was collected in a heparinized tube for measurement of blood troponin level. The other part was centrifuged at 3000 round / minutes for 15 minutes. The clear non haemolysed supernated sera were removed and kept at -20°C until analysis.

Biochemical investigations:

Serum irisin was assayed by ELISA kit, purchased from Sino Gene Cion Biotech co., ltd (Zhejiang, China), serum TNF-α was determined by ELISA kit purchased from Elabscience Company (Hubei, China), cardiac troponin I was determined by ELISA kit purchased from Mitsubishi chemical Europe GmbH (Duesseldorf, Germany), serum CK-MB was measured by ELISA kit purchased from Siemens Health care Diagnostics Ltd, Camberley, Germany), lipid profile assay (serum cholesterol, serum triglycerides and serum HDL-C) were purchased from Egyptian company for biotechnology, Egypt. LDL-cholesterol was estimated according to Friedewald's equation:-LDL in mg/dl= TC–(HDL -TG/5) (Friedewald et al. 1972).

Statistical analysis:

The data of each group were analyzed using the Statistics Package for Social Sciences (SPSS) version 20. The data were expressed as mean ± standard error (SE). The differences between groups were analyzed using one way analysis of variance (ANOVA) followed by Bonferroni post hoc test. The correlations among different variables were calculated using the Pearson's correlation test. P value ≤ 0.05 designates the presence of statistically significant difference.

Results:

Table (1) shows the demographic and laboratory data of normal controls, patients with MI and heart failure. The results showed that patients with MI and HF had significantly higher BMI, WHR, SBP & DBP in comparison to control group. Left ventricular ejection fraction was significantly lower in both groups of MI and HF compared to the control group and markedly decreased in HF patients in comparison to

Draft

MI patients. A significant elevation in the cardiac biomarkers (cardiac troponin-I and CK-MB) was evident in both MI and HF patients compared to the control group. Meanwhile, in HF patients, blood troponin-I level was significantly lower than in MI patients but serum CK-MB level was statistically insignificantly higher.

In both groups of MI and HF patients, serum irisin level decreased significantly compared to the control group with a slightly insignificant higher level in HF patients compared to MI patients. On the other hand, significant elevation of serum TNF-α was noticed in both groups in comparison with the control group with slight insignificant increase in HF patients compared to MI patients. Regarding the lipid profile, total serum cholesterol, triglycerides, LDL- cholesterol levels reduced significantly and serum HDL-cholesterol level increased markedly in both groups of patients versus the controls.

Table (2) shows the correlations between serum irisin level and all parameters in MI and HF patients. Significant negative correlations were found among each of BMI, WHR, SBP & DBP, cardiac biomarkers (CK-MB and troponin-I) (Fig.1) with serum irisin level in MI and HF patients while the correlation between serum irisin level and LVEF was significantly positive in both MI and HF patients

Noteworthy, there was a significant negative correlation between serum irisin level and TNF-α in MI and HF patients (Fig.1). Also, significant negative correlations were noticed between irisin and atherogenic lipids (total cholesterol, LDL-C and TG). On the contrary, a significant positive correlation between serum irisin level and HDL-C were observed in both MI and HF patients (Fig.2).

Discussion:

Draft

Acute myocardial infarction is the most common cause of death worldwide (Sarioglu et al. 2016). The present study was designed to evaluate serum irisin level in MI patients with or without HF and its relations with other cardiac biomarkers, inflammatory markers as TNF-α and lipid profile. In the current study, it was found that BMI, WHR, SBP, DBP, cardiac biomarkers (CK-MB, troponin-I), serum total cholesterol, triglycerides, LDL-C were markedly increased in MI & HF patients compared to the control group while LVEF, serum irisin & HDL-C level were significantly lower in both groups of patients compared to the control group. The decline in serum irisin level is in agreement with Aydin et al. 2014b ; Emanuele et al. 2014; Kuloglu et al. 2014; Anastasilakis et al. 2017. Besides that, the marked negative correlations between irisin and both BMI and WHR and between irisin & both SBP & DBP in MI cases and those with ischemic HF were observed & were in agreement with Moreno-Navarrete et al. 2013; Hou et al. 2015 & Hwang et al. 2016.

Irisin reduce ATP synthesis and release energy as heat. This heat may accelerate the biochemical reactions occurring in MI worsening the healing process. So, limiting irisin production increase ATP synthesis & energy supply to ischemic damaged cardiomyocytes hastening the healing process (Boström et al. 2012; Kuloglu et al. 2014) and this might clarify the reduced serum irisin level in both groups of patients observed in this study.

However, some authors hypothesized that lower irisin in MI may be the cause rather than the result of diminished coronary blood flow (Anastasilakis et al. 2017). In animals, irisin improves endothelial function (Han et al. 2015) and induces relaxation in

Draft

mesenteric arteries through endothelium-dependent and endothelium independent mechanisms (Jiang et al. 2015).

On the contrary Sarioglu et al. 2016 found increased cardiac tissue irisin mRNA levels and increased irisin expression at the end of the first & second weeks after the development of MI. They explained the increased irisin level by fibroblast activity which increased in the first and second weeks following MI resulting in increased formation of new connective tissue and scar tissue facilitating the process of healing. Moreover, Hsieh et al. 2018 reported that elevated serum irisin level within 28 days after AMI predisposes patients to several complications as recurrent MI, ischemic HF, ischemic stroke, recurrent angina, coronary revascularization and even death.

The discrepancy between decreased irisin level in MI reported by our study; Kuloglu et al. 2014; Aydin et al. 2014b and increased irisin level reported by Sarioglu et al. 2016 could be due to the length of the study.

The significantly decreased serum irisin level in ischemic HF patients compared to the control group agreed with Matsuo et al. 2015 who observed that the concentration of circulating irisin was significantly reduced in rats with HF. Also, the mRNA expression of both PGC-1α (the key regulator of FNDC5 expression) and the FNDC5 (the irisin precursor) were markedly reduced in HF rats (Strassburg et al. 2005). Moreover, it was postulated that a reduced expression of FNDC5 leads to a reduced expression of follistatin (inhibitor of myostatin), so with the increased myostatin level (inhibitor of muscle growth), it eventually resulted in a reduction in muscle mass (good source of irisin) (Mangner et al. 2013). In addition, the down-regulation of FNDC5

Draft

expression in HF could be considered as an adaptive response to prevent energy loss accompanying increased catabolic rate in HF patients (Matsuo et al. 2015).

In partial agreement with our results, Kalkan et al. 2018 found marked negative correlation between irisin & BMI, arm muscle area, skin fold thickness in cachectic HF patients with reduced ejection fraction. On the contrary, positive correlation between irisin and both BMI and WHR showed by Stengel et al. 2013 and Pardo et al. 2014. Stengel et al. 2013 found that obese patients had a significant higher circulating irisin levels and explained this as a physiological function of irisin to improve glucose tolerance which is often impaired in obese subjects. Furthermore, the negative correlation between irisin & both SBP & DBP are consistent with Hwang et al. 2016 who found that serum irisin was correlated with favorable metabolic parameters including blood pressure and revealed a negative correlation with both SBP & DBP and also in partial accordance with Al-Daghri et al. 2015 who found that DBP was negatively correlated with circulating irisin levels in T2DM patients. In contrast, positive correlations between irisin and blood pressure in metabolic syndrome patients had been observed by Park et al. 2013. This can be explained by that these studies include obesity and metabolic syndrome patients who had a higher irisin level (a state of resistance to irisin signaling). Xiong et al. 2015 indicated that FNDC5/irisin plays a beneficial role in attenuating hypertension via inhibiting sympathetic activation in obesity.

The present study showed marked reduction in LVEF in both AMI & HF patients compared to control group & this decrease was prominent in HF group versus MI group. This was in agreement with Ather 2008 & Matsuo et al. 2015. According to Lebeau et al. 2012, LVEF is an important indicator of left ventricular function, the severity and

Draft

prognosis of ischemic heart disease. In addition, the positive correlation between irisin and LVEF in both groups of patients was in the same line with that reported by Gloria-Bottini et al. 2016 & Anastasilakis et al. 2017 who observed correlation between decreased circulating irisin levels in MI patients, LVEF and the severity of coronary arteries stenosis. However, Silvestrini et al. 2019 reported no significant correlation between irisin and LVEF in heart failure with preserved or reduced ejection fraction.

Our study measured the cardiac biomarkers (cardiac CK-MB and troponin-I) which were significantly elevated in both groups of patients compared to the control group. This is in accordance with Aydin et al. 2014a; Kuloglu et al. 2014; Yilmaz et al. 2006 who demonstrated a relationship between clinical severity of the disease and elevation of myocardial enzymes (CK-MB and troponin I). The cause for elevation of serum CK-MB is its leakage into the circulation due to the increased permeability of the membrane of injured cardiomyocytes, while troponin-I which is present in the contractile apparatus is released into the circulation in HF with myofibrils degeneration (Yilmaz et al. 2006). This observation was demonstrated in the present study as blood troponin-I level in HF patients was significantly lower than MI patients. This could be explained that cardiac troponin-I might not still reach its peak which is 1-2 days after acute ischemic attack as all our samples were collected on admission and those patients may be presented earlier with the chest pain than MI patients (Reed et al. 2017). In addition, the prominent negative correlations between irisin level and cardiac biomarkers (troponin-I & CK-MB) after MI and HF were in agreement with Kuloglu et al. 2014. Thus, serum irisin level could serve as a marker for MI with accuracy similar to CK-MB and it is not inferior to CK-MB in predicting MI (Anastasilakis et al. 2017).

Draft

The obvious increase in TNF-α in MI and HF patients compared to the control group was associated with significant negative correlation between it & serum irisin level in both groups of patients. The increased serum TNF-α level is in accordance with the results of Francis et al. 2004; Hassanzadeh et al. 2006; Matsuo et al. 2015.; Hassanzadeh et al. 2006 reported an increase in serum TNF-α level during the first hours in patients of MI and suggested that it was produced, in the early stages of MI, due to initiation of an inflammatory process which result in tissue damage and myocardial necrosis.

Moreover, it was demonstrated that excessive cardiac-specific expression of TNF-α resulted in myocardial inflammation, increased apoptosis, progressive dilatation, cardiac hypertrophy which lead to heart failure and death (Kubota et al. 1997). The observed negative correlation between serum irisin level and TNF-α was consistent with Matsuo et al. 2015 who found a negative correlation between the serum concentration of TNF-α and serum irisin level, the mRNA expression of FNDC5 as well as PGC-1α in ischemic HF. The authors suggested that the lowered serum irisin level in HF might likely result from increased level of inflammatory cytokines as TNF-α. This was proved by the significant decrease in both PGC-1α and FNDC5 skeletal muscle expression by administration of TNF-α. Also, in supporting the relation between irisin and TNF-α, Mazur-Bialy et al. 2017 showed that irisin in high concentrations (50, 100nM) significantly decrease the release of pro-inflammatory cytokines as TNFα through suppressing phosphorylation of MAPK and activation of nuclear factor kappa B confirming an anti-inflammatory role of irisin.

The impaired lipid profile observed in MI & HF patients in the present study might be explained by Kumar et al. 2009 who found the increased susceptibility of

Draft

dyslipidemic patients to MI by the increased free radical generation producing a state of oxidative stress that lead to increase LDL-C oxidative form (Maritim et al. 2003). These oxidized forms of LDL-C were considered the most important risk factor for coronary artery disease as they promote foam cell formation which initiates the process of atherosclerosis (Berliner et al. 1995). The present study showed a significant correlation between irisin and dyslipidemia that was negatively correlated with TC, LDL-C and TGs and positively correlated with HDL-C. This is in agreement with Wen et al. 2013; Oelmann et al. 2016. Oelmann et al. 2016 stated an improved lipid profile in association with irisin suggesting an irisin-induced protection against lipid-related diseases. On the contrary, positive correlations between irisin, total cholesterol and triglycerides were reported by Liu et al. 2013 and also between irisin and both total cholesterol and LDL-C (Ebert et al. 2014).

Draft

Conclusions:

Irisin levels are decreased in patients with MI and HF. It is negatively correlated to troponin-I, CK-MB, TNF-α, TC, LDL-C and TGs and positively correlated with LVEF & HDL-C in MI and HF patients. It might be a useful biomarker in diagnosis of MI beside troponin-I and CK-MB & follow up of serum irisin can be used as useful biomarker in predicting the incidence of complications following MI. Irisin could have anti-inflammatory and hypolipidemic effects. Further studies are needed to clarify the possible mechanisms and the role of irisin as a promising prophylactic or therapeutic agent in different cardiovascular diseases.

Conflict of interest:

There are no conflict of interests in this work.

References:

Ahmed, E., Al Suwaidi, J., El-Menyar, A., AlBinali, H. A., Singh, R., & Gehani, A. 2014. Mortality trends in patients hospitalized with the initial acute myocardial infarction in a middle eastern country over 20 years. Cardiology research and practice, 2014.

Al-Daghri, N. M., Alokail, M. S., Rahman, S., Amer, O. E., Al-Attas, O. S., Alfawaz, H., et al. 2015. Habitual physical activity is associated with circulating irisin in healthy controls but not in subjects with diabetes mellitus type 2. European journal of clinical investigation. **45**(8): 775-781.

Alpert, J. S., Thygesen, K., Antman, E., & Bassand, J. P. 2000. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol. **36**(3): 959-969.

Anastasilakis, A. D., Koulaxis, D., Kefala, N., Polyzos, S. A., Upadhyay, J., Pagkalidou, E., et al. 2017. Circulating irisin levels are lower in patients with either stable coronary artery disease (CAD) or myocardial infarction (MI) versus healthy controls, whereas follistatin and activin A levels are higher and can discriminate MI from CAD with similar to CK-MB accuracy. Metabolism-Clinical and Experimental. **73**: 1-8.

Ather, M. 2008. Left ventricular ejection fraction after acute myocardial infarction. Professional Med J Jun. **15**(2): 234-239.

Aydin, S., & Aydin, S. 2016. Irisin Concentrations as a Myocardial Biomarker. Biomarkers in Cardiovascular Disease: 489-504.

Draft

Aydin, S., Aydin, S., Kobat, M. A., Kalayci, M., Eren, M. N., Yilmaz, M., et al. 2014a. Decreased saliva/serum irisin concentrations in the acute myocardial infarction promising for being a new candidate biomarker for diagnosis of this pathology. Peptides. **56:** 141-145. doi:10.1016/j.peptides.2014.04.002

Aydin, S., Kuloglu, T., Aydin, S., Eren, M. N., Celik, A., Yilmaz, M., et al. 2014b. Cardiac, skeletal muscle and serum irisin responses to with or without water exercise in young and old male rats: cardiac muscle produces more irisin than skeletal muscle. Peptides. **52**: 68-73.

Benjamin, E. J., Blaha, M. J., Chiuve, S. E., Cushman, M., Das, S. R., Deo, R., et al. 2017. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. **135**(10): e146-e603.

Berliner, J. A., Navab, M., Fogelman, A. M., Frank, J. S., Demer, L. L., Edwards, P. A., et al. 1995. Atherosclerosis: basic mechanisms: oxidation, inflammation, and genetics. Circulation. **91**(9): 2488-2496.

Boström, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., et al. 2012. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. **481**(7382): 463.

Buscemi, S., Corleo, D., Buscemi, C., & Giordano, C. 2017. Does iris(in) bring bad news or good news? Eat Weight Disord. doi:10.1007/s40519-017-0431-8

Ebert, T., Focke, D., Petroff, D., Wurst, U., Richter, J., Bachmann, A., et al. 2014. Serum levels of the myokine irisin in relation to metabolic and renal function. European journal of endocrinology. **170**(4): 501-506.

Draft

Emanuele, E., Minoretti, P., Pareja-Galeano, H., Sanchis-Gomar, F., Garatachea, N., & Lucia, A. 2014. Serum irisin levels, precocious myocardial infarction, and healthy exceptional longevity. The American journal of medicine. **127**(9): 888-890.

Francis, J., Chu, Y., Johnson, A. K., Weiss, R. M., & Felder, R. B. 2004. Acute myocardial infarction induces hypothalamic cytokine synthesis. American Journal of Physiology-Heart and Circulatory Physiology. **286**(6): H2264-H2271.

Friedewald, W. T., Levy, R. I., & Fredrickson, D. S. 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical chemistry. **18**(6): 499-502.

Gloria-Bottini, F., Saccucci, P., Banci, M., Neri, A., Magrini, A., & Bottini, E. 2016. The correlation between left ventricular ejection fraction and clinical severity of manifestations in subjects with Coronary Artery Disease. Cardiovasc Disord Med, **1**(2): 46-48.

Han, F., Zhang, S., Hou, N., Wang, D., & Sun, X. 2015. Irisin improves endothelial function in obese mice through the AMPK-eNOS pathway. American Journal of Physiology-Heart and Circulatory Physiology. **309**(9): H1501-H1508.

Hassanzadeh, M., Faridhosseini, R., Mahini, M., Faridhosseini, F., & Ranjbar, A. 2006. Serum levels of TNF-a, IL-6, and selenium in patients with acute and chronic coronary artery disease. Iranian Journal of Immunology. **3**(3): 142-145.

Hou, N., Han, F., & Sun, X. 2015. The relationship between circulating irisin levels and endothelial function in lean and obese subjects. Clinical endocrinology. **83**(3): 339-343.

Draft

Hsieh, I.-C., Ho, M.-Y., Wen, M.-S., Chen, C.-C., Hsieh, M.-J., Lin, C.-P., et al. 2018. Serum irisin levels are associated with adverse cardiovascular outcomes in patients with acute myocardial infarction. International journal of cardiology. **261**: 12-17.

Hwang, Y.-C., Jeon, W. S., Park, C.-Y., & Youn, B.-S. 2016. The ratio of skeletal muscle mass to visceral fat area is a main determinant linking circulating irisin to metabolic phenotype. Cardiovascular diabetology. **15**(1): 9.

Jiang, M., Wan, F., Wang, F., & Wu, Q. 2015. Irisin relaxes mouse mesenteric arteries through endothelium-dependent and endothelium-independent mechanisms. Biochemical and biophysical research communications. **468**(4): 832-836.

Kalkan, A. K., Cakmak, H. A., Erturk, M., Kalkan, K. E., Uzun, F., Tasbulak, O., et al. 2018. Adropin and Irisin in Patients with Cardiac Cachexia. Arquivos brasileiros de cardiologia. **111**(1):39-47. doi: 10.5935/abc.20180109. Epub 2018 Jul 2.

Kubota, T., McTiernan, C. F., Frye, C. S., Slawson, S. E., Lemster, B. H., Koretsky, A. P., et al. 1997. Dilated cardiomyopathy in transgenic mice with cardiac-specific overexpression of tumor necrosis factor-α. Circulation research. **81**(4): 627-635.

Kuloglu, T., Aydin, S., Eren, M. N., Yilmaz, M., Sahin, I., Kalayci, M., et al. 2014. Irisin: a potentially candidate marker for myocardial infarction. Peptides. **55:** 85-91.

Kumar, A., Nagtilak, S., Sivakanesan, R., & Gunasekera, S. 2009. Cardiovascular risk factors in elderly normolipidemic acute myocardial infarct patients-a case controlled study from India. Southeast Asian Journal of Tropical Medicine and Public Health. **40**(3): 581.

Draft

Lebeau, R., Serri, K., Morice, M.-C., Hovasse, T., Unterseeh, T., Piéchaud, J.-F., et al. 2012. Assessment of left ventricular ejection fraction using the wall motion score index in cardiac magnetic resonance imaging. Archives of Cardiovascular Diseases. **105**(2): 91-98. doi:https://doi.org/10.1016/j.acvd.2012.01.002

Liu, J.-J., Wong, M. D., Toy, W. C., Tan, C. S., Liu, S., Ng, X. W., et al. 2013. Lower circulating irisin is associated with type 2 diabetes mellitus. Journal of Diabetes and its Complications. **27**(4): 365-369.

Mangner, N., Matsuo, Y., Schuler, G., & Adams, V. 2013. Cachexia in chronic heart failure: endocrine determinants and treatment perspectives. Endocrine. **43**(2): 253-265.

Maritim, A., Sanders, a., & Watkins Iii, J. 2003. Diabetes, oxidative stress, and antioxidants: a review. Journal of biochemical and molecular toxicology. **17**(1): 24-38.

Matsumoto, S., Sakata, Y., Nakatani, D., Suna, S., Mizuno, H., Shimizu, M., et al. 2012. A subset of circulating microRNAs are predictive for cardiac death after discharge for acute myocardial infarction. Biochemical and biophysical research communications. **427**(2): 280-284.

Matsuo, Y., Gleitsmann, K., Mangner, N., Werner, S., Fischer, T., Bowen, T. S.**,** et al. 2015. Fibronectin type III domain containing 5 expression in skeletal muscle in chronic heart failure—relevance of inflammatory cytokines. Journal of cachexia, sarcopenia and muscle. **6**(1): 62-72.

Mazur-Bialy, A. I., Pocheć, E., & Zarawski, M. 2017. Anti-Inflammatory Properties of Irisin, Mediator of Physical Activity, Are Connected with TLR4/MyD88

Draft

Signaling Pathway Activation. International journal of molecular sciences. **18**(4): 701. doi:10.3390/ijms18040701

Moreno-Navarrete, J. M., Ortega, F., Serrano, M., Guerra, E., Pardo, G., Tinahones, F., et al. 2013. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. The Journal of Clinical Endocrinology & Metabolism. **98**(4): E769-E778.

Oelmann, S., Nauck, M., Völzke, H., Bahls, M., & Friedrich, N. 2016. Circulating irisin concentrations are associated with a favourable lipid profile in the general population. PloS one. **11**(4): e0154319.

Olesen, J., Larsson, S., Iversen, N., Yousafzai, S., Hellsten, Y., & Pilegaard, H. 2012. Skeletal muscle PGC-1α is required for maintaining an acute LPS-induced TNFα response. PloS one. **7**(2): e32222.

Pardo, M., Crujeiras, A. B., Amil, M., Aguera, Z., Jiménez-Murcia, S., Baños, R., et al. 2014. Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. International journal of endocrinology. 2014. article ID 857270.

Park, K.H., Zaichenko, L., Brinkoetter, M., Thakkar, B., Sahin-Efe, A., Joung, K. E., et al. 2013. Circulating irisin in relation to insulin resistance and the metabolic syndrome. The Journal of Clinical Endocrinology & Metabolism. **98**(12): 4899-4907.

Pedersen, B. K., & Febbraio, M. A. 2012. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nature Reviews Endocrinology. **8**(8): 457.

Draft

Piccini, J. P., Berger, J. S., & Brown, D. L. 2008. Early sustained ventricular arrhythmias complicating acute myocardial infarction. The American journal of medicine. **121**(9): 797-804.

Reed, G. W., Rossi, J. E., & Cannon, C. P. 2017. Acute myocardial infarction. The Lancet. **389**(10065): 197-210.

Sarioglu, G., Korkmaz, H., Onalan, E., Kuloglu, T., Yilmaz, M., Ozguler, M., et al. 2016. Irisin levels increase during experimentally induced acute myocardial infarction. Current Research: Cardiology. **3**(1): 9-12.

Silvestrini, A., Bruno, C., Vergani, E., Venuti, A., Favuzzi, A.M.R., Guidi, F., et al. 2019. Circulating irisin levels in heart failure with preserved or reduced ejection fraction: A pilot study. PLoS One. **14**(1): e0210320. doi: 10.1371/journal.pone.0210320. eCollection 2019.

Stengel, A., Hofmann, T., Goebel-Stengel, M., Elbelt, U., Kobelt, P., & Klapp, B. F. 2013. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity–correlation with body mass index. Peptides. **39:** 125-130.

Strassburg, S., Springer, J., & Anker, S. D. 2005. Muscle wasting in cardiac cachexia. The international journal of biochemistry & cell biology. **37**(10): 1938-1947.

Thygesen, K., Alpert, J. S., Jaffe, A. S., Simoons, M. L., Chaitman, B. R., White, H. D., et al. 2012. Third Universal Definition of Myocardial Infarction. Journal of the American College of Cardiology. **60**(16): 1581-1598. doi:http://dx.doi.org/10.1016/j.jacc.2012.08.001

Timmons, J. A., Baar, K., Davidsen, P. K., & Atherton, P. J. 2012. Is irisin a human exercise gene? Nature. **488(**7413): 463-468.

Draft

Tsuchiya, Y., Ando, D., Goto, K., Kiuchi, M., Yamakita, M., & Koyama, K. 2014. High-intensity exercise causes greater irisin response compared with low-intensity exercise under similar energy consumption. The Tohoku journal of experimental medicine. **233**(2): 135-140.

Valgimigli, M., Ceconi, C., Malagutti, P., Merli, E., Soukhomovskaia, O., Francolini, G., et al. 2005. Tumor necrosis factor-α receptor 1 is a major predictor of mortality and new-onset heart failure in patients with acute myocardial infarction: the Cytokine-Activation and Long-Term Prognosis in Myocardial Infarction (C-ALPHA) study. Circulation. **111**(7): 863-870.

Wen, M. S., Wang, C. Y., Lin, S. L., & Hung, K. C. 2013. Decrease in irisin in patients with chronic kidney disease. PloS one. **8(**5):e64025. doi:10.1371/journal.pone.0064025

Wrann, C. D., White, J. P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., et al. 2013. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell metabolism. **18**(5): 649-659.

Xiong, X.-Q., Chen, D., Sun, H.-J., Ding, L., Wang, J.-J., Chen, Q., et al. 2015. FNDC5 overexpression and irisin ameliorate glucose/lipid metabolic derangements and enhance lipolysis in obesity. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. **1852**(9): 1867-1875.

Yilmaz, A., Yalta, K., Turgut, O. O., Yilmaz, M. B., Ozyol, A., Kendirlioglu, O., et al. 2006. Clinical importance of elevated CK-MB and troponin I levels in congestive heart failure. Advances in therapy. **23**(6): 1060-1067.

Draft

Draft

Figure Captions:

Fig.1. Linear regression and correlation between irisin and blood troponin-I, creatine kinase-MB and tumor necrosis factor-alpha in myocardial infarction and heart failure patients

Fig.2. Linear regression and correlation between irisin and lipid profile (total cholesterol, triglycerides, low density lipoprotein-cholesterol; and high density lipoprotein-cholesterol) in myocardial infarction and heart failure patients

Draft

Table 1. The demographic and laboratory data of all subjects

	Control (n=20)	Myocardial infarction (n=33)	Heart failure (n=33)
Age (years)	54.15±1.04	57.67±1.50 a ns	57.24±1.70 a ns, b ns
BMI	26.45±0.59	27.84±0.16 a *	28.10±0.41 a *, b ns
WHR	0.90±0.01	0.93±0.01 a*	0.94±0.01 a*, b ns
SBP (mmHg)	122.25±2.13	135.30±3.81 a*	136.06±3.09 a*, b ns
DBP (mmHg)	76.75±2.00	85.15±2.31 a *	86.10±1.72 a *, b ns
Heart rate (beat/min)	73.85±0.66	76.58±1.77 a ns	79.67±1.85 a ns, b ns
LVEF (%)	61.95±1.00	52.97±0.92 a***	35.42±0.82 a***, b***
Irisin (ng/ml)	73.12±5.55	48.69±2.50 a***	54.31±3.11 a***, b ns
Troponin-I (ng/ml)	0.02±00	2.18±0.28 a***	0.97±0.13 a***, b ***
CK-MB (IU/L)	17.05±1.06	106.91±11.50 a***	128.91±15.83 a***, b ns
TNF-α (pg/ml)	4.6±0.38	8.86±1.20 a*	10.75±1.19 a***, b ns
TC (mg/dl)	161.1±4.45	187.24±5.21 a***	181.3±5.59 a*, b ns
TGs (mg/dl)	129.83±5.86	159.69±8.10 a*	163.59±6.66 a*, b ns
LDL-C (mg/dl)	82.28±4.92	109.37±5.50 a***	103.15±5.68 a*, b ns
HDL-C (mg/dl)	50.97±2.05	44.02±1.63 a*	44.69±1.48 a*, b ns

Note: Data are expressed as mean ± SE, BMI: Body Mass Index, WHR: waist/hip ratio, SBP and DBP: systolic and diastolic blood pressure, LVEF: left ventricular ejection fraction, CK-MB: creatin kinase-MB, TNF-α: tumor necrosis factor- α, TC: total cholesterol, TGs: triglycerides, LDL-C: low density lipoprotein-cholesterol; and HDL-C: high-density lipoprotein-cholesterol. a: Comparison of all groups vs. control, b: Comparison of heart failure vs myocardial infarction; *: significant at 0.05 level of probability, ***: significant at 0.001 level of probability, ns: not significant.

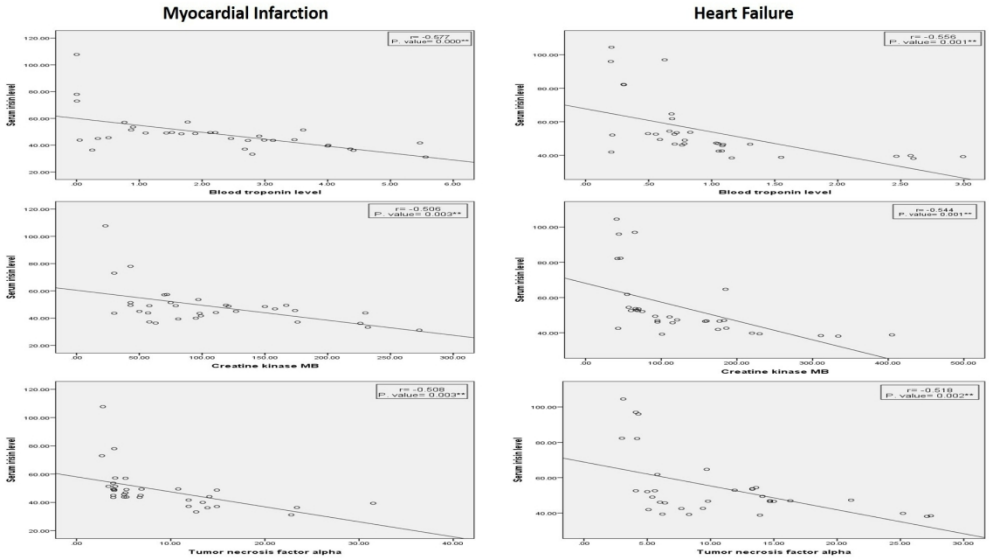
Draft

Table 2. Correlations between serum irisin level and all parameters

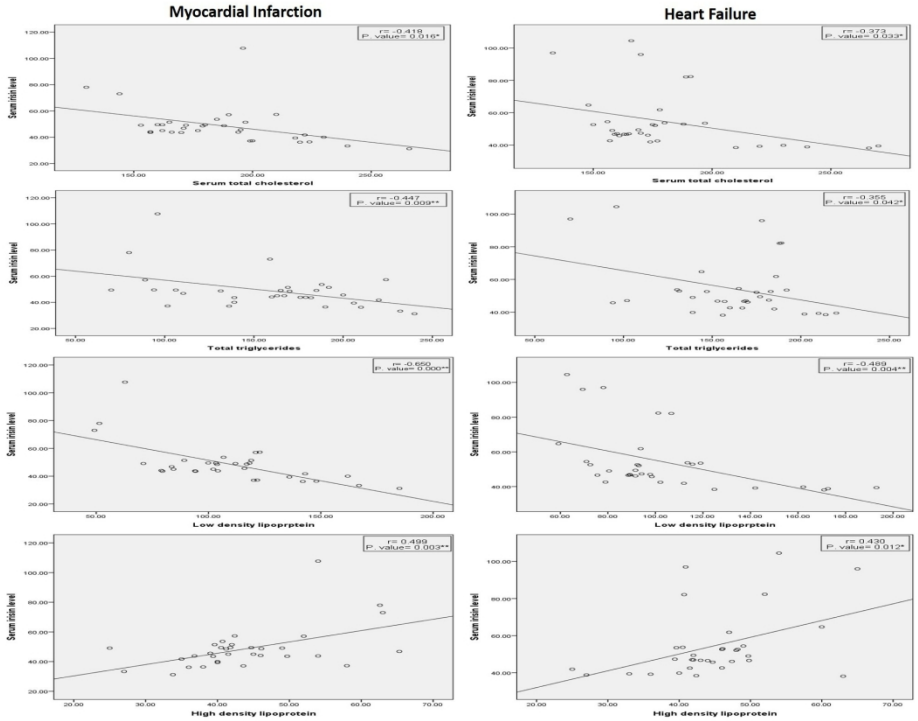
	Myocardial infarction (n=33)		Heart failure (n=33)	
	R	**P**	**r**	**P**
Age	0.043	0.814	-0.056	0.758
BMI	-0.433	**0.012***	-0.441	**0.010***
WHR	-0.513	**0.002****	-0.505	**0.003****
SBP	-0.405	**0.019***	-0.403	**0.020***
DBP	-0.361	**0.039***	-0.399	**0.021***
Heart rate	-0.061	0.737	-0.265	0.136
TNF- alpha	-0.508	**0.003****	-0.518	**0.002****
LVEF	0.686	**0.000*****	0.430	**0.013***
CK-MB	-0.506	**0.003****	-0.544	**0.001****
Troponin-I	-0.577	**0.000*****	-0.556	**0.001****
TC	-0.418	**0.016***	-0.373	**0.033***
TGs	-0.447	**0.009****	-0.355	**0.042***
LDL-C	-0.650	**0.000*****	-0.489	**0.004****
HDL-C	0.499	**0.003****	0.430	**0.012***

Note: BMI: Body Mass Index, WHR: waist/hip ratio, SBP and DBP: systolic and diastolic blood pressure, LVEF: left ventricular ejection fraction, CK-MB: creatin kinase-MB, TNF-α: tumor necrosis factor- α, TC: total cholesterol, TGs: triglycerides, LDL-C: low density lipoprotein-cholesterol; and HDL-C: high-density lipoprotein-cholesterol. *: significant at 0.05 level of probability, ***: significant at 0.001 level of probability, ns: not significant.

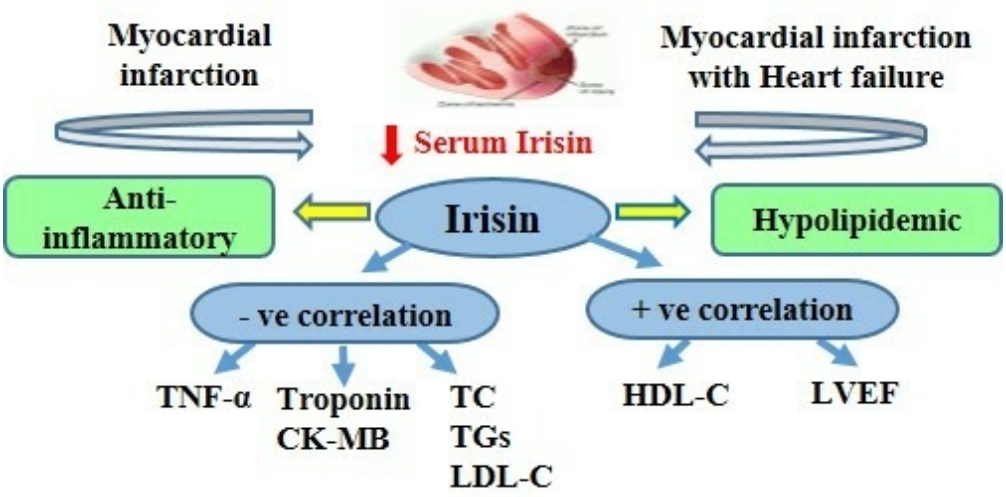
Draft



169x96mm (300 x 300 DPI)



184x133mm (300 x 300 DPI)



42x22mm (300 x 300 DPI)