The Roles of Myokines In Patients With Heart Diseases

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Abstract

Background: Myokines may act as protective or causative factors in the pathogenesis of cardiovascular diseases. Conflicting data have been published regarding abnormal levels of myokines in both angina pevtoris and heart failure (HF) patients.

Objective: The primary objective of this study was to evaluate the levels of decorin, myonectin, and irisin in individuals diagnosed with angina pectoris and congestive heart failure, and subsequent exposure to each of these conditions .

Methods: The present study was conducted at Salah Al-Din Hospital in Tikrit, which took place between ¹ˢᵗ from November in 2023 to ³⁰ᵗʰ from January in 2024. The study consisted of a sample of 300 male patients, including 100 diagnosed with congestive heart failure (G1).) and. 100 were diagnosed with angina pectoris (G2). Participants ranged in age from 35 to 55. After a comprehensive medical examination by a qualified physician in this area. After randomization, a control group (C) consisting of 75 healthy men between 35 and 55 years of age was included.

Results: When compared to the healthy volunteers (C), the sick groups (G1, G2) showed significantly higher serum concentrations of Decorin, Myonectin, and Irisin ($p < 0.01$). Regretfully, there was no discernible difference between patients with angina pectoris and those with congestive heart failure. Additionally, this study has provided additional evidence supporting the existence of negative associations between plasma Myonectin levels and Irisin in the same groups..

Conclusion: Myokines have been identified as predictive biological markers that exhibit an independent association with an elevated risk of heart failure (HF) and angina pectoris. However, further work is necessary to fully understand their role in predicting unfavourable cardiac remodelling and stratifying clinical outcomes through large-scale clinical studies..

Abbreviation: CHF: Congestive Heart Failure; CVD: Cardiovascular Diseases; CAD: coronary artery diseases; DCN: Decorin; CTRP15: Tumor necrosis factor-related protein15.

Keywords: Congestive Heart Failure, Angina Pectoris, Myokines, Decorin, Myonectin and Irisin.

INTRODUCTION

The striated muscles, which include the skeletal and cardiac muscles, are essential to metabolic activities. Pedersen and Hojman have discovered active tissues (2017). Hormones in the bloodstream and the synthesis and release of active substances into muscle cells control this phenomena of muscle plasticity. It happens as a result of both abnormal and typical physiological processes. These compounds are commonly referred to as myokines, which are hormones related to muscle function (Steensberg et al., 2020). Myocytes in muscle tissue produce and release cytokines, called myokines, in response to muscle contractions. The term "myokine" was introduced by Bengt Saltin in 2003 (Pedersen et al., 2003). Following the discovery of myostatin as a myokine in 1997, an extensive examination of secretome-based analysis has identified over 600 myokines from human myocyte culture media.

Even though a good number of these myokines are still under characterization, some molecules' biological activity and function have been investigated, and these findings indicate that these agents are released directly as a result of muscle contraction (Pedersen & Brandt, 2020).

The activation of this tissue is intricately connected to diverse organs, which includes the adipose tissue, liver, pancreas, bone, heart, immune cells, and mind cells. This connection is facilitated through receptors, which involve excitation-contraction coupling, metabolism, and muscle restore. These tactics collectively contribute to the continuous version of endocrine and paracrine muscle actions. The present knowledge indicates that skeletal myofibers and cardiac cells are chargeable for the synthesis and secretion of cytokines, myokines, and various different bioactive peptides. The molecules in question are of extreme importance in facilitating conversation between skeletal and cardiac muscle as well as different tissues. In conjunction with the regulation of synthesis and degradation by way of muscle metabolites, they serve as a vital mechanism for maintaining each neighborhood and general homeostasis (Pedersen, et al., 2017). The position of those organisms is not best confined to metabolic procedures, but they also contain themselves in a bunch of other physiological approaches, which include immunomodulation, tissue regeneration and restore, upkeep of body homeostasis, and mobile signaling, gene expression, and differentiation. With the mixing of hormone synthesis and secretion in various skeletal muscular tissues and cardiac muscle functions as one organism, it's far taken into consideration an part subject wherein endocrine and paracrine muscle movement emerges from bone thru molecular mechanisms (Pedersen and Febbraio, 2018)..

Cardiovascular Diseases (CVD)

Heart disease (HFD) is a group of medical conditions that affect the heart's or blood vessels' ability to function. One of the various diseases is cardiovascular diseases (CVD), which are a combination of a number of physiological conditions that comprise coronary artery diseases (CAD), for example, angina and myocardial infarction, otherwise known as a heart attack. Also considered cardiovascular diseases are conditions such as heart failure, rheumatic heart disease, hypertensive heart disease, cardiomyopathy, irregular heart rhythms, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic

illness, and venous thrombosis. In any given case, the particular disease denotes the variability in systems involved.

In the estimation, dietary risk factors account for about 53% of mortality from CVD. The development of PAD, CAD, and stroke has been linked to the emergence of atherosclerosis (Gimbrone, 2020).
Age, gender, smoking, physical inactivity, non-alcoholic fatty liver disease, excessive alcohol use, poor diet, obesity, genetic predisposition and family history of cardiovascular disease, high blood pressure (hypertension), high blood sugar (diabetes mellitus), high blood cholesterol (hyperlipidemia), undiagnosed celiac disease, psychosocial factors, poverty and low educational attainment, air pollution, and inadequate sleep are just a few of the risk factors associated with heart diseases. The aggregate impact of these risk factors remains considerable, even though the specific effects of each risk variable may change among other cultures or ethnic groups. Age, sex, and genetic susceptibility/family history are among the risk variables that are thought to be unchangeable. However, altering one's lifestyle, adjusting to new social situations, and utilising medication to prevent problems like high blood pressure, high cholesterol, and diabetes can all help to reduce a number of significant cardiovascular risk factors (Stamler, et al., 2020). The risk of atherosclerosis in the coronary arteries is higher in obese people. Studies conducted on multiple populations have shown that atherosclerosis, a recognised risk factor for cardiovascular disease, begins in childhood. Intimal lesions were discovered in all aortas and more than 50% of the right coronary arteries in individuals between the ages of 7-9 in a study by Kang-Decker et al. (2022), suggesting the existence of pathobiological reasons of atherosclerosis in young people.

MATERIALS AND METHODS

The present study was carried out at Salah Al-Deen Hospital, Tikrit between 1st from November in 2023 to 30th from January in 2024. A cohort of 100 male volunteers was enrolled in the study; 50 of them had a congestive heart failure diagnosis, and the remaining participants had an angina pectoris diagnosis. The age of all participants was between 25 and 55 years upon clinical and medical evaluation by a licensed physician in this field.

In addition to selecting an appropriate random group, another control group (C) comprising 75 healthy men in the age range of 25 – 55 years was also included in this study (Table 1). Seventy male subjects with angina pectoris and congestive heart failure, as well as a control group of healthy men between the ages of 25 and 55, had their blood samples taken for this investigation. Following a minimum 12-hour fast and a minimum 20-minute rest interval, venous blood was drawn in the early morning from both the patient and control groups.

An alternative vein was selected as a blood draw point in cases where the median cubital vein was inaccessible. The use of concentric rings to apply iodine to the venipuncture site ensured thorough disinfection before allowing it to dry. Five milliliters of blood was then collected into a

gel tube and sealed for transport. Carefully placed in a cool box with an ice bag, the gel tube was then delivered to the laboratory located within the emergency unit.

The gel tube was placed into the centrifuge and spun at 6000 revolutions per minute (rpm) for ten minutes. For the extraction of serum from the blood, a micropipette was employed. Three Eppendorf tubes, each with two milliliters of blood serum, were prepared for hormonal, immunological, and biochemical analyses. Following this, the specimen was stored in a deep freezer maintained at a temperature of -20°C.

Age, sex, weight, the patient's address, and some other relevant details served as the input for each participant in the form of a dataset with many variables. The quantification of serum Decorin, Myonectin, and Irisin was carried out using an enzyme-linked immunosorbent assay (ELISA) kit.

Table (1):- Demographic data of the sample population

Groups	No. of Individuals	Age (years)
G1	150	
G2	150	(25-55) years old
C	75	

STATISTICAL ANALYSIS

The statistical analysis was conducted using the statistical software Minitab. Group comparisons were performed using one-way analysis of variance (ANOVA), and the arithmetic means for parameters were examined using Duncan's multiple range test to determine significant differences, particularly between groups. The regression plots were utilised to report the Pearson correlation coefficient (R) between irisin and other metrics. The statistical significance criterion was determined to be $P \geq 0.01$, as reported by Popović (2021).

RESULTS

Myokine levels among patients suffering from Congestive Heart Failure, Angina Pectoris, and a control group are shown in Table 2 as well as in Figures 1, 2, and 3 representing averages with standard deviation. The decorin concentrations for the patients with angina pectoris were found to be 145.47 ± 23.31 pg/ml, for those suffering from congestive heart failure, and the control group had these values at mean ± SD, i.e., 155.33 ± 29.43 pg/ml, and finally, at 256.90 ± 30.90 pg/ml.

The Irisin levels of patients with CHF, angina, and the controls were 9.99±1.802 ng/ml, 8.65±2.169 ng/ml, and 5.81±1.851 ng/ml respectively by mean and standard deviation values. On the other hand, for the control group, myonectin level was (89.33±8.49) pg/ml, whereas the levels for CHF and angina are (41.36±8.27) and (44.27±8.43) respectively according to mean

values. The p-value was 0.00003 as an average value for the test groups used for finding these values..

Table No. (2) Arithmetic average for Myokines Concentrations in the studied groups

No. Group	Decorin (pg/ml)	Irisin (ng/ml)	Myonectin (pg/ml)
	Mean ± S.D	Mean ± S.D	Mean ± S.D
G1 n=35	145.47 ± 23.31 b	9.99 ± 1.802 a	41.36 ± 8.27 b
G2 n=35	155.33 ± 29.43 b	8.65 ± 2.169 a	44.27 ± 8.43 b
C n=20	256.90 ± 30.90 a	5.81 ± 1.851 b	89.33±8.49 a
P- value	P = 0.00003**		

Note: Whereas the presence of distinct letters denotes that there are statistically significant differences between vertical groups at a power level of $P \geq 0.01$(**), the presence of similar letters indicates that there are no statistically significant differences between vertical groups.Patients with congestive heart failure make up G1, patients with angina pectoris make up G2, and healthy people make up C (Control).

Previous studies examining the relationship between myokines and heart disease have produced inconsistent results, most likely due to differences in patient characteristics, lifestyle choices, autoimmune diseases, and possibly nutritional status. The results of this analysis showed statistically significant differences in decorin levels between the three groups. The investigation revealed significant differences in serum DCN levels between patients and controls. Although there were no significant differences between patient groups, DCN concentrations were significantly lower in the patient group than in the control group. The results of this study are consistent with those of Yang et al. agree. (2022), Nazemi et al. (2019) and Lightfoot and Cooper (2016). However, the present results contradict those of Jarvelainen et al. (2015) and Zhuang et al. (2021), who found that patients had significantly higher DCN levels than controls.
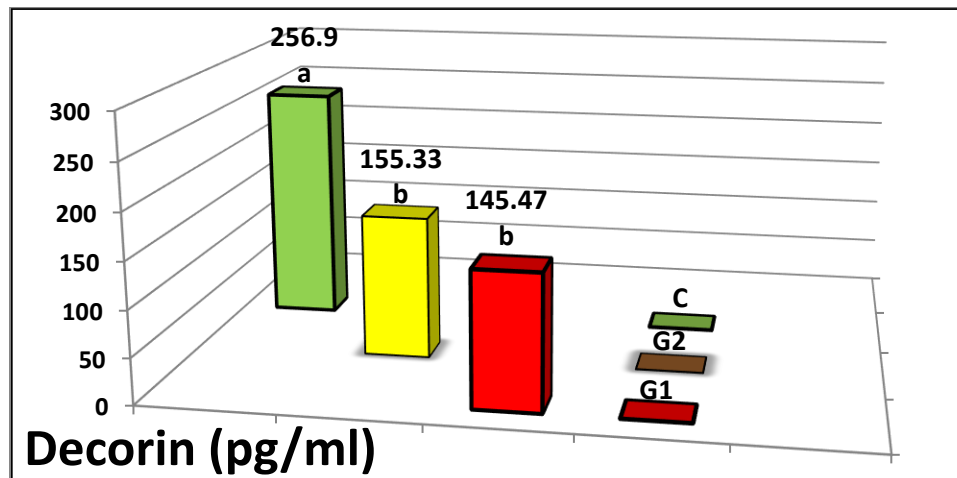

Decorin (pg/ml)

Figure (1): The concentrations of decorin in both the patient and control groups exhibited a range of pg/ml. Similar letters indicate the absence of statistically significant differences between the groups, whereas distinct letters reflect the presence of statistically significant differences at a potential level of P ≥ 0.01(**).Group G1 comprises persons diagnosed with Congestive Heart Failure, Group G2 comprises individuals diagnosed with Angina Pectoris, and Group C comprises individuals who are in good health (Control).

The linkage between myokines and heart diseases has had contradictory findings in past research studies mainly because of variations in patient characteristics, lifestyle preferences, autoimmune disorders, and probably malnutrition. Based on this result analysis, it is apparent that decorin concentrations in the three groups are statistically different. The study has shown a significant difference between patients and controls regarding serum DCN levels. While there were no significant differences between the groups of patients, the DCN concentration was significantly lower for these patients compared to the control group. This study result concurs with that of Yang et al.

In a similar manner, various researchers could also find it out; for example, while Jarvelainen and Zhuang discovered that patients showed higher DCN levels than healthy people, these results conflicted with the findings of Nazemi et al. and Lightfoot and Cooper..
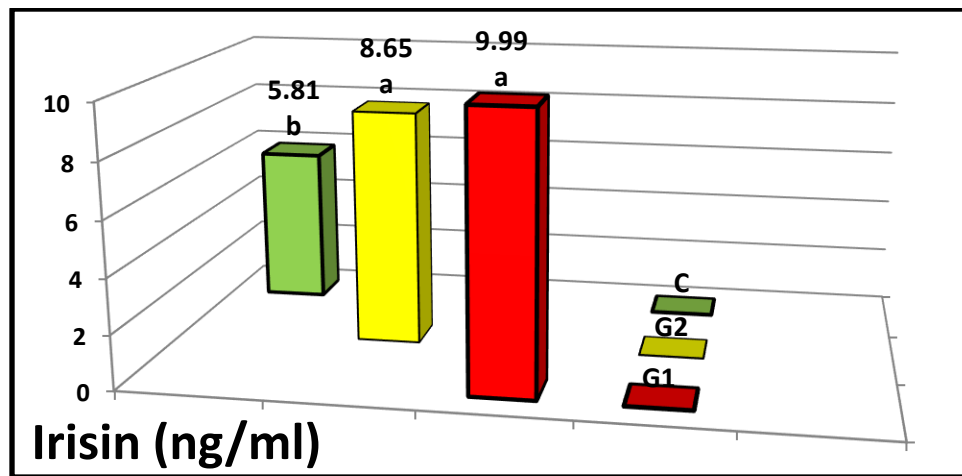

Figure (2): There was a measurement of irisin levels in the patient and control groups, given as ng/ml. Like letters indicate non-statistical differences between groups, and different letters show statistically significant differences at P ≥ 0.01(**) level. Group G1 consists of those who were diagnosed with Congestive Heart Failure; Group G2 consists of individuals diagnosed with Angina Pectoris; and Group C comprises healthy people.

Investigating the three groups, the present study discovered a statistically significant difference in myonectin levels. The results of this study revealed that CTRP15 was not statistically different between the patient groups, while it was lower in the control group. However, there were no statistically significant differences in the respective values between any two of those groups. According to academic studies by Takada et al., Berezin et al., and Leiherer et al., this research finding is in agreement with their work, but it is also not consistent with Piccirillo's data.

In 2019, Zhang et al. identified a statistically significant increase in CTRP15 levels in patients compared to the control groups in 2022.
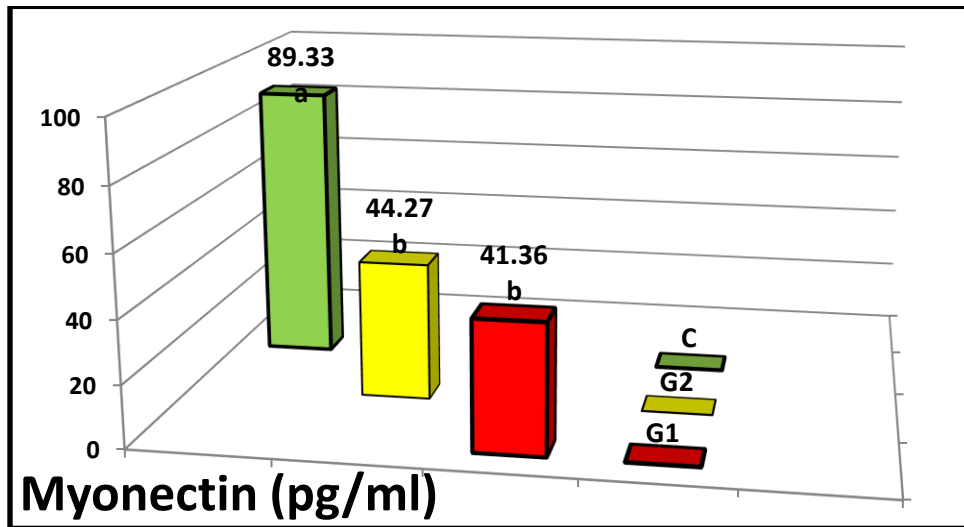

Figure (3): The quantities of Tumour necrosis factor-related protein15 (CTRP15/Myonectin) in both patients and control groups were quantified in picograms per millilitre (pg/ml). Similar letters indicate the absence of statistically significant differences between the groups, whereas distinct letters reflect the presence of statistically significant differences at a potential level of P ≥ 0.01(**).Group G1 comprises persons diagnosed with congestive heart failure, Group G2 comprises those diagnosed with angina pectoris, and Group C represents a control group consisting of healthy individuals.

The Pearson's correlation analysis, as shown in Tables 3, 4, and Figures 4, 5, 6, and 7, reveals a negative association between blood DCN concentrations and Myonectin in patients with CHF and Angina Pectoris. Conversely, positive correlations are detected between serum DCN concentrations and Myonectin in patients with CHF and Angina Pectoris. In contrast, there was a negative correlation observed between Irisin and both Myonectin and DCN within the same groups..

Table 3: Correlation coefficient (R) between irisin and parameters in patients with heart failure

Parameters	Statistical Variables	Irisin	DCN
DCN	R	-0.200	
	P	0.440^{ns}	
Myonectin	R	-0.643	0.376
	P	0.000^{**}	0.033^{*}

R: Correlation coefficient; **P**: p-value;* P≤0.05;** P≤0.01; **ns** :Not significant

Table 4: Correlation coefficient (R) between irisin and parameters in patients with angina pectoris

Parameters	Statistical Variables	Irisin	DCN
DCN	R	-0.332	
	P	0.055*	
Myonectin	R	-0.585	0.350
	P	0.000**	0.057*

R: Correlation coefficient; **P**: p-value;* P≤0.05;** P≤0.01; **ns** :Not significant
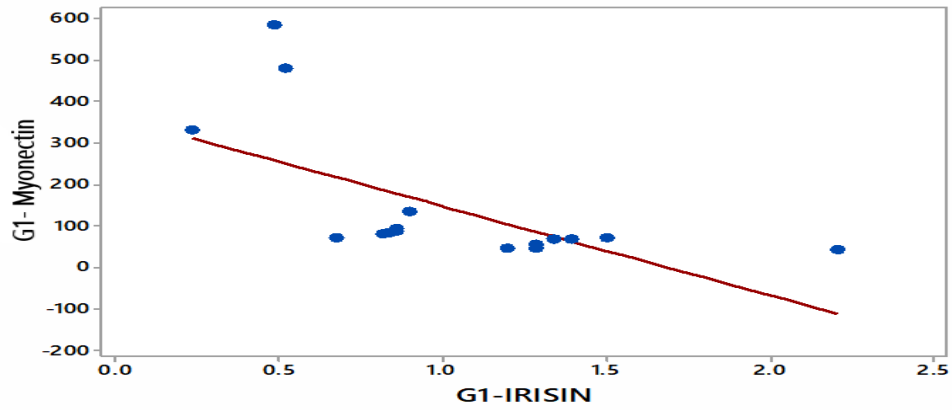

Figure (4): Myonectin and Irisin Correlation in Patients with Congestive Heart Failure
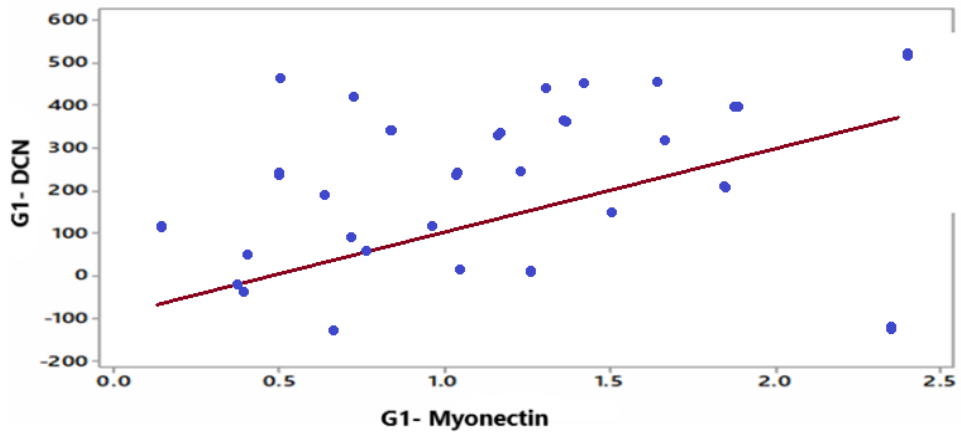

Figure (5): Correlation between Myonectin with DCN in congestive heart failure patients
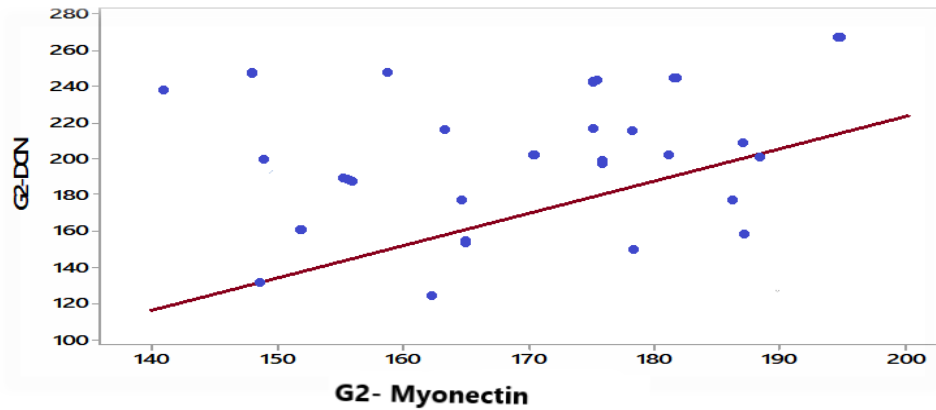
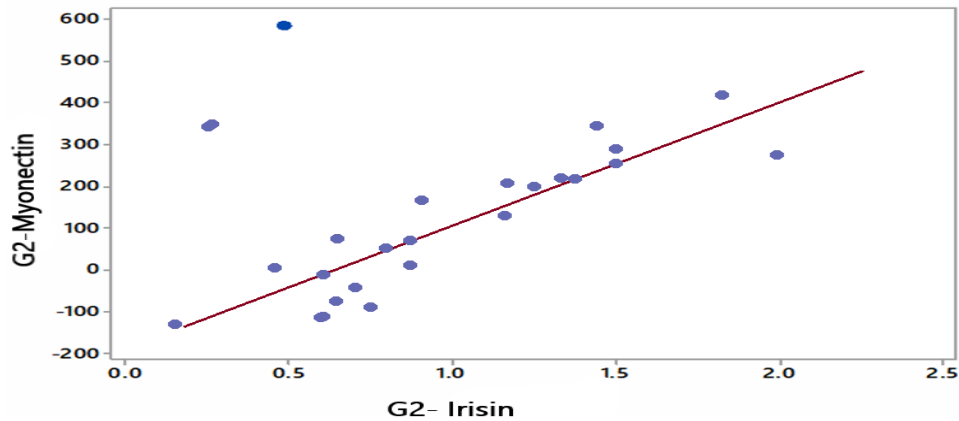**Figure (6):** Correlation between Myonectin with DCN in angina pectoris patients

Figure (7): Correlation between Myonectin with Irisin in angina pectoris patients

DISCUSSION:

Nowadays, it's far of important importance to become aware of folks that ought to broaden cardiovascular issues afterward of their lives, which includes atherosclerotic ailment. In this regard, biomarkers are beneficial tools. One of the techniques used for predicting coronary occasions in people with intermediate risk is a CAC scan. Among the various proteoglycans that must be referred to, decorin (DCN) deserves unique interest because of its compact shape and leucine-wealthy sequences. This was counseled via Fischer et al.

It has been observed that calcium deposits are brought about in the muscle cells of arteries because of plaque, which ends from atherosclerosis in human sufferers. Jens et al. (2014) have pronounced that decorin, one of the recognized additives of human atherosclerotic plaque, can be gift as properly and capable of stimulate the formation of calcium deposits in cultures of arterial easy muscle cells. According to Jens et al. (2014), decorin is an inducer that leads calcium deposits to shape within the artery's indoors layer. Nabel et al.

TGF-1 become pronounced in 2003 to stimulate the expression and deposition of extracellular matrix macromolecules such as collagen, elastin, and proteoglycan, which in the end serve in the development of atherosclerotic plaques. Moreover, TGF-1-caused huge proteoglycans had been proven to boom the binding affinity of low-density lipoprotein (LDL) (Little et al., 2012; Alkanaani, et al.,2020).

Homocysteine and vascular problems inclusive of atherosclerosis had been hypothesized to be associated within the 2018 empirical look at performed by way of Fujiwara et al. The investigators found that arterial clean muscle cells produced PGs as their principal elements concerned in atherosclerosis; therefore, PGs are key factors answerable for atherogenesis. In an in vitro have a look at, the researchers investigated the effect of homocysteine on peptide glycogen production via vascular smooth muscle cells, in which this remedy resulted in drastically decreased accumulation of PGs even if cell density changed into kept constant, and without having any adverse aspect effects on cellular viability.

The facts furnished by the researchers supported the speculation that homocysteine exerts a completely unique inhibitory effect on low rate density chondroitin/dermatan sulfate peptides (CS/DSPGs), especially the small CS/DSPGs biglycan and decorin, in conditioned media. Homocysteine has been tested to noticeably alter the disaccharide composition of iduronic acid sulfated N-acetylgalactosamine in chondroitin/dermatan sulfate chains using fluorophore-assisted carbohydrate electrophoresis studies. This suggests a opportunity for homocysteine to impair the synthesis of small CS/DSPGs, diagnosed with the aid of decreased charge density in blood vessel smooth muscle cells.

In addition, the homocysteine that is found influences the organization of the chondroitin/dermatan sulfate rings. The changes have been described as able to influence the development of atherosclerosis by Fu et al. (2022).

This study aims to explore the association between irisin and cardiovascular risk diagnostic standards. In mammals, adipose tissue can be identified as two different kinds: brown and white. In agreement with Frontera et al. (2020), brown adipose tissue contains an abundance of mitochondria resulting in a peculiar way of dividing mitochondrial respiration that provides energy in the form of heat. In their 2012 publication, Böstrom et al. conducted a study and found evidence that indicated that thermogenesis and oxygen consumption in cultured white adipocytes were stimulated by irisin. This was also noted by Böstrom et al.

The study conducted by Efe and colleagues (2018) showed that there is a direct association of the expression of irisin with TNF-α and IL-10 levels. According to De Meneck et al. (2020), obese children with high irisin levels also had increased systolic and diastolic blood pressure. Vascular endothelial cell dysfunction is associated with oxidative stress and endothelial cell death, two important factors in the pathophysiology of atherosclerosis. Additionally, I have found that an adenoviral vector expressing irisin can cause browning of the subcutaneous white fat in mice (2012).

Endothelial cells in particular experience apoptosis when subjected to oxidized low-density lipoprotein; however, this detrimental impact can be effectively countered through pre-irisin treatment (Zhang, et al., 2019). The connection of irisin with inflammation control plays a significant role in the process by which atherosclerosis evolves. Zheng et al. (2020) discovered that the addition of irisin during in vitro studies led to fewer foam cells made from oxidized low-density lipoprotein being produced. It was revealed that irisin was able to augment mitochondrial activity and serve as a protective agent against hypoxia/reoxygenation injury and myocardial infarction (MI).

Irisin prevented myocardial infarction by promoting SOD1 production and p38 phosphorylation as Wang and team (2017) suggested. The action was observed when irisin significantly inhibited mitochondrial permeability transition pores; hence, it is evident that irisin provided protective measures against MI through the induction of SOD1, which gave rise to the increase of superoxide dismutase 1 and then led to p38 phosphorylation.

Myokines are synthesized and released, which could result in irregularities in the protein metabolism of the heart and skeletal muscles. This aggravates manifestations such as heart palpitations, lower physical performance, and muscle loss. Additionally, when diabetes mellitus and abdominal obesity coexist with heart failure (HF), shifts within the myokine network, including irisin, myonectin, brain-derived neurotrophic factor (BDNF), and growth differentiation factor-11 (GDF-11), possibly contribute to muscular weakness, eventually leading to this problem (Philippou et al., 2020).

The major functions of myonectin are to boost skeletal muscle uptake of free fatty acids and promote the utilization of fat as well as carbohydrates by the adipose tissue. Nevertheless, it also exerts many pleiotropic benefits that include decreased inflammatory responses, protection against ischemia-reperfusion injury, and improvement in endothelial function (Chung & Choi, 2018).

Modification of the myokine circulation is an early sign in the pathophysiology of heart failure (HF). The alteration is related to systolic function depression, diastolic filling dysfunction, adverse cardiac remodeling, and the development of skeletal muscle myopathy. Myokines play a role in both the prognostication of progression to HF and in the pathophysiology of skeletal muscle myopathy. They may also be useful markers for identifying those individuals at higher risk before reaching the sarcopenia stage.

Currently, there is limited information regarding the superiority of these new biomarkers when compared with traditional circulating cardiac biomarkers, along with how well myokine signatures can predict heart failure-related mortality and outcomes. Nevertheless, it should be noted that alterations in certain myokine levels in the peripheral blood would result in metabolic imbalance subsequent to HF. Wang et al suggest Irisin, myonectin, BDNF, FGF-21, as well as osteonectin being likely good biomarkers for myopathy and cachexia associated with heart failure.

Hence, while the findings on echocardiography may offer valuable insight, it remains for future research to understand the full ability of these predictors in predicting significant cardiac remodeling and adverse events.

CONCLUSION

Myonectin may play a role in reducing inflammation. The low levels observed in patients can be attributed to factors such as insufficient physical activity, obesity, or diabetes. In addition, muscle weakness that is common in older men may contribute to this phenomenon. Another possible factor is taking lipid-lowering medications, such as statins. The potential utility of CTRP15 as a circulating biomarker for predicting cardiovascular disease (CVD) risk in individuals with obesity or diabetes deserves consideration. Further studies are needed to improve decorin's potential as a therapeutic agent for heart failure and angina. The heart muscle releases irisin and increases irisin levels in the blood. Therefore, an initial hypothesis proposed that heart failure (HF) may increase irisin release by directly affecting damaged cardiomyocytes. In conclusion, a growing body of research demonstrates the significant effects of irisin in mitigating risk factors associated with cardiovascular disease (CVD), underscoring its growing importance in the prevention and treatment of CVD.

Predictive biomarkers called myokines have been found to be independently associated with an increased risk of heart failure (HF) and angina. However, further studies are needed to fully understand their importance in predicting adverse cardiac remodeling and classifying clinical outcomes through large clinical studies. One potential area of research is changes in myokine profiles following aerobic and isometric interval exercise. Monitoring blood concentrations of myokines is a promising strategy for classifying heart failure (HF) patients at increased risk of myopathy progression. This is particularly important because heart failure is widely recognized as an important predictor of adverse clinical outcomes and there is a strong preference for physical activity. Additionally, myokines can be used as a useful tool to assess the adequacy of physical stimulation. Therefore, it is reasonable to consider myokines as potential targets for therapeutic intervention in heart failure and angina.

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