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OPTIMAL DIAGNOSTIC POINTS OF NESFATIN-1 AND CHEMERIN FOR PREDICTING SUPRAVENTRICULAR TACHYCARDIA CASES

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Abstract

background: Among all types of CVDs, arrhythmias are most often responsible for sudden deaths and are indicative of other high-risk diseases. Arrhythmia is the collective term for a variety of conditions that involve a heart rhythm other than sinus rhythm. Adipokines are produced from adipose tissues, which are considered endocrine organs involved in cardiovascular function causing electrophysiological effects such as ionic profiles, contractility in the atrium, and change in morphology of action potential. Nesfatin-1 and chemerin are a newly discovered adipokine, related to the inflammatory process.

The present study aims to examine the diagnostic ability of adipocytokines (Nesfatin-1 and chemerin) and their ratio in SVT arrhythmia cases.

Material and methods: The study recruited 60 patients and 30 healthy controls. These patients were divided into two subgroups of SVT, certain etiology of SVT cases with clear history of one or more of the risk factors such as (lipid disorder, thyroid disorder, DM, hypertension), and uncertain etiology of SVT cases without any previous history. Serum Nesfatin-1 and chemerin were measured using the ELISA technique. Some related parameters were also determined and correlated with the level of these adipokines.

Results: The mean level of serum nesfatin-1 was significantly higher in normal subjects than in both certain & un-certain SVT etiology groups.

Estimation plot of determination serum level of Chemerin was indicted a massive increased level in un-certain SVT patients compared the other groups.

Binary logistic regression was performed. It was found that chemerin in certain and uncertain etiology SVT patient (OR: 1.008 and 1.018; 95% CI: (0.998 - 1.018), (1.008 - 1.028) respectively, were independent risk factors. while Nesfitin (OR: 0.960 and 0.946, 95% CI: (0.929 - 0.992), (0.913 - 0.980) were independent protective factors for arrhythmia SVT patient. Results of the receiver operating curve (ROC) curve and AUC analysis for the optimal diagnostic points for predicting uncertain etiology of SVT cases was indicated that chemerin was demonstrated the most interesting prediction (sensitivity = 0.60.%, specificity = 0.89%) at a level = 733.55).

Conclusions: Nesfatin-1 and chemerin levels are affected by SVT arrhythmia disease when adjusted for other cofounders. The present results suggest that serum chemerin can be used as an

inflammatory marker of SVT arrhythmia patients as it has good sensitivity and specificity.

Introduction

Supraventricular tachycardia (SVT) is a dysrhythmia originating at or above the atrioventricular (AV) node and is defined by a narrow complex The Pathophysiology was proposed to be due to The atrioventricular (AV) node that serves as the starting point for electrical conduction in the heart, which then passes through the sinoatrial (SA) and adjacent atrial tissue. The electrical signal is delayed by around 100 milliseconds at the AV node. The His-Purkinje system, which distributes the electrical signal to the left and right bundles and, eventually, to the myocardium of the ventricles, is where the electrical signal goes after passing through the AV node. Prior to ventricular contraction, the atria can contract and empty during the AV node pause. A short QRS complex (less than 120 milliseconds) shows that the ventricles are being triggered more quickly than the His bundle using the His-Purkinje system as usual. This suggests that the AV node, the His bundle, the atrial myometrium, or the sinoatrial (SA) node are the sources of the arrhythmia. (1). Since A specialized organ called adipose tissue secretes several indicators that function as paracrine and endocrine regulators, recently a wide range of these adipokines were reported to be involved in a variety of physiological processes (2)

Chemerin is a powerful chemoattractant molecule. A recently discovered adipokine called chemerin has a physiologically active molecule with cytokine-like effects that is mostly released by adipose tissue (3). In an experimental research, chemerin was found to increase macrophage adherence to extracellular matrix proteins and adhesion molecules in vitro (4). According to this finding, chemerin may increase inflammation by attracting and keeping macrophages at the sites of inflammation. In an animal model of acute lung damage, chemerin has also been found to limit neutrophil recruitment and the release of pro-inflammatory cytokines and chemokines, exhibiting strong anti-inflammatory effects. (5) on the other hand, An adipokine recently also identified called nesfatin-1 (NF-1) which reduces the inflammatory response, has been linked to the Atrial fibrillation's process which includes inflammation (AF), the study was confirmed that serum nesfatin-1 concentrations were inversely correlated with AF development. (6) Also, other findings demonstrated a novel method by which NF-1 influences L-type Ca2+ channels in adult rat ventricular myocytes. Importantly, these channels are modulated by a variety of hormones, neurotransmitters, and cytokines, operating via G-protein coupled receptors and second messengers. The effect of NF-1 on cardiac function, particularly ventricular contraction, in the mammalian cardiovascular system may be directly attributed to this unique method. (7)

Certain adipokines are linked to play a significant role in the contraction of the heart. A novel predictive predictor of major adverse cardiac events is serum nesfatin-1 and chemerin. Chemerin in circulation can enhance patients with arrhythmias' early risk categorization. The significance of these adipokines within the cellular context and their connection to the disease of cardiac channelopathies may be underlined by this investigation (8) Therefore, the present study aims to examine the diagnostic ability of adipocytokines (Nesfatin-1 and chemerin) in SVT arrhythmia cases.

Material and methods: A cross-sectional study for a total 60 patients and 30 healthy controls was performed. patients were divided into two subgroups of SVT, certain etiology of SVT cases with clear history of one or more of the risk factors such as (lipid disorder, thyroid disorder, DM, hypertension), and 30 patients with uncertain etiology of SVT cases without any previous history. Serum Nesfatin-1 and chemerin were measured using the ELISA technique.
The data analysis for this work was generated using the Statistical Package for the Social Sciences software, version 28.0 (IBM, SPSS, Chicago, Illinois, USA) and the Real Statistics Resource Pack software for Mac (Release 7.2) of the resource pack for Excel 2016. Copyright (2013 – 2020). The univariate analysis was performed using an independent Kruskal Wallis Test for continuous variables. Biomarkers were compared using Sparman rank test to evaluate the relationship within the case study. The optimal threshold with high specificity and sensitivity for critical cases was detected using receiver operating characteristic (ROC) analysis. a P value < 0.05 was considered to be statistically significant.

Results & Discussion:

Distribution of serum level of Nesfitin & Chemerin:

A box plot was used to visually show the distribution of data through displaying the data quartiles and averages. Figure (1) demonstrated a across distribution of serum level of Nesfitin & Chemerin in SVT patients group and healthy control group. Throughout the results, the quartiles and range levels of Nesfitin was decreased markedly in arrhythmia patients, while Chemerin was estimated to have great variability in patients compared to control. The range levels in patients groups were (86.6-183.7) & (487.6-986.9) ng/ml respectively.
Adipokines are cardiovascular disease (CVD) mediators or biomarkers that affect the heart as well as blood vessels, by increasing the cardiac contractility and action potential duration, which result in the extent of left ventricular and atrial remodeling. adipokines play a significant role in the development and progress of atrial fibrillation. The pathophysiological role in atrial fibrillation by causing cardiac hypertrophy is manifested by increasing the cardiac contractility and action potential duration, atrial fibrosis, electrical and structural remodeling of atrial tissue. (9)
Zhu et al. (2021) also found that serum adiponectin (chemerin) was associated with the markers of cardiac autonomic, inflammation as well as cardiac remodeling. Moreover, subsequent multivariate analysis showed a significant independent link between elevated adiponectin levels and atrial fibrillation in the overall participants (10) In addition, Kourliouros et al. also explained that a greater inflammation environment could provide a substrate for the development of arrhythmia (11).

Additionally, Kusayama et al. study had revealed that inflammation has been associated with the presence of paroxysmal atrial fibrillation (12). In atrial fibrillation-related structural remodeling, the predominant pathologic abnormality is the atrial fibrosis and also clinical significance has a degree of fibrosis. Epicardial fat is a metabolically active tissue that generates a variety of bioactive molecules including TNF-α and adiponectin which can be the key mediators of atrial fibrosis as

well as structural remodeling (11).

Adiponectin influences the functioning of the heart through central nervous system when adiponectin enters through the blood–brain barrier. Adipocytokine imbalance including a lower level of adiponectin (Nesfitin) which results in the development of hyperinsulinemia, dyslipidemia, endothelial dysfunction, fibrosis, abdominal obesity, arterial hypertension, impaired glucose tolerance, and atrial fibrillation (13).

Similarly, Linberg and Karas studies have shown a connection between quite high levels of chemerin and heart failure, coronary heart disease, and even mortality (14)
On the other hand, Endogenously expressed NF-1 was recently identified in the heart of mammals, suggesting that NF-1 may be an endogenous modulator of cardiac performance. Indeed, NF-1 has been shown to induce negative inotropism and lusitropism in vitro (15). Nesfitin attenuates cardiac performance as indicated by decreases in left ventricular (an index of myocardial contractility) and left ventricular fractional shortening in perfused hearts (16). However, the mechanisms underlying these effects of NF-1 in cardiomyocytes remain unknown.

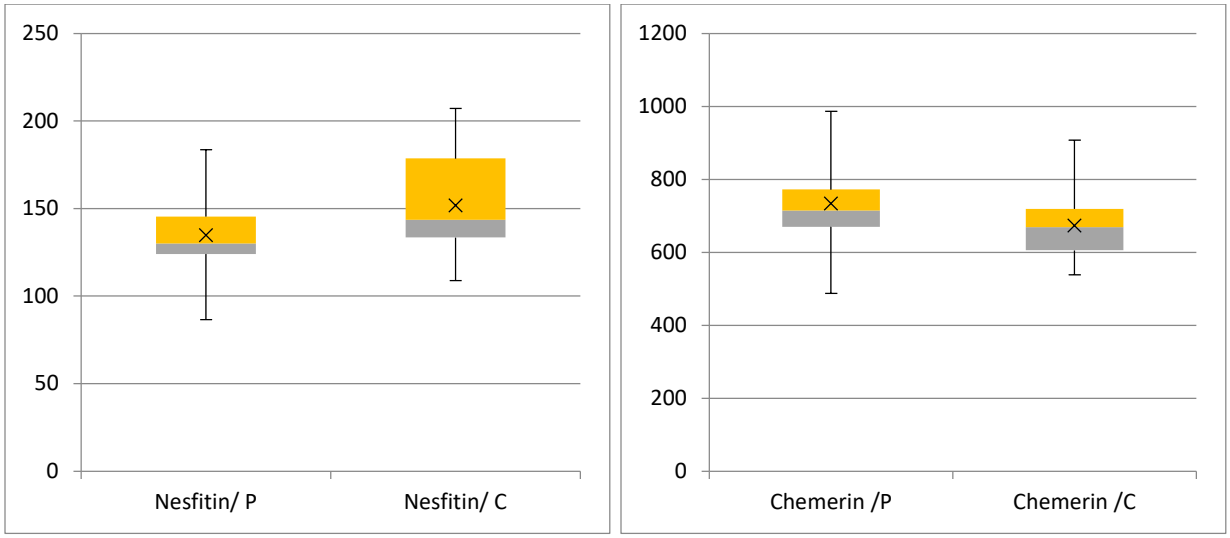

Figure 1: Boxplot of the Distribution of serum level of Nesfitin & Chemerin in SVT patients & Healthy control group.

Study the correlation of Adipokines and patients' groups

Considering the important role of the measured biomarkers in the, the spearman rank test analysis of SVT patient was used to analyze the response relationship between parameters.
The correlation study shows many significant correlations among the measured parameters.The most important correlations were between serum Nesfitin levels which was positively related to the *Chemerin and creatinine levels.* In addition, *Chemerin* was significantly associated with BMI of the patients. These correlations may be due to many effects of chemerin on various biological processes involved in arrhythmia cases, which increased with the progression of the disease.

Chemerin regulates adipogenesis, angiogenesis, and inflammation (17). As a risk factor of arrhythmia cases indicator, serum TG was highly significant positively related to high levels of VLDL (all $P < 0.001$). Similarly, serum Cholestreol values were correlated with LDL levels. The relationship between the parameters and study cases was presented in Figure (2)
It has been reporting by Pearson correlation analysis that there was a positive relation of serum concentrations with diastolic blood pressure, body mass index (BMI), systolic blood pressure, triglycerides, low-density lipoprotein cholesterol (LDL-C), and creatinine. As a result, they showed an association of serum chemerin concentration with atrial remodeling (18)

Also, circulating levels was correlate positively with the severity dilated cardiomyopathy. Because of its chemotactic effects mediated reduction in NO production and negative effects on plasma lipids, chemerin is linked to progression of atherosclerosis (19). Low serum levels of cardio-protective adipokines(nesfitin) or increased levels of pro-inflammatory adipokines (chemerin) might be useful biomarkers of different cardiovascular diseases. Despite the vigorous research in the field of adipokines, it may take some more time to very clearly establish the role of each adipokine in health and disease conditions. (20).
Kaur et al. (21) validated that recombinant chemerin significantly induced tube formation in endothelial cells. Moreover, associations with high-sensitivity C-reactive protein (hsCRP), white blood cell count, markers of endothelial activation intercellular cell adhesion molecule-1 (ICAM-1) and E-selectin suggests a link of chemerin not only with obesity and inflammation but also to endothelial activation markers (22).

	Nesfitin	Chemerin	TG	Cholestreol	HDL	LDL	VLDL	Urea	Creatinin	BMI
Nesfitin										
Chemerin										
TG										
Cholestreol										
HDL										
LDL										

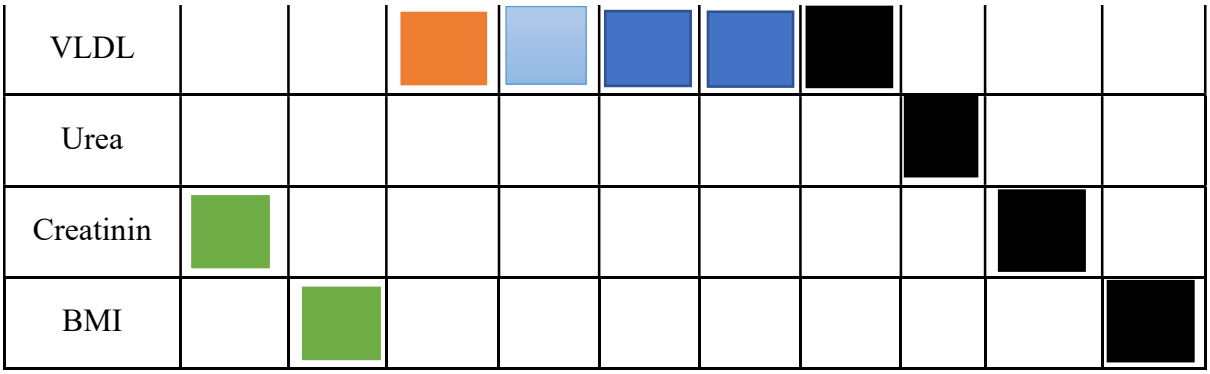

Figure 2: Heatmap of the spearman rank test analysis of SVT patient. white boxes indicate a lack of correlation (p>0.05) while in coloured boxes were reported statistically significant direct and indirect correlations, respectively. The intensity of the colour indicates the following relation: green (r=0.4); blue (r=0.5) light blue (r=0.7); orang(r=0.9).

Receiver operating curve (ROC) curve of serum Adepokines levels to diagnosis of SVT cases

Results of the receiver operating curve (ROC) curve and AUC analysis for the the Nesfitin and chemerin besides their ratio as possible diagnostic parameters. only chemerin was shown a good diagnostic performance for prediction arrhythmia Patients compared to control group, data are presented in Table (1).

For chemerin levels: (sensitivity = 0.65.%, specificity = 0.67%) at a level = 690.1 , Accordingly, the distribution of patients using chemerin cutoff values was presented in Table (2).

The p-values of the AUC were <0.05 and statistically significant. Youden's J statistics of the parameters in Figures (3) confirm these results.

Table 1: AUC, optimal threshold, Sensitivity and specificity of proposed marker obtained by the ROC curves for prediction of arrhythmia patients

Test Variable	Chemerin
AUP	0.7
Sensitivity %	65%
Specificity %	67%
Youden index	0.313
Cut-off points	690.1
CI (95%)	0.55 – 0.81
PPV	79.48%
NPV	48.48
Accuracy	65.27%

P value	0.012

Table 2. Distribution of patients according to the CNR cutoff values in the studied groups

Chemerin/ Nesfitin ratio cutoff values	Patients	Control
<4.6066	55	10
>4.6066	5	20
Total	60	30

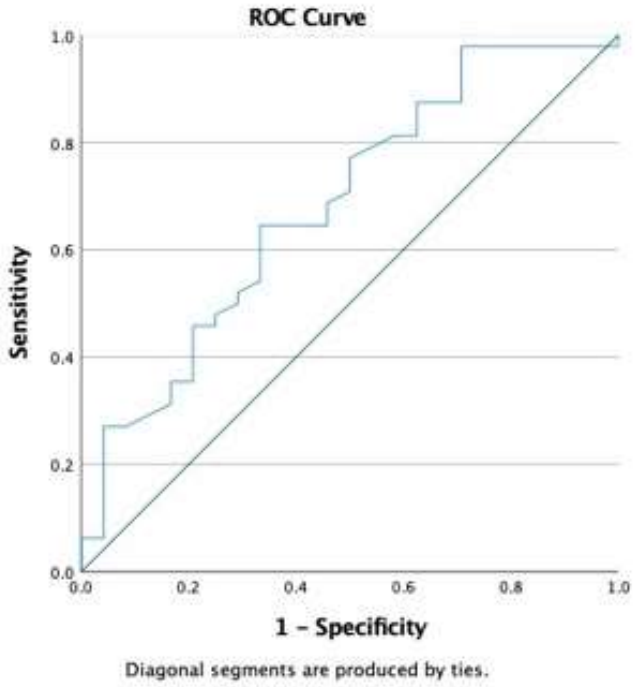

Figure 3: ROC curves for chemerin in arrhythmia patients to analyse the optimal diagnostic points for predicting SVT cases compared to control group, The area under ROC curve:0.7; 95%CI (0.55 – 0.81); p value <0.05

Furthermore, the analysis of the optimal diagnostic points for predicting uncertain etiology of SVT cases compared to certain group was performed.

Results were indicated that chemerin was demonstrated the most interesting prediction about uncertain etiology of SVT cases. The optimal threshold and diagnostic performance was presented in Table (3) ROC curves were presented in Figures (4), (5)

Acorrdingly, the distribution of patients using chemerin cutoff values was presented in Table (4).

Table 3: AUC, optimal threshold, Sensitivity and specificity of proposed marker obtained by the ROC curves for prediction uncertain etiology of SVT cases compared to certain

group.

Test Variable	Chemerin	Nesfitin
AUP	0.74	0.6
Sensitivity %	0.6	0.4
Specificity %	0.889	0.778
Youden index	0.489	0.178
Cut-off points	733.55	139.25
CI (95%)	0.597 - 0.875	0.396 - 0.734
PPV	57.14%	43.75%
NPV	90%	54.16%
Accuracy	70.83%	75%
P value	<0.001	0.206

Table 4: Distribution of patients according to the Chemerin cutoff value in subgroups

Chemerin	Certain Etiology Of SVT	Uncertain Etiology Of SVT
<733.55	27	12
>733.55	3	18
Total	30	30

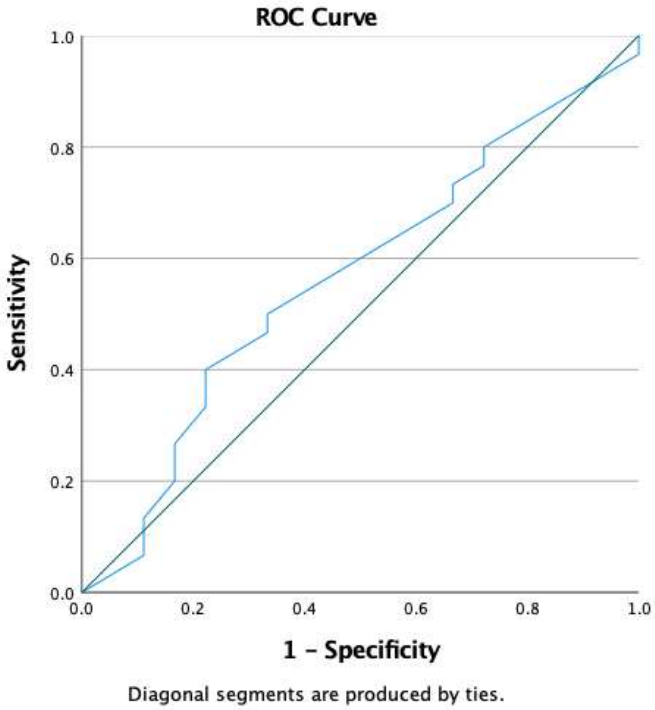

***Figure 4: ROC curves for Nesfitin in arrhythmia patients to analyse the optimal diagnostic points for predicting of* uncertain etiology of SVT cases compared to certain group.**

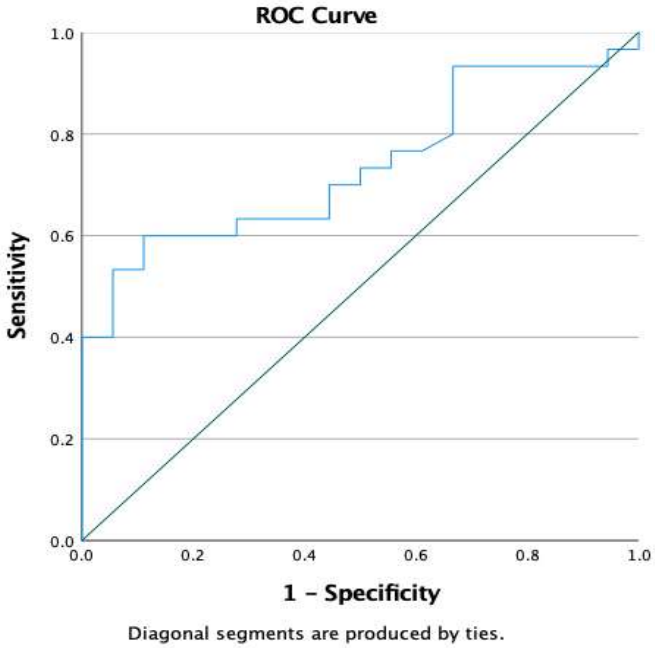

Figure 5: ROC curves for Chemerin in arrhythmia patients to analyse the optimal diagnostic points for predicting of uncertain etiology of SVT cases compared to certain group.

Results of this study confirmed the association of chemerin to SVT arrhythmia cases. To the best

of our knowledge, this is an unique study about the analysis of the optimal diagnostic points for predicting arrhythmia (SVT) cases.

During the last years, an increasing number of clinical studies have investigated the relation of circulating chemerin levels with heart disease.

Investigations have mainly reported on the strong correlation between inflammatory factors and AF development. (23). Moreover, inflammation factor could be utilized as a predictive marker of development or recurrence of AF. Therefore, inflammation plays a key role in AF development and progression. studies have demonstrated the important role of nesfatin-1 in inflammation inhibition (24).

ROC analysis indicated that these biomarkers might be a reliable result for this purpose. In spit the role of individual markers, it might be a tool of inflammation in SVT cases along with the previous reported markers.

References:

1. *Oct, Ho RT. A narrow complex tachycardia with atrioventricular dissociation: What is the mechanism? Heart Rhythm. 2017 and 14(10):1570-1573.*

2. Vegiopoulos A., Rohm M., Herzig S. Adipose tissue: Between the extremes. EMBO J. 2017 and 10.15252/embj.201696206., 36:1999–2017. doi:.

3. Helfer G., Wu Q.-F. Chemerin: A multifaceted adipokine involved in metabolic disorders. J. Endocrinol. 2018 and 10.1530/JOE-18-0174, 238:R79–R94. doi:.

4. Hart R., Greaves D.R. Chemerin Contributes to Inflammation by Promoting Macrophage Adhesion to VCAM-1 and Fibronectin through Clustering of VLA-4 and VLA-5. J. Immunol. 2010 and 185:3728–3739.

5. Luangsay S., Wittamer V., etal., , Parmentier M. Mouse ChemR23 Is Expressed in Dendritic Cell Subsets and Macrophages, and Mediates an Anti-Inflammatory Activity of Chemerin in a Lung Disease Model. J. Immunol. 2009 and 183:6489–6499.

6. Duan XL, Li L, Li YN. Association of serum nesfatin-1 concentrations with atrial fibrillation. Kaohsiung J Med Sci. 2018 Jun and 34(6):348-351.

7. Ying, J., Zhang, Y., Gong, S., Chang, Z., Zhou, X., Li, H., Tao, J. and Zhang, G., 2015. Nesfatin-1 suppresses cardiac L-type Ca2+ channels through melanocortin type 4 receptor and the novel protein kinase C theta isoform pathway. Cellular Physiology and Biochemistry, 36(2), pp.555-568.

8. Fatima SS, Rehman R, Baig M, Khan TA. New roles of the multidimensional adipokine: chemerin. Peptides. 2014 and 62:15–20. 2014.

9. Rafaqat, S., Rafaqat, S. & Rafaqat, S. Pathophysiological role of major adipokines in Atrial Fibrillation. Int J Arrhythm 22, 18 (2021). 2021.

10. Zhu T, Wang Z, Wang S, Hu W, Chen H, Xie J, Wang M, Ma K, Jiang H. Association between serum adiponectin and atrial fibrillation: a case-control study stratified by age and gender. Cardiol Res Pract. 2021 and 2021. 2021.

11. Kourliouros A, Karastergiou K, Nowell J, Gukop P, Tavakkoli Hosseini M, Valencia O, Mohamed Ali V, Jahangiri M. Protective effect of epicardial adiponectin on atrial fibrillation following cardiac surgery. Eur J Cardiothorac Surg. 2011 and 39(2):228–32. 2011.

12. Kusayama T, Furusho H, Kashiwagi H, Kato T, Murai H, Usui S, Kaneko S, Takamura M. Inflammation of left atrial epicardial adipose tissue is associated with paroxysmal atrial fibrillation. J Cardiol. 2016 and 68(5):406–11. 2016.

13. Bilovol O, Shaposhnikova Y, Ilchenko I, Shalimova A. Relationship between peculiarities of atrial fibrillation, body mass index and adipokines levels. Vessel Plus. 2017 and 1:196–201. 2017.

14. Karas MG, Benkeser D, Arnold AM, Bartz TM, Djousse L, Mukamal KJ, Ix JH, Zieman SJ, Siscovick DS, Tracy RP, Mantzoros CS. Relations of plasma total and high-molecular-weight adiponectin to new-onset heart failure in adults≥ 65 years of age (from the Cardi. 2014.

15. Angelone T, Filice E, Pasqua T, Amodio N, Galluccio M, Montesanti G, Quintieri AM, Cerra MC: Nesfatin-1 as a novel cardiac peptide: Identification, functional characterization, and protection against ischemia/ reperfusion injury. Cell Mol Life Sci 2013 and 70. 2013.

16. Angelone T, Filice E, Pasqua T, Amodio N, Galluccio M, Montesanti G, Quintieri AM, Cerra MC: Nesfatin-1 as a novel cardiac peptide: Identification, functional characterization, and protection against ischemia/reperfusion injury. Cell Mol Life Sci 2013 and 70:.

17. Lu B, Zhao M, Jiang W, et al. Independent association of circulating level of chemerin with functional and early morphological vascular changes in newly diagnosed type 2 diabetic patients. Medicine (Baltimore) 2015 and e1990, 94:. 2015.

18. Zhang G, Xiao M, Zhang L, Zhao Y, Yang Q. Association of serum chemerin concentrations with the presence of atrial fibrillation. Ann Clin Biochem. 2017 and 54(3):342–7. 2017.

19. Neves KB, Lobato NS, Lopes RA, et al. Chemerin reduces vascular nitric oxide/cGMP signalling in rat aorta: a link to vascular dysfunction in obesity? Clin Sci (Lond) 2014 and 127:111-122. 2014.

20. Muralidhara, D.V., Adipose Tissue, Adipokines and Cardiac Health–An overview.Indian Journal of Basic and Applied Medical Research and June 2019: Vol.-8, Issue- 3, P. 132 - 141. 2019.

21. Kaur J, Adya R, Tan BK, Chen J, Randeva HS. Identification of chemerin receptor(ChemR23) in human endothelial cells: chemerin-induced endothelial angio-genesis. Biochem Biophys Res Commun 2010 and 391:1762–8. 2010.

22. Landgraf K, Friebe D, Ullrich T, Kratzsch J, Dittrich K, Herberth G, et al. Chemerinas mediator between obesity and vascular inflammation in children. J ClinEndocrinol Metab 2012 and 97:E556–64. 2012.

23. O. Gedikli, A. Dogan, I. Altuntas, A. Altinbas, M. Ozaydin, O. Akturk, et al. Inflammatory markers according to types of atrial fibrillation Int J Cardiol, 120 (2007), pp. 193-197. 2007.

24. Xing-Liang Duan, Lei Li, Ya-Ni Li, Association of serum nesfatin-1 concentrations with atrial fibrillation, The Kaohsiung Journal of Medical Sciences, Volume 34, Issue 6, 2018, Pages 348-351,. 2018.