Biomedical Research and Therapy 2024, 11(4):6289-6296

Open Access Full Text Article

Research Article

Impact of Anthropometric and Genetic Factors on Plasma SIRT1 Level in Men with Essential Hypertension and Heart Failure

Starzhynska Olha Leonidivna*, Donets Andrii Oleksandrovych, Maiko Olena Vyacheslavivna, Zhebel Vadym Mykolayovych

National Pirogov Memorial Medical University, Vinnytsya, Ukraine

Correspondence

Starzhynska Olha Leonidivna, National Pirogov Memorial Medical University, Vinnytsya, Ukraine

Email: docstarzhynska@gmail.com

History

- Received: Dec 26, 2023
- Accepted: Mar 19, 2024
- Published Online: Apr 30, 2024

DOI : 10.15419/bmrat.v11i4.875

Check for updates

ABSTRACT

Introduction: Sirtuin 1 (SIRT1) emerges as a promising biomarker for heart remodeling in the context of essential arterial hypertension (EAH). Additionally, the levels of certain plasma peptides might signal myocardial fibrosis and the progression of heart failure (HF) in hypertensive patients. Despite this potential, conflicting data exist regarding the marker's diagnostic value in HF patients. This study aims to explore the impact of anthropometric factors on plasma SIRT1 levels in men diagnosed with EAH and HF, considering the rs7069102 single nucleotide polymorphism (SNP) in the SIRT1 gene. **Methods**: The study included an examination of 190 Ukrainian men aged between 40 and 65. The participants were divided into two groups: a control group, consisting of 70 individuals without cardiovascular disease (CVD), and a study group comprising 120 men with EAH, 60 of whom displayed signs of HF. Plasma SIRT1 levels were quantified using an enzyme-linked immunosorbent assay (ELISA), while the rs7069102 C/G polymorphism in the SIRT1 gene was detected through allele-specific polymerase chain reaction (PCR). The research employed various statistical methods, including correlation analysis, T-test, Mann-Whitney U test, one-way ANOVA, and analysis of contingency tables for data analysis. **Results**: The investigation revealed that men suffering from EAH and HF exhibited significantly reduced plasma SIRT1 levels (1.550 ± 0.084 ng/ml) compared to those with EAH but without HF (3.271 ± 0.238 ng/ml, $p < 0.001$). Notably, hypertensive men with concurrent HF and obesity or those with an early onset of hypertension showed even lower plasma SIRT1 concentrations. Interestingly, the analysis found no significant difference in plasma SIRT1 levels among individuals in the control group and EAH patients without HF across different rs7069102 C/G SNP variants. However, among hypertensive men with HF, individuals with the GG genotype displayed considerably lower plasma peptide levels compared to those with either the CC or CG genotype (1.390 ± 0.092 ng/ml *vs.* 1.744 ± 0.126 ng/ml, $p = 0.032$). **Conclusion**: This study highlights a significant association between reduced plasma SIRT1 levels and heart failure in male patients with EAH. Factors contributing to decreased plasma peptide levels include obesity, early onset of hypertension, and possessing the GG variant of the rs7069102 SNP in the SIRT1 gene. These findings underscore the potential of SIRT1 as a marker for HF and may guide future therapeutic strategies.

Key words: essential hypertension, heart failure, obesity, SIRT1 gene (rs7069102), sirtuin 1

INTRODUCTION

Currently, there's a concerning trend in the global increase of heart failure (HF) and associated mortality rates. For instance, approximately 6.7 million Americans are afflicted with HF. This number is predicted to rise, with the lifetime risk of complications soaring to 24%[1]. Arterial hypertension (AH) emerges as the most frequent cause or comorbidity linked with HF. Indeed, 80-90% of HF patients exhibit some form of AH, as hypertension-induced myocardial damage critically impairs heart function[2]. Therefore, the early detection of HF in individuals with hypertension is crucial. Utilizing biomarkers has proven to be an effective diagnostic approach. Of particular interest is the peptide sirtuin 1 (SIRT1), an enzyme protein that plays a key role in moderating apoptosis, energy metabolism, and influences life expectancy of cardiomyocytes by acting at both subcellular and epigenetic levels[3–5]. Research has linked SIRT1 expression with fibrotic processes in the heart and vascular wall[6,7], suggesting that plasma levels of this peptide could serve as indicators of myocardial dysfunction. The diagnostic potential of plasma SIRT1 levels for HF is supported by clinical studies, which show significant changes in patients with AH or those exhibiting clinical signs of HF[8–11]. Yet, the data on its diagnostic utility among HF patients are mixed and sometimes contradictory, leaving several questions unanswered. Notably, factors such as age[12,13], and distinct effects of obesity across genders[14,15], can influence

Cite this article : Leonidivna S O, Oleksandrovych D A, Vyacheslavivna M O, Mykolayovych Z V. **Impact of Anthropometric and Genetic Factors on Plasma SIRT1 Level in Men with Essential Hypertension and Heart Failure**. *Biomed. Res. Ther.* 2024; 11(4):6289-6296.

SIRT1 levels. Furthermore, the findings on plasma SIRT1 levels vary across different cardiovascular diseases (CVD), suggesting the need for targeted evaluation of plasma peptide levels in HF patients, considering potential genetic, age, gender, and anthropometric differences.

A crucial factor in a biomarker's clinical application is understanding the genetic basis of its production. The gene controlling SIRT1 is located on chromosome 10q21.3 (ENSG00000096717). Research has explored several single nucleotide polymorphisms (SNPs) potentially impacting SIRT1 expression or structure: rs11599176, rs12413112, rs33957861, rs35689145, rs7896005[16,17]. Among these, the SNP with a cytosine to guanine substitution (C>G) at position rs7069102 stands out due to its significant impact on peptide expression and consequent plasma SIRT1 levels[18]. Studies reveal considerable variation in the prevalence of this SNP's variants across different populations (data sourced from the 1000 Genomes Project on https://www.ensembl.org), underscoring the importance of conducting region-specific research.

Given the multiple factors influencing plasma SIRT1 levels, we embarked on a cross-sectional study to delve into some of these aspects. The study's objective was to explore potential anthropometric influences on plasma SIRT1 levels in hypertensive men with chronic HF, specifically considering the rs7069102 C>G polymorphism within the SIRT1 gene.

METHODS

Patients

In planning our study groups, we drew inspiration from the designs of similar studies. Using the G*Power calculator (http://www.gpower.hhu.de/), we estimated a statistical power of 0.85 and a significance level of $p < 0.05$ to determine the minimum necessary group size. Accordingly, we enrolled 120 hypertensive men and 70 non-cardiovascular disease (CVD) men, who underwent examinations at the Vinnytsya Regional Diagnostic and Disease Prevention Center (VRDDP) in Vinnytsya, Ukraine, as our protocol dictates. The National Pirogov Memorial Medical University's (NPMMU) ethical committee, located in Vinnytsya, Ukraine, sanctioned our research protocol. Prior to commencing any procedure, informed consent was duly obtained from all participants who signed the required documents. We set the inclusion criteria to male individuals aged 40 to 65 years, residing in the Podil region of Ukraine, and diagnosed with essential arterial hypertension (EAH). Exclusion criteria were individuals with symptomatic arterial hypertension (AH), a history of myocardial infarction or unstable angina, significant congenital heart defects, arrhythmia, non-coronary myocardial diseases, pulmonary arterial hypertension, and severe kidney or liver dysfunction, alongside known rheumatological, endocrine, or oncological diseases. Data influencing our exclusion criteria included age, sex, and concurrent diseases' impact on plasma SIRT1 levels. The primary study group had an average age of 50.93 $\pm$ 0.449 years with an EAH diagnosis. Seventy control group participants showed no CVD signs, averaging 49.03 $\pm$ 0.794 years. Diagnoses followed the 2018 and 2021 European Society of Cardiology (ESC) guidelines, segregating 120 hypertensive men based on heart failure (HF) signs into two groups of 60: one showing no HF symptoms and the other displaying NYHA class II-III HF symptoms. Participants underwent extensive evaluations, including physicals, lab tests, blood pressure measurement, electrocardiography, echocardiography, and plasma SIRT1 level and SIRT1 gene rs7069102 C/G polymorphism analysis. Body mass index (BMI) calculations used the Quetelet formula (BMI = body weight (kg)/height^2 (cm)), classifying obesity according to WHO guidelines.

Blood Samples

We assessed plasma SIRT1 levels and the rs7069102 SNP variant in the SIRT1 gene from venous blood samples of all participants. The SIRT1 plasma concentration was measured using the standard ELISA method with RayBiotech, Inc. (USA) reagents and a Humareader single enzyme analyzer (Germany). This choice was backed by ELISA's proven accuracy, specificity, and widespread clinical use.

Genomic DNA extracted from whole blood was used to determine the rs7069102 C/G polymorphism in the SIRT1 gene, employing the DNA-EXTRAN-1 reagent kit for extraction. The allele-specific polymerase chain reaction (PCR), a method renown for SNP analysis effectiveness, facilitated the detection of SIRT1 gene alleles at the rs7069102 position by tracking the fluorescent signal of the amplified products (Thermo Fisher Scientific, USA).

Statistical Analysis

We presented our findings as mean (M $\pm$ SEM) or percentages. Depending on the data distribution, we applied appropriate statistical methods to discern correlations or differences between groups. These

included parametric (Pearson correlation, t-test) and non-parametric (Spearman correlation, Mann-Whitney U test) methods, one-way ANOVA with the Tukey criterion for parametric data, or the Kruskal–Wallis test for non-parametric data. We employed the $\chi 2$ Pearson criterion with Yates correction to assess differences in observation frequencies, especially for smaller group analyses. Differences were considered significant at $p < 0.05$.

RESULTS

Analysis of plasma SIRT1 concentrations in our study groups showed that men with essential arterial hypertension (EAH) not taking heart failure (HF) into account had significantly higher SIRT1 levels (2.414 ± 0.152 ng/ml) compared to the control group (1.891 ± 0.089 ng/ml, p = 0.014). Yet, among men with both EAH and HF, SIRT1 levels were notably lower (1.550±0.084 ng/ml) than in those with EAH alone (3.271 ± 0.238 ng/ml, p < 0.001) as illustrated in **Figure 1**.

Investigating further, we found a clear link between plasma peptide levels and either age or obesity. Upon reviewing the clinical characteristics, we confirmed all study groups were matched by age. However, differences in body weight and BMI were observed, particularly that individuals with both EAH and HF presented higher values compared to either men without any cardiovascular diseases (CVD) or those with EAH but no HF (**Table 1**).

Interestingly, the incidence of obesity was highest in the group suffering from both EAH and HF compared to either the control group or those with solely EAH. This group also displayed distinct hypertension profiles, characterized by earlier disease onset and prolonged duration, alongside notably lower glomerular filtration rates (GFR) than seen in other groups.

Subsequent correlation analyses between group differences and plasma SIRT1 levels uncovered no age correlation (R=-0.11, p=0.25). Nevertheless, significant correlations emerged regarding GFR (positive, R=+0.22, p=0.02), BMI (negative, R=-0.22, p=0.01), and disease duration (negative, R=-0.33, p<0.001). Exploration into the impact of moderate GFR reduction (60-90 ml/min) revealed no significant deviation in SIRT1 levels from those with normal renal function, suggesting SIRT1 plasma levels could serve as a reliable biomarker unaffected by age or renal status.

However, the presence of obesity drastically reduced plasma SIRT1 levels (1.432±0.117 ng/ml in obese men *vs.* 2.813±0.190 ng/ml in non-obese men, p<0.001) as shown in Figure 2. Early-onset EAH (up to age 35) was associated with lower SIRT1 levels (1.842±0.172 ng/ml) compared to later onset (2.665±0.187 ng/ml, p=0.009). These observations suggest that a prolonged history of hypertension and a higher prevalence of obesity might explain the decreased SIRT1 levels in patients with both EAH and HF.

Further analysis delved into the genetic influence on SIRT1 production, focusing on the rs7069102 SNP within the SIRT1 gene. Predominantly, in the Podil region of Ukraine, individuals carrying the mutant G allele were prevalent (70.26%). While CG and GG variants were equally distributed (both 46.84%), the CC homozygous variant was rare (6.32%). A detailed exploration of rs7069102 SNP variants revealed that, except for those with HF, SIRT1 plasma concentrations did not significantly differ among the groups, including between GG homozygotes and individuals carrying the CC or CG variants.

In conclusion, our research indicates that lower plasma SIRT1 levels in patients with both EAH and HF could be attributed to the interplay between disease duration, obesity, and specific genetic backgrounds. These findings underscore the complex nature of SIRT1 as a biomarker in hypertensive disorders, suggesting a need for more detailed studies to unravel the genetic underpinnings influencing its expression.

DISCUSSION

We discovered that the plasma SIRT1 level in patients with EAH significantly differs from levels found in healthy volunteers. Research by Duman *et al.* suggests that in hypertensive patients, plasma peptide levels are notably higher than those in individuals with normal blood pressure[19–22]. Conversely, other studies have indicated that hypertensive patients exhibit significantly lower plasma peptide concentrations compared to a control group[9,23]. The assessment of SIRT1 in patients with heart failure (HF) showcases varied methodological approaches among researchers. Some studies have examined peptide expression levels in tissues, revealing experimental evidence that cardiomyocyte peptide expression in HF patients is nearly half that of healthy hearts[8]. Other analyses, focusing on SIRT1 expression in peripheral blood mononuclear cells, found significantly reduced levels in HF patients[19]. Despite the use of differing methodologies in these studies, our findings align closely. However, research conducted by Italian scientists reported higher peptide expression in HF patients than in healthy volunteers[24]. No studies were

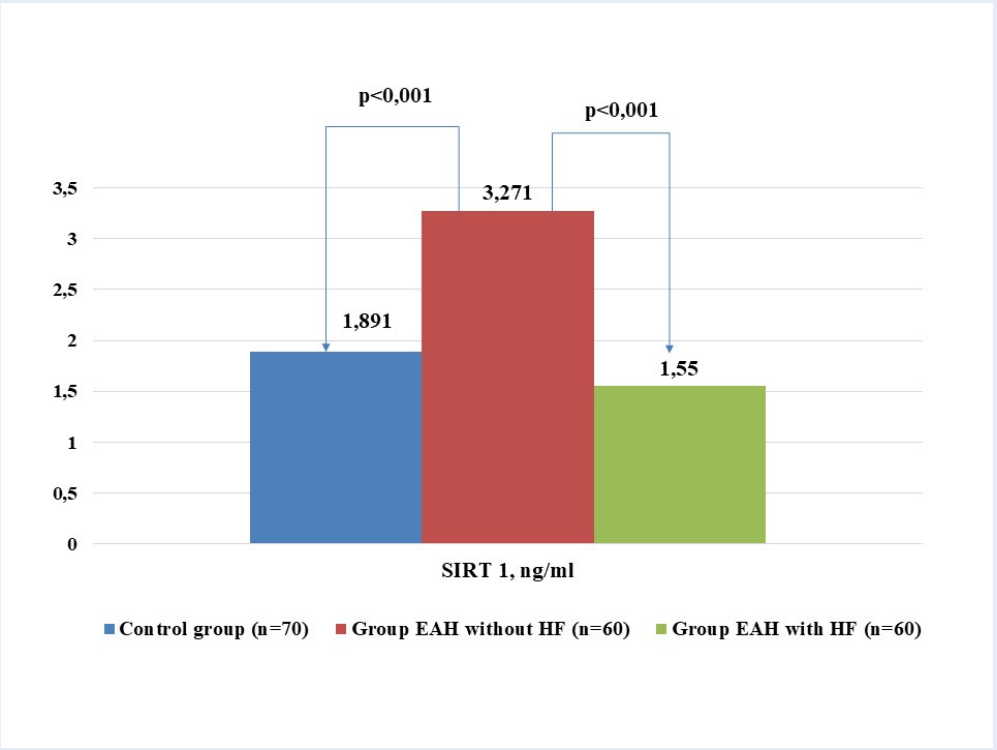

Figure 1: **Plasma concentration of SIRT1 in the study groups**.
Abbreviations: **CHF**: and chronic heart failure, **EAH**: essential arterial hypertension, **SIRT1**: sirtuin 1. Data are shown as Mean.

Table 1: Clinical characteristics of the study groups (M ± m, %)

Parameters	Control group (n=70)	Group EAH without CHF (n=60)	Group EAH with CHF (n=60)
Age, years	49.03±0.792	50.03±0.675	52.02±0.757
Body weight, кg	79.06±1.014	80.12±1.307	88.67±1.510*#
BMI, кg/m^2	25.23±0.268	25.92±0.394	29.38±0.547*#
GFR, ml/min/1.73 m^2	111.4±2.473	105.7±2.673	95.63±1.709*#
Age of EAH onset, years	-	48.98±1.119	35.77±1.120#
Duration of EAH, years	-	9.14±0.773	13.53±0.771#
Obese persons, n (%)	3 (4.29%)	8 (13.34%)	31 (57.67%)&

Notes: * differences are significant when compared with the control group, $p < 0.01$; # the differences are significant when compared with the EAH group without CHF, $p < 0.01$; & differences are reliable when comparing between groups, $\chi^2 = 47.74$, $p < 0.001$; **BMI**: body mass index, **CHF**: chronic heart failure, **EAH**: essential arterial hypertension, **GFR**: glomerular filtration rate.

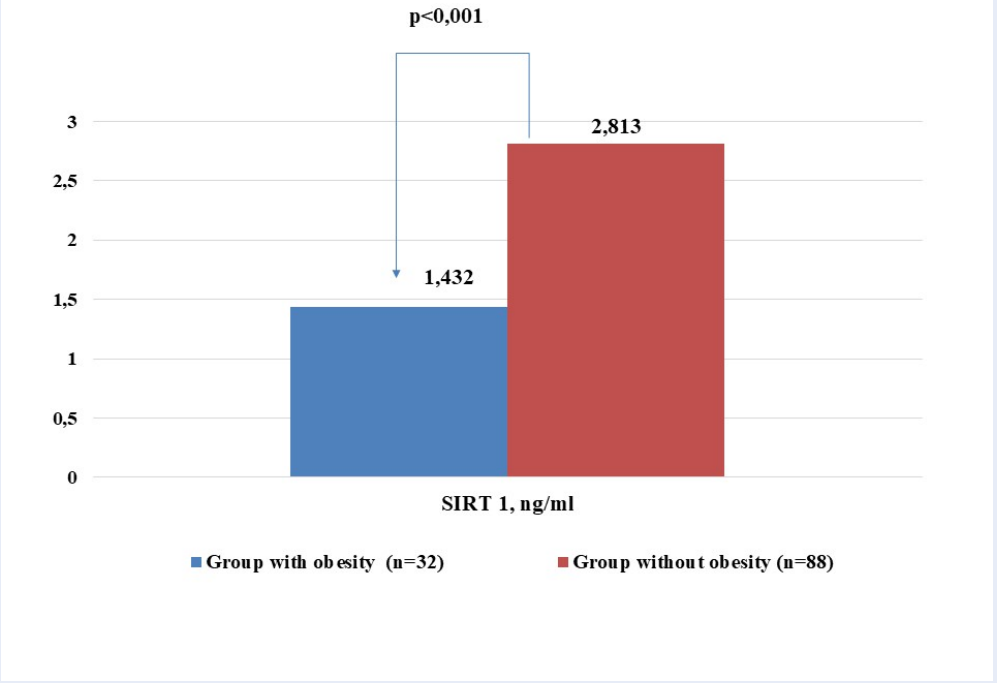

Figure 2: **Plasma concentration of SIRT1 in hypertensive men with different BMI**. **Notes**: **BMI**: body mass index, **SIRT1**: sirtuin 1. Data are shown as Mean.

Table 2: Plasma SIRT1 levels in individuals with different variants of SNP of the SIRT1 gene (rs7069102), (M ± m)

Groups	Control group (n = 70)	Group EAH without CHF (n = 60)	Group EAH with CHF (n = 60)
Individuals with variant CC+CG (n = 101)	2.024±0.113	3.474±0.370$^{\#}$	1.744±0.126$^{\&}$
Homozygotes GG (n = 89)	1.668±0.160	3.091±0.308$^{\#}$	1.390±0.092$^{*\&}$

Notes: * differences are significant when compared with individuals with CC+CG variant, p = 0.032; # significant differences when compared with the control group, p = 0.002; &- the differences are significant in comparison with the EAH group without CHF, p = 0.018; CHF: chronic heart failure, EAH: essential arterial hypertension, SIRT1: sirtuin 1, SNP: single nucleotide polymorphism.

found examining plasma SIRT1 concentration in hypertensive patients with HF.

This diversity in results likely stems from the various study designs. When research includes participants of differing genders, ages, and HF etiologies, and employs varied methods for SIRT1 evaluation, interpreting or reproducing study findings becomes challenging. In planning our study, we minimized several variables by ensuring homogeneity in gender, age, and HF etiology within our groups. This approach allowed us to identify potential factors influencing plasma peptide levels: the duration of hypertension, disease severity, presence of obesity, and genetic components.

We observed that plasma SIRT1 concentration in patients with EAH and HF was significantly lower in those with early disease onset and obesity. This contrasts with findings in coronary heart disease (CHD) patients, where plasma peptide levels showed no correlation with anthropometric measures[25,26]. Interestingly, Norwegian research identified a correlation between SIRT1 expression and obesity in women, but not in men[14]. The design of our cross-sectional study limits the generalization of our results, suggesting that men with EAH and HF may exhibit lower SIRT1 levels if obesity is present or if EAH appears early.

This could impact the use of this peptide as a diagnostic marker for HF. However, our data supports a hypothesis that early EAH onset and obesity comorbidity could accelerate HF development through more significant early hypertensive damage to the myocardium, depleting cardiomyocyte SIRT1 reserves. Experimental evidence links low SIRT1 expression in cardiomyocytes to advancing myocardial fibrosis[27]. Thus, reduced plasma SIRT1 levels could signal depleted myocardial functional reserves in HF development, meriting further longitudinal research.

We also explored the phenotypic significance of the rs7069102 C/G SNP in the SIRT1 gene concerning plasma activity and concentration levels. Minimal available literature exists on this topic. Kilic et al. found no significant differences in plasma peptide levels between carriers of different SNP variants in a general Turkish population[12]. Yet, in a CHD patient cohort, GG homozygotes exhibited significantly higher plasma SIRT1 levels compared to other variants[28]. In acute coronary syndrome patients, a higher plasma peptide concentration was linked to the C allele[29]. Little to no information exists on the rs7069102 C/G SNP's effect on plasma SIRT1 levels in HF patients. Our findings indicate low plasma peptide levels among homozygous GG variant carriers in patients with EAH and HF, offering new insights into the rs7069102 C/G polymorphism's phenotypic manifestations in Ukrainian hypertensive men. Given the minor allele G's varying prevalence across populations, its potential impact on plasma SIRT1 levels could differ globally.

Our results lay the groundwork for further exploring plasma peptide concentrations in EAH patients, considering various heart structure and function disorders that lead to hypertensive heart and HF. The cross-sectional nature of our study precluded investigating other HF progression factors in EAH patients, such as lifestyle or treatment approaches. Consequently, our findings open avenues for detailed analysis of plasma SIRT1 level changes in patients with EH and varied HF phenotypes across different clinical scenarios. This could enhance the diagnostic and prognostic utility of SIRT1, refining the biomarker's application by accounting for significant influences and limitations.

CONCLUSIONS

In male patients diagnosed with exercise-associated hyponatremia (EAH), there was a significant association between lower plasma SIRT1 levels and heart failure (HF). Several factors contributing to reduced plasma peptide levels were identified, including obesity, the early onset of hypertension, and the presence of the GG variant within the rs7069102 single nucleotide polymorphism (SNP) in the SIRT1 gene. These findings enhance our understanding of SIRT1's diagnostic value and its potential limitations as a biomarker for HF in clinical settings. Furthermore, they underscore the necessity for and guide the direction of future research in this area.

ABBREVIATIONS

BMI - Body Mass Index, CHD - Coronary Heart Disease, CVD - Cardiovascular Disease, EAH - Essential Arterial Hypertension, ELISA - Enzyme-Linked Immunosorbent Assay, ESC - European Society of Cardiology, GFR - Glomerular Filtration Rate, HF - Heart Failure, NPMMU - National Pirogov Memorial Medical University, NYHA - New York Heart Association, PCR - Polymerase Chain Reaction, SEM - Standard Error of the Mean, SIRT1 - Sirtuin 1, SNP - Single Nucleotide Polorphism, VRDDP - Vinnytsya Regional Diagnostic and Disease Prevention Center, WHO - World Health Organization

ACKNOWLEDGMENTS

This research received no specific grant from any funding agency in the public, commercial or non-profit sectors. We thank all patients for their participation in the investigation, and the doctors, nurses, and administrative staff of VRSRPD (Vinnytsia, Ukraine) that assisted with the study.

AUTHOR'S CONTRIBUTIONS

Starzhynska O.: developed data collection and assessment tools, analysis and interpretation of data, drafting of the manuscript. Donets A.: conducted the initial analysis of the problem, coordinated and supervised data collection on the site. Maiko O.: wrote review, edited of the manuscript. Zhebel V.: developed the study concept and design, edited and approved the final manuscript. All authors read and approved the final manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Data and materials used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research protocol was approved by the ethical committee of NPMM, Vinnytsya, Ukraine, which found no deviations from the requirements of the Declaration of Helsinki and the Council of Europe Convention on Human Rights and Biomedicine (1977) and requirements of the current legislation of Ukraine. Before initiating any procedures, all patients provided Informed Consent by signing the appropriate documentation.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Bozkurt B, Ahmad T, Alexander KM, Baker WL, Bosak K, Breathett K, et al. Writing Committee Members. Heart Failure Epidemiology and Outcomes Statistics: A Report of the Heart Failure Society of America. Journal of Cardiac Failure. 2023;29(10):1412–1451. PMID: 37797885. Available from: https://doi.org/10.1016/j.cardfail.2023.07.006.
2. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nature Reviews Nephrology. 2020;16(4):223–37. PMID: 32024986. Available from: https://doi.org/10.1038/s41581-019-0244-2.
3. Opstad TB, Berg TJ, Holte KB, Arnesen H, Solheim S, Seljeflot I. Reduced leukocyte telomere lengths and sirtuin 1 gene expression in long-term survivors of type 1 diabetes: A Dialong substudy. Journal of Diabetes Investigation. 2021;12(7):1183–92. PMID: 33249778. Available from: https://doi.org/10.1111/jdi.13470.
4. Vargas-Ortiz K, Pérez-Vázquez V, Macías-Cervantes MH. Exercise and Sirtuins: A Way to Mitochondrial Health in Skeletal Muscle. International Journal of Molecular Sciences. 2019;20(11):2717. PMID: 31163574. Available from: https://doi.org/10.3390/ijms20112717.
5. Wyman AE, Atamas SP. Sirtuins and Accelerated Aging in Scleroderma. Current Rheumatology Reports. 2018;20(4):16. PMID: 29550994. Available from: https://doi.org/10.1007/s11926-018-0724-6.
6. Mengozzi A, Costantino S, Paneni F, Duranti E, Nannipieri M, Mancini R. Targeting SIRT1 Rescues Age- and Obesity-Induced Microvascular Dysfunction in Ex Vivo Human Vessels. Circulation Research. 2022;131(6):476–91. PMID: 35968712. Available from: https://doi.org/10.1161/CIRCRESAHA.122.320888.
7. Paramesha B, Anwar MS, Meghwani H, Maulik SK, Arava SK, Banerjee SK. Sirt1 and Sirt3 Activation Improved Cardiac Function of Diabetic Rats via Modulation of Mitochondrial Function. Antioxidants. 2021;10(3):338. PMID: 33668369. Available from: https://doi.org/10.3390/antiox10030338.
8. Lu TM, Tsai JY, Chen YC, Huang CY, Hsu HL, Weng CF. Downregulation of Sirt1 as aging change in advanced heart failure. Journal of Biomedical Science. 2014;21(1):57. PMID: 24913149. Available from: https://doi.org/10.1186/1423-0127-21-57.
9. Martinez-Arroyo O, Ortega A, Galera M, Solaz E, Martinez-Hervas S, Redon J. Decreased Urinary Levels of SIRT1 as Non-Invasive Biomarker of Early Renal Damage in Hypertension. International Journal of Molecular Sciences. 2020;21(17):6390. PMID: 32887498. Available from: https://doi.org/10.3390/ijms21176390.
10. Waldman M, Cohen K, Yadin D, Nudelman V, Gorfil D, Laniado-Schwartzman M. Regulation of diabetic cardiomyopathy by caloric restriction is mediated by intracellular signaling pathways involving 'SIRT1 and PGC-1α'. Cardiovascular Diabetology. 2018;17(1):111. PMID: 30071860. Available from: https://doi.org/10.1186/s12933-018-0754-4.
11. Yan J, Wang J, He JC, Zhong Y. Sirtuin 1 in Chronic Kidney Disease and Therapeutic Potential of Targeting Sirtuin 1. Frontiers in Endocrinology (Lausanne). 2022;13. PMID: 35795148. Available from: https://doi.org/10.3389/fendo.2022.917773.
12. Kilic U, Gok O, Elibol-Can B, Uysal O, Bacaksiz A. Efficacy of statins on sirtuin 1 and endothelial nitric oxide synthase expression: the role of sirtuin 1 gene variants in human coronary atherosclerosis. Clinical and Experimental Pharmacology & Physiology. 2015;42(4):321–30. PMID: 25582759. Available from: https://doi.org/10.1111/1440-1681.12362.
13. Zhong Y, Chen AF, Zhao J, Gu YJ, Fu GX. Serum levels of cathepsin D, sirtuin1, and endothelial nitric oxide synthase are correlatively reduced in elderly healthy people. Aging Clinical and Experimental Research. 2016;28(4):641–5. PMID: 26462844. Available from: https://doi.org/10.1007/s40520-015-0472-7.
14. Opstad TB, Kalstad AA, Pettersen AÅ, Arnesen H, Seljeflot I. Novel biomolecules of ageing, sex differences and potential underlying mechanisms of telomere shortening in coronary artery disease. Experimental Gerontology. 2019;119:53–60. PMID: 30684534. Available from: https://doi.org/10.1016/j.exger.2019.01.020.
15. Doulamis IP, Tzani AI, Konstantopoulos PS, Samanidis G, Georgiopoulos G, Toutouzas KP. A sirtuin 1/MMP2 prognostic index for myocardial infarction in patients with advanced coronary artery disease. International Journal of Cardiology. 2017;230:447–53. PMID: 28043667. Available from: https://doi.org/10.1016/j.ijcard.2016.12.086.
16. Clark SJ, Falchi M, Olsson B, Jacobson P, Cauchi S, Balkau B. Association of sirtuin 1 (SIRT1) gene SNPs and transcript expression levels with severe obesity. Obesity (Silver Spring, Md). 2012;20(1):178–85. PMID: 21760635. Available from: https://doi.org/10.1038/oby.2011.200.
17. Dardano A, Lucchesi D, Garofolo M, Gualdani E, Falcetta P, Bornez VS. SIRT1 rs7896005 polymorphism affects major vascular outcomes, not all-cause mortality, in Caucasians with type 2 diabetes: A 13-year observational study. Diabetes/Metabolism Research and Reviews. 2022;38(4). PMID: 35092334. Available from: https://doi.org/10.1002/dmrr.3523.
18. Yamac AH, Uysal O, Ismailoglu Z, Ertürk M, Celikten M, Bacaksiz A. Premature Myocardial Infarction: Genetic Variations in SIRT1 Affect Disease Susceptibility. Cardiology Research and Practice. 2019;2019. PMID: 31143479. Available from: https://doi.org/10.1155/2019/8921806.
19. Akkafa F, Altiparmak IH, Erkus ME, Aksoy N, Kaya C, Ozer A. Reduced SIRT1 expression correlates with enhanced oxidative stress in compensated and decompensated heart failure. Redox Biology. 2015;6:169–73. PMID: 26233702. Available from: https://doi.org/10.1016/j.redox.2015.07.011.
20. Conti V, Corbi G, Manzo V, Malangone P, Vitale C, Maglio A. SIRT1 Activity in Peripheral Blood Mononuclear Cells Correlates with Altered Lung Function in Patients with Chronic Obstructive Pulmonary Disease. Oxidative Medicine and Cellular Longevity. 2018;2018. PMID: 29861836. Available from: https://doi.org/10.1155/2018/9391261.
21. Starzhynska O, Donets A. Prevalence of the single nucleotide polymorphism (sSNP) rs7069102 of the SIRT1 gene among hypertensive residents of the Podil region of Ukraine. Precarpathian bulletin of the Shevchenko scientific society. Pulse. 2023;19(67):7–18. Available from: https://doi.org/10.21802/2304-7437-2023-19(67)-7-15.
22. Duman H, Bahçeci I, Çinier G, Duman H, BakıEM, Çetin M. Left ventricular hypertrophy is associated with increased sirtuin level in newly diagnosed hypertensive patients. Clinical and

Experimental Hypertension (New York, NY). 2019;41(6):511–5. PMID: 30230925. Available from: https://doi.org/10.1080/10641963.2018.1510946.

23. Prola A, Silva JPD, Guilbert A, Lecru L, Piquereau J, Ribeiro M. SIRT1 protects the heart from ER stress-induced cell death through eIF2α deacetylation. Cell Death and Differentiation. 2017;24(2):343–56. PMID: 27911441. Available from: https://doi.org/10.1038/cdd.2016.138.
24. Corbi G, Conti V, Troisi J, Colucci A, Manzo V, Pietro PD. Cardiac Rehabilitation Increases SIRT1 Activity and β-Hydroxybutyrate Levels and Decreases Oxidative Stress in Patients with HF with Preserved Ejection Fraction. Oxidative Medicine and Cellular Longevity. 2019;2019. PMID: 31885811. Available from: https://doi.org/10.1155/2019/7049237.
25. Samant SA, Pillai VB, Gupta MP. Cellular mechanisms promoting cachexia and how they are opposed by sirtuins. Canadian Journal of Physiology and Pharmacology. 2019;97(4):235–45. PMID: 30407871. Available from: https://doi.org/10.1139/cjpp-2018-0479.
26. Yang P, Dai T, Liu B, Huang L, Yin J, Zhao F, et al. The Predictive Value of NGF, TMAO, SIRT1 and apoA1 in Patients With Ischemic Heart Failure. Alternative Therapies in Health and Medicine. 2023;2023:AT9328. PMID: 37944962.
27. Liu YP, Wen R, Liu CF, Zhang TN, Yang N. Cellular and molecular biology of sirtuins in cardiovascular disease. Biomedicine and Pharmacotherapy. 2023;164. PMID: 37263163. Available from: https://doi.org/10.1016/j.biopha.2023.114931.
28. Kilic U, Gok O, Bacaksiz A, Izmirli M, Elibol-Can B, Uysal O. SIRT1 gene polymorphisms affect the protein expression in cardiovascular diseases. PLoS One. 2014;9(2). PMID: 24587358. Available from: https://doi.org/10.1371/journal.pone.0090428.
29. Kızıltunç E, Kösem A, Özkan C, Ilgın BU, Kundi H, Çetin M, et al. Serum Sirtuin 1, 3 and 6 Levels in Acute Myocardial Infarction Patients. Arquivos Brasileiros de Cardiologia. 2019;113(1):33–9. PMID: 31291416. Available from: https://doi.org/10.5935/abc.20190114.