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Abstract

Visfatin is an adipocytokine that exists in two forms, intracellular and extracellular. Circulating visfatin, which lacks the nicotinamide phosphoribosyltransferase (NAMPT) enzyme activity, functions as adipocytokine. Increased concentration of circulating visfatin is associated with several diseases, including cardiovascular disease. However, therapeutic strategies to normalize the circulating visfatin concentration are less understood. In heart failure (HF) patients with obesity and insulin resistance (IR), the routine HF therapy, trimetazidine (TMZ), which is a sirtuin1 (sirt1) activator, is known to normalize the circulating visfatin concentration. Besides this preferred effect of TMZ, an adjuvant therapy including N-acetylcysteine (NAC, antioxidant and anti-inflammatory molecule), niacin (vitamin B3, NAD+ booster) and magnesium (sirt1 activator and anti-inflammatory molecule) can be considered to address the underlying molecular mechanisms that are associated with the pathogenesis of HF. Such mechanisms include excess oxidative stress, increased circulating visfatin concentration, NAD+ deficiency, sirt1 down regulation and elevated systemic and cardiac inflammation. Together, the **proposition** is that TMZ and the suggested adjuvant therapy could improve the clinical symptoms and normalize the circulating visfatin concentration by addressing the underlying mechanisms associated with HF.

Keywords: Heart failure, trimetazidine, magnesium, N-acetylcysteine, oxidative stress, visfatin

1. Introduction

Visfatin is an adipokine that elicits paracrine and autocrine effects on the cardiovascular system. Previously, visfatin has been considered to be identical to pre-B cell colony-enhancing factor (PBEF) that promotes the maturation of early B-lineage precursor cells [1]. Further, visfatin has intrinsic enzyme activity as nicotinamide phosphoribosyl transferase (NAMPT) [2]. NAMPT catalyses the rate-limiting step in NAD+ (nicotinamide adenine dinucleotide) biosynthetic salvage pathway, wherein NAD+ is an essential cofactor in several redox reactions [3]. As shown in Figure.1, NAMPT converts nicotinamide to nicotinamide mononucleotide (NMN); then nicotinamide/nicotinic acid mononucleotide adenyl transferase (NMNAT) transforms NMN to NAD+ [4].

Visfatin exists in two forms, intracellular and extracellular. Intracellular form exhibits NAMPT enzyme activity so as to maintain the enzyme activities of NAD+-dependent enzymes, hence, the intracellular visfatin regulates cellular metabolism and energy homeostasis [5]. Whereas the extracellular form, which is synthesised and secreted by adipocytes and several other cell types [6] (including cardiac fibroblasts, cardiomyocytes, vascular smooth muscle cells, endothelial cells, cells in the atherosclerotic plaque, activated immune cells, circulating blood cells), is an adipocytokine which is associated with hormone-like signalling pathways and intracellular signalling cascades [7]. As circulating visfatin has been considered as a biomarker of inflammation and endothelial dysfunction [6], here the focus is on the extracellular circulating visfatin and its association with the pathogenesis of heart failure (HF). Interestingly, a recent report has shown that extracellular circulating visfatin does not elicit enzymatic activity (for NMN biosynthesis) due to the insufficient concentration of ATP (the activator of enzymatic activity of visfatin/NAMPT) in the extracellular spaces [8], which shows that circulating visfatin functions as an adipocytokine rather than an enzyme (NAMPT).

The physiological relevance and function of circulating visfatin remains controversial. However, enhanced circulating visfatin concentration has been reported in several pathologies [6] including, obesity, type 2 diabetes (T2D), hypoxia, chronic kidney disease, preeclampsia, acute coronary syndromes, cerebrovascular diseases and non-metabolic chronic inflammatory diseases, among the others. Further, strategies to normalize the elevated circulating visfatin concentration are less explored.

Trimetazidine (TMZ), a cytoprotective and an anti-ischemic agent, is a pharmacological drug that was previously approved for angina pectoris [9]. Eventually, the direct influence of TMZ in improving myocardial metabolism *via* beta oxidation was established [10], besides the other benefits of TMZ. Hence, the European Society of Cardiology (ESC, 2016 guidelines) has included TMZ for the treatment of angina pectoris with HF [9]. Since then, experimental and clinical studies have reported on the efficacy of TMZ in HF [11]. Different mechanisms by which TMZ exerts its cardioprotective effect includes sirt1 activation [11], energy metabolism [12], apoptosis of cardiomyocytes, myocardial autophagy [13], myocardial interstitial fibrosis, myocardial inflammation, expression of atrial natriuretic peptide [14], modifying the phosphate levels in left ventricle [15] and electrophysiological influence [16]. Nevertheless, whether or not TMZ can influence the circulating visfatin concentration is yet to be understood.

2. Mechanisms associated with circulating visfatin and heart failure

Abdominal obesity occurs due to an imbalance between the energy intake and energy expenditure. Further, obesity is associated with T2D and insulin resistance (IR) [17]. The two major cellular events that occur in abdominal obesity are white adipose tissue (WAT) inflammation and hypoxia, as shown in Figure 2. In cardiovascular disease, classically excessive oxidative stress occurs as an underlying molecular mechanism. Such elevated oxidative stress leads to more tissue inflammation and reduced ejection fraction, which cumulatively leads to HF development. Majority of the reports [8, 18, 19] show that visfatin concentration is up-regulated in HF. Besides these oxidative stress induced effects, excess reactive oxygen species down-regulates

the sirt1 enzyme activity and expression which in-turn leads to increase in circulating visfatin concentration [20]. Therefore, it is possible that excess circulating visfatin contributes to HF development.

2.1 White adipose tissue inflammation and adipocyte dysfunction

The excess energy, which is stored in the adipose tissue, leads to adipocyte enlargement. Eventually, these hypertrophic adipocytes produce chemotactic adipocytokines, such as leptin, adiponectin, resistin, and visfatin, among the others. The secreted adipocytokines, in turn, attract the macrophages into the adipose tissue, to trigger inflammation (WAT inflammation) in the adipose tissue (Fig. 2). In WAT inflammation, lipolysis in the hypertrophic adipocytes causes leakage of free fatty acids. These free fatty acids directly contribute to apoptosis of non-adipose tissue, microvascular inflammation and altered adipose tissue perfusion to result in hypoxia and necrosis. These cellular events in turn promote several pro-inflammatory signalling pathways in adipocytes, fibroblasts and immune cells [21]. Besides these events, an imbalance in the biosynthesis and secretion of pro- and anti-inflammatory adipocytokines is created, which causes adipocyte dysfunction. Adipose tissue dysfunction then becomes an underlying factor for several systemic and metabolic consequences such as, IR, systemic low grade inflammation, hyperlipidemia and hypercoagulability which cumulatively furthers the pathogenesis of cardiovascular disease and T2D [22].

2.2 White adipose tissue inflammation, reactive oxygen species and circulating visfatin

Excess circulating visfatin stimulates the pathogenesis of atherosclerosis and HF [18] through multiple mechanisms, including, cell proliferation, cell survival, extracellular matrix, vascular reactivity, inflammation and myocardial fibrosis. However, pre-treatment with visfatin exhibits cardioprotective effect under hypoxia-reperfusion [23]. Hence, visfatin may have potential therapeutic benefits in the pathologies associated with ischemia.

Elevated concentration of circulating visfatin activates NADPH (nicotinamide adenine dinucleotide phosphate, Fig. 2) oxidase in endothelial cells to contribute to endothelial dysfunction in the coronary vessels [6]. Activated NADPH oxidase generates excessive reactive oxygen species. Excess oxidative stress successively influences several critical molecules and cellular events including the following i) aggravated cell death of cardiomyocytes. Such an excessive cardiomyocyte cell death is one of the fundamental reasons for the pathogenesis of HF with reduced ejection fraction (HFrEF) [24]; ii) degradation of the circulating NAD+ level [25]. It has been reported that, in HF patients, NAD+ deficiency is prevalent [26], whose restoration reverses HF [26]. As NAD+ is an essential co-factor for the deacetylase enzyme, sirt1, the deacetylase enzyme activity gets compromised in NAD+ deficiency, which leads to accumulation of acetylated proteins in HF [26]. On the other hand, acetylation of endothelial nitric oxide synthase (eNOS) resulted in impaired enzyme activity, thereby contributing to nitric oxide (the primary vasodilator) deficiency, endothelial dysfunction and atherosclerosis [27]; and iii) in response to excess oxidative stress, activation of JNK, p38 and ERK pathways occurs in cardiomyocytes. Such cumulative activation of different pathways, eventually, results in cardiac hypertrophy, adverse left ventricle remodeling, cardiac fibrosis and HF [6]. Many of the visfatin-elicited effects (proliferative, proinflammatory and proangiogenic), on the cardiovascular system are through activation of several signalling pathways, such as PI3K, NFkB, STAT3 and ERKs [28].

Besides the production and release of visfatin from the primary source (adipocytes and activated immune cells), apical epicardial adipose tissue, periadventitial adipose tissue, cardiac fibroblasts, myocytes and the cells in the vascular walls contribute to the up-regulated local cardiac visfatin concentration [29], which has been reported to have an autocrine effect in the cardiovascular system [6]. In support, experimental studies have shown that in addition to the influence of circulating visfatin, visfatin that is secreted from rat cardiac cells becomes a local source of the adipocytokine that leads to cardiac fibrosis [19].

Circulating visfatin, besides eliciting its proliferative effects on the cells in the vascular wall, it mediates the proliferation of cardiac fibroblasts. Proliferating fibroblasts synthesise and release more collagen (type-1 and -2), which eventually promotes cardiac fibrosis [19]. Moreover, visfatin up-regulates the mRNA and protein levels as well as enzyme activity of matrix metalloproteinases (MMP-2 and -9) in monocytes and endothelial cells. MMPs promote angiogenesis by two simultaneous cellular events, degradation of the extracellular matrix and reduction in the concentrations of the tissue inhibitors of MMPs (TIMP-1 and -2) [6]. Importantly, as these MMPs degrade the matrix, this degradation furthers the plaque vulnerability [30]. Besides, the presence of more cardiac fibroblasts, excess collagen and accumulation of extracellular matrix promotes myocardial fibrosis and remodeling [31]. In endothelial cells, visfatin up-regulates the biosynthesis of pro-angiogenic soluble factors including VEGF, FGF-2, MPC-1 and IL-6 [32], which play a crucial role in the initiation of atherosclerosis.

Experimental and clinical studies have reported on the pro-inflammatory role of visfatin. Exposure human vascular smooth muscle cells to exogenous visfatin activated ERK1/2 and NFkB, which up-regulated the expression of a pro-inflammatory molecule, inducible nitric oxide synthase (iNOS). Consequent to iNOS induction, the biosynthesis of nitric oxide and peroxynitrite ($ONOO^-$) were up-regulated. The potent oxidant, $ONOO^-$ then expedites the occurrence of endothelial dysfunction, vascular injury and vascular inflammation [33].

Based on these observations, it is clear that, in patients with obesity, IR and HF, circulating concentrations of visfatin, biomarkers of inflammation and oxidative stress are elevated; and that the

concentration of NAD+ is down-regulated. However, therapeutic strategies to cumulatively normalize these factors are few. Yet, one study [34] has reported that exercise training lowers circulating visfatin concentrations.

2.3 Abdominal obesity, hypoxia and heart failure

In obesity-mediated WAT inflammation, excessive circulatory visfatin from the adipocytes and activated immune cells becomes the underlying factor for the occurrence of hypoxia [35]. Hypoxia occurs due to enhanced utilization of oxygen or attenuated perfusion of the hypertrophic adipocytes. Hypoxic environment further leads to the over-expression of pro-inflammatory genes (including hypoxia-inducible-factor-1), excessive oxidative stress, lipotoxicity in adipose tissue and altered adipocytokines secretion. These cellular events cumulatively facilitate the self-propagative vicious cycle as well as WAT inflammation to foster the development of IR, skeletal muscle wasting, cardiac and vascular remodelling and eventually to HF development [36].

3. Potential strategies to alter the concentration of circulating visfatin for ameliorative effect in cardiovascular disease

In obesity, adipose tissue dysfunction and hypoxia, among the other cellular events, are crucial factors in creating imbalances in the ratio of oxidants/antioxidants and pro-/anti-inflammatory molecules. It is evident that TMZ, one of the established conventional drugs in HF therapy, normalizes the circulating visfatin concentration [11]. Further, the effect of selected nutritional supplements, such as niacin (as NAD+ booster) [37], magnesium (as sirt1 activator and anti-inflammatory molecule) [38, 39] and NAC (as anti-oxidant and anti-inflammatory) [40] are well established. In this context, our **proposition** is that along with TMZ, inclusion of an adjuvant therapy which comprises of a multi-ingredient nutritional supplement [such as niacin (vitamin B3 form; an NAD+ booster), magnesium (sirt1 activator and anti-inflammatory) and N-acetylcysteine (anti-inflammatory and anti-oxidant)] could improve the adverse outcomes in patients with HF, obesity and IR, than TMZ alone. Possibly, TMZ + multi-ingredient nutritional supplement could address the unfavourably altered biochemical parameters (circulating concentrations of visfatin, NAD+ and biomarkers of oxidative stress and inflammation) and cardiac structure and function (Fig. 2).

In support of the inclusion of nutritional supplements, one study has reported that Quercetin, a sirt1 activator, reduces visfatin secretion [20]. Hence it is possible that TMZ as a sirt1 activator could directly reduce the circulating concentration of visfatin. Interestingly, exercise is known to activate sirt1 [41] and TMZ has been reported to improve HF symptoms by sirt1 activation [9]. Therefore, based on these reports, it is only logical to consider sirt1 activators as adjuvants for therapeutic effect in HF.

Deficiencies of magnesium and NAD+ are prevalent in HF [42]. In this regard, based on our hypothesis, supplementation of NAC and magnesium could address the elevated oxidative stress and pro-inflammatory *milieu*. Parallelly, as a consequence of elevated circulating visfatin and locally generated visfatin in the cardiovascular system, cardiomyocyte cell death could be triggered. Such an apoptosis-induced augmented *in vitro* cell death has been reported to be abrogated by exogenous NAD+ treatment [42]. Thus, therapeutically, NAD+ booster could potentially mitigate the excess visfatin-induced cell death. Besides this *in vitro* cytoprotective effect of NAD+, repletion of NAD+ in mice fed with nicotinamide riboside (NAD+ precursor and direct activator of NAD+ biosynthesis) resulted in the reversal of HF with preserved ejection fraction (HFpEF) [26]. For these HF-associated cellular events, supplementation of magnesium for anti-inflammatory effect and niacin as NAD+ booster could potentially mitigate the onset or pathogenic progression in HF.

In HF, oxidative stress induces a reduction in the expression and activity of sirt1 (the deacetylase enzyme). This sirt1-deficiency then leads to hyper-acetylated proteins. In addition to the sirt1-deficiency-induced hyper-acetylated proteins, myocardial hyper-acetylated proteins accumulate due to impaired NAD+ biosynthesis pathway (causing NAD+ deficiency) and compromised sirt3 expression [26]. Besides the NAD+ deficiency-mediated hyperacetylation, elevated oxidative stress compromises the sirt1 enzyme activity [43] which consequently results in accumulation of hyperacetylated proteins. To counter the hyperacetylation *milieu*, magnesium as sirt1 activator has been reported to be effective. Thus, magnesium supplementation could restore the physiological status of acetylated/de-acetylated proteins in the myocardium.

Together, TMZ and the nutritional supplements including sirt1 activators, antioxidants, anti-inflammatory molecules and NAD+ booster could potentially normalize the concentrations of visfatin, NAD+, free radicals and pro-inflammatory molecules, to eventually improve the adverse symptoms of HF. Besides the influences of nutrient supplements, it is possible that TMZ could reduce the excess circulating visfatin level *via* potential sirt1 activation.

4. Conclusion

To sum up, while the routine HF therapy with TMZ supports the improvement of clinical manifestations of HF and cardiac function, in terms of ejection fraction[11] and the potential reduction of circulating visfatin concentrations, the adjuvant therapy with multiple nutritional supplements could have an additive effect to TMZ, as the individual supplement(s) is/are known for their effect to normalize the adverse cellular events associated with oxidative stress, inflammation, mitigated sirt1 activity and modified circulating

concentrations of analytes (visfatin and NAD+) that leads to the development and progression of HF (Fig. 2). Hence, TMZ with the said nutritional supplements may have therapeutic and preventive effects in HF.

Compliance with ethical standards

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Conflict of Interest The authors declare no potential conflict of interest with respect to research content, authorship and/or publication of this article.

Ethical Approval Not applicable

Research involving human participants and/or animals Not applicable

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Abbreviations

HF – Heart Failure; HFrEF- Heart failure with reduced ejection fraction; HFpEF - Heart failure with preserved ejection fraction; TMZ – Trimetazidine; PBEF - pre-B cell colony-enhancing factor; NAMPT - Nicotinamide phosphoribosyl transferase; NAD+ - Nicotinamide adenine dinucleotide; NMN - Nicotinamide mononucleotide; NMNAT- Nicotinic acid mononucleotide adenyl transferase;NADPH - nicotinamide adenine dinucleotide phosphate; eNOS - endothelial nitric oxide synthase; iNOS - inducible nitric oxide synthase; IR – Insulin Resistance; WAT – White adipose tissue; T2D – Type 2 Diabetes; JNK - Jun N-terminal kinase; ERK - extracellular signal-regulated kinases; P13K - Phosphoinositide 3-kinase; NFkB - Nuclear factor kappa B; STAT 3 - Signal transducer and activator of transcription 3; MMP - Matrix metalloproteinases; VEGF - Vascular endothelial growth factor; FGF - Fibroblast growth factor; MPC1 - Mitochondrial pyruvate carrier 1; IL6 – Interleukin 6; ONOO- - Peroxynitrite; Mg – Magnesium; NAC- N-acetyl cysteine;

Figures

Figure 1 NAD+ biosynthesis by salvage pathway. CD38-cyclic ADP ribose hydrolase; NAD+ -Nicotinamide adenine dinucleotide; NAM-nicotinamide; NR-nicotinamide riboside; NMN-nicotinamide mononucleotide'; iNAMPT-intracellular nicotinamide phosphoribosyltransferase (visfatin); NMNAT-nicotinate mononucleotide adenylyltransferase' PARP-poly-ADP ribose polymerase; PPi-pyrophosphate; Vit B3-vitamin B3.

Figure 2 Flowchart summarizes the reported effects of circulating visfatin in the cardiovascular system and the potential cardioprotective effects of trimetazidine (TMZ) and adjuvant therapy. EC-endothelial cells; ED-endothelial dysfunction; eNOS-endothelial nitric oxide synthase; FGF2-fibroblast growth factor-2; HFrEF-heart failure with reduced ejection fraction; IL-6-interleukin-6; iNOS-inducible nitric oxide synthase; LV-left ventricle; MCP-1-Monocyte chemoattractant protein-1; Mg-magnesium; MMP-matrix metalloproteinase; NAC-N-acetylcysteine; NAD+ - Nicotinamide adenine dinucleotide; NO-nitric oxide; NOx-NADPH oxidase; ONOO-peroxynitrite; ROS-reactive oxygen species; Sirt1-siruin-1; TNFα-tumor necrosis factor-alpha; VSMC-vascular smooth muscle cells; WAT-white adipose tissue; ↑-upregulation; ↓-downregulation.

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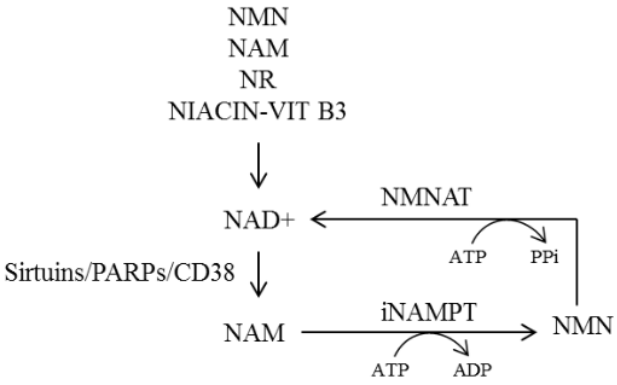
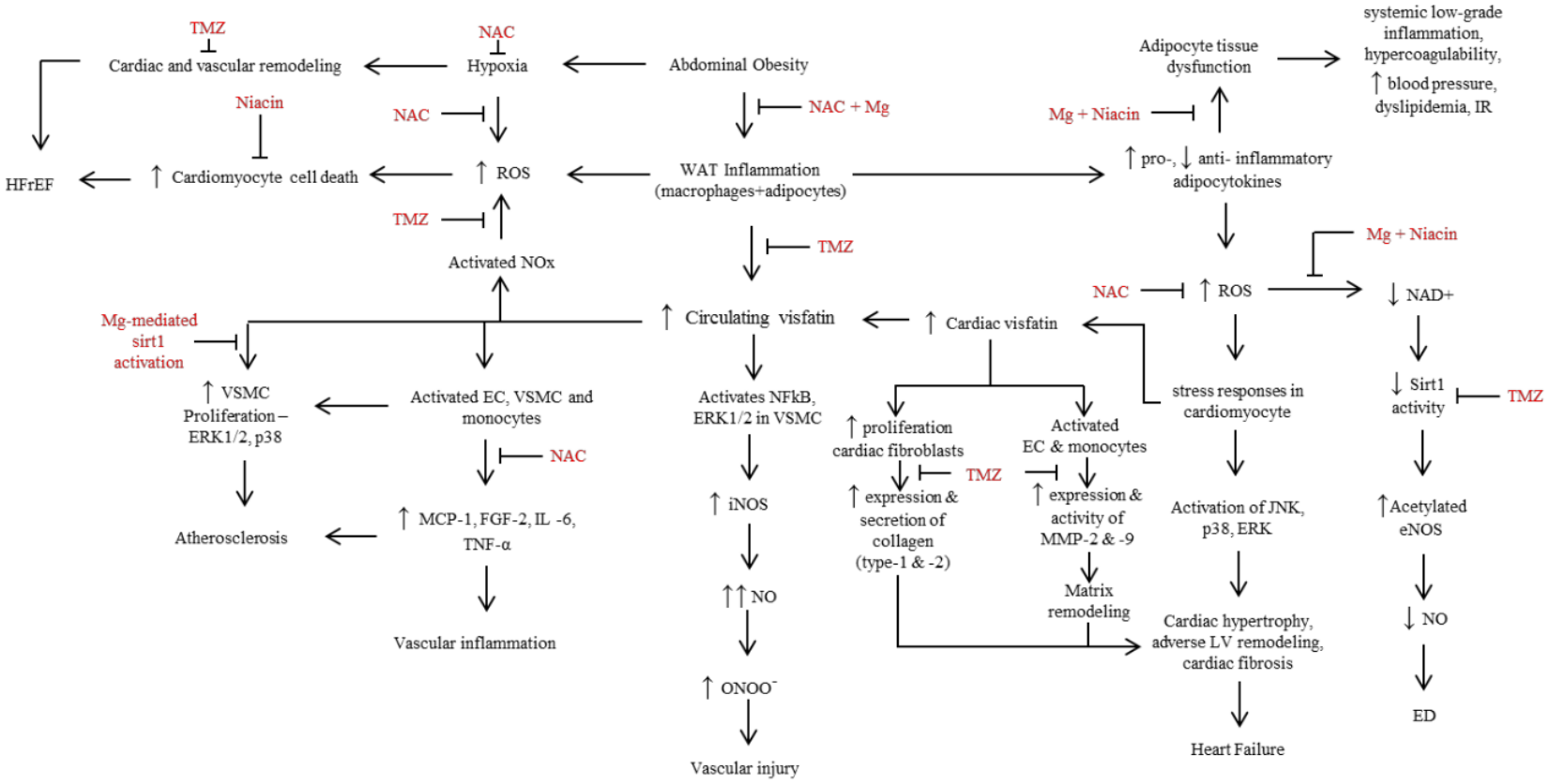


Figure 2 Flowchart summarizes the reported effects of circulating visfatin in the cardiovascular system and the potential cardioprotective effects of trimetazidine (TMZ) and adjuvant therapy. EC-endothelial cells; ED-endothelial dysfunction; eNOS-endothelial nitric oxide synthase; FGF2-fibroblast growth factor-2; HFrEF-heart failure with reduced ejection fraction; IL-6-interleukin-6; iNOS-inducible nitric oxide synthase; LV-left ventricle; MCP-1-Monocyte chemoattractant protein-1; Mg-magnesium; MMP-matrix metalloproteinase; NAC-N-acetylcysteine; NAD+ - Nicotinamide adenine dinucleotide; NO-nitric oxide; NOx-NADPH oxidase; ONOO-peroxynitrite; ROS-reactive oxygen species; Sirt1-siruin-1; TNFα-tumor necrosis factor-alpha; VSMC-vascular smooth muscle cells; WAT-white adipose tissue; ↑-upregulation; ↓-downregulation.



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