REVIEW ARTICLE

MCBS
Mol Cell Biomed Sci. 2024; 8(1): 15-22
DOI: 10.21705/mcbs.v8i1.367

Molecular Adaptation of Cardiac Remodeling in Metabolic Syndrome: Focus on AMPK, SIRT1 and PGC-1α

Andika Yusuf Ramadhan[1], Vivian Soetikno[2]

[1]*Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*
[2]*Department of Pharmacology and Therapeutic, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*

Obesity, lack of physical activity, and genetic predisposition might play a pivotal role in pathogenesis of metabolic syndrome. Cardiac function alteration including hemodynamic changes, contractility function, arrhythmia, and cellular respiratory function, might happen due to chronic condition in metabolic syndrome. Insulin resistance, neurohormonal activation and chronic inflammation might contribute to these changes. Cardiomyocyte had capabilities to adapt from these abnormalities, one of them is the activation of cellular pathway to resist cardiac injury from metabolic syndrome. This molecular pathway involves three proteins, including AMP-activated protein kinase (AMPK), sirtuin-1 (SIRT1) and peroxisome proliferator-activated receptor γ coactivator-α (PGC-1α). The aim of this narrative review is to elucidate role of AMPK, SIRT1, and PGC-1α in cardiac adaptation against cardiac dysfunction in metabolic syndrome. AMPK, SIRT-1, and PGC-1α contribute to adapt and to repair the cardiac injury resulting from celullar and mechanical stress from metabolic syndrome and prevent cardiac remodeling event. Several pathological events, such as insulin resistance, induce alteration of switching energy fuel to the heart, causing cardiomyocte to rely on glucose metabolism and lipotoxicity, leading to damages of cardiomyocyte through reactive oxygen species (ROS) generation and lipid peroxidation. Increase of ROS promotes cardiac injury followed by necrotic and apoptotic events. AMPK, SIRT1, and PGC-1α act as cardioprotector molecule against metabolic syndrome insults to several mechanism such as: AMPK play role as counter act of lipotoxicity and insulin resistance through increasing insulin sensitivity and regulate redox reaction. SIRT1 plays role in regulating apoptotic genes and PGC-1α repairs cardiac fuel sources. Activation of AMPK/SIRT1/PGC-1α prevent cardiac remodeling due to metabolic syndrome by increasing insulin sensitivity, increases mitochondrial biogenesis and reduce pro-apoptotic signals in cardiomyocte.

Keywords: *AMPK/SIRT1/PGC-α, cardiac remodeling, metabolic syndrome*

Introduction

Metabolic syndrome remains a significant medical burden in Indonesia and is one of the highest risk factors for cardiovascular disease. The prevalence of metabolic syndrome in Indonesia has reached 23.34% and is predicted to continue increasing every year.[1] Metabolic syndrome is a clinical condition that encompasses several risk factors

Submission: August 21, 2023
Last Revision: November 18, 2023
Accepted for Publication: November 20, 2023

Corresponding Author:
Vivian Soetikno
Department of Pharmacology and Therapeutic
Faculty of Medicine, Universitas Indonesia
Jl. Salemba Raya No.6, Jakarta 10430, Indonesia
e-mail: vivian.soetikno@ui.ac.id

Cell and Biopharmaceutical Institute

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v8i1.367

for cardiovascular disease, including obesity, hypertension, insulin resistance, and albuminuria.[2] The etiology of metabolic syndrome is not well understood, but factors such as obesity, lack of physical activity, and genetic predisposition may play a pivotal role in its development.[2,3] Metabolic syndrome can cause damage to the heart due to cellular and mechanical stress, with vascular calcification being the most commonly observed damage, although damage or destruction to other cardiac cells and tissues remains possible.[3]

The alterations in the heart associated with metabolic syndrome have wide-ranging effects, including changes in hemodynamic function, contractility, cardiac rhythm, and cellular destruction. Oxidative stress is believed to be the primary cause of heart function alterations resulting from insulin resistance in metabolic syndrome.[4] Insulin resistance is a condition in which cells are unable to respond adequately to normal levels of insulin, leading to disruptions in energy balance within cellular respiratory mitochondria and abnormalities in cardiac metabolism, ultimately resulting in alterations in cardiac function.[5]

Changes in cardiac function in metabolic syndrome are further exacerbated by neurohormonal activation and chronic inflammation due to oxidative stress and insulin resistance.[5,6] These mechanisms are regulated and activated by mitochondrial dysfunction. One of the molecular pathways that plays a crucial role in cellular adaptation to these metabolic insults from metabolic syndrome in the heart is the AMP-activated protein kinase (AMPK)/sirtuin-1 (SIRT1)/peroxisome proliferator-activated receptor γ coactivator-α (PGC-1α) pathway. This molecular pathway is pivotal in the cellular adaptation against the metabolic challenges posed by metabolic syndrome in the heart. While the conventional theory suggests that cardiac adaptation is mediated by the renin-angiotensin-aldosterone system (RAAS), leading to vasoconstriction, hypertension, left ventricular hypertrophy, and fibrosis, the blockade of the RAAS pathway has shown promise in improving cardiac status and is already being utilized in clinical settings. Beyond this, there is another molecular adaptation pathway that plays a pivotal role in cardiac adaptation alongside RAAS.[7] The AMPK/SIRT1/PGC-1α pathway acts intracellularly and has beneficial downstream effects on cardiac cells. Activation of this pathway can help repress cardiac damage resulting from metabolic syndrome.[8,9] A narrative literature review, or a review method that summarize and synthesize the key point and theory from previous articles, was conducted to elucidate the role of AMPK/SIRT1/PGC-1α pathway in cardiac adaptation to metabolic syndrome insults. The articles that are cited in this literature review were gathered from journal database PubMed, EMBASE, and Cochrane Library.

Metabolic syndrome and cardiac dysfunction

Metabolic syndrome is a form of cluster metabolic dysregulation that consists of insulin resistance, dyslipidemia, obesity, hypertension, and microalbuminuria.[2] The prevalence of metabolic syndrome continues to increase over the years, and lifestyle changes and lack of physical activity are believed to be the main contributing factors. Most patients with metabolic syndrome are at a higher risk of cardiovascular events.[3,4] Metabolic syndrome has a complex pathogenesis and pathophysiology, but the main mechanism is not yet fully understood. However, lipotoxicity, insulin resistance, chronic inflammation, and neurohormonal activation are assumed to play roles in the pathogenesis of metabolic syndrome.[5]

Metabolic syndrome has several clinical diagnoses, with the primary diagnosis typically based on the presence of elevated blood pressure, increased insulin resistance, obesity, and dyslipidemia (Table 1). The pathogenesis of metabolic syndrome is initiated by overeating and a lack of physical activity, which leads to the development of visceral adiposity.[2,3] Visceral adiposity causes three major events: neurohormonal activation, chronic inflammation, and insulin resistance.[2] Neurohormonal activation is induced by an imbalance in the levels of leptin and adiponectin (increased leptin and decreased adiponectin), activation of the RAAS, and an increase in angiotensin II type 2 (AT2) receptor.[10-12] Chronic inflammation is induced by an increase in the levels of reactive oxygen species (ROS) due to lipid peroxidation in visceral adiposity and an increase in pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-6, and fibrinogen.[10] Mainly, the presence of insulin resistance is due to a high level of free fatty acids and reduced insulin levels in the systemic circulation, which may impact increased gluconeogenesis, lipogenesis, and triglyceride synthesis in the liver, ultimately contributing to insulin resistance in metabolic syndrome.[2-4]

Cardiovascular disease is the primary complication of metabolic syndrome progression. It can range from atherogenic changes in blood vessels to heart failure. Cardiac dysfunction is the leading cause of cardiovascular

Table 1. Metabolic syndrome criteria according to WHO 1998, IDF 2005, ATP III and 2001.

Clinical Findings	World Health Organization 1998[5]	International Diabetes Federation 2005[5]	Adult Treatment Panel III of the National Cholesterol Education Program 2001[5]
Metabolic syndrome criteria	Insulin resistance + any other 2	Increase weight circumference (specific population)	Any 3 of 5
Insulin resistance	Impaired glucose tolerance/Impaired fasting glucose (indicate insulin resistance)	-	-
Blood glucose	Impaired fasting glucose/Impaired glucose tolerance/Type 2 diabetes melitus	≥100 mg/dL	≥110 mg/dL (include diabetes melitus)
Dyslipidemia	Triglyceride ≥150 mg/dL and HDL-C <35 mg/dL (for men) HDL-C <39 mg/dL (for women)	Triglyceride ≥150 mg/dL or on treatment for dyslipidemia and HDL-C <40 mg/dL (for men) HDL-C <50 mg/dL (for women) or on HDL-C treatment	Triglyceride ≥150 mg/dL and HDL-C <40 mg/dL (for men) HDL-C <50 mg/dL (for women)
Hypertension	≥140/90 mmHg	≥130/85 mmHg or on antihypertension treatment	≥130/85 mmHg or on hypertension medication
Obesity	Waist/hip ratio men >0.9 and women >0.85. BMI >30 kg/m^2	Waist circumferences >94 cm	Waist circumferences men ≥102 cm and women ≥88 cm
Other	Microalbuminuria	-	-

events in metabolic syndrome. The heart is a vulnerable yet crucial organ in human life, necessitating a high level of energy to maintain functioning throughout one's lifespan.[13-15] The mitochondrial respiratory chain plays a pivotal role in providing bioenergy to the human heart and maintaining the balance of redox reactions at the intracellular level.[15-17] Pathological conditions and metabolic stress states can target mitochondrial function, reducing the number of mitochondria by disrupting mitochondrial DNA, mitochondrial RNA, membranes, lipids, and proteins. In most cases, oxidative stress plays a significant role in this process, resulting in the disruption of the mitochondrial respiratory chain reactions and utilization (Figure 1).[17,18]

Cardiac dysfunction caused by metabolic syndrome manifests as cardiomyopathy in a chronic state. Lipotoxicity, neurohormonal activation, oxidative stress, and chronic inflammation are the primary mechanisms of cardiac dysfunction in metabolic syndrome.[8,14] Prolonged insulin resistance in metabolic syndrome has several effects on other organs, including the heart. One hallmark of insulin resistance is an increase in insulin levels in the blood.[15,19]

Hyperinsulinemia promotes the uptake of free fatty acids in the heart due to the upregulation of cluster of differentiation (CD)36, a fatty acid transporter. During metabolic stress, there is an increased expression of CD36 and hyperactivation of CD36, leading to an increased uptake of fatty acids and induced cardiac lipotoxicity. Insulin resistance also shifts cardiac energy utilization towards fatty acid metabolism, causing a decrease in glucose utilization.[19] The heart and other supporting organs undergo specific alterations in cardiomyopathy in metabolic syndrome.[8,9] Changes in the cardiovascular system begin with alterations in the hemodynamic profile in obese patients, followed by insulin resistance, dyslipidemia, and hypertension. In metabolic syndrome, activation of the sympathetic nervous system causes an increased heart rate, sodium retention, increased preload, and elevated blood pressure.[9] Increased levels of adipocytokines also play a role in the pathogenesis of cardiac dysfunction in metabolic syndrome, leading to anatomical and structural changes such as the formation of concentric hypertrophy, disarray of myocardial fibers, microvascular dysfunction, atherogenic lesions, and, ultimately, heart failure.[9,13,14]

Cardiac remodeling is the final step in the genesis of diabetic cardiomyopathy. Diabetic cardiomyopathy is characterized by an increase in cardiac mass, especially in the left ventricle, and myocardial fibrosis. This process is initiated when cardiomyocyte injury is followed by cardiomyocyte necrosis, which is then replaced by fibroblasts, ultimately leading to cardiac fibrosis.[17] Diabetic cardiomyopathy manifests as diastolic dysfunction, increased ventricular wall thickness, prolonged diastolic

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v8i1.367

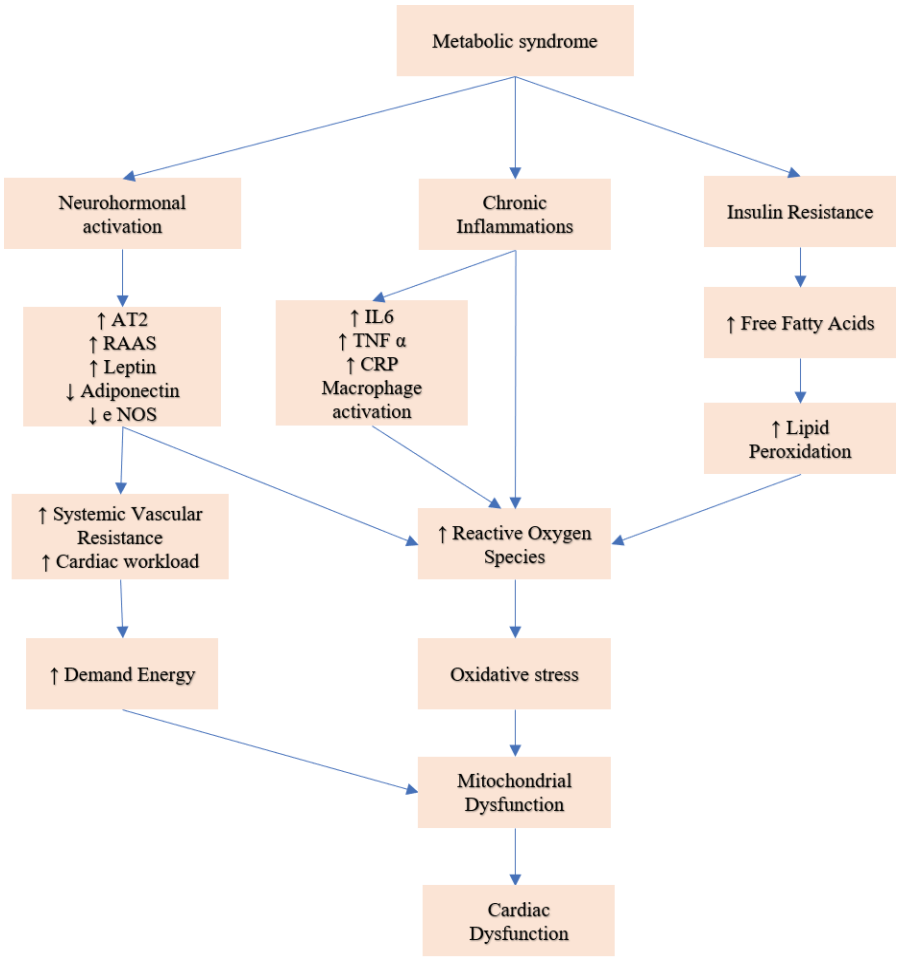

Figure 1. Metabolic syndrome induces neurohormonal activation, chronic inflammation, and insulin resistance. a) Neurohormonal activation leads to an elevation of AT2, activation of renin-angiotensin-aldosterone system (RAAS), an increase in leptin, a decrease in adiponectin, and reduced endothelial nitric oxide synthase (eNOS) synthesis. This mechanism results in an increased systemic vascular resistance and cardiac workload. b) Chronic inflammation is characterized by elevated levels of IL-6, TNF-α, C-reactive protein (CRP), and the activation of macrophages. Chronic inflammation leads to an increased level of ROS and induces cardiac dysfunction. c) Insulin resistance increased free fatty acids, and resulting lipid peroxidation generate ROS and induce oxidative stress. All three of these mechanisms share the same pathway, leading to mitochondrial dysfunction.

relaxation time, and impaired cardiac conduction system (Figure 2).[20,21]

The heart itself has several mechanisms of adaptation to resist cardiac insults, injuries, or ischemic events. These mechanisms consist of molecular pathways that produce cardioprotective molecules to safeguard the heart. Some of these mechanisms are activated through AMPK/SIRT1/PGC-1α. As explained in the previous section, metabolic syndrome is known to cause several damages to the heart.[13,14] Activation of this pathway can prevent cardiac remodeling.

Role of AMPK in cardiac metabolic syndrome

AMPK plays a vital role in cellular energy metabolism and serves as a sensor. It acts as the primary metabolic regulator activated by an increase in AMP levels and a decrease in ATP levels.[22,23] AMPK is a protein kinase with multifunctional roles that regulate microtubule dynamics and intracellular metabolism.[22,23] This heterotrimeric protein can be activated by various stimuli, such as increased levels of calcium, oxidative stress, and genotoxic stress.[14,18]

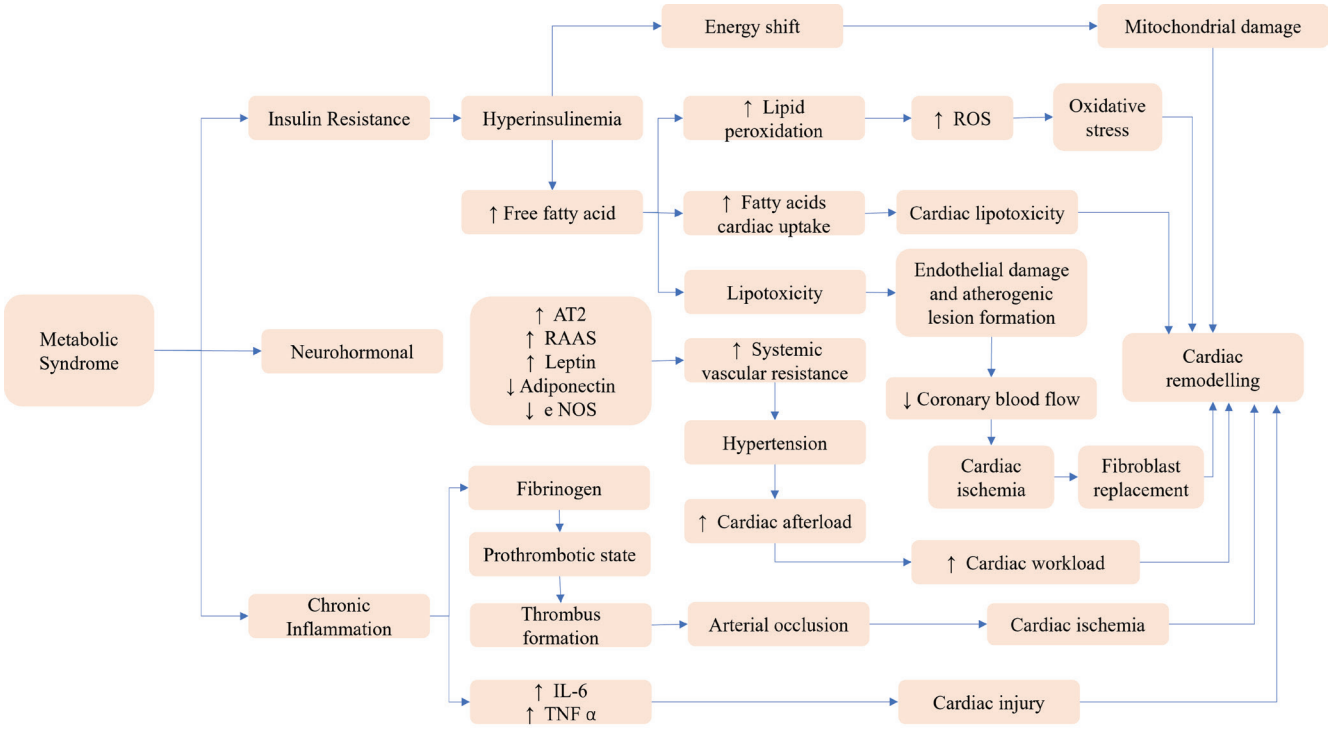

Figure 2. Metabolic syndrome can induce cardiac remodeling through several mechanisms. Insulin resistance causes hyperinsulinemia in the cardiac organ, leading to a shift in the energy utilization of cardiomyocytes and mitochondrial damage. Activation of RAAS and expression of AT2 lead to increased systemic vascular resistance and hypertension, contributing to increased cardiac workload. Lipotoxicity and chronic inflammation contribute to cardiomyocyte damage through oxidative stress and induce a prothrombotic state.

AMPK serves multiple functions in cell cycle regulation, membrane polarity, and membrane excitability. In some conditions, AMPK controls the migration of organelles within cells mediated by microtubules. Downstream mechanisms of AMPK have several targets, including the metabolism of lipids, carbohydrates, cell signaling, and ion transporters.[20,21]

In the heart, AMPK acts as a major regulator of cardiac metabolism and plays a specific role in adapting to various stress conditions, such as cardiac stress. Cardiac stress can be triggered by an increased blood volume load, myocardial ischemia, and oxidative stress.[22,23] Activation of AMPK leads to the activation of glycolysis through the phosphorylation of ATP and an increase in the translocation of glucose transporter-4 (GLUT-4) to the plasma membrane of cardiomyocytes. This increased translocation of GLUT-4 leads to increased glucose uptake as the primary energy substrate. In acute conditions, AMPK stimulates glucose transport, and chronically AMPK increases the expression of genes associated with glucose metabolism.[24,25] AMPK's effects on energy metabolism are also influenced by the insulin signaling pathway. Insulin inhibits AMPK phosphorylation and stimulates the activation of Acetyl-CoA carboxylase (ACC), leading to insulin-mediated suppression of mitochondrial lipid oxidation in cardiovascular endothelia. Activation of AMPK has vascular tone effects and induces vasorelaxation, which is crucial in blood pressure regulation.[23,24]

In response to the stress caused by metabolic syndrome on cardiomyocytes, such as pressure overload, increased ROS, ischemic events, and energy stress, activation of AMPK leads to increased gene expression, enhanced fatty acid oxidation, increased autophagy, reduced apoptosis, and increased mitochondrial biogenesis.[26-28] The critical role of AMPK in mitochondrial biogenesis is mediated by downstream pathways involving PGC-1α. In endothelial cells, AMPK has an effect on reducing the inflammation process in atherogenic blood vessels.[28,29]

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v8i1.367

Atherosclerosis is a chronic inflammatory vascular condition formed by several events, including lipoprotein oxidation, endothelial activation, and macrophage infiltration. This condition leads to the formation of atherogenic plaques that narrow coronary artery perfusion.[26,28] AMPK reduces redox reactions through the regulation of redox status and attenuates the inflammation process in atherosclerotic plaques, serving as a regulator in plaque progression. The mechanism by which AMPK attenuates the inflammation process is introduced by its capability to change the phenotype of monocytes.[28]

Role of SIRT1 in cardiac metabolic syndrome

SIRT1, also known as the mammalian homolog of silent information regulation 2 in yeast *Saccharomyces cerevisiae* 1, is a class III NAD-dependent histone deacetylase that plays a pivotal role in responding to oxidative stress.[30] SIRT1 is widely expressed in mammalian organs, and its expression is regulated by pathological stress. SIRT1 plays a role in the deacetylation of several genes (forkhead box O transcription factors (FOXOs), p53, and poly-adenosine 5-diphosphate-ribose polymerase) and is involved in controlling gene expression.[30,31] In the heart, SIRT1 has cytoprotective effects by promoting cardiomyocyte growth under pathological stress and is found to be higher in states of hypertrophy.[29,30] The protective mechanisms of SIRT1 in the heart are also mediated by its anti-atherosclerotic effects, contributing to cardioprotection during ischemic-reperfusion injury and preserving cardiac contractility.[30]

In metabolic syndrome, insulin resistance acts as the basic pathogenesis of cardiac function decline by inducing apoptosis in cardiomyocytes.[31,32] Advanced glycation end products resulting from chronic hyperglycemia induce myocardial stiffness, impaired cardiac relaxation, and propagate cellular oxidative stress.[30,32] This mechanism leads to cellular damage in cardiomyocytes. Activation of SIRT1 triggers several cardioprotective mechanisms, including the downregulation of pro-apoptotic molecules, reduction of oxidative stress, and inhibition of the apoptosis process.[27]

Besides cardiac stiffness, advanced glycation end products also cause vascular stiffness, which induces ischemic injury to cardiomyocytes. Upregulation of SIRT1 plays a pivotal role in regulating endothelial nitric oxide synthase (eNOS) activity. As is known, eNOS has vasodilatory activity in the vascular system. Increased eNOS activity reduces cardiac infarct size and improves myocardial function by increasing blood flow to the myocardium.[31,32]

In other organs that support the cardiac system, such as blood vessels and the liver, activation of SIRT1 leads to the activation of several proteins, such as PGC-1α, FOXO1, peroxisome proliferator-activated receptor (PPAR)-α, p53, and liver kinase B1 (LKB1). By activating these proteins, SIRT1 induces several mechanisms, such as increased insulin activity, enhanced stress resistance, angiogenesis protection, inhibition of cardiac hypertrophy, and inhibition of inflammation and apoptosis.[30-32]

Role of PGC-1α in cardiac metabolic syndrome

PGC-1 consists of three main groups: PGC-1α, PGC-1β, and PGC-related coactivator (PRC). PGC-1α is a transcription coactivator involved in and interacting with various biological responses, such as mitochondrial biogenesis, glucose/fatty acid metabolism, and heart development.[31]

PGC-1α acts as a major contributor to cardiac mitochondrial biogenesis. In most healthy cardiac organs, PGC-1α is found to be highly expressed in the myocardium, rather than in the sick heart. As we know, the heart is the most energy-demanding organ due to its vital activity. Most of the energy used by the heart is derived from fatty acid oxidation. Increased expression of PGC-1α leads to increased mitochondrial biogenesis, resulting in optimal cellular respiratory functions.[29,33,34]

Metabolic syndrome is associated with defective mitochondrial biogenesis. This alteration is caused by a shift in the source of bioenergy and chronic oxidative stress in the heart.[33,34] Downregulation of PGC-1α causes changes in redox reactions and chronic inflammation. In the heart, decreased expression of PGC-1α induces a reduction in fatty acid oxidation, low ATP production, and an increase in ROS, leading to a decline in cardiac function.[29,35,36]

Cardiac remodeling is the final step in the progression of diabetic cardiomyopathy. As we know, cardiac hypertrophy, and cardiac fibrosis can occur in diabetic cardiomyopathy. Left ventricular enlargement, followed by cardiac fibrosis, is a complication of increased pressure, volume overload, and cardiomyocyte necrosis. PGC-1α activity is suppressed during the overload and can cause an increase in morbidity. Decreased activity of PGC-1α can affect cardiomyocyte fuel use.[37] Cardiomyocytes typically can consume glucose, fatty acids, lactate, pyruvate, ketones, and amino acids. In

cardiac hypertrophy, there is a shift in fuel use, primarily to β-oxidation of fatty acids, with a decrease in the use of glucose. This shift mechanism is related to the decreased expression of PGC-1α.[37]

AMPK/SIRT1/PGC-1α as an adaptation to cardiac metabolic syndrome

Cardiac remodeling is the result of a sequence of pathological insults to the heart. Oxidative stress, lipotoxicity, and neurohormonal activation play a role in the progression of cardiac remodeling. A critical hallmark of cardiac remodeling genesis is the decreased cardioprotective molecules, followed by the replacement of cardiomyocytes with fibroblasts. Cardiac hypertrophy, left ventricular enlargement, reduced diastolic function, and increased systemic resistance contribute to the formation of diabetic cardiomyopathy, ultimately leading to heart failure. The switching of cardiac fuel sources in cardiomyocytes also plays a role in this process.[8,9,18]

Oxidative and mechanical stress on the heart in metabolic syndrome can be countered by the activation of the molecular pathway of AMPK/SIRT1/PGC-1α. As we know, the fundamental mechanism of cardiac remodeling in metabolic syndrome is initiated by insulin resistance and lipotoxicity. Insulin resistance induces an alteration in the switch of energy sources for the heart, causing cardiomyocytes to rely on glucose metabolism. Lipotoxicity causes damage to cardiomyocytes through the generation of ROS and lipid peroxidation. An increasing number of ROS promotes cardiac injury followed by necrotic and apoptotic events. AMPK plays a role in countering lipotoxicity and insulin resistance by increasing insulin sensitivity and regulating redox reactions. SIRT1 plays a role in regulating apoptotic genes and PGC-1α repairs the cardiac fuel source.[37,38,39]

Intracellular repair mechanisms play a pivotal role in reducing the risk of cardiac remodeling. Through the activation of AMPK/SIRT1/PGC-1α, cardiac remodeling is preventable.[7,23,33] Activation of AMPK is triggered by an imbalance in energy sensing in cardiomyocytes and an increase in the expression of GLUT-4. The downstream effects of AMPK also increase the availability of nitric oxide (NO), contributing to a reduction in systemic vascular resistance and an increase in vascular dilation of coronary arteries. Additionally, AMPK activation leads to the activation of SIRT1, which has several molecular pathways that play a role in cardiac remodeling.[23,24,33] By regulating p53, SIRT1 reduces apoptosis, inhibits the activation of matrix metalloproteinases that induce cardiac fibrosis, and activates PGC-1α.

Defective mitochondrial biogenesis causes the inability of cardiomyocytes to produce a respiratory chain reaction, resulting in a lack of ATP in cardiomyocytes. Mitochondrial defects happen to be the cause of cardiac dysfunction in metabolic syndrome, as the heart becomes unable to contract adequately and simultaneously. Downstream activation of PGC-1α plays a pivotal role in increasing mitochondrial biogenesis and repairing cardiomyocyte metabolism. Activation of PGC-1α reduces defective mitochondrial respiration and increases cardiac function.[37,38,39]

Conclusion

Cardiac dysfunction due to chronic metabolic syndrome results in high morbidity and mortality. Cardiomyocytes have several mechanisms to repair the damage caused by metabolic syndrome, and one of them is through the activation of the AMPK/SIRT1/PGC-1α pathway. Activation of AMPK/SIRT1/PGC-1α prevents cardiac remodeling due to metabolic syndrome by increasing insulin sensitivity, increasing mitochondrial biogenesis, and reducing pro-apoptotic signals in cardiomyocytes.

Authors Contribution

AYR and VS were involved in conceptualizing the manuscript's topic and prepared the manuscript draft. AYR performed the literature survey and collection. All authors participated in giving critical revisions of the manuscript.

References

1. Driyah S, Oemiati R, Rustika, Haratati NS. Prediktor sindrom metabolik: Studi kohor prospektif selama enam tahun di Bogor, Indonesia. Media Penelit Pengemb Kesehat. 2019; 29(3): 215-24.
2. Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, *et al.* Metabolic syndrome: Updates on pathophysiology and management in 2021. Int J Mol Sci. 2022; 23(2): 786. doi: 10.3390/ijms23020786.
3. Catharina AS, Modolo R, Ritter AMV, Sabbatini AR, Lopes HF, Moreno Junior H, *et al.* Metabolic syndrome-related features in controlled and resistant hypertensive subjects. Arq Bras Cardiol. 2018; 110(6): 514-21.
4. Lebovitz HE. Insulin resistance: Definition and consequences. Exp Clin Endocrinol Diabetes. 2001; 109 (Suppl 2): S135-48.
5. Bovolini A, Garcia J, Andrade MA, Duarte JA. Metabolic syndrome pathophysiology and predisposing factors. Int J Sports Med. 2021; 42(3): 199-214.

Print ISSN: 2527-4384, Online ISSN: 2527-3442
DOI: 10.21705/mcbs.v8i1.367

6. Cantó C, Auwerx J. PGC-1α, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. Curr Opin Lipidol. 2009; 20(2): 98-105.
7. Ma TK, Kam KK, Yan BP, Lam YY. Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: Current status. Br J Pharmacol. 2010; 160(6): 1273-92.
8. Silveira Rossi JL, Barbalho SM, Reverete de Araujo R, Bechara MD, Sloan KP, Sloan LA. Metabolic syndrome and cardiovascular diseases: Going beyond traditional risk factors. Diabetes Metab Res Rev. 2022; 38(3): e3502. doi: 10.1002/dmrr.3502.
9. Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. Transl Res. 2017; 183: 57-70.
10. Febriza A, Ridwan, As'ad S, Kasim VN, Idrus HH. Adiponectin and its role in inflammatory process of obesity. Mol Cell Biomed Sci. 2019; 3(2): 60-6.
11. Lukito AA, Bakri S, Kabo P, Wijaya A. The mechanism of coronary artery calcification in centrally obese non-diabetic men: Study on the interaction of leptin, free leptin index, adiponectin, hs-C reactive protein, bone morphogenetic protein-2 and matrix Gla protein. Mol Cell Biomed Sci. 2020; 4(2): 88-93.
12. Ambarwati R, Santosa D, Pangarsa EA, Setiawan B, Tobing ML, Sofro MAU, *et al.* High leptin and low adiponectin levels in the metabolic syndrome patients with malignancy. Indones Biomed J. 2023; 15(5): 297-303.
13. Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: Defining their role in the development of insulin resistance and β-cell dysfunction. Eur J Clin Invest. 2002; 32 (Suppl 3): 14-23.
14. Lewis GF, Steiner G. Acute effects of insulin in the control of VLDL production in humans. Implications for the insulin-resistant state. Diabetes Care. 1996; 19(4): 390-3.
15. Juhan-Vague I, Alessi MC, Mavri A, Morange PE. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. J Thromb Haemost. 2003; 1(7): 1575-9.
16. Li A, Zheng N, Ding X. Mitochondrial abnormalities: A hub in metabolic syndrome-related cardiac dysfunction caused by oxidative stress. Heart Fail Rev. 2022; 27(4): 1387-94.
17. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and mitochondrial DNA damage in heart failure. Circ J. 2008; 72 (Suppl A): A31-7.
18. Peoples JN, Saraf A, Ghazal N, Pham TT, Kwong JQ. Mitochondrial dysfunction and oxidative stress in heart disease. Exp Mol Med. 2019; 51(12): 1-13.
19. Mandavia CH, Aroor AR, Demarco VG, Sowers JR. Molecular and metabolic mechanisms of cardiac dysfunction in diabetes. Life Sci. 2013; 92(11): 601-8.
20. Hayden MR, Tyagi SC. Myocardial redox stress and remodeling in metabolic syndrome, type 2 diabetes mellitus, and congestive heart failure. Med Sci Monit. 2003; 9(7): SR35-52.
21. Shirwany NA, Zou MH. AMPK in cardiovascular health and disease. Acta Pharmacol Sin. 2010; 31(9): 1075-84.
22. Allard MF, Parsons HL, Saeedi R, Wambolt RB, Brownsey R. AMPK and metabolic adaptation by the heart to pressure overload. Am J Physiol Heart Circ Physiol. 2007; 292(1): H140-8.
23. Kandula N, Kumar S, Mandlem VKK, Siddabathuni A, Singh S, Kosuru R. Role of AMPK in myocardial ischemia-reperfusion injury-induced cell death in the presence and absence of diabetes. Oxid Med Cell Longev. 2022; 2022: 7346699. doi: 10.1155/2022/7346699.
24. Webster I, Friedrich SO, Lochner A, Huisamen B. AMP kinase activation and glut4 translocation in isolated cardiomyocytes. Cardiovasc J Afr. 2010; 21(2): 72-8.
25. Long YC, Zierath JR. AMP-activated protein kinase signaling in metabolic regulation. J Clin Invest. 2006; 116(7): 1776-83.
26. Cao K, Xu J, Pu W, Dong Z, Sun L, Zang W, *et al.* Punicalagin, an active component in pomegranate, ameliorates cardiac mitochondrial impairment in obese rats via AMPK activation. Sci Rep. 2015; 5: 14014. doi: 10.1038/srep14014.
27. Gray S, Kim JK. New insights into insulin resistance in the diabetic heart. Trends Endocrinol Metab. 2011; 22(10): 394-403.
28. Marino A, Hausenloy DJ, Andreadou I, Horman S, Bertrand L, Beauloye C. AMP-activated protein kinase: A remarkable contributor to preserve a healthy heart against ROS injury. Free Radic Biol Med. 2021; 166: 238-54.
29. Meiliana A, Dewi NM, Wijaya A. Mitochondria in health and disease. Indones Biomed J. 2019; 11(1): 1-15.
30. Chong ZZ, Wang S, Shang YC, Maiese K. Targeting cardiovascular disease with novel SIRT1 pathways. Future Cardiol. 2012; 8(1): 89-100.
31. Ma L, Li Y. SIRT1: Role in cardiovascular biology. Clin Chim Acta. 2015 Feb 2;440:8-15.
32. Karbasforooshan H, Karimi G. The role of SIRT1 in diabetic cardiomyopathy. Biomed Pharmacother. 2017; 90: 386-392.
33. Liang H, Ward WF. PGC-1α: A key regulator of energy metabolism. Adv Physiol Educ. 2006; 30(4): 145-51.
34. Cheng CF, Ku HC, Lin H. PGC-1α as a pivotal factor in lipid and metabolic regulation. Int J Mol Sci. 2018; 19(11): 3447. doi: 10.3390/ijms19113447.
35. Oka SI, Sabry AD, Cawley KM, Warren JS. Multiple levels of PGC-1α dysregulation in heart failure. Front Cardiovasc Med. 2020; 7: 2. doi: 10.3389/fcvm.2020.00002.
36. Zhu X, Shen W, Yao K, Wang H, Liu B, Li T, *et al.* Fine-tuning of PGC1α expression regulates cardiac function and longevity. Circ Res. 2019; 125(7): 707-19.
37. Brainard RE, Facundo HT. Cardiac hypertrophy drives PGC-1α suppression associated with enhanced O-glycosylation. Biochim Biophys Acta Mol Basis Dis. 2021; 1867(5): 166080. doi: 10.1016/j.bbadis.2021.166080.
38. Li W, Cao J, Wang X, Zhang Y, Sun Q, Jiang Y, *et al.* Ferruginol restores SIRT1-PGC-1α-mediated mitochondrial biogenesis and fatty acid oxidation for the treatment of DOX-induced cardiotoxicity. Front Pharmacol. 2021; 12: 773834. doi: 10.3389/fphar.2021.773834.
39. D'Onofrio N, Servillo L, Balestrieri ML. SIRT1 and SIRT6 signaling pathways in cardiovascular disease protection. Antioxid Redox Signal. 2018; 28(8): 711-32.