https://doi.org/10.48047/AFJBS.6.2.2024.4448-4455

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

# Genetic Insights into Metabolic Syndrome and Ischemic Heart Disease: The Role of Renalase and Sirt1 Polymorphisms

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Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 5 July 2024

Accepted: 15July 2024

Published: 15 July 2024

*doi:10.48047/AFJBS.6.2.2024.4448-4455*

**Abstract:** Metabolic syndrome (MetS) and ischemic heart disease (IHD) are interrelated conditions contributing to significant cardiovascular morbidity and mortality worldwide. Emerging evidence highlights the role of genetic polymorphisms in modulating susceptibility to these disorders. This review focuses on the impact of *Renalase* and *Sirt1* gene polymorphisms in patients diagnosed with MetS and IHD. *Renalase*, a secreted flavoprotein, plays a pivotal role in blood pressure regulation, glucose metabolism, and cardiovascular protection, while *Sirt1*, a NAD+-dependent deacetylase, regulates energy metabolism, inflammation, and oxidative stress. Polymorphic variations in these genes may influence their expression and functionality, exacerbating metabolic and cardiovascular derangements observed in MetS with concurrent IHD. This review synthesizes current findings regarding the genetic variants of *Renalase* and *Sirt1* and their association with metabolic dysregulation, endothelial dysfunction, and atherosclerosis progression. Additionally, it explores the potential for these polymorphisms to serve as predictive biomarkers and therapeutic targets. Understanding the genetic interplay of *Renalase* and *Sirt1* polymorphisms could provide insight into personalized medicine approaches, enhancing risk stratification and management of MetS patients predisposed to IHD.

**Keywords:** *Metabolic Syndrome, Ischemic Heart Disease, Renalase, Sirt1, Gene Polymorphisms, Cardiovascular Disease*

## Introduction.

Metabolic syndrome (MetS) is a complex condition characterized by a constellation of interrelated metabolic abnormalities, including central obesity, insulin resistance, dyslipidemia, and hypertension. These abnormalities synergistically contribute to increased risks of cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM) [1]. Its prevalence continues to rise globally, influenced by sedentary lifestyles, high-calorie diets, and genetic predispositions [2].

The global incidence of metabolic syndrome rises almost parallel to the incidence of obesity. However, the incidence of metabolic syndrome is slightly higher in children of low-income countries, which suggests the high economy of the country is not a predictor of metabolic syndrome**.** The prevalence of metabolic syndrome increases with increasing age; almost 40% of people have metabolic syndrome in the 6th decade of their lives.

Although metabolic syndrome involves both men and women equally, it is slightly more prevalent in women than men in certain ethnic groups [2].

The underlying etiology of metabolic syndrome is multifactorial. The proposed causes include genetic predisposition and multiple environmental or lifestyle factors, including obesity, lack of physical activity, and unhealthy dietary habits. The crux of the syndrome is a buildup of fatty tissue, especially in the abdomen, leading to insulin resistance [3].

Proinflammatory cytokines, such as tumor necrosis factor, leptin, adiponectin, plasminogen activator inhibitor, and resistin, are released from the enlarged adipose tissue, which adversely alters and impacts insulin. Insulin resistance can be acquired or due to genetic predisposition. Impairment of the signaling pathway, insulin receptor defects, and defective insulin secretion can all contribute to insulin resistance. Visceral obesity has been identified as the main trigger of all pathways involved in the pathogenesis of metabolic syndrome, and high-calorie intake is the primary cause of visceral fat accumulation [3].

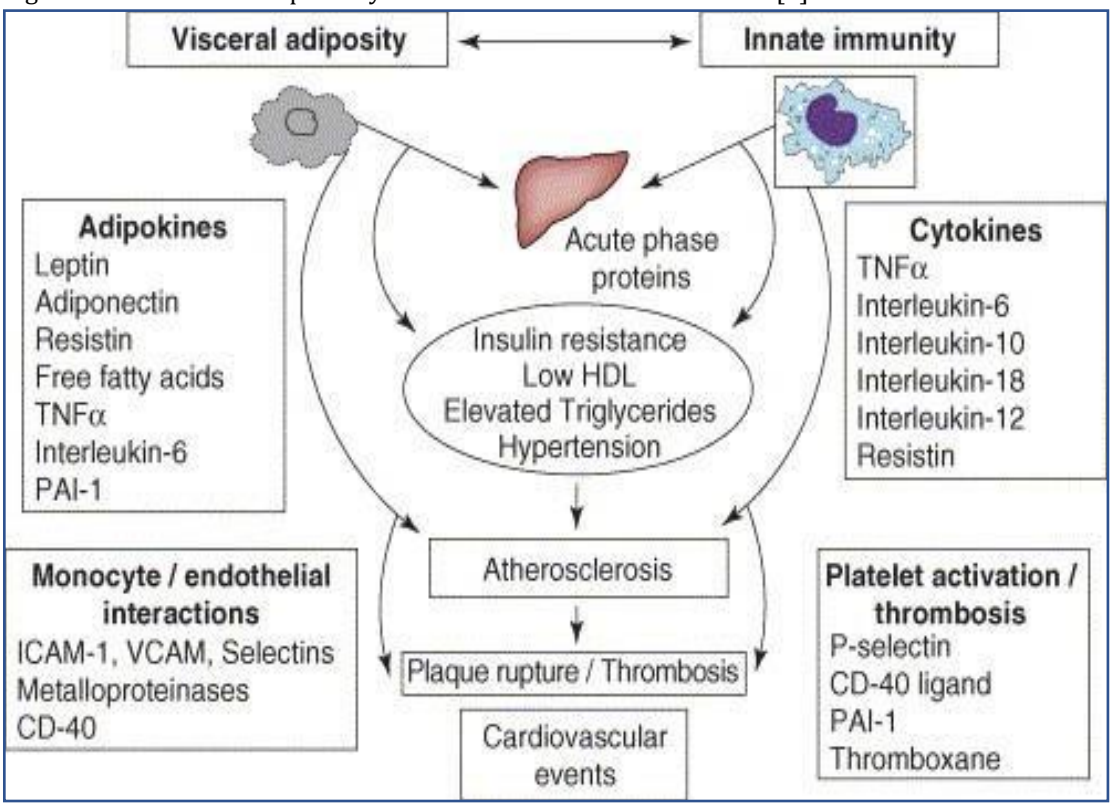


Figure (1): Etiology of metabolic syndrome [3].

Metabolic syndrome has been studied extensively over the past few decades. Insulin resistance, adipose tissue dysfunction and chronic inflammation have been proposed as the basic components of the pathogenesis of metabolic syndrome. Under normal circumstances, a sudden rise in serum glucose level triggers insulin secretion from the pancreatic β-cells, which promote cellular glucose uptake via glucose transporters. However, in those with insulin resistance, tissues are less sensitive to this acute rise in insulin, resulting in a higher serum glucose level and hyperinsulinemia. The impairment in insulin secretion and abnormal insulin signaling results in impaired glucose metabolism, fat deposition, cardiotoxicity, and chronic inflammation, the characteristic features of metabolic syndrome [3].

Visceral obesity is another essential component of metabolic syndrome. Free fatty acids released by the adipose tissues promote insulin resistance and inhibit insulin secretion from the pancreatic beta cells. The high-free fatty acids inhibit glucose uptake in skeletal muscles and increase hepatic gluconeogenesis and lipid synthesis by inducing protein kinases [4].

Both insulin resistance and free fatty acids play a major role in the pathogenesis of hypertension, prothrombotic state, and chronic inflammation. Visceral adipose tissues also secrete multiple active metabolites and various pro-inflammatory cytokines, C-reactive protein, leptin, and resistin, which induce chronic inflammation, a possible mechanism of various complications of metabolic syndrome [3].

The inflammatory cytokines further increase insulin resistance in skeletal muscles, liver, and adipose tissues by inhibiting the insulin signaling pathway in these tissues. These cytokines, especially tumor necrosis factor-alpha, promote insulin resistance by inactivating insulin receptors in the skeletal muscles. Insulin resistance further activates inflammatory cytokines and promotes thrombogenesis by increasing the fibrinogen level. Metabolic syndrome adversely influences several body systems. Insulin resistance causes microvascular damage, predisposing patients to endothelial dysfunction, vascular resistance, hypertension, and vessel wall inflammation. Endothelial damage can impact the body's homeostasis, causing atherosclerotic disease and the development of hypertension [4].

Furthermore, hypertension adversely affects several body functions, including increased vascular resistance and stiffness, causing peripheral vascular disease, structural heart disease comprising of left ventricular hypertrophy and cardiomyopathy, and leading to renal impairment. Accumulated effects of endothelial dysfunction and hypertension due to metabolic syndrome can further result in ischemic heart disease [5].

Endothelial dysfunction due to increased levels of plasminogen activator inhibitor-1 and adipokine levels can cause thrombogenicity, while hypertension causes vascular resistance by which coronary artery disease can develop. Dyslipidemia associated with metabolic syndrome can drive the atherosclerotic process, leading to symptomatic ischemic heart disease [5].

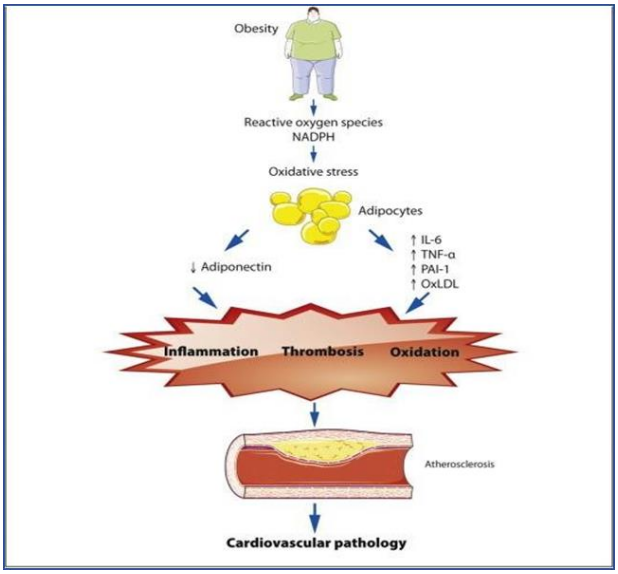


Figure (2): Pathophysiology of metabolic syndrome [6].

The diagnostic criteria for MetS, as defined by the International Diabetes Federation (IDF), underscore the central role of abdominal obesity and its metabolic consequences. Insulin resistance, a hallmark feature of MetS, results from impaired insulin signaling pathways, particularly in skeletal muscle, liver, and adipose tissue. This disruption causes hyperglycemia and compensatory hyperinsulinemia, leading to beta-cell exhaustion and systemic metabolic imbalance [3]. These changes contribute to dyslipidemia, with elevated

triglycerides, reduced HDL cholesterol levels, and an increased prevalence of small, dense LDL particles, all of which potentiate atherogenesis [4].

A significant contributor to the pathogenesis of MetS is the proinflammatory state mediated by adipokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and resistin, released from visceral adipose tissue. These cytokines disrupt endothelial function and increase oxidative stress, forming a vicious cycle that promotes vascular inflammation and atherogenesis [5]. Oxidative stress biomarkers, such as malondialdehyde and reduced glutathione, are markedly elevated in MetS, correlating with disease severity [6].

Genetic susceptibility is increasingly recognized as a critical factor in MetS development. Variants in genes related to lipid metabolism (e.g., APOE), glucose regulation (e.g., PPARG), and inflammation (e.g., TNFA) have been implicated [7]. Of particular interest are genes like *Renalase* and *Sirt1*, which regulate metabolic and oxidative stress pathways, providing potential therapeutic targets for mitigating disease progression [8].

Identifying genetic and molecular biomarkers of MetS, including emerging players such as *Renalase* and *Sirt1*, is crucial for the development of precision medicine. Early recognition of high-risk individuals through genetic profiling can facilitate timely interventions to prevent associated complications like ischemic heart disease (IHD) [9].

**Ischemic Heart Disease**

Ischemic heart disease (IHD), also known as coronary artery disease (CAD), represents the most common manifestation of cardiovascular disease and a leading cause of death worldwide. It primarily results from atherosclerosis, where lipid deposition, endothelial dysfunction, and chronic inflammation lead to coronary artery narrowing and impaired myocardial oxygen delivery [10].

IHD is very common in both developed and developing worlds. It was estimated that IHD represented 2.2% of the overall global burden of disease and 32.7% of cardiovascular diseases. The incidence of IHD is observed to rise with age, regardless of gender. In the ONACI registry, the incidence of IHD was about 1% in the 45 to 65 age group, which increased to about 4% as the age group reached 75 to 84 years [10].

IHD is a multifactorial phenomenon. Etiologic factors can be broadly categorized into non-modifiable and modifiable factors. Non-modifiable factors include gender, age, family history, and genetics. Modifiable risk factors include smoking, obesity, lipid levels, and psychosocial variables [10].

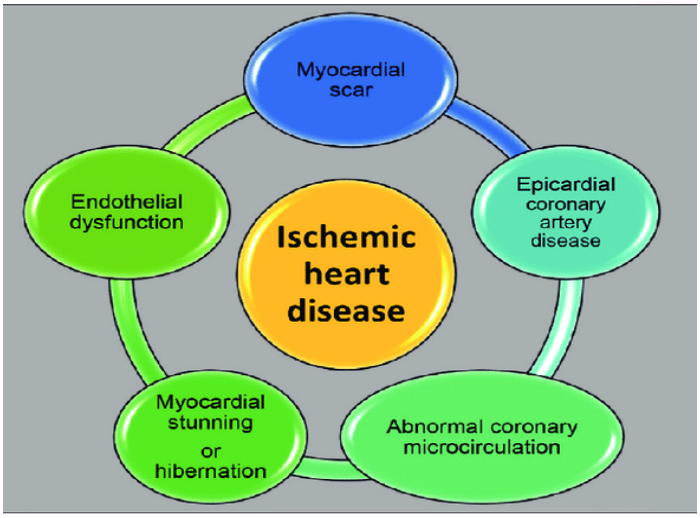


Figure (3): Etiology of IHD [10].

The hallmark of the pathophysiology of IHD is the development of atherosclerotic plaque. Plaque is a build-up of fatty material that narrows the vessel lumen and impedes the blood flow. The first step in the process is the formation of a "fatty streak." Fatty streak is formed by subendothelial deposition of lipid-laden macrophages, also called foam cells. When a vascular insult occurs, the intima layer breaks, and monocytes migrate into the subendothelial space where they become macrophages [11].

These macrophages take up oxidized low-density lipoprotein (LDL) particles, and foam cells are formed. T cells get activated, which releases cytokines only to aid in the pathologic process. Growth factors released activate smooth muscles, which also take up oxidized LDL particles and collagen and deposit along with activated macrophages and increase the population of foam cells. This process leads to the formation of subendothelial plaque [11].

Over time, this plaque could grow in size or become stable if no further insult occurs to the endothelium. If it becomes stable, a fibrous cap will form, and the lesion will become calcified over time. As time passes, the lesion can become hemodynamically significant enough that not enough blood would reach the myocardial tissue at the time of increased demands, and angina symptoms would occur [11].

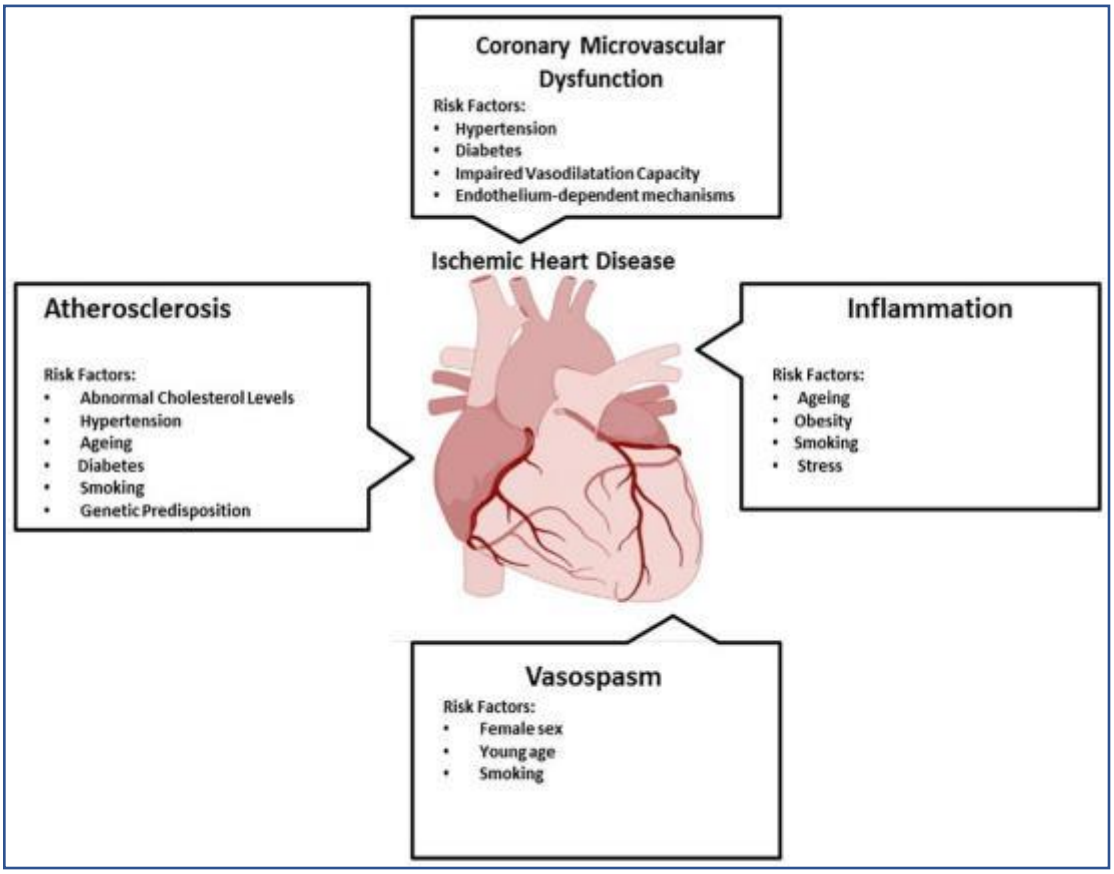


Figure (4): Pathophysiology of IHD [11].

The interplay between MetS and IHD is well-established. Insulin resistance, hyperglycemia, dyslipidemia, and systemic inflammation inherent to MetS accelerate atherosclerosis, plaque instability, and thrombosis, increasing the risk of acute coronary syndromes [11]. This intricate relationship highlights the importance of understanding shared genetic and molecular pathways between MetS and IHD [12].

Atherosclerosis, the pathological substrate of IHD, is characterized by the accumulation of oxidized LDL within the intima, triggering monocyte recruitment and foam cell formation. Proinflammatory cytokines and reactive oxygen species (ROS) perpetuate this cycle, destabilizing plaques and predisposing them to rupture. Key regulators, such as endothelial nitric oxide synthase (eNOS), are inhibited in MetS, further impairing vascular homeostasis [13].

Advances in genomic medicine have identified numerous genetic polymorphisms associated with IHD. Variants in genes regulating lipid metabolism (e.g., LDLR), inflammation (e.g., IL6), and oxidative stress (e.g., NOS3) have been linked to disease susceptibility. Notably, polymorphisms in *Renalase* and *Sirt1* genes emerge as critical

determinants of cardiovascular outcomes in MetS patients, offering novel insights into IHD pathophysiology [14].

By elucidating the genetic determinants of IHD in MetS patients, particularly the contributions of *Renalase* and *Sirt1*, researchers aim to refine risk prediction models and develop targeted therapies to mitigate disease burden [15].

**The Role of Renalase Polymorphisms**

Renalase is an FAD-dependent amine oxidase primarily secreted by the kidneys and heart. It degrades circulating catecholamines, such as dopamine, epinephrine, and norepinephrine, thereby modulating sympathetic tone, blood pressure, and cardiovascular homeostasis [16]. Beyond its enzymatic activity, Renalase exhibits anti-inflammatory, antioxidative, and cytoprotective properties, making it a pivotal player in metabolic and cardiovascular regulation [17].

Polymorphisms in the *Renalase* gene have been implicated in the pathogenesis of hypertension, MetS, and IHD. The rs10887800 variant, located in exon 2, is the most studied. Individuals with the GG genotype demonstrate reduced Renalase activity, leading to heightened sympathetic tone, oxidative stress, and endothelial dysfunction, all of which exacerbate MetS and IHD risk [18].

Decreased Renalase levels have been observed in MetS patients, correlating with elevated markers of oxidative stress (e.g., ROS) and inflammation (e.g., TNF-α, CRP). This deficiency exacerbates metabolic dysregulation by impairing insulin sensitivity and glucose homeostasis, establishing a direct link between Renalase dysfunction and MetS progression [19].

Experimental models further underscore Renalase's cardioprotective effects. In ischemia-reperfusion injury, exogenous administration of Renalase attenuates myocardial apoptosis, inflammation, and oxidative damage, highlighting its therapeutic potential in IHD management [20].

Variants like rs10887800 in the promoter region of *Renalase* influence gene transcription and expression. Reduced expression is associated with impaired antioxidative defense and heightened cardiovascular risk in MetS patients [21]. Combining genetic and environmental insights, such as dietary patterns, provides a comprehensive understanding of Renalase's role in cardiometabolic disorders.

The interplay between *Renalase* polymorphisms and hypertension is particularly noteworthy. Elevated norepinephrine levels due to impaired Renalase activity amplify vascular resistance and stress-induced endothelial damage, fostering atherosclerosis and left ventricular hypertrophy in MetS patients [22].

Future research focusing on Renalase-targeting therapies, such as small molecules that enhance its activity, holds promise for managing cardiometabolic diseases. Genetic testing for *Renalase* polymorphisms may refine patient stratification, facilitating personalized treatment approaches [23].

**Role of Sirt1 Polymorphisms**

Sirtuin 1 (Sirt1), a NAD+-dependent histone deacetylase, regulates gene expression involved in metabolism, inflammation, and oxidative stress. By modulating pathways such as PGC-1α and FOXO, Sirt1 enhances mitochondrial biogenesis, insulin sensitivity, and antioxidative defense, making it a key player in metabolic and cardiovascular health [24].

Polymorphisms in the *Sirt1* gene, such as rs7895833 and rs3758391, influence its enzymatic activity and expression levels. Reduced Sirt1 activity due to these variants impairs glucose and lipid metabolism, increases inflammation, and predisposes individuals to MetS and its cardiovascular complications [25].

In the context of IHD, Sirt1's deacetylation of eNOS promotes nitric oxide production, improving endothelial function and reducing atherosclerosis risk. Polymorphic variations that impair this mechanism exacerbate vascular dysfunction, highlighting Sirt1's central role in IHD prevention [26].

Clinical studies demonstrate that individuals with Sirt1 polymorphisms exhibit elevated levels of oxidative stress markers (e.g., 8-isoprostane) and proinflammatory cytokines (e.g., IL-6), correlating with greater cardiovascular morbidity and mortality in MetS patients [27].

Experimental evidence supports Sirt1 activation as a therapeutic strategy. Compounds like resveratrol and SRT1720 enhance Sirt1 activity, ameliorating insulin resistance, inflammation, and endothelial dysfunction in preclinical models. Understanding the genetic variability in Sirt1 function could optimize the use of these agents in clinical practice [28].

Sirt1 also regulates adipogenesis through deacetylation of PPAR-γ, suppressing visceral fat accumulation and improving lipid profiles. Polymorphisms impairing this pathway contribute to central obesity and dyslipidemia in MetS [29].

The interaction between Sirt1 polymorphisms and environmental factors, such as high-fat diets and sedentary behavior, further modulates cardiometabolic risk. This gene-environment interplay underscores the need for lifestyle interventions tailored to genetic profiles [30].

The identification of Sirt1 polymorphisms as potential biomarkers for MetS and IHD enables early diagnosis and risk stratification. Incorporating genetic testing into routine clinical care may improve outcomes through personalized prevention strategies [31].

Conclusion

Metabolic syndrome and ischemic heart disease share overlapping genetic and molecular mechanisms, with Renalase and Sirt1 polymorphisms playing pivotal roles. These genetic variations influence oxidative stress, inflammation, and metabolic regulation, offering valuable insights into disease pathogenesis and potential therapeutic targets Advancing research into these polymorphisms, particularly their functional consequences and interactions with environmental factors, is essential to harness the full potential of personalized medicine in cardiometabolic disease management

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