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Review Article

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# Multifaceted Mechanisms of Adiponectin on Cardiovascular Health: A Comprehensive Review

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## ABSTRACT

Cardiovascular diseases (CVDs) remain the leading cause of mortality globally, accounting for 19.8 million deaths annually (31.0% of all fatalities). Obesity serves as an independent risk factor for CVD development through the increased production of proinflammatory adipokines due to dysfunctional adipose tissue expansion. Adiponectin, an endocrine hormone synthesized by adipose tissue, exhibits multifaceted protective mechanisms including anti-inflammatory, anti-atherogenic, and insulin-sensitizing properties. Clinical evidence from fundamental scientific research demonstrates that hypoadiponectinemia represents an independent risk factor for cardiovascular disease development. This comprehensive review examines adiponectin's diverse mechanisms of action on cardiovascular health, encompassing its regulatory effects on carbohydrate metabolism through AMPK activation and GLUT4 translocation, lipid metabolism via PPARα pathway modulation, and anti-inflammatory responses through suppression of TNF-α and IL-6. Additionally, we discuss adiponectin's antiatherogenic effects mediated through endothelial nitric oxide synthase enhancement and endothelial progenitor cell functionality. A better understanding of these multifaceted mechanisms could provide insights into novel therapeutic targets and biomarker applications for cardiovascular disease management. Variations in adiponectin levels can serve as valuable indicators for monitoring the effectiveness of lifestyle and pharmacological interventions aimed at improving cardiovascular outcomes.

**KEYWORDS** adiponectin, coronary artery disease, atherosclerosis, anti-atherogenic, anti-inflammation, metabolic regulation

## INTRODUCTION

Despite significant advances in early detection, therapeutic interventions, and pharmacological approaches, cardiovascular disease (CVD) remains the predominant cause of mortality worldwide. The increasing prevalence of CVD has intensified clinical interest in understanding the complex pathophysiological mechanisms contributing to cardiac and vascular diseases, as well as identifying effective therapeutic strategies for CVD prevention and management (1).

The cardiovascular system comprises the heart and vascular network, including arteries, veins, and capillaries (2). CVDs encompass a spectrum of conditions affecting this system, primarily including coronary artery disease (CAD), cerebrovascular disease, peripheral artery disease (PAD), and aortic atherosclerosis (3). Among these, CAD

is marked by insufficient oxygen and blood supply to the myocardium, resulting from an imbalance between myocardial oxygen supply and demand caused by coronary artery stenosis. Atherosclerotic plaque formation within coronary artery lumens creates flow-limiting obstructions, making CAD both preventable and the leading cause of cardiovascular mortality (4).

## EPIDEMIOLOGY

Multiple nationwide epidemiological studies conducted from 1968 to 2016 indicate that coronary heart disease (CHD) prevalence varies between 1.6% and 13.2% across different Indian populations. A comprehensive 1990 survey demonstrated a CHD prevalence of 9.7% in Delhi, highlighting the significant disease burden in urban Indian populations (5).

CVDs result in approximately 19.8 million fatalities annually, representing 31.0% of global mortality and establishing CVD as the leading cause of death worldwide (6). Approximately 80.0% of these deaths occur in low- and middle-income countries, with the World Health Organization reporting that one-fifth of CVD-related fatalities, particularly among younger populations, occur in India (7).

India has an age-standardized CVD mortality rate of 272 per 100,000 individuals, exceeding the global average of 235 according to the Global Burden of Disease Study (8). Notably, Indians develop CVDs approximately one decade earlier than Western populations (9).

### Etiology of coronary artery disease

*Non-modi-fiable risk factors*

- Age progression
- Male gender
- Ethnic background
- Family history of premature CAD

*Modifiable risk factors*

- Type 2 diabetes mellitus
- Systemic hypertension
- Tobacco use and smoking
- Dyslipidemia
- Chronic kidney disease
- Obesity and metabolic syndrome

*Risk-enhancing factors*

- Early menopause
- Preeclampsia history
- Chronic inflammatory diseases
- Persistently elevated triglyceride levels (10)

Male gender demonstrates higher CAD susceptibility compared to females, with elevated inflammatory markers serving as significant independent predictors for CAD development. The 10-year atherosclerotic CVD risk can be assessed using validated ASCVD risk calculators (11).

## PATHOPHYSIOLOGY

A defining feature of the pathophysiology of CAD is the formation of atherosclerotic plaque. These lipid-rich deposits progressively narrow arterial lumens and obstruct coronary blood flow. The pathogenic process initiates with fatty streak formation, where lipid-laden macrophages (foam cells) accumulate sub-endothelially. Vascular endothelial injury creates intimal layer disruption, facilitating monocyte migration into the sub-endothelial space where they differentiate into macrophages. These macrophages transform into foam cells upon consuming oxidized low-density lipoprotein (ox-LDL) particles. Activated T-lymphocytes contribute to the pathogenic process through cytokine production.

Growth factor release stimulates smooth muscle cell contraction and proliferation, which is further enhanced by ox-LDL particles, collagen deposition, activated macrophages, and increased foam cell formation. This complex inflammatory cascade ultimately results in subendothelial plaque development and arterial luminal narrowing (12).

### Classification of coronary artery disease (13)

1. Stable ischemic heart disease (SIHD)
2. Acute coronary syndrome (ACS)
   - ST-elevation Myocardial Infarction (STEMI)
   - Non-ST elevation myocardial infarction (NSTEMI)
   - Unstable angina

### Adiponectin in obesity and cardiovascular disease

Adipose tissue functions as both an endocrine and paracrine organ, synthesizing physiologically active adipocytokines including adiponectin, leptin, and various inflammatory mediators. The relationship between obesity and CVD etiology has been extensively investigated in contemporary research. Obesity increases proinflammatory

adipokine production, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), and plasminogen activator inhibitor type 1, due to dysfunctional adipose tissue expansion (14).

Notably, obese individuals demonstrate significantly lower adiponectin levels compared to other adipokines, and adiponectin specifically suppresses inflammation (15). Clinical and experimental evidence indicates that reduced adiponectin levels contribute to obesity-related complications including chronic inflammation, insulin resistance, and CVD development (16). The effects of adiponectin on inflammation and the cardiovascular system are the main focus of this review.

## Adiponectin

Adiponectin is often referred to as adipocyte complement-related protein of 30 kDa (Acrp30). Fundamental scientific research has established that adiponectin has anti-inflammatory, anti-atherogenic, and insulin-sensitizing characteristics (17). Consequently, comprehensive understanding of adiponectin is essential for scientists. This insight might result in novel therapeutic strategies for conditions such as obesity, metabolic syndrome, CVD, and type 2 diabetes.

## The structural characteristics

The 30-kDa multimeric protein, adiponectin, is released mostly by white adipose tissue, although modest quantities are also generated in other tissues. Full-length human adiponectin has 244 amino acid residues, including an $NH_2$-terminal variable region, a collagenous domain, and a COOH-terminal globular domain (Figure 1). In contrast to human adiponectin, mouse adiponectin comprises a protein consisting of 247 amino acids (18). Adipocytes secrete three oligomeric structures into the bloodstream: a high molecular weight (HMW-300 kDa) biologically active isoform, a trimer (67 kDa), and a hexamer (140 kDa). The monomeric form of adiponectin is indistinguishable in its early state (19).

## Adiponectin receptors

Two structurally homologous seven transmembrane receptors, AdipoR1 and AdipoR2, have been demonstrated to serve as receptors for adiponectin. Their structural makeup differs from that of traditional G-protein coupled receptors (GPCR). In contrast to all other documented GPCRs, AdipoR1 and AdipoR2 possess an inverted membrane architecture, characterized by a cytoplasmic $NH_2$ terminus and an extracellular COOH terminal domain. The AdipoR1 receptor has a high affinity for globular adiponectin and a low affinity for full-length adiponectin. (Figure 1)

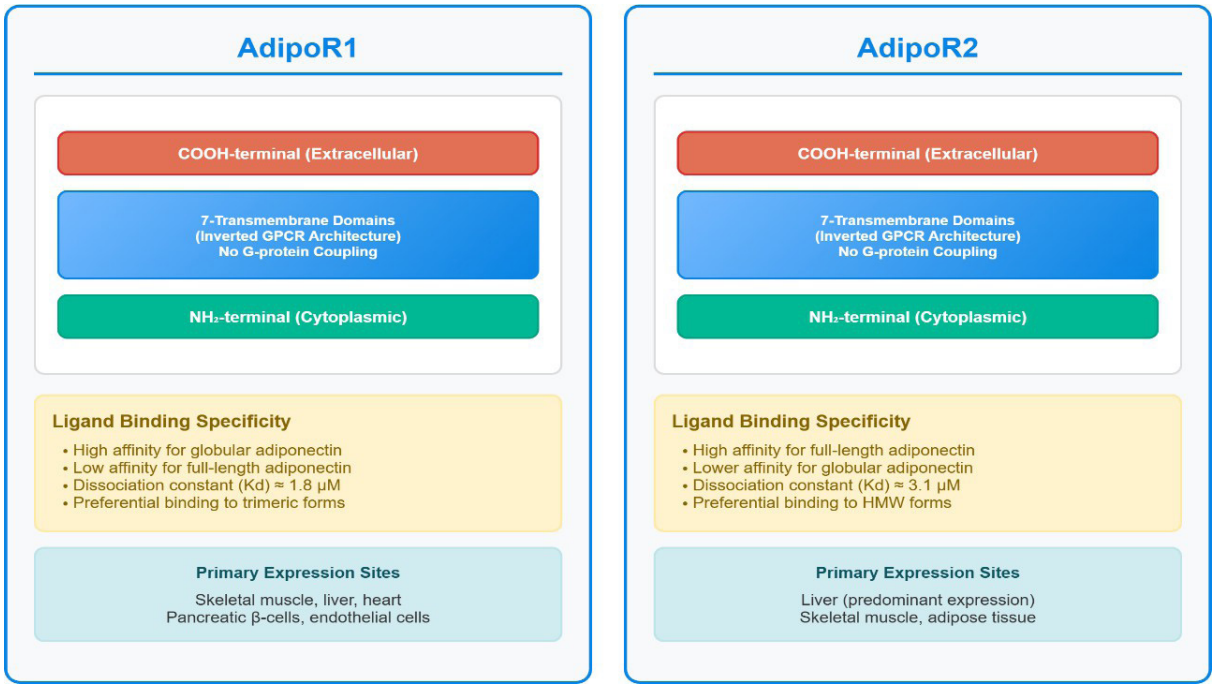


**Figure 1.** AdipoR1 and AdipoR2 receptor structure

In contrast, AdipoR2 predominantly identifies full-length adiponectin and is mostly expressed in the liver (20). In addition to AdipoR1 and AdipoR2, T-cadherin has also been found to be an adiponectin receptor. It specifically functions as a receptor for hexameric or high molecular weight (HMW) adiponectin (21).

## METABOLIC ACTIONS OF ADIPONECTIN

### Effects of adiponectin on carbohydrate metabolism

Adiponectin significantly influences the regulation of lipid and glucose metabolism. Adiponectin promotes glucose absorption via the activation of AMP-activated protein kinase (AMPK). Globular adiponectin has demonstrated the ability to enhance glucose transport in isolated skeletal muscle and cultured myocytes (22, 23).

Research demonstrates that globular adiponectin enhances glucose absorption in skeletal muscle cells by promoting the translocation of glucose transporter 4 (GLUT4) to the cell membrane. Moreover, adiponectin decreased both the baseline and insulin-induced rates of cellular glycogen production (24).

AMPK activation leads to direct phosphorylation and inactivation of glycogen synthase, which explains the reduction in glycogen synthesis after adiponectin treatment. Moreover, it has been demonstrated that in myocytes treated with adiponectin, lactate production takes the place of glucose metabolism (25, 26). Adiponectin deficiency is associated with insulin resistance, poor glucose metabolism, and the eventual onset of heart failure (27).

Adiponectin activates AMPK and AMPK inhibits PEPCK and G-6-Pase, thereby reducing hepatic gluconeogenesis (Figure 2). The phosphorylation of AMPK is most likely the source of adiponectin's inhibitory action on gluconeogenesis. AMPK activation is necessary for the adiponectin-dependent inhibition of PEPCK and G6Pase gene expression and hepatic glucose production (28, 29). These mechanisms demonstrate adiponectin's crucial role in preventing insulin resistance and type 2 diabetes development through enhanced glucose utilization and reduced hepatic glucose production.

### Effects of adiponectin on lipid metabolism

Multiple studies have shown that treating isolated muscle and cultured skeletal muscle cells with the globular domain of adiponectin increases their consumption of fatty acids (30). Peroxisome proliferator-activated receptor alpha (PPARα) activity rises and myocytes' uptake of glucose and fatty acid oxidation is encouraged when full-length and globular adiponectin binds to adiponectin receptors. PPARα activation by adiponectin promotes muscle fatty acid uptake through transcriptional regulation of genes involved in fatty acid oxidation pathways, including carnitine palmitoyl transferase 1, acyl-CoA dehydrogenases, and 3-hydroxyacyl-CoA dehydrogenase, ultimately enhancing cellular energy production from lipids.

Adiponectin also increases the phosphorylation of AMP-activated protein kinase (AMPK) in skeletal muscle, and fatty acid oxidation in skeletal muscle cells is dependent upon AMPK activation (31). The activation of AMPK dependent on adiponectin in skeletal muscle was shown to be linked to an elevation in acetyl-CoA carboxylase (ACC) phosphorylation and a reduction in malonyl-CoA levels. Since carnitine palmitoyl transferase 1 (CPT-1) is subject to allosteric inhibition by malonyl-CoA, decreased malonyl-CoA levels following adiponectin administration enhance fatty acid oxidation in muscle (Figure 2) (32).

Adiponectin also influences the metabolism of myocardial fatty acids. The globular domain of adiponectin markedly enhances fatty acid oxidation in the myocardium. This impact has been suggested to be independent of AMPK activity (33). Prolonged adiponectin treatment has been shown to reduce hepatic triglyceride concentrations and to enhance insulin sensitivity (34).

In summary, adiponectin enhances fatty acid oxidation in both skeletal and cardiac muscle through AMPK-dependent and independent mechanisms, while reducing hepatic triglyceride synthesis, collectively improving metabolic health and cardiovascular outcomes.

### Adiponectin and insulin resistance

Insulin resistance, characterized by a subnormal response to physiological insulin concentrations, complicates the ability of insulin targets to meet the body's metabolic requirements, distinguishing type 2 diabetes. Clinical symptoms of

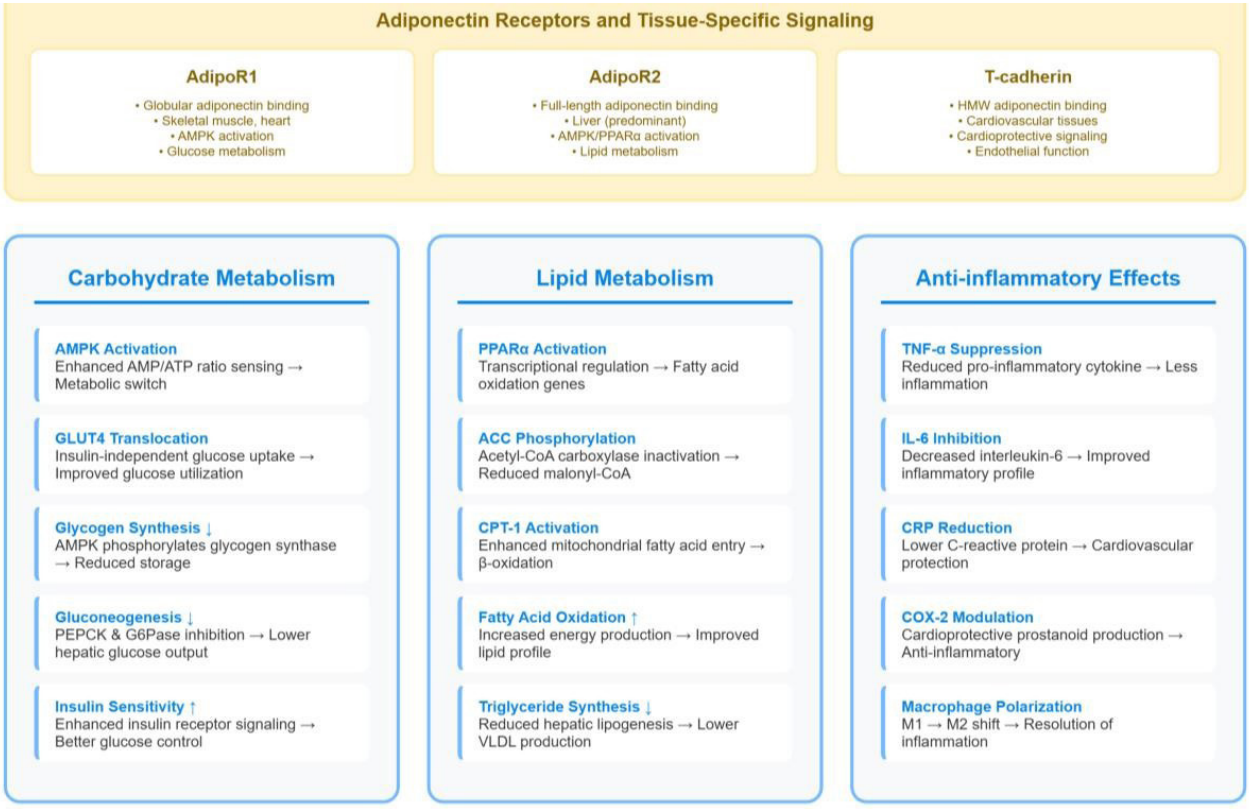


**Figure 2.** Adiponectin role in carbohydrate and lipid metabolism

this condition include hyperglycemia, hyperinsulinemia, dyslipidemia, decreased plasma adiponectin levels, elevated inflammatory markers, and heightened morbidity and mortality associated with liver and renal failure, as well as cardiovascular and neurological illnesses (35). Insulin resistance arises from many mechanisms at the cellular level, including compromised insulin signal transduction, enhanced insulin antagonistic pathways, and damaged effector molecules within insulin- dependent pathways (36).

Adiponectin is a prominent insulin sensitizer. A variety of methods have been employed to ascertain and delineate its insulin-sensitizing properties, in vivo target tissues, and fundamental processes. The plasma glucose levels in rats after intraperitoneal administration of full-length adiponectin are reduced. The influence of insulin levels on the rate of glucose clearance in peripheral organs is minimal; this effect arises mostly from a decrease in hepatic glucose synthesis. Secondly, adiponectin suppresses gluconeogenesis by reducing the expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. Consequently, the liver serves as a principal target tissue for full-length adiponectin (37).

Elevating HMW adiponectin via fat-specific overexpression of DsbA-L, a prevalent adipose protein that facilitates adiponectin multimerization, phosphorylates hepatic AMPK-α at Thr172, essential for 5′-AMP-activated protein kinase (AMPK) activation, and mitigates hepatosteatosis and insulin resistance induced by a high-fat diet (38), without influencing skeletal muscle AMPK activation (39). An additional independent experiment revealed that adiponectin treatment enhances fatty acid oxidation in skeletal muscle and inhibits lipid accumulation in the liver by activating AMPK. This enhances overall in vivo insulin sensitivity and reduces triglyceride levels in the muscle and liver (Figure 3) (30).

These results indicate that skeletal muscle is an additional significant target of adiponectin. Multiple investigations in 2001 independently established adiponectin's insulin-sensitizing properties (31).

Independent of plasma insulin concentrations, recombinant adiponectin overexpression or administration mitigates insulin resistance and lowers blood glucose levels in obese mice (40). Although adiponectin alone is not an optimal target for insulin-sensitizing pharmaceuticals, the

elements of the signaling cascade present interesting opportunities. Recent studies have shown that the small-molecule adiponectin receptor activator AdipoR enhances glucose tolerance and insulin resistance in mice subjected to a high-fat diet (41, 42).

## Adiponectin's antiatherogenic effects

Numerous clinical investigations indicate a correlation between atherosclerosis and plasma adiponectin levels. Plasma adiponectin concentrations below 4.0 mg/mL were recognized as an independent risk factor for CAD in Japanese males, even controlling for other coronary risk factors (43). In prospective investigations, increased plasma adiponectin levels correlated with reduced risks of acute myocardial infarction in healthy individuals and CAD in individuals with type 2 diabetes (44, 45). Adiponectin inhibits atherosclerosis through many mechanisms affecting the heart and blood vessels.

Adiponectin modulates endothelial nitric oxide synthase (eNOS), a crucial element of endothelial function and angiogenesis. Adiponectin facilitates the phosphorylation of extracellular nitric oxide synthase in endothelial cells through signaling pathways dependent on AMP-activated protein kinase (AMPK) (46, 47). Adiponectin counteracts the inhibitory effect of OxLDL on eNOS activity and augments both eNOS production and activity in endothelial cells (48, 49).

Adiponectin enhances the quantity and functionality of endothelial progenitor cells (EPCs), hence facilitating angiogenesis and endothelial repair, as evidenced by studies conducted on humans and animals (50). Adiponectin inhibits the migration and proliferation of vascular smooth muscle cells, hence preventing neointima formation. In addition to its beneficial effects on endothelial function and EPC-mediated endothelial repair, it also suppresses inflammation and the generation of macrophage foam cells (Figure 3) (51).

## Adiponectin's anti-inflammatory properties

The association between adiponectin levels and pro-inflammatory markers in various populations has been the subject of several studies. Research indicates that the inflammatory marker C-reactive protein (CRP) is an independent predictor of future cardiovascular risk and a risk factor for the development of the metabolic syndrome (52). Plasma adiponectin levels and plasma CRP levels in males are negatively correlated (53). Two important proinflammatory adipokines that aid in regulating the hepatic production of CRP are TNF-α and IL-6 (54).

Experimental studies have demonstrated that adiponectin affects the production and function of TNF-α in many organs, whereas pro-inflammatory cytokines like TNF-α and IL-6 have a negative effect on adiponectin expression. As a result,

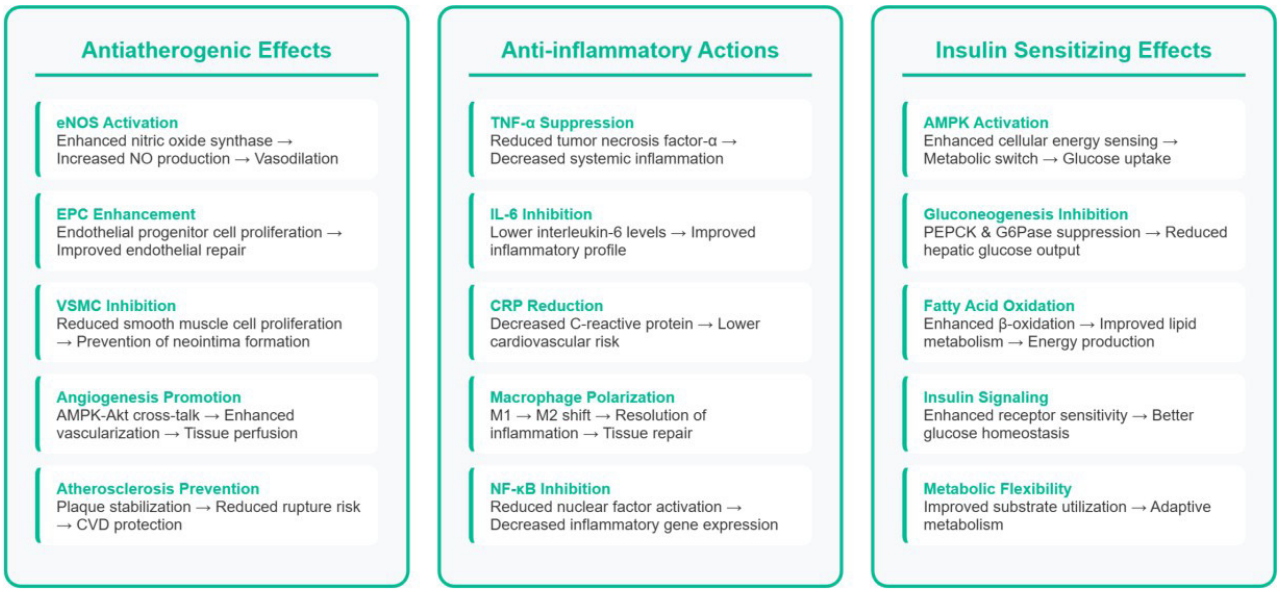


**Figure 3.** Protective effect of adiponectin

several investigations show that association between hypoadiponectinemia and increased IL-6 levels (55).

The rate-limiting enzyme COX-2, which is involved in the production of prostanoid, appears to be the mechanism by which adiponectin inhibits cardiac ischemia/reperfusion (I/R)-induced inflammation. Through sphingosine kinase-1, adiponectin increases the activity of COX-2 and promotes its synthesis in cardiomyocytes, while also reducing reactive oxygen species (ROS) production through enhanced antioxidant enzyme expression and mitochondrial function improvement (Figure 3) (56, 57).

## CLINICAL IMPLICATIONS AND THERAPEUTIC POTENTIAL

Understanding adiponectin's multifaceted mechanisms provides valuable insights for CVD management. Adiponectin analysis can enhance patient treatment approaches and improve outcomes for individuals with CAD. Lower adiponectin levels may indicate higher atherosclerosis risk, while variations in adiponectin concentrations serve as indicators of lifestyle or medication intervention effectiveness.

Elevating plasma adiponectin levels through pharmacological or lifestyle interventions represents a promising therapeutic approach for CVD treatment. Recent developments include adiponectin receptor agonists such as AdipoRon and ALY688, which have shown promise in preclinical studies for treating metabolic and CVDs (58, 59). Several pharmaceuticals and compounds with anti-diabetic and cardiovascular protective properties have been shown to increase plasma adiponectin levels in both human and animal studies, supporting the therapeutic potential of adiponectin pathway modulation. In contrast, several other studies have indicated that higher adiponectin levels correlate with adverse outcomes in heart failure (60, 61).

## CONCLUSIONS

Adiponectin is an adipokine released by adipose tissue. Current research suggests that adiponectin may have a role in several biological processes and metabolic activities. These encompass lipid metabolism, insulin sensitivity, inflammation, and energy management. Diabetes and CVD have a negative correlation with adiponectin levels.

Previous clinical and experimental research has evidenced the numerous beneficial effects of adiponectin on metabolic and cardiovascular issues related to obesity. This is attributable to the close proximity of cardiovascular tissue and adiponectin. Adiponectin regulates circulatory function via paracrine and endocrine mechanisms. Adiponectin is a significant component that modifies the relationship among adipose tissue, cardiac cells, and the vasculature.

The therapeutic potential of elevating plasma adiponectin levels through pharmacological and/or lifestyle interventions offers promising novel approaches for CVD treatment as well as providing epidemiological data establishing a definite association between adiponectin and the condition. Several pharmaceuticals and other substances exhibiting anti-diabetic and cardiovascular protective properties elevate plasma adiponectin levels in both humans and animals.

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## CONFLICT OF INTEREST

The authors declare no competing interests related to this work.

## ADDITIONAL INFORMATION

### Author contributions

All authors participated in literature review, data analysis, manuscript preparation, and revisions, and consent to assume responsibility for all aspects of this study.

### Ethical considerations

This publication adhered to all ethical standards for research without direct human subject interaction.

## Data availability

Data sharing is not applicable to this review article as no new data were generated or analyzed.

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