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ASSOCIATION OF ADIPONECTIN & T- CADHERIN WITH CARDIOVASCULAR DISEASE – A REVIEW ARTICLE

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Manuscript running title: Association of Adiponectin & T- Cadherin with CVD

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ABSTRACT
Adipose tissue secretes adipokines like adiponectin during physiological and pathological states. Adiponectin is related with diet-induced and inflammation – induced obesity, which has secondary adverse effects on cardiovascular system.
T-cadherin is the receptor of adiponectin which is expressed in the heart and blood vessels. Various Experimental studies show that T-cad is linked with adiponectin in cardiovascular tissues and is essential for adiponectin-associated cardio-protection.
Recent studies and the analysis of data reflect that T-cadherin (encoded by CDH13 gene) is concern with the onset of atherosclerosis and coronary heart disease (CHD) and its development. Single nucleotide polymorphisms (SNPs) in CDH13 gene are associated with T-cadherin & adiponectin and with the levels of lipid, but their role in coronary artery disease and its development is yet to be investigated.
This review suggests that the mechanism of action and the association of adiponectin and T-cadherin in relation to cardiovascular diseases (CVDs) may play a significant role to reduce the CVDs complications and associated mortality. Furthermore, studies are required to find out the association of adiponectin and T-cadherin with CVDs.
Keywords: Adiponectin, Cardiovascular diseases, CDH13 gene, T-cadherin

INTRODUCTION

Adipose tissue secretes a hormone with an anti-inflammatory, anti-atherogenic, and anti-diabetic properties called adiponectin**.**[1]
Abdominal fat tissue generally composed of large adipocytes that can produce pro-inflammatory cytokines and low levels of anti-inflammatory factors, such as adiponectin, maintaining chronic inflammation and insulin resistance**.**[2]
Adiponectin, a multimeric protein and one of the most abundant gene products expressed in adipose tissue,[3] is well known to play a critical role in metabolic regulation, affecting obesity, insulin sensitivity, and atherosclerosis**.** Structure of adiponectin and its receptors are summarized in **figure 1.**
Several studies have shown that adiponectin is involved in numerous biological effects, including anti-diabetic, anti-oxidant, and anti-atherosclerotic actions.[4] By contrast, elevated systemic and local levels of adiponectin are present in patients with immune-mediated and inflammatory diseases.[5]
Various studies reveal the multifactorial effects of adiponectin in adipocytes of adipose tissue and energy homeostasis which shows a great impact on circulatory levels and storage sugar levels.[6]
Adiponectin produced from adipocytes is the important molecule to inhibit the development and progression of atherosclerosis. It is analyzed that the hypoadiponectinemia had various risk factors for coronary artery disease, like

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visceral fat obesity, hypertension, impaired glucose tolerance and dyslipidemia, including low HDL–cholesterol.[7]One of the major mechanisms by which HDL protects against atherosclerosis is postulated to be so-called reverse cholesterol transport (RCT).[8]

T-cadherin is a receptor for the adipocytokine adiponectin, indicating that it can modulate metabolism; its function here is only beginning to be elucidated.[9]

It was previously shown that LDL stimulates the production of short-lived T-cadherin clusters and assures the cholesterol-dependence signaling of the calcium.[10]

Suppression of macrophage-to-foam cell transformation is one of the anti-atherosclerotic effects of adiponectin.[11]

T-cadherin, unlike other cadherins, is not responsible for cell adhesion but participates in intracellular signal transmission.[12] It has been demonstrated that T-cadherin is essential for the cardio-protective effect of adiponectin, and has been associated with insulin secretion.

T-cadherin, of the trans-membrane proteins that facilitate calcium-dependent intercellular adhesion, is the receptor for hexameric and high molecular weight (HMW) adiponectin expressed in the vasculature[13] and cardiac myocytes.[14]

T-cadherin is a glycosylphosphatidylinositol-anchored protein; it belongs to the cadherin superfamily and is a receptor for low density lipoproteins (LDL).[15]

Various studies show that Single nucleotide polymorphisms (SNPs) in T-cadherin gene (CDH13) can affect adiponectin concentrations in blood and thus be a part of the mechanism of cardiovascular disorders.

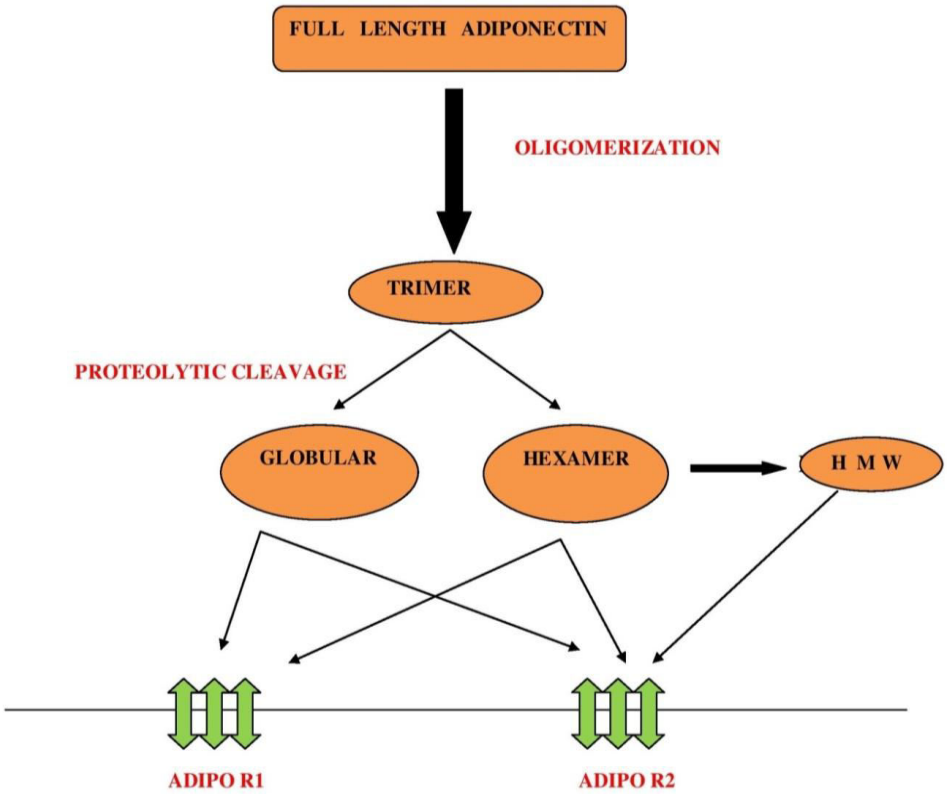

FIGURE 1: STRUCTURE OF ADIPONECTIN AND ITS RECEPTORS

ADIPO R1: Adiponectin receptor 1, ADIPO R2: Adiponectin receptor 2, HMW: High molecular weight adiponectin.

PREVALENCE OF CVD

As per World Health Organization (WHO) analysis in 2008, that out of 17.3 million CVD deaths worldwide, heart attacks (myocardial infarction) and strokes were responsible for 7.3 and 6.2million deaths, respectively.[16]

Recent reports of three studies (prospective study) done in India shows a higher mortality proportion attributable to CVD i.e., 30% - 42% and an age- standardized mortality rate due to CVD was 225-525 per 100,000 population in men and 225-299 per 100,000 population in women was noted by the global burden of disease study 2010.[17]

MECHANISM OF ADIPONECTIN AND CVD ASSOCIATION

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Adiponectin is a multifunctional molecule which protects the vessel wall in early process of the atherosclerosis inhibiting neointimal, smooth muscle cell proliferation, and lipid deposition on the vascular wall.[18]
Studies reported that serum adiponectin level was seen to be lower in T2DM patients when compared with healthy controls and hypoadiponectinemia was strongly associated with T2DM, insulin resistance, obesity and other metabolic diseases.[19]
Adiponectin is a protein hormone with 244 amino acids derived from adipose tissue and mainly target adiponectin receptors and exerts functions such as anti-atherogenic, anti- inflammatory, anti- diabetic and cardioprotective effects.[20]
It is primarily found in white adipose tissue (WAT) and also could be found in cardiomyocytes. It has two widely expressed receptors (AdipoR1) and (AdipoR2) which cross the cerebrospinal fluid in the brain**.**[21]
Both receptors are critical in inducing AMP-activated protein kinase (AMPK) activity for regulating metabolism of fatty acids, carbohydrate, cholesterol, cell growth etc.
Hypertrophic cardiomyopathy studies show that overexpression of adiponectin had reduced the hypertrophy by activating the AMPK and inhibits the hypertrophic response to α – adrenergic receptor stimulation.
Adiponectin's anti-hypertrophic activities on AMPK are thought to occur via the receptors of AdipoR1 and AdipoR2**.**[22] Mechanism of adiponectin and its receptors are elucidated in **figure 2.**
Adiponectin resistance in skeletal muscle and liver tissue causes development of systemic hyperglycemia and hyperlipidemia resulting in vascular injury and cardiovascular complications.

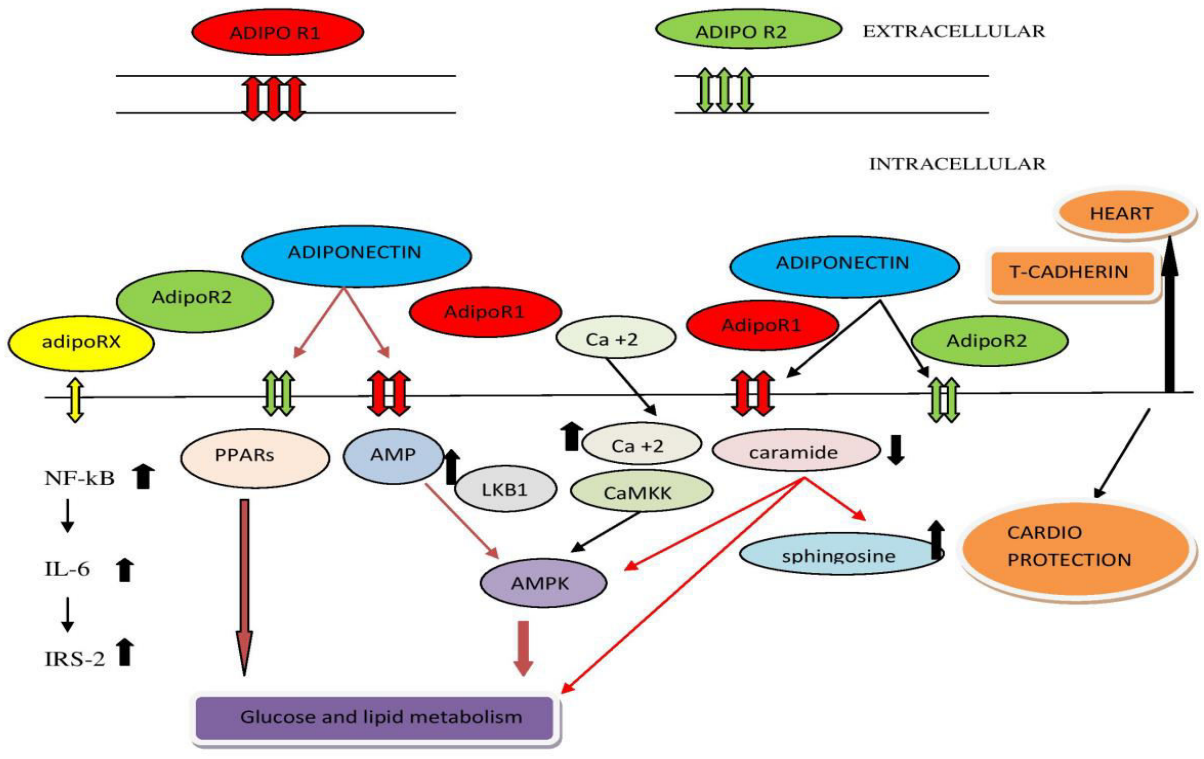

FIGURE 2: MECHANISM OF ACTION OF ADIPONECTIN AND T – CADHERIN THROUGH ITS RECEPTORS
ADIPO R 1: Adiponectin receptor 1, ADIPO R 2: Adiponectin Receptor 2, AMP: Adenosin mono phosphate, AMPK: AMP activated protein kinase, CaMKK: Calcium dependent Mitogen – activated protein kinase kinase, IL-

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6: Interleukin - 6, IRS – 2: Insulin receptor substrate - 2, LKB1: Liver kinase B1, NF-kB – Nuclear factor kappa light chain enhancer of activated B cells, PPARs: Peroxisome proliferator- activated receptors.

RISK FACTORS FOR CVD

CVD is currently one of the main causes of morbidity and mortality worldwide. Findings support the hypothesis that adiponectin levels could be a predictive factor in addition to traditional cardiovascular risk factors and that low adiponectin values may indicate the development of atherosclerosis.[23]

A recent study reflects that in a population of 240 Mexican children serum levels of adiponectin, but not those of other adipocytokines, were inversely associated with high blood pressure values. These results were confirmed after adjustment for BMI and waist circumference.[24]

Obesity as well as insulin resistance both involved in the development of the metabolic syndrome. The metabolic syndrome is characterized by hypertension, impaired fasting glucose levels, central obesity, and dyslipidemia. Its prevalence is continuously increasing in children and adolescent worldwide. Low plasma adiponectin levels indicate the development of metabolic syndrome in both adults.[25]

Studies published over the last ten years, reflects that adipokines play an important role in glucose and lipid metabolisms, and in the development of cardiovascular and metabolic complications of obesity.[26]

T- CADHERIN AND RISK FACTORS FOR CVD

Anchoring a low-density lipoprotein or adiponectin to T-cadherin can stimulate a nuclear factor kappa light chain enhancer of activated B cells (NFκB) signaling pathway, which plays a key role in inflammation and links obesity and vascular disease.[27]

The mechanism of formation of atherosclerotic plaque has not been fully studied. Some studies reflect that T-cadherin plays an important role in the development and progression of atherosclerosis and CHD.[28]

Recent reports have shown that an adiponectin receptor (T-cadherin receptor) that is characteristically expressed on endothelial and vascular smooth muscle cells, is involved in several inflammatory diseases such as coronary artery disease (CAD)**.**[29]

It has been shown that adiponectin suppressed neointimal and atherosclerotic plaque formations through T-cadherin**.**[30] Studies have also shown the importance of adiponectin/T-cadherin association in cardiovascular protection.

Experimental studies have shown that deregulation of T-cadherin expression in vascular cells is associated with disorders such as hypertension, restenosis and atherosclerosis**.**[31]

T-cadherin protects vascular endothelial cells against oxidative stress-induced apoptosis and facilitates vascular remodeling**.**[32]

Furthermore, studies showed that SNPs closer to the T-cadherin gene correlates strongly with plasma adiponectin level and CVDs in human subjects.

Through the association with T-cadherin, adiponectin seems to diminish pathological cardiac remodeling, promote re-vascularization, and exert vasculo-protective actions.[33]Association of adiponectin and T- cadherin with CVD is shown in **figure 3.**

SNPs near the T-cadherin gene strongly correlated with circulating adiponectin levels in humans**.**[34] The decrease in myocardial T-cadherin levels might be related to an increased concentration of circulating adiponectin, and the diminished anti-inflammatory activity of this adipokine**.**[35]

Several studies have shown that SNPs in T-cadherin gene (CDH13) may influence the level of adiponectin in blood, thus some CDH13 gene SNPs possibly may lead to the development of CVDs.

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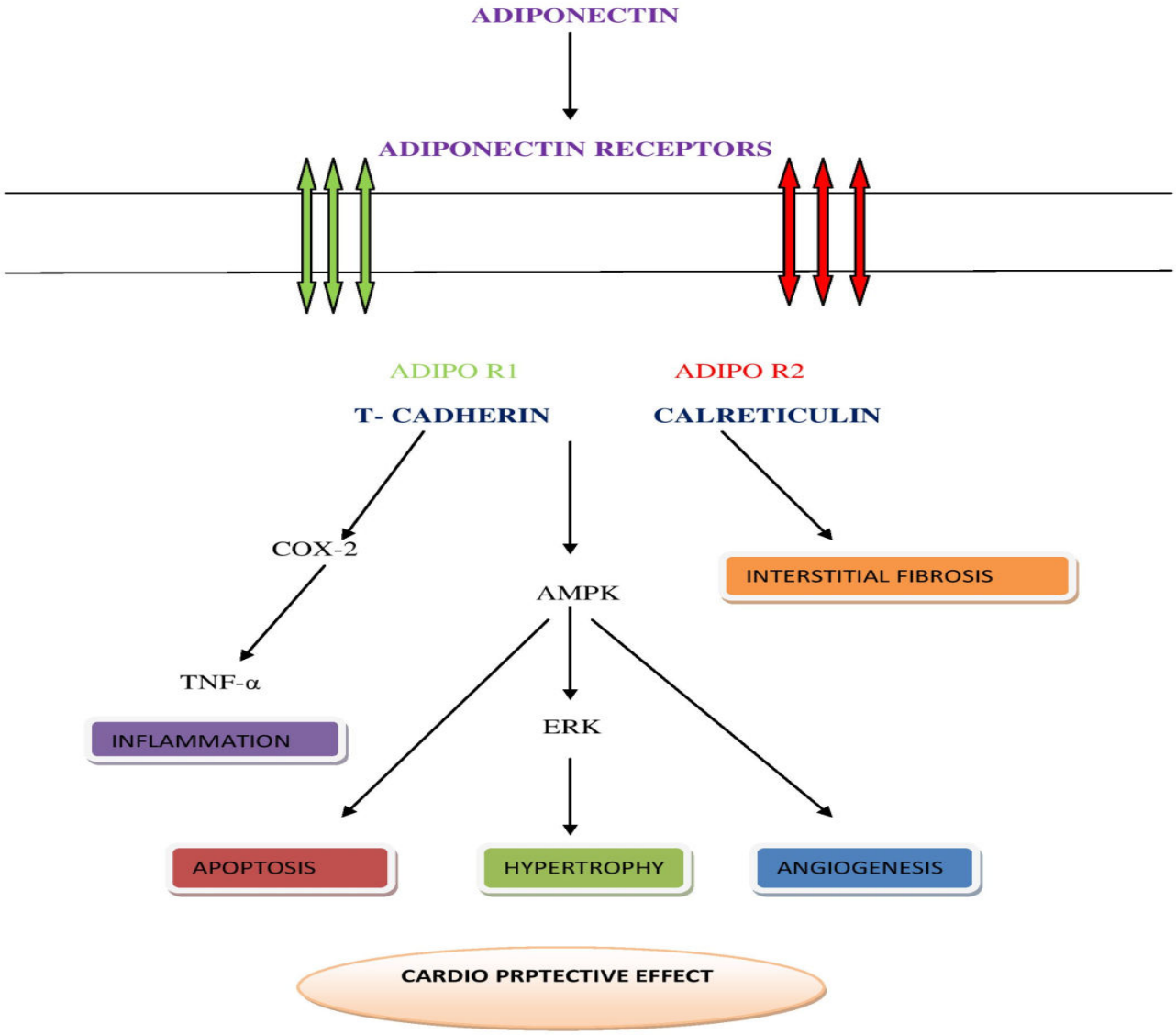

FIGURE 3: ASSOCIATION OF ADIPONECTIN AND T-CADHERIN WITH CVD

AMPK: AMP activated protein kinase, COX – 2: Cyclooxygenase -2, ERK: Extracellular – signal- regulated kinase, TNF –α: Tumor necrosis factor - alpha.

Several SNPs in *CDH13 gene* affect the expression of T-cadherin and the levels of adiponectin and lipids in blood plasma, but the connection between these SNPs and CHD development has not been studied yet.

This article shows that the association of adiponectin receptors and T-cadherin for the cardio-protection. Furthermore, CDH13 gene SNPs studies are required to investigate the circulatory level of T cadherin and its genetic association in CVDs patients. This review highlighted that T-cadherin and its association with CVD may be major footsteps towards finding a genetic link and therapeutic approaches that may help to significantly reduce CVDs complications and associated mortality.

CONCLUSION

Previous studies indicated that the multiple mechanisms are involved in the association between adiponectin and inflammatory markers levels, in which T-cadherin plays an important role in circulating adhesion molecule levels. Low level of adiponectin would contribute to the CVD via AMPK activity.

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Reduced cardiac T-cadherin levels might be an additional indicator of heart failure severity and lead to the diminished anti-inflammatory role of adiponectin in the myocardium of patients with chronic non- ischemic dilated cardio- myopathy.

Reviewing previous studies, it can be concluded that adiponectin receptors are associated with glucose and lipid metabolism which in future may results in type 2 diabetes mellitus (T2DM) and CVDs. T-cadherin is the receptor for LDL and is essential for cardio- protective effect of adiponectin. Further study is required to elucidate the association of T-cadherin and development of CVDs.

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