Research article

Circulatory T-cadherin is a potential biomarker for atherosclerosis

Mohd Danish Khan¹, Mohammad Kaleem Ahmad², Roshan Alam³, Fahad Khan⁴, Mohammad Mustufa Khan¹,⁴

¹Department of Biochemistry, Integral Institute of Medical Sciences & Research (IIMSR), Integral University Lucknow, 226026, Uttar Pradesh, India
²Department of Biochemistry, King George’s Medical University (KGMU), Lucknow, 226003, Uttar Pradesh, India
³Department of Biotechnology, Noida Institute of Engineering and Technology (NIET), Greater Noida, 201306, Uttar Pradesh, India
⁴Department of Basic Medical Sciences, Integral Institute of Allied Health Sciences & Research (IIAHSR), Integral University, Lucknow, 226026, Uttar Pradesh, India

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ABSTRACT

T-cadherin, a special member of cadherin family, expresses with blood circulation involving the heart i.e. CVS. Cadherin is connected with the healthy conditions of an individual and normal functioning of cardio-vascular metabolism. T-cadherin is mainly associated with blood vascular system of human. Previous studies analysed this cadherin been unexpressed within the fat storing tissues i.e. adipose tissue of peri-aortic and peri-coronary, it is present within endothelium as well as in vascularized smooth muscular cells which includes the area nearby coronary vessels and aorta. The area and site of this cadherin is attention-grabbing because it particularly related to atherosclerosis and cardiovascular disease (CVD). T-cadherin - a protein acting as the receptor for low density lipoproteins (LDL). It may act as a special biomarker for atherosclerosis. Previous studies on T-cadherin showed that it has cardio-protective role. Furthermore, research is essential to enumerate the cardio-protective function of T-cadherin. It can be an important therapeutic target in developing new medicine to decrease incident of heart disease and its complications.

Keywords: Atherosclerosis; cardiovascular disease; cardio-protective; low density lipoproteins; T-cadherin.

INTRODUCTION

Atherosclerosis is basically a long term slow progressive inflammatory disease involving large arteries that may starts by the activating and injury to vascular tissues and vascular endothelium after exposure to different risk factors related to cardiovascular diseases (CVD) (1). The key mechanism of atherosclerosis is the build-up of low-density lipoprotein (LDL) within vessel wall, the progress of inflammation, increasing the quantity of extra-cellular matrix (ECM) within the affected area and formation of plaque. LDL affects the vascular cells because of the carriage of cholesterol inward the cells and also due to their capability to induce intracellular signalling (2).

LDL has binding affinity with a G-protein coupled receptor (GPCR). This receptor is a glycosyl-phosphatidyl-inositol (GPI)-anchored protein that binds with T-cadherin or H-cadherin or cadherin-13 or CDH13. T-cadherin expressing cells when it binds with LDL (3), It is seen on surface of cells, it does not have any intracellular domain. T-cadherin presents predominantly in aorta, iliac, carotid, and in heart (4).

T-cadherin increases or decreases the functions of the endothelium cells (ECs) (5). In-vitro appearance of T-cadherin is related with the proliferation of ECs and smooth muscle cells (SMC). It is also linked with the cell organelle endoplasmic reticulum (ER) and stress condition during oxidative stress in the cells of endothelium. Several studies revealed that T-cadherin involves in multi-functional work for the vascular system (6). Collected evidence reflects the significance related to T-cadherin in survival and damage of vascular cells (VC) (7).

Cadherin (T cadherin)

A GPI-anchored protein and presents on the cell-surface and is not present at the position of inter-cellular junction. It consists of the extra-cellular structure of type I cadherin, which does not have cytoplasmic and trans-membranous domains. T-cadherin in cells is related with disorders like hypertension, restenosis, and atherosclerosis. The participation of T-cadherin is reported in angiogenesis and vascular alteration (8). According to the Genome-wide association study i.e. (GWAS), T-cadherin affects metabolism of glucose as well as diseases linked with coronary artery (9).

The high levels of T-cadherin in heart might be related with the better local control of inflammation, consequently conserving cardiac function. The joining between T-cadherin and adiponectin (APN) is essential within myocardium. Reduced cardiac T-cadherin levels may deteriorate the anti-inflammatory action of adipokine (10).

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Biomedicine- Vol. 42 No. 3: 2022

417
**T-cadherin structure**

T-cadherin has an adhesive structure that involves Ca2+ dependent cell to cell union in tissues of an organism. T-cadherin-mediated cell to cell junctions get produced via interaction in between extra-cellular domains between similar cadherin, those are localized on the membranes of the adjacent cells. Stability of adhesion junctions are confirmed by the union of intracellular cadherin with actin cytoskeleton.

Most of the proteins of cadherin family are trans-membrane glycol-proteins which can cross the domain of the membrane once. T-cadherin protein chain N- termini is located outer region of cell and C- termini is located inside the cell. The structure of T-cadherin is shown in Fig. 1. The portion outer-side of cell of T-cadherin molecule contains various number of cadherin domains which are homologous. Each domain comprises of approximately 110 amino acids residues.

![Structure of Cadherin](Image)

**Fig. 1: Structure of Cadherin (T-cad) (33).** It is a GPI-anchored classical form that lacks C-terminal trans membrane and cytosolic domain. T-cad 130 kDa; T-cadherin 130 kilo-daltons; T-cad 100 kDa; T-cadherin 100 kilo-daltons (Figure created in Biorender.com).

Classical cadherins, structurally have five domains which are EC1- EC5 (starting with the N-termini of the molecule). Cadherin molecule is stable only in calcium ion (Ca2+) presence, and the Ca2+ binding with extra-cellular portion of polypeptide chain is needed for cadherin-associated cell–cell adhesion. Calcium binding region contains of short sequences of amino acid located between adjacent extracellular repeats.

Comparing with the above class, this cadherin is not found to be present at zonula adherence, but in inside of lipids present on cell membrane, re-distributed again as required through primary cells which are migratory in function.

**Atherosclerosis**

Atherosclerosis is major factor involved in diseases related with vascular system throughout the world. Key diagnostic findings may be ischaemic disease related to heart, various diseases associated with artery, and stroke (11).

Fatty streaks which are adhered in the wall of the arteries form clots called plaques. When these plaques raptured, they results in thrombus formation which may leads to the obstruction of artery involved (12). Atherosclerosis occurs due to chronic inflammation and accumulation of plaques within the arteries. Plaques are composed of lipid that initiates an inflammation which results in turbulent flow that results in atherosclerotic cardio-vascular disease (ASCVD) (13).

The common risk factors may include increased LDL-cholesterol, blood pressure, diabetes mellitus, smoking etc, and age (male above 45 years & post-menopausal female), and most importantly is the family history of diseases. Dietary intake of high saturated and trans-fatty acids, sedentary lifestyle, obesity, and genetic predisposition contribute to risk for atherosclerosis. While a reduce level of high-density lipoprotein-cholesterol (HDL-cholesterol) is also counted as an alarming risk factor. Some pharmacological therapy increasing HDL-cholesterol yields opposite results raising attentions about the function of HDL in ASCVD (14).

The causes of the atherosclerotic lesions, its formation and methods related to preventing atherosclerosis have been studied previously. It was illustrated that the main cause of atherogenesis is the aggregation of LDL-cholesterol in wall of vessel with the progression of inflammation when there is increased quantity of extra-cellular matrix in that area which is affected and results in development of plaque (15).

**T-cadherin and atherosclerosis**

T-cadherin is elevated in atherosclerosis lesions of human aorta, in restenotic lesions of carotid artery, and in multiplying cells of smooth muscle and endothelium. T-cadherin regulation among ECs takes place during oxidative stress which decreases stress-induced apoptosis. T-cadherin is a regulating protein of ECs (16). T-cadherin regulates endothelial permeability that is elucidated in Fig. 2.

Atherosclerosis involves lipid alteration, activation of platelets, thrombosis, oxidative stress, smooth muscle initiation of vascular cells, changed matrix metabolism, and resistance vessels. It mostly takes place in intima (medium size) arteries where there is altered blood flow, provoked by associating with the altered functioning of endothelium and holding of lipoprotein (17).
T-cadherin is the third receptor of adiponectin and it has cardio-protective benefits. Aggregation of adiponectin which is dependent on T-cadherin within vessels shows defensive function in relation to atherosclerosis (18).

Adipocyte initiated adiponectin collects in endothelial cells via cadherin-T to avoid the initiation of atherosclerotic proliferation. This cadherin presents in synthetic smooth muscle cells, but absent in contractile Smooth muscle cells while adiponectin aggregates via T-cadherin on synthetic Smooth muscle cells. Adiponectin and T-cadherin in coordination protects the progress of atherosclerosis (19).

It should be noted that variations in T-cadherin level can affect sensitivity to insulin, activity of endothelium nitric oxide synthase, ECs migration and angiogenesis, contractile activity of vascular SMCs and organization of extracellular matrix (ECM) (20). These factors may alter the pattern related to development of atherosclerosis. T-cadherin prevents development and progression of atherosclerosis that are illustrated in Fig. 3.

**Prevalence of CVD**

The total burden of CVD has estimated to 523 million in the year 2019. The CVD-associated deaths have estimated to 18.6 million in the year 2019 (21). In India, prevalence of CVDs has estimated to 29.4% in the middle age to older population (≥45years age) (22). Arterial hypertension increases the events of atherosclerosis and CVD (23). It is observed that the systolic blood pressure (SBP) increases by approx. 7 mm of Hg / 10 years of adult age. In addition, SBP increases by approx. 8 mm of Hg/5 kilogram/m² rise in BMI. Experimental study reported that the prolonged hypertension induces the atherosclerotic plaques, vulnerable plaque, and prevalence of myocardial infarction (MI)-associated mortality (24).
Epidemiological studies have reported that arterial hypertension is the significant modifiable risk factors for CVD, all strokes and all coronary events. So that management of arterial hypertension may play a significant role to reduce the incident of atherosclerosis and CVD. Atherosclerosis affects the heart and brain mainly and leading to IHD and stroke, respectively. IHD is ranked first and stroke is ranked fifth for the sources of death worldwide (25).

T-cadherin linked with the development of atherosclerosis and further chronic heart disease (CHD) (26). Low levels of plasma T-cadherin is connected with the atherosclerotic damage of coronary arteries disease (CAD) development (27). T-cadherin expression usually associated with pattern of chronic cardiac disease onset, myocardial infarction (MI) or stable angina. This indicates T-cadherin participation in atherogenesis and its effect on the atherosclerotic lesions (28).

Cardio-protective function of T-cadherin is channels through adiponectin and raised triglyceride (TG) and very low-density lipoprotein (VLDL) in patients of T2DM. ADIPOQ gene variants alter circulatory adiponectin levels and cause hypo adiponectinemia (29, 30). Risk associated for cardio-vascular disease in type 2 diabetes mellitus patients increases with resistance in insulin, low plasma adiponectin and altered lipid profile (31).

T-cadherin is the third receptor for adiponectin that has beneficial metabolic and cardiovascular properties. Low adiponectin serum levels correlate with progress of cerebrovascular disease, CAD, MI, hypertension, left ventricular hypertrophy (LVH) and CVD. Low levels of cardiac T-cadherin act as an independent indicator of MI and heart disease severity. Low levels of cardiac T-cadherin leading to diminished anti-inflammatory function of adiponectin in myocardium of chronic non-ischemic dilated cardiomyopathy patients (32).

This review advocates for reduced circulatory values of adiponectin and T-cadherin for obesity, hypertension, dyslipidemia and T2DM. Lower cadherin (T) and adiponectin range further increase the accumulation of LDL in arterial wall and increasing the prevalence of atherosclerosis and CVD. This review emphasizes the T-cadherin may act as a potential biomarker for atherosclerosis and CVD. T-cadherin could become a beneficial agent therapeutically to develop new medicine for reduction/treatment/management of atherosclerosis and CVD.

**Limitations and future visions**

For this review, more than 80% articles included from the last 05 years. However, very limited studies have reported the association between T-cadherin and atherosclerosis. The percentage of ongoing research related to T-cadherin and atherosclerosis is also very low. This review emphasized the need of further more research related to T-cadherin and atherosclerosis because T-cadherin may act as a potential biomarker for atherosclerosis.

**CONCLUSION**

T-Cadherin is the receptor for LDL that can be an effective biomarker for atherosclerosis. Previous studies on T-cadherin showed that it has cardioprotective role. Its circulatory levels indicate the early patterns of atherosclerosis, CVDs and their complications. Furthermore studies are required to strengthen the hypothesis that T-cadherin has cardioprotective function. It may be a potential target for developing new therapy and medicine to decrease the incidents of atherosclerosis and CVD.

**CONFLICT OF INTEREST**

Authors declare that there is no conflict of interest.

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