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Association of Circulatory T-cadherin with the Risk Factors for Cardiovascular Disease in Patients with Type-2 Diabetes Mellitus

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Abstract

Circulatory T-cadherin is one of the adiponectin receptors that is associated with cardiovascular functions. T-cadherin may act as a potential biomarker for screening cardiovascular disease (CVD) risk factors in type 2 diabetes mellitus (T2DM) patients. In this case–control study, 100 T2DM patients with CVD as cases and 100 aged-matched healthy subjects as controls were enrolled, aged between 30-70 years. Clinical parameters such as fasting blood sugar (FBS), glycated hemoglobin (HbA1c), and lipid profile were estimated along with blood pressure and BMI i.e., body mass index in each subject. The correlation of circulatory T- cadherin with various clinical and anthropometric parameters was analyzed among cases. The minimum value(cut-off) of circulatory T-cadherin was calculated by the receiver operator characteristic curve (ROC). The mean of FBS, HbA1c, lipid profile parameters and systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, and circulatory T-cadherin were significantly raised in cases compared to controls ($p<0.01$). A positive correlation was found significant between circulatory T-cadherin and HbA1c among cases ($r= 0.230$, $p<0.05$). ROC analysis indicates that the minimum cut-off value of circulatory T-cadherin level 5.5ng/ml was found suitable for early screening of CVD risk factors in individuals with T2DM.T2DM patients with CVD have shown abnormal lipid profile, elevated blood sugar, blood pressure, body weight and circulatory T-cadherin levels as compared to controls. A significant positive correlation was found between circulatory T-cadherin and HbA1c indicating that elevated circulatory T-cadherin and HbA1c increases the risk for cardiovascular diseases in patients having T2DM.

Keywords: Body mass Index, Cardiovascular disease, Glycated hemoglobin, T-cadherin, T2DM

Full-length article **Corresponding Author*, e-mail: ***mustufakhan@iul.ac.in***

1. Introduction

According to World Health Organization, the global burden of CVD is about 10% and it is the foremost cause of death [1]. The prevalence of CVD in India is estimated to be 29.4% in the middle age group when compared to older population (≥45 years age) [2]. Ischemic heart disease (IHD) is ranked first and stroke is ranked fifth for the causes of death in association with CVD worldwide [3]. It was recorded that the death rate due to CVD has increased fivefold when it is associated with diabetes [4]. About 32.2% of type 2 diabetes mellitus (T2DM) individuals were affected by CVD [5].In addition, about 77 million people are living with diabetes in India. The current total prevalence of diabetes mellitus in India is about 9.3% [6]. In T2DM the variations in blood sugar levels were in positive correlation with the development of CAD i.e., coronary artery disease and damage in endothelium of blood vessel by chronic hyperglycaemia [7]. Increasing burden of diabetes along with CVD is the alarming condition to find suitable biomarkers for prediction/screening of disease in the early stage.

1.1. T-cadherin

T-cadherin acts as an important biomarker during screening of diabetes and CVD in the early stage. T-cadherin is linked with CVD as it is the 3rd receptor of protein adiponectin (APN) and it has cardio-protective role. Accumulation results of adiponectin which is dependent on T-cadherin within blood vessels show protective function in consideration of atherosclerosis [8]. T-cadherin lacks a trans-membrane domain, but T-cadherin is required to exhibit the protective effect of APN on various organs [9].

T-cadherin and APN both work in association and modulate glucose and lipid metabolism. The exact role of circulatory T-cadherin is still to be investigated [10]. It was seen that the removal of cellular ceramide is done by high molecular weight (HMW) APN in association with T-cadherin and this process causes a further fall of insulin resistance [11]. Previous studies, shown that low-density lipoprotein stimulates the assembly of short-lived T-cadherin clusters and assures the signaling of calcium which is cholesterol-dependent [12]. T-cadherin also acts as a receiving protein for LDL, and it expresses the cells when it binds with LDL [13]. The occurrence of protein T -cadherin is predominantly seen in aorta, iliac, carotid, and in heart [14]. Study has showed that circulatory T-cadherin is associated with multiple functions for the cardio-vascular system [15].

1.2. Association of T-cadherin and CVD

T-cadherin inside the cells is linked with hypertension, restenosis, and atherosclerosis. In addition, T-cadherin actively participates in the mechanism of angiogenesis and vascular alteration [16]. GWAS-The Genome-wide association study stated that T-cadherin affects the metabolism of glucose as well as diseases linked with coronary arteries [17].

T-cadherin is also connected with the development of atherosclerosis which may lead to chronic heart disease (CHD) in future [18]. Low levels of plasma circulatory T-cadherin is related with atherosclerotic damage which is the cause of development of CAD [19]. T-cadherin expression in blood circulation is connected with chronic cardiac disease, myocardial infarction or stable angina. This shows that T-cadherin contributes in atherogenesis and has an effect on atherosclerotic lesions [20]. Low circulatory levels of cardiac T-cadherin act as indicator of myocardial infarction (MI) and severity of heart disease. It is also noted that low levels of circulatory cardiac T-cadherin leads to diminishing anti-inflammatory functions related with protein APN in myocardium of the patients having chronic non-ischemic dilated cardiomyopathy [21]. Arterial hypertension is also considered to be among the CVDs. It causes few or almost no symptoms but is considered to be a significant risk factor in MI, stroke, renal failure, and peripheral vascular disease [22]. Atherosclerosis mostly takes place in the intima of arteries where there is alteration in blood flow, which is initiated by the association with the changed functioning of endothelium & holding of lipoprotein [23]. T-cadherin is one of the receptor of APN, binding of APN and T-cadherin results in promotion of exosome biogenesis that helps in enhancing cardio-protective role of APN along with T-cadherin [24] shown in figure 1.

T-cadherin is mainly located on the surfaces of vascular cells (endothelial cells, smooth muscle cells, and pericytes) also in the heart; these competitive relationships may underlie the development of atherosclerosis and other cardiovascular pathologies [25]. Therefore, this study is designed to find the association of circulatory T-cadherin with the risk factors for CVD in patients with T2DM.

2. Materials and Methods

2.1. Subject Selection

In this study (case-control), total of 200 subjects, 100 subjects as controls (healthy) and 100 subjects as cases (T2DM with CVD) age in between 30-70 years were enrolled after taking proper case history and medical history. This study has approval of the Institutional Research Committee (IRC) and Institutional Ethical Committee (IEC) and followed the ethical standards with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (WMA, 2013). Written informed consent was taken from each study subject.

2.2. Study Design

Two groups, cases (T2DM with CVD) and controls (healthy controls) were taken. Anthropometric parameters - BMI, SBP and DBP were measured in both the groups. Clinical parameters such as FBS, HbA1c, Total Cholesterol (TC), Triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) and very low-density lipoprotein-cholesterol (VLDL-C) were investigated in both the groups. Level of circulatory T cadherin was estimated in both the groups.

2.3. Anthropometric Parameters

2.3.1. BMI

This was calculated by using the formula, BMI = weight in kg / height in meter^2.For measuring the weight and height digital weighing machine and stadiometer were used, respectively. BMI: interpretations are, Underweight BMI<18.5 kg/m^2; normal weight BMI = 18.5–22.9 kg/m^2; overweight BMI > 23–24.9 kg/m^2; and obese, ≥25 kg/m^2 [26].

2.3.2. Blood Pressure (BP)

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured after 5 minutes rest period by using mercury sphygmomanometer after making sure that the participants had not consumed caffeine, tobacco, or exercised in the last 30 minutes. Two readings were taken at 1-min interval and the average of the two readings was taken as the blood pressure reading of the participant [27].

2.4. Laboratory Investigations

Fasting blood sugar (FBS) was estimated by using commercially available kits –ERBA, by GOD-POD method on semi auto analyzer Erba chem7. Glycated haemoglobin (HbA1c) was estimated by D10 HPLC based HbA1c Analyzer (Bio-Rad). Lipid profile was also done using commercially available kits ERBA using Erba chem7. Circulatory level of T-cadherin was estimated and recorded with the help of ELISA kit.

2.5. Statistical analysis

All the data analysis was done using the software IBM SPSS version 20.0 (Armonk, NY, USA). All the data were compared between the two groups by using analysis of variance (ANOVA) or unpaired t-test. Values were represented as mean ± SD (Standard Deviation). Pearson correlation coefficient was calculated among cases. The receiver operator characteristic curve (ROC) and area under curve (AUC) was analyzed among cases. A p-value <0.05 was considered as statistically significant for all data analyzed.

Table 1: Clinical characteristics of controls and cases.

Parameters	**Controls (Healthy controls) n=100 Mean ± SD**	**Cases (T2DM with CVD) n=100 Mean ± SD**	***p*-Value**
Age (years)	44.9±10.8	49.9±11.0	0.001**
SBP (mm of Hg)	132.8±6.9	143.3±10.5	0.001**
DBP (mm of Hg)	81.8±5.6	85.5±7.9	0.001**
BMI (kg/m^2)	23.1±2.0	24.9±3.1	0.001**
FBS (mg/dl)	100.1±12.2	158.6±34.3	0.001**
HbA1c (%)	5.4±0.5	7.1±1.07	0.001**
TC (mg/dl)	179.7±34.4	219.0±45.6	0.001**
TG (mg/dl)	113.0±30.8	182.5±54.2	0.001**
HDL-C (mg/dl)	45.4±5.3	40.1±4.3	0.001**
LDL-C (mg/dl)	75.2±24.9	141.5±44.6	0.001**
VLDL-C (mg/dl)	22.5±6.1	36.5±10.8	0.001**
T-cadherin(ng/ml)	1.06±0.34	7.1±0.6	0.001**

*** Statistically significant at 0.01 level (2-tailed), p<0.01*
** Statistically significant at 0.05 level (2-tailed), p<0.05*
FBS: Fasting blood sugar, HbA1c: glaciated hemoglobin, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, VLDL-C: Very low-density lipoprotein-cholesterol, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index.

Table 2: Correlation of T- cadherin with parameters of cases.

Parameters	**AGE (years)**	**FBS (mg/dl)**	**HbA1c (%)**	**TC (mg/dl)**	**TG (mg/dl)**	**HDL-C (mg/dl)**	**LDL-C (mg/dl)**	**VLDL-C (mg/dl)**	**SBP (mmHg)**	**DBP (mmHg)**	**BMI (kg/m^2)**
T-cadherin (ng/ml)	0.107	0.114	**0.230***	0.030	-0.064	-0.073	0.091	-0.057	0.026	0.107	0.111

*** Correlation is significant at the 0.01 level (2-tailed).*
** Correlation is significant at the 0.05 level (2-tailed).*
FBS: Fasting blood sugar, HbA1c: glaciated hemoglobin, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, VLDL-C: Very low-density lipoprotein-cholesterol, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index.

Table 3: Cut-off value of circulatory T-cadherin among cases by ROC analysis.

Variables	**Mean ± SD**	**Cut-off value**	**AUC**	**SE**	**p-value**	**95% CI**	
						Lower bound	**Upper bound**
Circulatory T- cadherin (ng/ml)	7.1±0.6 ng/ml	5.5ng/ml	0.656	0.039	0.001**	0.580	0.732

*** Statistically significant at 0.01 level (2-tailed), p<0.01*
**Statistically significant at 0.05 level (2-tailed), p<0.05*
AUC: Area under the ROC curve, SE: standard error, CI: confidence Interval

Table 4: Clinical characteristics of study subjects based on circulatory T-cadherin cut-off value (5.5ng/ml).

Parameters	Group 1 (< 5.5 ng/ml) (n=100) Mean ± SD	Group 2 (≥ 5.5 ng/ml) (n=100) Mean ± SD	p- Value
Age (years)	44.9±10.8	49.9±11.0	0.001**
SBP (mm of Hg)	132.8±6.9	143.3±10.5	0.001**
DBP (mm of Hg)	81.8±5.6	85.5±7.9	0.001**
BMI (kg/m^2)	23.1±2.0	24.9±3.1	0.001**
FBS (mg/dl)	100.1±12.2	158.6±34.3	0.001**
HbA1c (%)	5.4±0.5	7.1±1.07	0.001**
TC (mg/dl)	179.7±34.4	219.0±45.6	0.001**
TG (mg/dl)	113.0±30.8	182.5±54.2	0.001**
HDL-C (mg/dl)	45.4±5.3	40.1±4.3	0.001**
LDL-C (mg/dl)	75.2±24.9	141.5±44.6	0.001**
VLDL-C (mg/dl)	22.5±6.1	36.5±10.8	0.001**

***. Correlation is significant at the 0.01 level (2-tailed).*
**. Correlation is significant at the 0.05 level (2-tailed).*
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, FBS: Fasting blood sugar, HbA1c: glaciated hemoglobin, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, VLDL-C: Very low-density lipoprotein-cholesterol

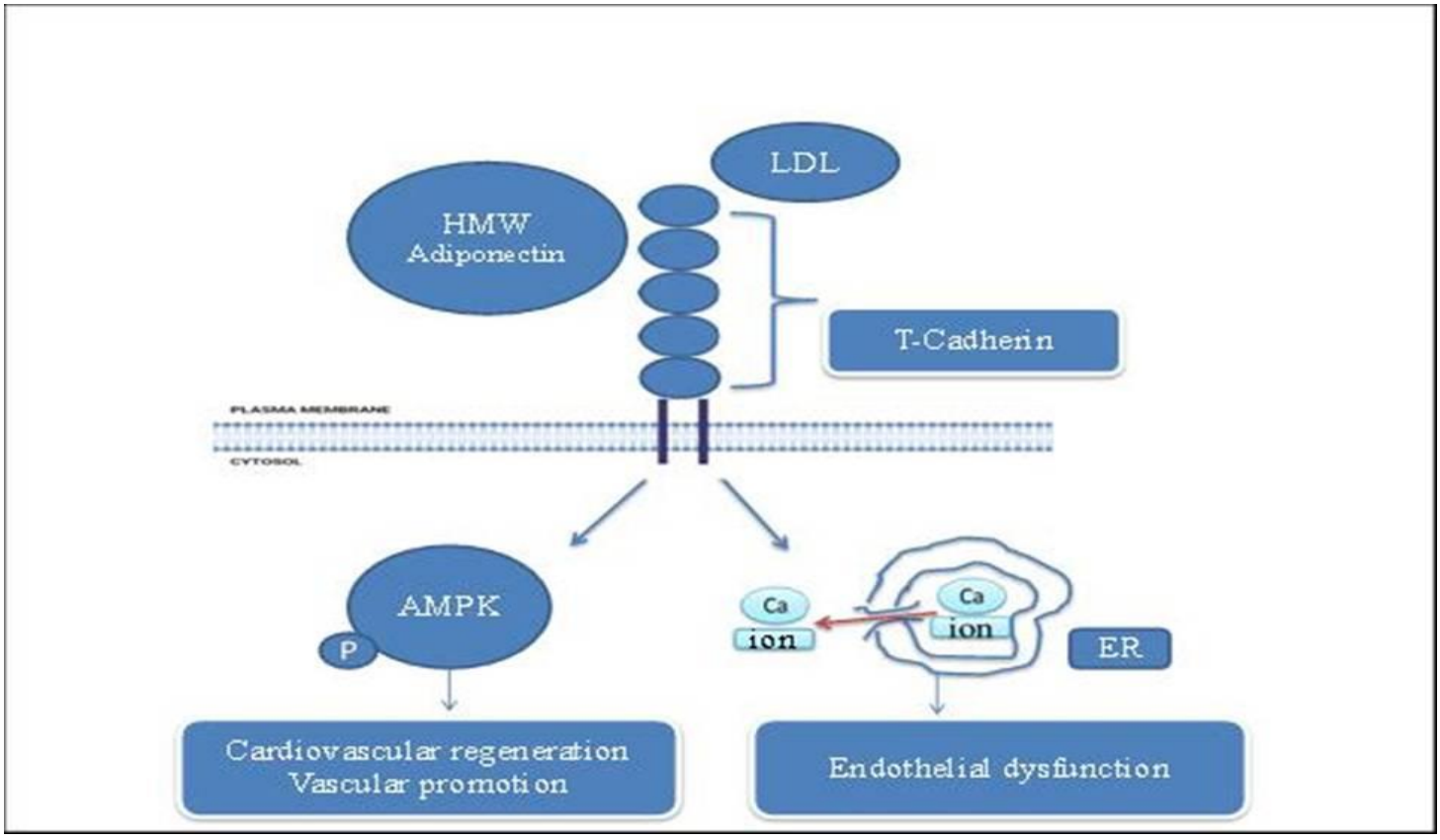

Figure 1: Association and mechanism of T-cadherin in T2DM with CVD

AMPK – Adenosine monophosphate-activated protein kinase, Ca – calcium ion, ER – endoplasmic reticulum, HMW – high-molecular-weight, LDL- low-density lipoprotein, P - phosphate.

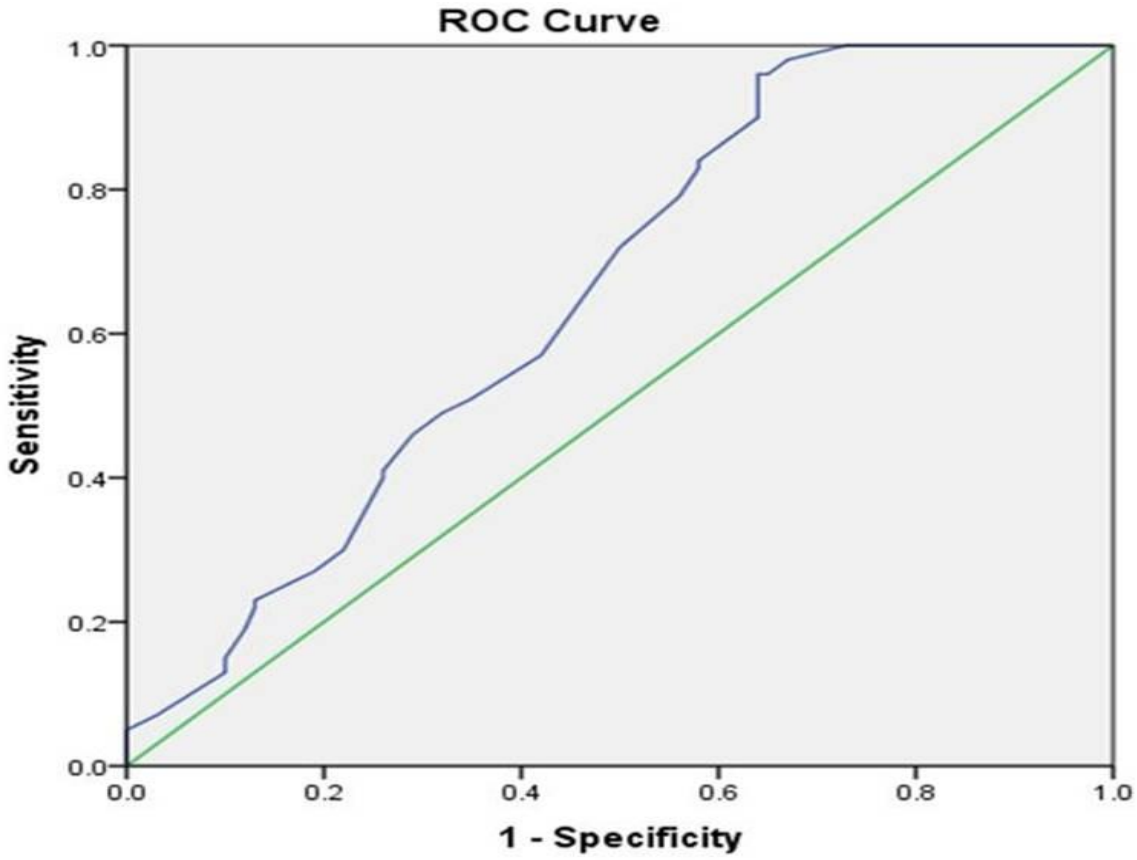

Figure 2: ROC Curve for circulatory T-cadherin

3. Results and Discussions

The mean of age, SBP, DBP, BMI, FBS, HbA1c, TC, TG, LDL-C, VLDL-C, and circulatory T- cadherin were significantly raised in cases when compared to controls ($p<0.01$). However, the mean of HDL-C was found significantly low in cases as compared to controls($p<0.01$), shown in Table 1. When the correlation of circulatory T-cadherin among the different parameters of cases is calculated and analyzed, it was found that the circulatory level of T-cadherin is correlated positively with HbA1c and that was statistically significant ($p<0.05$) shown in Table 2.

When Receiver Operator characteristic curve (ROC) is drawn and analyzed it was found that the cut-off value for circulatory T-cadherin is 5.5ng/ml, and AUC was 0.656and the analysis was statistically significant ($p< 0.01$) shown in Table 3. Study subjects were further grouped based on the ROC results and cut-off value of circulatory T-cadherin. Group 1; having circulatory T-cadherin levels < 5.5ng/ml(n=100) and Group 2; having circulatory T-cadherin levels ≥ 5.5ng/ml (n=100). The mean value of age, SBP, DBP, BMI, FBS, HbA1c, TC, TG, LDL-C, and VLDL-C was found significantly elevated in group 2 as compared to group 1 ($p<0.01$). However, the mean value of HDL-C was found significantly low in group 2 than group 1 ($p<0.01$), shown in Table 4.

Philippova et al. (2011) showed that T-cadherin can be released from the cells of endothelium and the amount of release may determine the degree of damage or activation [28]. They also stated T-cadherin as a biomarker for atherosclerosis at early stage and that is clinically not reflected by sign and symptoms but characterized by disturbances in the functioning in the endothelium. Interestingly, it was demonstrated that there was elevation of circulatory T-cadherin in plasma of subjects with atherosclerosis when a comparison was done with healthy subjects. This present study also shows the significant raised level of circulatory T-cadherin in patients of T2DM with CVD when compared with healthy controls ($p<0.01$). This might be an indication of endothelial cell damage. T-cadherin can be in association with other molecules those are related with metabolism such as lipoprotein [29] and insulin [30]. This indicated the relation and association of T-cadherin with T2DM. When various clinical parameters and anthropometric parameters were analyzed in cases and controls, it was found that FBS, HbA1c, TC, TG, LDL-C, VLDL-C, BMI, SBP, and DBP were significantly elevated in cases as compared to controls. However, HDL-C was found significantly low in cases when compared to controls. This indicated that the patients of T2DM with CVD are at greater risk of CVD-associated mortality in future. In addition, elevated levels of LDL-C and decreased levels of HDL-C are the basic characteristics of dyslipidaemia. Altered lipid profile i.e., dyslipidaemia is the independent risk factor for atherosclerotic CVD in patients with T2DM [31, 32].

The mean BMI was found significantly elevated in cases as compared to controls. This indicated that obesity is increasing the risk for T2DM and CVD [5, 33]. When correlation of circulatory T-cadherin with clinical parameters of case group is done it was found that T-cadherin is significantly associated with HbA1c ($p< 0.05$),

which shows the association of circulatory T-cadherin with T2DM as T-cadherin is one of the receptors of APN [34].

The study reported that the high level of circulating APN can reduce the risk for obesity, insulin resistance, T2DM and its complications such as atherosclerosis and CVD [35]. The mean value of circulatory T-cadherin was significantly elevated in cases as compared to controls. This indicates that the greater the level of circulatory T-cadherin, the greater the risk of CVD and its complications. Elevated circulatory T-cadherin levels in plasma during the early stage of CVD and its complications indicated that it may act as a diagnostic marker for screening of atherosclerosis at early stage [36].

When clinical and anthropometric characteristics of group 1 (circulatory T-cadherin < 5.5 ng/ml), and group 2 (circulatory T-cadherin ≥ 5.5 ng/ml) were analysed on the basis of cut-off value of circulatory T cadherin (5.5 ng/ml), it was found that mean value of all the clinical and anthropometric parameters were elevated in group 2 (≥ 5.5 ng/ml), except HDL-C. Circulatory T-cadherin was strongly associated with angiogenic activities of endothelial cells and it can act as a pro-angiogenic molecule [37]. Asian Indians have high prevalence of T2DM and its associated macrovascular complications such as CVD [38]. So, early diagnosis of disease is the necessary to reduce T2DM and CVD-associated mortality mainly in Asian Indians. Therefore, searching new biomarkers and therapeutic strategies is required to prevent endothelial dysfunction and risk of developing CAD and its complications mainly in patients with T2DM [39]. *Khan et al. (2023)* reported that people having a sedentary lifestyle are at greater risk of becoming obese and developing diabetes and continuation of sedentary lifestyle may lead to CVD, MI and heart failure [40]. Circulatory T-cadherin may act as potential tool for early screening and diagnosis of T2DM and CVD-associated risk factors.

4. Conclusion

Results showed that circulatory T-cadherin is significantly associated with the risk factors for T2DM and CVD. This study strengthens the hypothesis that circulatory T-cadherin may be used as a potential biomarker for the screening of T2DM and CVD-associated risk factors.

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Conflicts of Interest

Authors M. D. Khan, M. K. Ahmad, S. Khan, R. Alam, G. Jaiswal, M.M. Khan declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (IEC Approval No. IEC/IIMS&R/2021/20) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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