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Assessment of serum sirtuin 1 levels in type 2 diabetes mellitus with coronary artery disease patients

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Abstract

Background and objective. *Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia and insulin deficiency, and is accompanied by multiple complications, including cardiovascular disease. Silent information regulator 1 (SIRT1) plays a role in diverse physiological and pathological processes. This study aimed to evaluate serum SIRT1 levels in patients with T2DM and in those with T2DM and coronary artery disease (CAD), and to explore their correlation with cardiovascular risk factors.*

Methods. *A case–control study was conducted on 225 participants, divided into three groups (n = 75 each): healthy controls, T2DM, and T2DM with CAD. Serum SIRT1 levels were measured by ELISA, along with standard biochemical and cardiac markers. Data were analyzed using ANOVA with post-hoc tests, Pearson correlations, multiple regression, and ROC analysis.*

Results. *Mean serum SIRT1 levels were 1.23 ng/mL in controls, 2.07 ng/mL in T2DM, and 5.77 ng/mL in T2DM-CAD patients ($p < 0.001$). ROC analysis identified a cut-off value of 3.4 ng/mL, with 68% sensitivity, 93.3% specificity, and 80.7% accuracy for detecting CAD in T2DM patients. Serum SIRT1 levels were significantly higher in T2DM-CAD patients compared with both controls and T2DM patients ($p < 0.001$). SIRT1 levels showed positive correlations with glycemic and lipid parameters, and a negative correlation with CK-MB in controls and T2DM patients. In the T2DM-CAD group, SIRT1 levels correlated positively with most biochemical and cardiac markers, except HDL-cholesterol.*

Conclusion. *Serum SIRT1 levels were significantly elevated in T2DM patients with CAD, suggesting a potential role as a non-invasive biomarker for cardiovascular risk stratification in diabetes. Further longitudinal studies are needed to validate SIRT1 as a biomarker.*

Keywords: sirtuin, type 2 diabetes mellitus, coronary artery disease, cholesterol, triglycerides

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and ischemic or coronary artery disease (CAD) are two major health problems that frequently coexist in developing countries [1,2]. Diabetes accelerates the process of atherosclerosis through multiple mechanisms, making it an independent risk factor for CAD [3]. In patients with diabetes, the majority of morbidity and mortality is attributable to cardiovascular disease (CVD). Individuals with both T2DM and CAD are particularly challenging to manage, and their risk of CVD-related complications is

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substantially increased. Genetic factors and polymorphisms in certain genes may also contribute to the risk of coronary heart disease (CHD) [4].

In India, CVD accounts for more than 10.5 million deaths annually, representing 20.3% of deaths in men and 16.9% in women [5]. According to the World Health Organization, 24.8% of annual deaths in India are due to CVD, with CAD as a major contributor. In 2016, CVD represented 28% of all deaths nationwide. T2DM, a major risk factor for CVD, not only increases CAD risk but also worsens outcomes after myocardial infarction. Globally, the prevalence of CVD among patients with T2DM is estimated at 32.2% [6]. T2DM is now considered a CAD risk equivalent, contributing substantially to morbidity and premature mortality. Individuals with diabetes have more than a twofold higher risk of death from CVD compared with non-diabetic individuals [7].

Sirtuin 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase that regulates diverse metabolic pathways [8]. It stimulates insulin secretion, promotes fat metabolism, and improves insulin sensitivity. SIRT1 can also inhibit the progression of atherosclerosis and protect against CHD [9,10]. It has been shown to improve endothelial function by activating eNOS, thereby reducing oxidative stress [11]. In addition, SIRT1 exerts anti-inflammatory effects by inactivating pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, thus limiting macrophage activation [12,13]. Taken together, these findings suggest that SIRT1 may play a protective role in both metabolic regulation and cardiovascular health.

Previous studies have investigated serum SIRT1 levels in CAD patients, but findings remain inconsistent. Some reported reduced SIRT1 levels in advanced CAD, suggesting a loss of protective effects [14], while others found significant associations between SIRT1 and major adverse limb events (MALE) or major adverse cardiac events (MACE), proposing SIRT1 as a potential independent predictor in T2DM [15]. In contrast, studies in acute myocardial infarction (AMI) patients reported no protective association of SIRT1, 3, and 6 [16]. Furthermore, circulating SIRT1 levels were inversely correlated with epicardial fat thickness, a marker of CAD severity [17].

Given these conflicting results, the present study aimed to quantify serum SIRT1 levels in patients with T2DM and in those with T2DM and CAD, and to explore their potential role as predictive markers for CAD risk. In addition, we sought to investigate correlations between SIRT1 levels and biochemical parameters relevant to cardiovascular risk in a tertiary care teaching hospital in South India.

METHODS

This case-control study included 225 patients aged 30-65 years. Participants were divided into three groups: 75 healthy controls (Group I), 75 patients with T2DM without coronary heart disease (Group II), and 75 patients with T2DM and coronary heart disease (Group III). Written informed consent was obtained from all participants before study enrollment. The study protocol was approved by the Institutional Ethical Committee of Swamy Vivekanandha Medical College Hospital & Research Institute (IEC-SVMCHRI).

Selection criteria

Inclusion criteria

- Group I (controls): fasting blood sugar (FBS) <110 mg/dL and HbA1c <5.7%, with no history of diabetes.
- Group II (T2DM): patients with T2DM of <5 years' duration, without microvascular or macrovascular complications.
- Group III (T2DM + CAD): patients with T2DM and CAD. All enrolled CAD patients was confirmed by coronary angiography, defined as ≥50% stenosis in at least one major coronary branch (diameter ≥2 mm). Patients with a history of coronary artery bypass graft surgery or percutaneous coronary intervention were also included.

Exclusion criteria

Patients with type 1 diabetes (T1DM), active or chronic inflammatory disorders, autoimmune diseases, malignancies, hematological disorders, use of immunosuppressive drugs, or pregnancy were excluded. A detailed clinical history and physical examination were obtained for all participants.

Data collection and analysis

Venous blood samples (5 mL) were collected from all participants after overnight fasting. Biochemical parameters measured included fasting blood sugar (FBS), postprandial blood sugar (PPBS), urea, creatinine, lipid profile (total cholesterol, LDL cholesterol, triglycerides), glycated hemoglobin (HbA1c), uric acid, creatine kinase-MB (CK-MB), and troponin I, using an automated analyzer (Vitros Chemistry 5.1/FS, Japan). Serum samples were stored at −80 °C until analysis.

Serum SIRT1 concentrations were measured using a commercial ELISA kit (GENELISA, Krishgen Biosystems, USA), according to the manufacturer's instructions. The diagnostic cut-off value was determined using the 95% confidence interval (mean ± 2 SD) method [18].

Statistical analysis

Data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD). Group comparisons were performed using one-way ANOVA, fol-

lowed by post-hoc Tukey's test for pairwise differences. Correlations between serum SIRT1 and demographic/biochemical parameters were assessed using Pearson's correlation coefficient. A p-value <0.05 was considered statistically significant, and p <0.001 highly significant.

RESULTS

Demographic and biochemical characteristics

The mean ages were 47.85 ± 9.65 years in Group I, 53.44 ± 9.44 years in Group II, and 59.83 ± 10.91 years in Group III, with significant between-group differences. Fasting blood glucose was significantly higher in Groups II and III versus Group I, and postprandial glucose differed significantly across all three groups. Lipid parameters (total cholesterol, triglycerides, LDL-C) were highest in Group III, intermediate in Group II, and normal in Group I. VLDL-C was significantly elevated in Groups II and III compared with Group I, whereas HDL-C did not differ among groups.

Urea, creatinine, and uric acid were normal in Groups I and II but significantly increased in Group III. CK-MB and troponin I were also significantly higher in Group III compared with Groups I and II. Serum SIRT1 levels rose progressively across groups and were significantly higher in T2DM-CAD than in both controls and T2DM alone ($p < 0.001$). The overall demographic and biochemical data are summarized in Table 1.

Statistical testing

One-way ANOVA demonstrated significant overall differences, and post-hoc Tukey tests identified pairwise group differences. Mean serum SIRT1 concentrations were 1.23 ng/mL in controls, 2.07 ng/mL in T2DM, and 5.77 ng/mL in T2DM-CAD, with significantly higher levels in the T2DM-CAD group compared to the other groups (Figure 1).

Correlations

In the T2DM-CAD group, Pearson correlation analysis (Prism) showed significant positive correlations between SIRT1 and FBS ($p = 0.02$) and uric acid ($p = 0.039$), with no significant correlations with PPBS or HbA1c (Figure 2).

Across Groups I and II, SIRT1 correlated negatively with CK-MB ($r = -0.264$, $p = 0.001$) and positively with PPBS, HbA1c, total cholesterol, and triglycerides (Table 2). In Groups I and III, SIRT1 showed significant positive correlations with all parameters except HDL-C.

Multiple regression

Multiple linear regression was performed using SIRT1 as the dependent variable. No predictors were identified in the control group. In T2DM, CK-MB ($p = 0.02$) emerged as an independent predictor of SIRT1. In T2DM-CAD, uric acid ($p = 0.009$) was a significant independent predictor (Table 3).

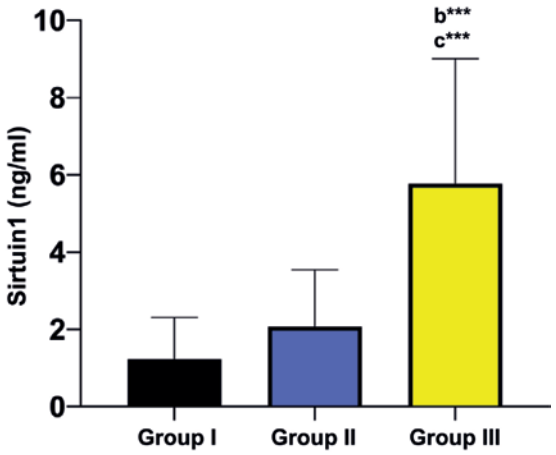

FIGURE 1. *Quantification of serum SIRT1 across groups. The significance was considered $p < 0.05$. b - indicates significance between group I and III (*** $p < 0.001$).; c - indicates significance between group II and III (*** $p < 0.001$)*

Diagnostic performance

A SIRT1 cut-off of 3.4 ng/mL (mean ± 2 SD method) yielded 68% sensitivity, 93.3% specificity, and 80.67% accuracy for identifying CAD among T2DM patients (Table 4).

Receiver operating characteristic (ROC) curve analyzed to diagnose the CAD-T2DM group with SIRT 1 level by prism software. The area under the curve (AUC) was about 0.945 with a 95% confidence interval (95% CI - 0.9100 to 0.9803) by the P value of < 0.05 (Figure 3).

Based on this cut-off, SIRT1 < 3.4 ng/mL was observed in 70/75 (93.3%) controls, 61/75 (81.3%) T2DM, and 24/75 (32.0%) T2DM-CAD; SIRT1 ≥ 3.4 ng/mL was observed in 5/75 (6.7%) controls, 14/75 (18.7%) T2DM, and 51/75 (68.0%) T2DM-CAD (Table 5).

DISCUSSION

This study compared serum SIRT1 levels among patients with T2DM, T2DM with CAD, and healthy controls, providing evidence of SIRT1 involvement in CAD regulation. Coronary artery luminal obstruction and plaque rupture due to atherosclerosis are the most common causes of CAD [19]. SIRT1 has also been implicated in cardiomyocyte apoptosis and cellular stress responses [20].

In the present study, glucose and lipid parameters (except HDL-C) were significantly elevated in the T2DM-CAD group, followed by the T2DM group, whereas controls had normal values. CK-MB, troponin I, and SIRT1 levels were also significantly higher in T2DM-CAD patients compared with the other groups ($p = 0.001$). These findings are consistent with previous reports showing increased CK, total cholesterol, and LDL-C in CAD patients compared with controls [21].

TABLE 1. *Means and standard deviations of demographic and biochemical parameters by group*

Parameters	Group	Mean	Std. Deviation	P value
Age	Control	47.85	9.65 ± 1.11	
	T2DM	53.44	9.44±1.09	0.002[a]**
	T2DM-CAD	59.83	10.91±1.26	<0.001[b]***
FBS (mg/dL)	Control	96.07	8.31 ±0.96	
	T2DM	160.76	53.87±6.22	<0.001[a]***
	T2DM-CAD	161.33	39.88±4.60	<0.001[b]***
PPBS (mg/dL)	Control	124.09	13.59 ±1.57	
	T2DM	260.37	70.14±8.09	<0.001a***
	T2DM-CAD	239.53	59.45±6.86	<0.001[b]*** 0.048[c]*
HbA1C (%)	Control	5.42	0.28 ±0.033	
	T2DM	10.7792	1.98±0.229	<0.001[a]***
	T2DM-CAD	9.197	2.239±0.258	<0.001[b]*** <0.001[c]***
Cholesterol (mg/dL)	Control	177.40	25.311 ±2.923	
	T2DM	198.56	38.573±4.454	<0.001[a]***
	T2DM-CAD	209.30	31.728±3.664	<0.001[b]***
TGL (mg/dL)	Control	130.32	27.866 ±3.218	
	T2DM	177.00	56.236±6.494	<0.001[a]***
	T2DM-CAD	182.68	66.581±7.688	<0.001[b]***
HDL (mg/dL)	Control	41.55	8.765 ±1.012	
	T2DM	42.72	8.681±6.494	0.763
	T2DM-CAD	43.96	7.011±0.810	
LDL (mg/dL)	Control	106.09	14.602 ±1.686	
	T2DM	101.85	27.349±1.002	0.005[a]**
	T2DM-CAD	129.91	30.099±3.476	<0.001[b]*** <0.001[c]***
VLDL (mg/dL)	Control	28.79	12.736 ±1.471	
	T2DM	36.52	8.312±3.158	<0.001[a]***
	T2DM-CAD	35.08	10.817±1.249	<0.001[b]**
Urea (mg/dL)	Control	21.43	5.907 ±0.682	
	T2DM	22.92	6.384±.960	
	T2DM-CAD	27.13	10.712±1.237	<0.001[b]*** 0.004[c]**
Creatinine (mg/dL)	Control	0.765	0.237 ±0.027	
	T2DM	0.871	0.705±0.737	
	T2DM-CAD	0.997	0.572±0.066	0.025[b]*
Uric acid (mg/dL)	Control	4.911	0.705 ±0.081	
	T2DM	4.74	0.944±0.081	
	T2DM-CAD	5.96	1.108±0.127	<0.001[b]*** <0.001[c]***
CK-MB (IU/L)	Control	17.8533	7.048 ±0.813	
	T2DM	17.7092	6.628±0.109	
	T2DM-CAD	42.26	29.337±3.387	<0.001[b]*** <0.001[c]***
Troponin I (ng/mL)	Control	0.018	0.016±0.001	
	T2DM	0.03852	.0473±0.765	
	T2DM-CAD	0.67231	1.101±0.127	<0.001[b]*** <0.001[c]***
Sirtuin 1 (ng/mL)	Control	1.238	1.080±0.124	
	T2DM	2.07236	1.489±0.172	
	T2DM-CAD	5.77	3.240±0.374	<0.001[b]*** <0.001[c]***

The significance was considered $p < 0.05$ (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). a - significance between group I and II; b - significance between group I and III; c - significance between group II and III.

Abbreviations: T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; FBS, fasting blood sugar; PPBS, postprandial blood sugar; HbA1c, glycated hemoglobin; TGL, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; CK-MB, creatine kinase-MB

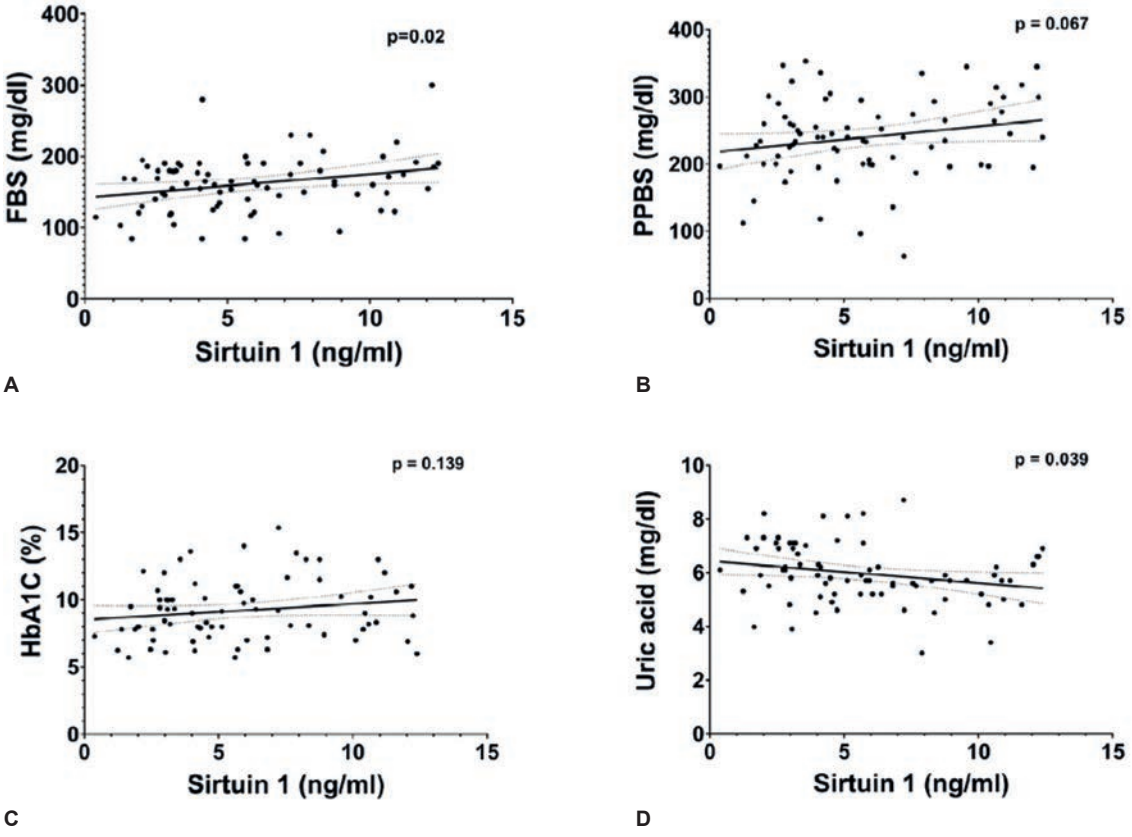

FIGURE 2. *Correlations between serum SIRT1 and (A) FBS, (B) PPBS, (C) HbA1c, and (D) uric acid in T2DM-CAD. Pearson correlation; p < 0.05 indicates statistical significance*

TABLE 2. *Pearson correlations of SIRT1 with clinical and biochemical variables (Group I vs II; Group I vs III)*

Variables	Group 1 Vs Group 2 Sirtuin-1 N =150		Group 1 Vs Group 3 Sirtuin-1 N =150	
	r	Sig (p)	r	Sig (p)
Age	0.089	0.276	0.364	<0.001***
FBS	0.128	0.119	0.628	<0.001***
PPBS	0.187	0.022*	0.638	<0.001***
HbA1c	0.273	0.001**	0.603	<0.001***
TC	0.163	0.046*	0.426	<0.001***
TGL	0.247	0.002**	0.451	<0.001***
HDL	-0.028	0.738	0.055	0.500
LDL	0.066	0.420	0.504	<0.001***
VLDL	0.093	0.256	0.227	0.005**
Urea	0.018	0.824	0.275	<0.001***
Creatinine	-0.044	0.591	0.245	0.003**
Uric acid	-0.069	0.398	0.212	0.009**
CK- MB	-0.264	0.001**	0.313	<0.001***
Troponin	0.024	0.767	0.331	<0.001***

The significance consider at *p<0.05; ** p < 0.01; *** p < 0.001.

Abbreviations: T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; FBS, fasting blood sugar; PPBS, postprandial blood sugar; HbA1c, glycated hemoglobin; TGL, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; CK-MB, creatine kinase-MB

The mean serum SIRT1 levels were 1.23 ng/mL in controls, 2.07 ng/mL in T2DM, and 5.77 ng/mL in T2DM-CAD patients. Although SIRT1 increased in T2DM, the rise was significant only in T2DM-CAD. As a member of the sirtuin family of NAD+-dependent histone deacetylases, SIRT1 plays a critical role in glucose and lipid metabolism and exerts anti-atherosclerotic effects [22].

TABLE 3. *Multiple linear regression of SIRT1 on study variables by group (standardized β, p values)*

Predictor variables	Group I (SIRT1)		Group II (SIRT1)		Group III (SIRT1)	
	Standardized coefficients Beta (B)	Significance (p)	Standardized coefficients Beta (B)	Significance (p)	Standardized coefficients Beta (B)	Significance (p)
Age	-0.046	0.723	0.005	0.496	0.029	0.813
FBS	-0.246	0.067	-0.276	0.980	0.149	0.415
PPBS	0.065	0.670	0.140	0.238	0.172	0.279
HbA1C	-0.030	0.802	0.122	0.427	-0.085	0.651
Cholesterol	0.014	0.921	0.161	0.426	-0.080	0.849
TGL	-0.137	0.404	-0.029	0.242	0.393	0.205
HDL	0.006	0.967	-0.039	0.818	-0.087	0.570
LDL	-0.026	0.848	0.038	0.782	0.177	0.684
VLDL	0.025	0.862	0.026	0.780	-0.374	0.219
Urea	-0.126	0.392	-0.097	0.853	0.287	0.227
Creatinine	-0.128	0.421	-0.032	0.505	-0.052	0.794
Uric acid	-0.022	0.877	-0.286	0.823	-0.360	0.009*
CK-MB	-0.225	0.071	-0.064	0.022*	-0.162	0.224
Troponini	0.116	0.346	0.005	0.603	0.126	0.348

The significance consider at $p < 0.05$

Abbreviations: T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; FBS, fasting blood sugar; PPBS, postprandial blood sugar; HbA1c, glycated hemoglobin; TGL, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; CK-MB, creatine kinase-MB

TABLE 4. *Validity indices for serum sirtuin 1 levels for the prediction of coronary artery disease*

	Sensitivity	Specificity	+ VE predictive	-VE predictive	Accuracy
Sirtuin1 cutoff < 3.4	68	93.3	91.07%	74.47%	80.67%

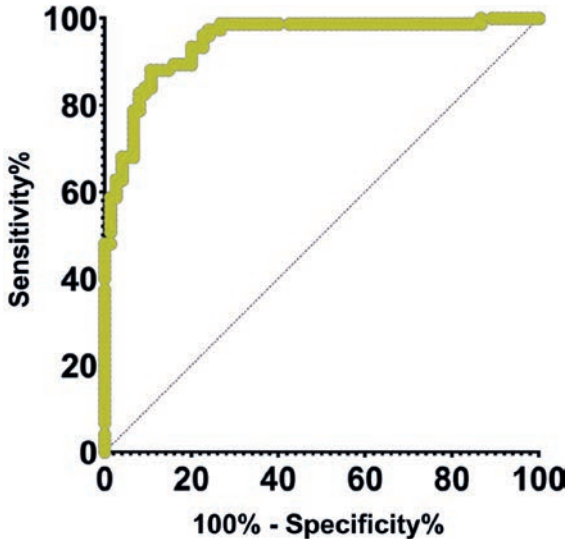

FIGURE 3. *Receiver operating characteristic (ROC) curve analyses for the diagnosis of CAD-T2DM group by Sirtuin 1 levels*

SIRT1 gene constitutive over expression was deteriorates cardiac involvement [23] and another study reported that increase in SIRT1 expression is observed in atrial fibrillation may be inhibiting the process of oxidative stress [24]. Our results showed that serumlevels of SIRT1 were significantly increased in the T2DM-CAD group than control and T2DM groups.

TABLE 5. *Association of sirtuin1 cutoff levels in control, T2DM and T2DM-CAD groups*

SIRT1 ng/ml Cut off		Control	T2DM	T2-DM-CAD
< 3.4	N	70	61	24
	%	93.3	81.3	32
> 3.4	N	5	14	51
	%	6.7	18.7	68
Total	N	75	75	75
	%	100	100	100

Studies reported that plasma SIRT1 levels were lower in chronic coronary syndrome (CCS) patients than in the control group and also they found that significantly lower in patients with both acute myocardial infarction and unstable angina than control and CCS group [25] (Abdelnabi et al., 2021). Study also reported a significantly low serum level of SIRT1 in advanced CAD and noticed an increased AMI [14]. But this result was controversy between those studies and our study. In our study, patients with T2DM and CAD were not subdivided into acute and chronic CAD or other cardiac conditions. This lack of subgroup stratification may explain why we observed higher SIRT1 levels compared with other reports. The increase in the SIRT1 level may also propose that a compensatory mechanism to upsurge

the antioxidants against oxidative stress in CAD patients. A study reported that after supplements treatment increased SIRT1 expression was observed in CAD patients [26], this could be one of thereasons for the increased SIRT1 levels of our study. Also study evidenced that SIRT1 involved in atheroprotective effects by downregulating numbers of proinflammatory cytokines expression of and intervene vasodilatation actions through eNOS-derived nitric oxide and scavenging reactive oxygen species [27].

There was a significant negative correlation of serum SIRT1 levels and CK-MB (r = -0.264, p = 0.001) observed between group I and group II. Also there was a significant positive association between serum SIRT1 levels and PPBS, HbA1C, total cholesterol, and triglycerides. A study reported that plasma SIRT1 was positively associated with platelets and negatively associated with cholesterol and triglycerides [25]. But in our study group I and group III correlations showed a significant positive correlation between SIRT1 levels with all the studied variables except HDL-C. Multiple linear regression analysis, CK-MB (p=0.02) was significantly correlated in the T2DM group, and uric acid was correlated in the T2DM-CAD (0.009) group.

In the present diagnostic performance analysis showed that a cut-off of 3.4 ng/mL for SIRT1 yielded 68% sensitivity, 93.3% specificity, and 80.7% accuracy for predicting CAD in T2DM patients. This is broadly consistent with other studies, although reported cut-offs and diagnostic validity vary. For example, a study of Egyptian patients with CAD for the validity of SIRT1 found that 75% sensitivity, and 55% specificity, with an accuracy of 65% with a 2.4 ng/mL cut-off [25], whereas other studies identified thresholds around 3.7 ng/mL for predicting major adverse cardiac or limb events [28]. Another study analyzed the ROC curvefor SIRT1 and identified that a cutoff of 3.79 ng/mL for predicting the risk of MALE and MACE. Also, a study report suggested that the serum levels of SIRT1 may not be associated with T2DM [28]. Another report stated that expression of the SIRT1 gene in peripheral blood mononuclear cells was not correlated with the rigorousness of coronary lesions of the patients with T2DM but significantly correlated with inflammatory cytokines [29].

SIRT1 expressions were significantly increased in CAD patients who received statin therapy, and inferred that SIRT1 may have a cardioprotective role after AMI [30]. Through the studies and our research, SIRT1 can involve a regulatory role in T2DM and CAD.

Limitations

This study has several limitations. First, its case-control design identifies associations but cannot establish causality. Second, it was conducted in a single center with a relatively small sample size, limiting generalizability. Third, patients with CAD were not stratified into acute versus chronic subgroups, and treatment regimens (antidiabetic drugs, statins, and other cardiovascular therapies) were not controlled for. Lifestyle factors such as diet, BMI, and smoking status were not assessed, which may act as potential confounders. Finally, laboratory analyses were limited to serum SIRT1 levels, without molecular validation or longitudinal follow-up.

Future perspectives

Further large-scale, multicenter, longitudinal studies are needed to clarify the role of SIRT1 in CAD among diabetic patients, to evaluate temporal changes, and to test its integration into multimarker predictive models. Genetic and molecular investigations could also help establish whether SIRT1 might serve not only as a biomarker but also as a therapeutic target.

CONCLUSION

Serum SIRT1 levels were significantly elevated in T2DM patients with CAD, suggesting potential utility as a non-invasive biomarker for cardiovascular risk stratification. Further longitudinal and interventional studies are warranted to establish causality and to assess the clinical applicability of SIRT1 in predicting cardiovascular outcomes in diabetes.

Ethical approval

This study was approved by the Institutional Ethical Committee of Swamy Vivekanandha Medical College Hospital and Research Institute, Elayampalayam, Namakkal, Tamil Nadu, India.

Written informed consent was obtained from all participants prior to inclusion in the study.

Conflict of interest

The authors declare no conflicts of interest.

Financial support

None declared

Author's contributions

Conceptualization, H.S. and S.G.; methodology, H.S. and S.G.; N.NE.;software, H.S. and S.K.; validation, H.S. and S.K.; S.G.; formal analysis, H.S. and S.K.; investigation, H.S. and S.K.;resources: H.S. and S.G.; N.NE.;data curation: H.S. and S.K.; S.G.; writing—original draft preparation: H.S. and S.K.; writing—review and editing: H.S. and S.K.; S.G.; visualization: H.S.; S.K.;supervision: S.G. and N.NE.; project administration: H.S.; funding acquisition: H.S. All authors have read and agreed to the published version of the manuscript.

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