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Serum endocan levels in patients with coronary artery disease and association of serum endocan levels with severity of coronary artery disease

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Abstract

Background: Coronary artery disease (CAD) is the single most frequent cause of death worldwide. Over 7 million people every year die of CAD, accounting for 12.8% of all deaths. Atherosclerosis is the primary cause of ACS, with most cases occurring from the disruption of plaque from a non-severe lesion. Endothelial dysfunction is considered as an early change in atherogenesis. Cardiovascular disease is associated with raised levels of systemic inflammatory markers. Endocan (previously known as Endothelial cell specific molecule-1, ESM-1), is a potential immuno-inflammatory marker that may be linked to cardiovascular disease. It plays a role in endothelial dependent pathologic diseases, such as inflammatory disorders, tumour progression and adhesion, and migration and angiogenesis. It is accepted as a potential endothelial cell marker. Aim: To estimate Serum endocan levels in patients without Acute Coronary Syndrome and in patients with acute Coronary Syndrome and association of its levels with severity of Coronary Artery Disease based on Coronary Angiogram. **Methodology:** This was a rural based teaching hospital cross sectional study in ACS patients. Sample size was calculated to be 74 (37 in each group). Group 1 included patients diagnosed with acute coronary syndrome based on clinical presentation and investigations and Group 2 were those without any clinical and investigatory evidence of ACS. The patient baseline characteristics, serum glucose level, lipid profile, ECG and severity of ACS assessed by coronary angiogram. The serum endocan levels were estimated in the study population by ELISA method, and it was compared between the two groups. **Results:** *The Serum Endocan level was significantly elevated with p value of <0.001 in group 1 with mean serum Endocan levels of 1130.95± 680.55pg/ml. Minimum endocan levels observed was 220 pg/ml and maximum value observed in our study was 2120 pg/ml. when compared with patients with ACS and without ACS, serum Endocan levels was significantly elevated in ACS group with a p value of < 0.001. When serum endocan levels was assessed with the severity of coronary artery disease (based on CAG), there was not a statistically significant correlation with a p value of 0.47.* **Conclusion:** Serum Endocan levels was significantly elevated in patients with acute coronary syndrome and can be used as marker in diagnosis of ACS. This shows the role of inflammation in the pathogenesis of ACS helping in widening the concept of atherosclerosis.

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Keywords: Acute coronary syndrome, serum endocan, troponin, coronary angiogram, atherosclerosis.

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Introduction

Coronary artery disease (CAD) is the most common cause of mortality and morbidity in both developed and developing countries.[1] It is a leading cause of death in India.[2] The risk in Indians is 3 to 4 times higher than in western countries.[2][3] CAD occurs 5 to 10 years earlier in Indians compared to western people. Previously it was thought that atherosclerosis was merely a lipid storage disorder.[3] But now the concept behind atherosclerosis is understood better, inflammation also plays a major role.[4] Atherosclerosis is the primary cause of ACS, with most cases occurring from the disruption of plaque from non-severe lesion. Endothelial dysfunction is considered as an early change in atherogenesis.[5] Cardio vascular disease is associated with raised levels of systemic inflammatory markers.[6]

Endocan (previously known as Endothelial cell specific molecule-1, ESM-1), is a potential immuno-inflammatory marker that may be linked to cardiovascular disease.[7] It plays a role in endothelial dependent pathologic diseases, such as inflammatory disorders, tumour progression and adhesion. It is accepted as a potential endothelial cell marker.

The endothelium plays a major role in controlling vascular tone and maintaining vascular homeostasis by secreting vasoactive factors.[1][8] Endothelial cell specific molecule-1 (ESM-1) or endocan, is a soluble proteoglycan (50 kDa), secreted by human vascular endothelial cells.[10] Endocan can be detected in the circulation and is an indicator of angiogenesis and endothelial cell activation.[12][13] Endocan is also thought to play a role in the pathogenesis of vascular disorders, inflammation and endothelium dysfunction.[12][13] Recent studies have found that serum Endocan may be a surrogate endothelial dysfunction indicator that also plays a role in endothelium-dependent pathology.[13][16][17][18] This suggests that the vascular endothelium may play an important role in CAD development.[13][18][19] Therefore, we wanted to correlate the distribution of serum Endocan in CAD patients, as there are less studies regarding positive correlation of these levels in CAD patients. Studies have also shown that serum endocan levels were significantly altered in endothelial inflammation leading to ACS, Diabetes Mellitus, Dyslipidemia and Systemic Hypertension.[15][19][20] Hence in this study we are verifying the role of endocan and its relationship with endothelial dysfunction in ACS and comparing its level with number of vessels involved based on coronary angiogram.

Aims and Objectives

1. To estimate the serum Endocan levels in patients with Acute Coronary Syndrome.
2. To find out the Association of serum Endocan levels with severity of coronary artery disease, based on Coronary Angiogram.

Materials and Methods

Study Design

The study design employed was a cross sectional study, conducted at Sri Manakula Vinayagar medical college and hospital, Puducherry from May 2017 to October 2020 for a period of 18 months, after obtaining IEC approval (SMVMCH-EC/DO/AL/1251/2017).

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Study Participants:

Group 1: All patients with acute coronary syndrome above 18 years including acute ST elevation myocardial infarction, non ST elevation myocardial infarction, unstable angina attending as inpatients in cardiology and internal medicine department.

Group 2: Individuals with age above 18 without acute coronary syndrome.

Inclusion Criteria:

Patients with Acute Coronary Syndrome above 18 years of age, including

1. Acute ST elevation Myocardial Infarction
2. Non ST elevation Myocardial Infarction
3. Unstable Angina

Exclusion Criteria:

1. Rheumatoid Arthritis
2. AIDS
3. Chronic Kidney Disease

Sample Size: Sample size is calculated to be 74 (37 in each group) using software Open-Epi software version 3.2, taking into account mean endocan levels among coronary artery disease patients and normal volunteers as 0.75 (SD 0.13) and 0.86 (SD 0.2) respectively from previous studies[17] with 95% confidence interval and 80% power, calculated by formula n=(2.8.0.5/(p-p0))2, by assessing the endocan levels in both control and study groups.

Methodology

Patients admitted as inpatient in Sri Manakula Vinayagar Medical College and Hospital with ACS diagnosed by history, examination, ECG and laboratory investigations are included in the study. After getting informed consent from the patient and patient's attenders, blood sample were collected for routine investigations and along with it, blood sample of 3 ml will be collected for measuring Seum Endocan levels. This group is considered as Cases Group/ Group 1. Patients aged 18 years without Acute Coronary syndrome is taken as Group 2 . Both groups were matched and were compared. Patient in Group 1 were subjected to Coronary Angiography and were divided into three groups based on involvement of blood vessels(SVD, DVD and TVD) and Serum Endocan levels association with severity of CAD will be assessed.

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analysed using SPSS 22m version software. Categorical data was represented in the form of frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. p value (probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. MS Excel and MS Word was used to obtain various types of graphs such as pie diagram and ROC curve. SPSS version 22 (IBM SPSS statistics, Somers NY, USA) was used to analyse data.

Results

Table 1: Comparison of distribution of age among the study population

Variable	**Group 1**	**Group 2**	**p-value**
	Mean (SD)	**Mean (SD)**	
Age in years	56.8 (10.1)	46.7 (13.8)	<0.001
Total	37	37	

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In our study the mean age group in cases were found to be 56.8 and in controls were 46.7 with p value of <0.001, which was statistically significant using independent t test.

Table 2: Comparison of various risk factors between the groups

Variable		Cases N (%)	Controls N (%)	Chi-Square Value	P Value
Gender	Male	31 (83.8)	17 (45.9)	11.6	0.001
	Female	6 (16.2)	20 (54.1)		
Diabetes Mellitus	Yes	20(54.1)	2(5.4)	20.9	<0.001
	No	17(45.9)	35(94.6)		
Systemic Hypertension	Yes	9 (24.3)	7 (18.9)	0.32	0.57
	No	28(75.7)	30 (81.1)		
Dyslipidemia	Yes	10(27.0)	6 (16.2)	1.3	0.26
	No	27(72.9)	31 (83.8)		
Alcohol Use	Yes	23(62.2)	10 (27.0)	9.2	0.002
	No	14(37.8)	27 (73.0)		
Smoking status	Yes	23(62.2)	6 (16.2)	16.4	<0.001
	No	14(37.8)	31 (83.8)		

Among the study population, Male preponderance of 83.8% was seen in our study in the cases. In the control group both sexes were similar in number. Chi-squared test showed a male preponderance statistically with a p value of 0.001.54.1% of our study cases had Diabetes mellitus. When we compared the diabetic status between the two groups with chi-squared test we got a p value of <0.001. This shows that Diabetes has a strong association with ACS. Comparison of Hypertension in both cases and controls was 0.57 using chi-squared which was not statistically significant.10 % of our cases had dyslipidemia. On comparing Dyslipidemia in both cases and controls, p value was 0.26 using chi-squared test.
The use of alcohol was more in cases with 62.2%. The p value was 0.002 by using chi-squared test and statistically significant implying the role of alcohol in ACS and the need for deaddiction.In this study, it is observed that 62.2% prevalence of smoking in cases and 16.2% in the controls with a significant co-relation between smoking and ACS with a p value of <0.001using chi squared test.

Table 3: Comparison of TROPONIN-I between the groups

TROPONIN-I	Cases N (%)	Controls N (%)	Chi-Square Value	P Value
Positive	26 (70.3)	0	40.1	<0.001
Negative	11 (29.7)	37 (100)		
Total	**37 (100)**	**37 (100)**		

The above table shows the comparison of Troponin-I between the two groups. We observed that 70.3% had positive test result. Chi –squared test was used, p value was <0.001 which was statistically significant (Troponin I done here is a Qualitative test).

Table 4: Comparison of ECG between the groups

ECG	Cases N (%)	Controls N (%)	Chi-Square Value	P Value
Normal	6 (16.2)	37 (100)	53.3	<0.001

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ST	23 (62.2)	0		
ST depression and T wave changes	8 (21.6)	0		
Total	**37 (100)**	**37 (100)**		

On comparing the ECG findings between the two groups, 16.2% had normal ECG findings, 62.2% had ST elevation changes and 21.6% had ST, T wave changes in the cases group. We compared it with the control groups using Chi-squared test with pvalue of <0.001 which was statistically significant.

Table 5: Comparison of BP between the groups

BP	**Cases N (%)**	**Controls N (%)**	**Chi-Square Value**	**P Value**
120/80	30 (81.1)	29 (78.4)	2.7	0.26
140/80	5 (13.5)	8 (21.6)		
>160	2 (5.4)	0		
Total	**37 (100)**	**37 (100)**		

The above table shows the comparison of Blood pressure between the two groups. We got a p value of 0.26 using chi-squared test which was not statistically significant.

Table 6: Comparison of BMI between the groups

Variable	**Cases**	**Controls**	**t-Value**	**p-value**
	Mean (SD)	**Mean (SD)**		
BMI	25 (3.2)	25.4 (1.8)	0.67	0.51

In the above table, comparing the BMI between the two groups was done using independent t test, shows no statistical difference.

Table 7: Comparison of RBS between the groups

Variable	**Cases**	**Controls**	**p-value**
	Mean (SD)	**Mean (SD)**	
RBS *	152 (120-250)	98 (78-112)	<0.001

The above table shows the comparison of Random blood sugar between the groups using Median (IQR), Mann Whitney Test., which was statistically significant with p value of <0.001.

Table 8: Comparison of CK-MB between the groups

Variable	**Cases**	**Controls**	**p-value**
	Mean (SD)	**Mean (SD)**	
CKMB	22 (17-57)	15 (12-16)	<0.001

The above table shows the comparison of ck-mb levels between the two groups using Median (IQR), Mann Whitney Test. p value was <0.001, which was statistically significant.

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Table 9: Comparison of fasting lipid profile between the groups

Variable	Cases	Controls	t-Value	p-value
	Mean (SD)	Mean (SD)		
Cholestrol	188.8 (51.4)	198.3 (48.3)	0.8	0.41*
HDL	36.0 (6.6)	38.6 (8.5)	1.5	0.14*
LDL*	106 (68-38)	129 (104-148)		0.04**
TGLS*	104 (80-163)	148(73-248)		0.12**

*Independent t test was used **Median (IQR), Mann Whitney Test was used.

The above table shows the comparison of different parameters of FLP between the groups and the p value of LDL of 0.04 was statistically significant.

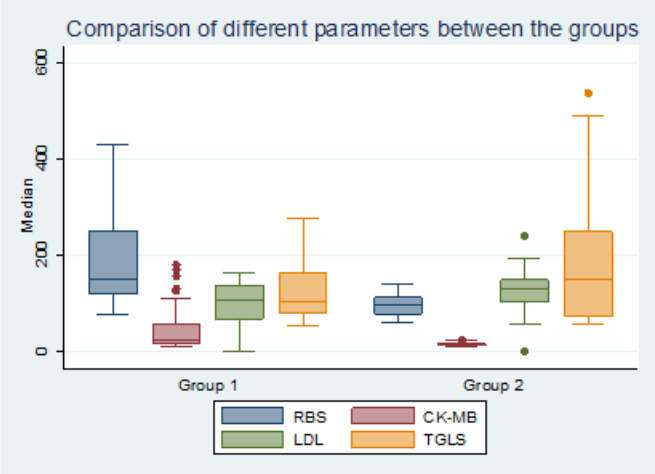

Figure 1: showing comparison of different parameters between the groups

The above figure is a Boxplot graph showing the median and inter-quartile range. The line inside the box is showing the median range. The top and bottom borders are inter-quartiles (25 and 75%). Boxplot graph was used as the data were non-normally distributed.

Table 10: Comparison of S. ENDOCAN between the groups

Variable	Cases	Controls	z	p-value
	Mean (SD)	Mean (SD)		
S. ENDOCAN	2000(1400-2000)	560(370-820)	6.3	<0.001

The above table shows the mean values of Serum Endocan levels were significantly different in cases 2000 and controls 560. Z score of 6.3 and P value is <0.001 using Mann Whitney test, which is significant.

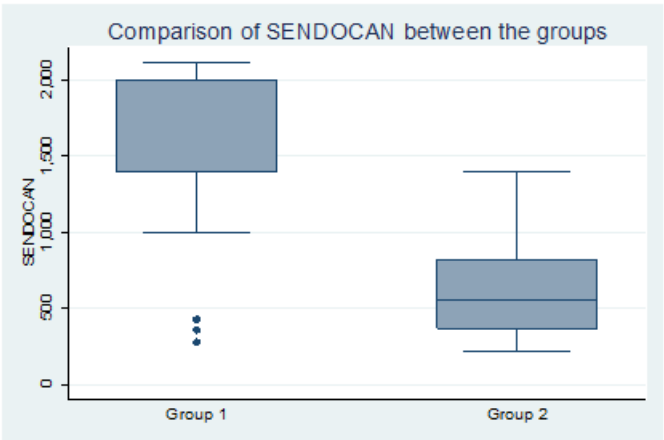

Figure 2: showing comparison of Serum Endocan levels between the groups.

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The above figure shows boxplot graph of serum endocan levels which was more in cases belonging to group 1 when compared with group 2 controls.

Table 11: Comparison of ENDOCAN between CAG among group 1. (1. Single vessel disease, 2. Double vessel disease, 3. Triple vessel disease.)

CAG	n	Mean	SD	F	P Value
1	24	1772	475.6	1.05	0.36
2	8	1555	613.2		
3	5	1402	662.8		

The above table shows the comparison of serum endocan levels between coronary angiogram in group 1 depending on the number of vessels involved using ANOVA test.
p value was 0.36 which was statistically not significant.

Discussion

A total of 74 patients (37cases, 37 controls) were taken into study, who fit into the inclusion criteria. Most of the patients in our study had smoking tobacco products and alcohol beverages usage as the risk factor which is the leading cause for coronary artery disease. Estimation of serum endocan level was done using ELISA method. Results showed elevated serum endocan levels in ACS patients, which is statistically significant. LDL cholesterol levels were statistically significant in the cases of our study. Male gender prevalence was more in our cases with acute coronary syndrome. Serum endocan level was significantly elevated in cases with acute coronary syndrome with statistically significant p value of <0.001.

Inflammation plays an important role in the pathogenesis of atherosclerosis. Inflammatory cells, proteins, and responses from vascular cells play a central role in the pathogenesis of different stages of atherosclerosis including the initiation and progression of atheroma, plaque instability, and rupture.[16][17]

Endocan is thought to play a role in vascular diseases, organ-specific inflammation, and endothelium-dependent pathological disorders. Serum endocan levels are increased in diseases with vascular involvement or invasion.[18] So we conducted this study to assess the serum endocan levels in patients with acute coronary syndrome.

In this study, total population of 74 patients 37 cases with ACS and 37 patients without ACS as controls were taken. The majority subjects in case group were in age group of 41-55 years (21 subjects), followed by 15 patients in group between >55 years, which is followed by 1 patient in age group of 25-40 years. This correlates with the findings in a number of previous studies that ACS is more prevalent after the 4^{th} decade of life. The mean age group in cases was 56 ± 10 years which was similar to the study done by kose et al where patients with coronary artery disease were in the mean age group of 56 years.[19]

Coming to gender distribution of cases in this study, 31 were males (83.8%) and 6 were females (16.2%). While the control group had 17 males (45.9%) and 20 females (54.1%). This data suggests that most of the cases in this study was males which was correlating with the similar studies of Sevil Fisekci et al and other studies which showed male preponderance of 81.2%. [116] Chi- square test was used to compare the gender distribution in both the groups and got male preponderance with p value of 0.001, which was statistically significant. Although we had a data of 6% of females in cases they were all in the post-menopausal age group, which correlates with similar study done by kose et al. [19][20]

As in most of the previous studies the following risk factors were seen in most of the ACS patients.[21] The most commonly seen risk factor in this study was smoking tobacco products 62.2% in the cases and 37.8 % of cases didn't use alcohol. In control group 27% had used

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alcohol and 73 % did not use alcohol. Similar study done by Himbert et al showed 61% of smokers had coronary artery disease. This data showed a significant risk factor in relation to alcohol use and the development of acute coronary syndrome. It is observed that a similar distribution in relation to smoking status of individuals in cases with 62.2% smoking cigarettes or beedi and 16.2 % in controls without smoking.

Similar study done by Gok et al showed 60% cases with CAD were smokers. While in control group only 16.2% of individuals were smokers and the remaining 83.8% were non-smokers. So, On comparing the two groups using chi-square test, it was statistically significant with p value of <0.001. Both the risk factors had similar distribution in this study and it was seen in male gender only. Following this, the next commonly found risk factor was Diabetes mellitus. It is seen in about 54.1% of cases in both genders.

Following this was systemic hypertension, seen in 24.3% of the cases. Dyslipidemia was seen in 27% of the case group. Body Mass Index was also included in our study was 25 $\pm$(3.2) in cases, which was not statistically significant.

Lipid profile of the cases show mean LDL values of 106 with (SD) 68-38. The mean LDL in controls was 129 with (SD) 104-148. It is found that a similar correlation with the study done by kose et al with mean LDL levels in Acute coronary syndrome being 125$\pm$ 31. HDL levels in the cases are reduced when compared to that of control group. Mean HDL value is 36mg/dl and the SD is 6.6. LDL cholesterol levels were statistically significant in this study. It correlates with most of the previous studies, where elevated LDL is the single most risk factor for coronary artery disease.[2]

Serum Endocan levels in acute coronary syndrome were significantly elevated in cases group, when compared with controls. The mean Endocan levels in cases were 2000 pg/ml with SD (1400-2000). The mean endocan levels in controls were 560pg/ml with SD (370-820). Similar study done by cimen et al showed serum endocan levels were in a mean range of 268.0 (226.4-336.5) in the control group and was significantly elevated in acute coronary syndrome patients. Mann Whitney test was used and z value of 6.3 and P value <0.001 which was statistically significant. This study had the same findings as that of the study done by kose et al., where serum Endocan levels were significantly elevated in patients with coronary artery diseases.[21][22]

Sl. no	Author's name and year	Place of study	Number of subjects	Objective	Conclusion
1.	Kose M et al., & 2015	Istanbul, Turkey	53 patients & 30 control	To demonstrate the association of Serum Endocan levels and ACS and its severity	Serum levels of endocan, a new biomarker of endothelial pathologies, is significantly increased in patients with ACS, but clinical usage to predict the severity of CAD in patients with ACS needs further investigation
2.	Zhao T et al.	Meta-analysis	1839 patients &1258	Endothelial dysfunction was widely regarded as the	In this meta-analysis, we further confirmed that serum endocan level was

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	& 2018		control	initial lesion in the multifactorial pathogenesis of cardiovascular disease (CVD). Serum endocan, a novel endothelial dysfunction biochemical marker, is involved in the development of CVD. Here, we fulfilled a meta-analysis to evaluate the association between CVD and serum endocan levels.	significantly increased in the CVD population. The high serum endocan level may be one of the risk factors for CVD.
3	Aşkın L, Tanrıverdi O & 2021	Overview of many studies	941 patients	To present a review of the biological functions of the endocan and the prevention of atherosclerosis.	Endocan is a promising new inflammatory marker in CVD. Serum endocan level monitoring may be an important step forward in predicting the occurrence and development of CVD, and serial measurements may shed light on the effect of therapy on endothelial functions
4	Turan T et al & 2016	Trabzon, Turkey	54 CAE patients & 30 control	To investigate the association p between coronary artery ectasia (CAE) and endocan	There was a significant correlation between endocan levels and severity of isolated CAE according to the Markis classification. Plasma endocan levels may reflect the presence and severity of isolated CAE, suggesting that endocan may be involved in pathogenesis of isolated CAE.
5	Arman Y at al & 2022	Istanbul, Turkey	42 patients & 42 control	To reveal the usability of serum endocan levels as a biomarker in the diagnosis of subclinical atherosclerosis in patients with prediabetes, based on CIMT measurements.	Carotid intima media thickness was found to be high and the serum endocan level was low in patients with prediabetes. Decreased serum endocan levels in patients with prediabetes may be a contributing factor to atherosclerosis

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					formation mechanisms.
6	Ziae e M, Mas haye khi S, Ghaf fari S, Mah mou di J, Sarb akhs h P, Garj ani A & 2019	Tabriz, Iran	320 patients	To assess the prognostic value of serum levels of endocan in patients with the acute coronary syndrome (ACS) through its correlation with the Thrombolysis in Myocardial Infarction (TIMI) risk score and compared the possible association with clinical outcomes.	A high endocan level on hospital admission is an independent predictor of worse cardiovascular outcomes and higher TIMI risk score in patients with ACS.
7	Pres ent Stud y	Puducherry, India	37 cases & 37 control	***To estimate the serum Endocan levels in patients with Acute Coronary Syndrome and to find out the Association of serum Endocan levels with severity of coronary artery disease, based on Coronary Angiogram.***	This study shows a significant association between Serum Endocan levels in cases and controls. Serum Endocan level was significantly elevated in cases with Acute coronary syndrome. Hence, Serum Endocan levels can be used as a marker in cases with Acute coronary syndrome.

In addition to finding out the Serum Endocan levels in between groups, the severity of coronary artery disease was assessed based on the number of vessels involved by coronary angiogram. On comparing Serum Endocan levels between coronary angiogram in cases, 24 cases had single vessel disease and the mean serum endocan levels were 1772 with SD of 475.6. Other 8 cases had double vessel disease with mean serum endocan levels of 1555 with SD of 613.2. Rest of 5 cases had triple vessel disease with mean serum endocan values of 1402 with SD of 662.8. ANOVA test was used the p value was 0.36, which was not statistically significant.[23][24]Severity of CAD with respective to serum Endocan levels was done by modified Gensini stenosis and by using syntax scoring system in other studies, which did not correlate in their study.

Strengths of the study

Serum endocan levels was significantly elevated in ACS patients and can be used as a marker in patients with acute coronary syndrome. As this study was a comparative cross-sectional study the causal relationship of endocan with ACS was established.

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Limitations of the study

This study was done with small sample size. Serum Endocan levels do not have a normal detectable range for assessing as it varies with the kit. ELISA method was taken as per availability in our research lab facility.

Conclusion

This study shows a significant association between Serum Endocan levels in cases and controls. Serum Endocan level was significantly elevated in cases with Acute coronary syndrome. Hence, Serum Endocan levels can be used as a marker in cases with Acute coronary syndrome.

But, this study couldn't establish the severity of acute coronary syndrome based on coronary angiogram with serum endocan levels. This also throws insight into the concept of inflammation in acute coronary syndrome.

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