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To evaluate HS-CRP and Osteoprotegerin as risk factors in acute coronary syndrome in patients of type 2 DM

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Abstract
Background: Osteoprotegerin (OPG), a key factor in vascular calcification and atherosclerosis has been suggested to be associated with cardiovascular events particularly in patients with Type 2 DM. This study sought to assess the relationship between Osteoprotegerin and hs-CRP with other conventional cardiovascular disease risk factors in Type 2 Diabetes Mellitus patients.
Methods: A total of 80 consecutive type 2 diabetes mellitus patients with symptoms of acute coronary syndrome were enrolled in this cross-sectional study. They were divided into two groups each with reference to age, Group A (40-60yr), Group B (>60yr). Blood samples were taken for laboratory tests. OPG, hs-CRP and other conventional risk factors were measured.
Results: OPG levels were in direct association with smoking (p=0.046), STEMI (mean-7.33 ng/ml) and inversely related to age (Group A>B; p=0.02). Hs-CRP level was in direct association with STEMI and low ejection fraction (%). After adjusting for variables like Hb, ESR and total cholesterol (p=0.048) was significant indicator of hs-CRP. Total cholesterol (p=0.002) has direct linear association with acute coronary syndrome. Serum hs-CRP and serum OPG in type 2 diabetic patients were not associated (p>0.05) with the conventional risk factors like alcohol abuse, duration of diabetes, BMI, waist circumference and HbA1C.
Conclusion: Increased levels of OPG is associated with smoking and in patients with STEMI. Severe LV systolic dysfunction was observed in patients with high hs-CRP levels and mild LV systolic dysfunction in patients with high OPG levels.

Keywords: Atherosclerosis, Type 2 Diabetes Mellitus, Acute coronary syndrome, Conventional risk factors, Osteoprotegerin, highly sensitive C-reactive protein (hs-CRP).

1. Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors [1]. Type 2 DM has a strong genetic component. Individuals with a parent with type 2 DM have an increased risk of diabetes; if both parents have type 2 DM, the risk approaches 40% [2]. A high proportion of asymptomatic diabetic patients have significant subclinical atherosclerosis [3]. The mortality from Acute Myocardial Infarction is increased five-fold in diabetic patients (Hansen *et al*. 2007) [4]. Arterial hypertension and dyslipidemia frequently coexist with diabetes and contribute to the increased prevalence of CVD in diabetic patients [5].

The Cardiovascular disease (CVD) risk is high in Type 2 DM [6] and it has been proved that in those patients with high hsCRP, there is increased risk of CVD events and increased risk of mortality [7]. Hs-CRP is also a potential adjunct for global risk assessment in the primary prevention of cardiovascular disease [8].

Recently another CVD risk–Osteoprotegerin has been detected particularly in patients with Type 2 DM. Osteoprotegerin (OPG) is a glycoprotein that acts as a decoy receptor for receptor activator of nuclear factor B ligand (RANKL) and tumor necrosis factor-related apoptosis-inducing ligand that have been consistently associated with the incidence and prevalence of coronary artery disease [9].

The main purpose of this study is to determine Osteoprotegerin association in Type 2 DM patients with ACS (Acute coronary syndrome) and in Type 2 DM in comparison to hsCRP and other conventional CVD risk factors

2. Patients and Methods

2.1. Participants

80 patients were selected consecutively who fulfilled the inclusion and exclusion criteria and were divided into 2 groups of 40 each. GROUP A: Age 40-60yr M/F; Type 2 DM patients with/without ACS (20 each respectively), GROUP B: Age >60yr M/F; Type 2 DM patients with/without ACS (20 each respectively). Data were collected in a pretested proforma meeting the objectives of the study. A detailed proforma was made for each patient after their consent, which included age, sex, and IP and OP number, relevant present, past, personal and drug history and clinical examination was done. The study protocol was approved by research ethics committee of JSS University.

2.2. Measurements and laboratory investigations

The patients' weight, height, and waist circumference were measured precisely. The systolic and diastolic blood pressures were taken twice with at least 10 minutes interval. Body mass index (BMI) was calculated as weight (Kg) divided by height squared (m^2). Diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association, 2011. Fasting and postprandial blood sugars, HbA1C, Lipid profile were all done in our laboratory using standard techniques. For measurement of highly sensitive C-reactive protein (hs-CRP), the blood was centrifuged immediately at 4°C and stored at –

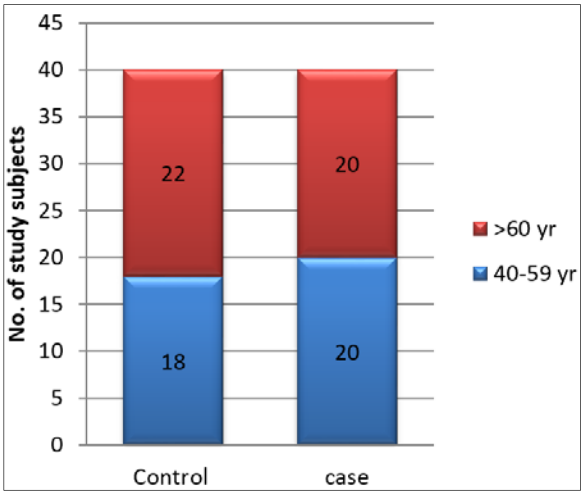
20 °C and were processed by immunoturbid assay with an interassay variation coefficient of <5%. Serum concentrations of Osteoprotegerin (OPG) were determined by available commercial kits (Elabsciences diagnostic kit, China) using Sandwich-Enzyme Linked Immunosorbid assay method for which the blood was centrifuged immediately after drawing at 3,500 rpm for 10 min, stored at -20 °C and kept frozen at −80 °C until analysis.

2.3. Statistical analysis

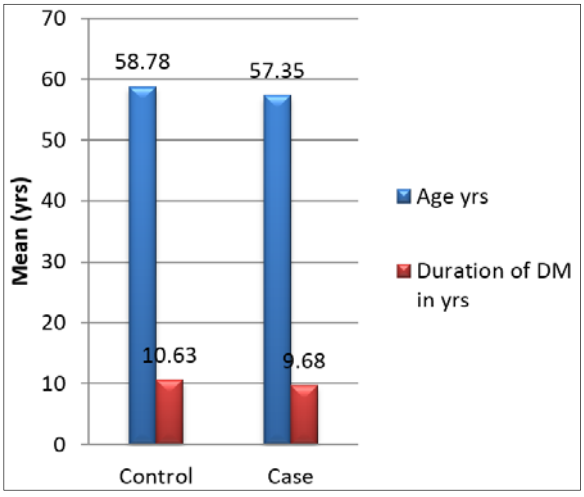
Statistical analysis was performed using SPSS software (v.16). Normally distributed variables were expressed as mean, median and standard deviation (SD). Independent t-test was performed to evaluate difference in continuous variables across different groups. Chi-square test or Fisher exact tests were employed to assess the difference between distributions of the categorical variables. Mann Whitney test was used to compare medians between two independent groups. Statistically significant level was considered to be P value < 0.05.

3. Results

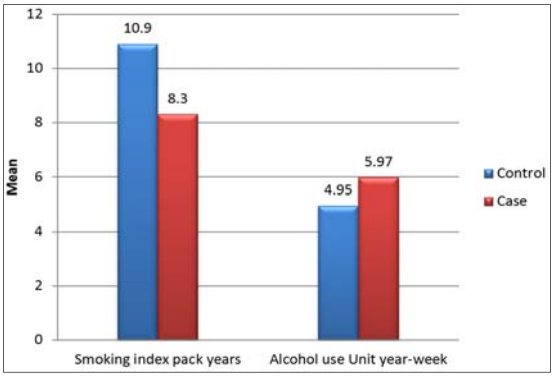
Characteristics of the study population with respect to Conventional risk factors:



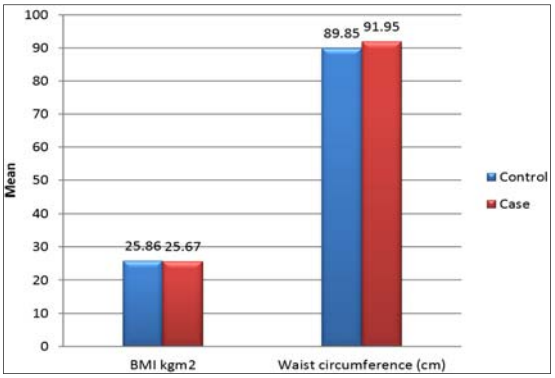
Graph 1: Age distribution of study subjects



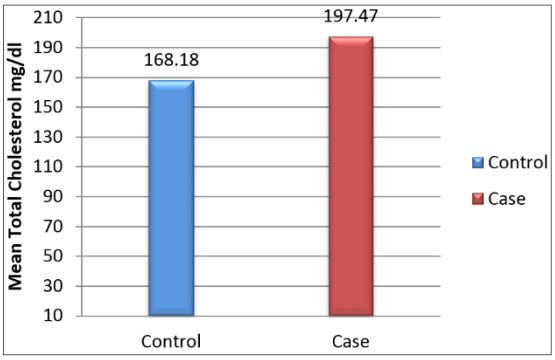
Graph 2: Distribution of mean age and duration of Diabetes among controls and cases



Graph 3: Distribution of mean smoking index and alcohol intake in cases and controls



Graph 4: Distribution of mean BMI and Waist circumference in cases and controls



Graph 5: Comparison of mean total cholesterol in controls and cases.

Table 1: Mean lipid profile, HbA1C, renal functions and serum uric acid in the study group

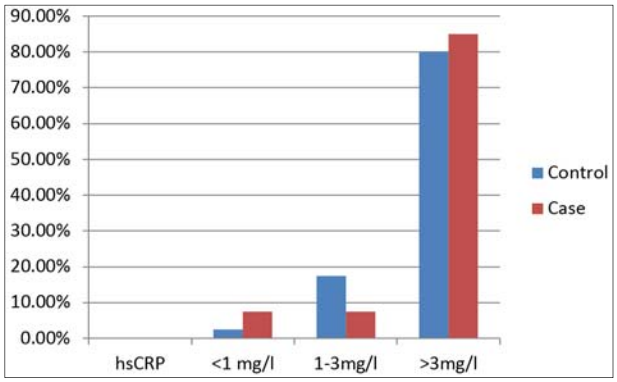
	Group					
	Control			Case		
	Mean	SD	Median	Mean	SD	Median
HbA1C	9.27	2.13	8.95	9.86	2.46	9.60
Total cholesterol	168.18	40.17	174.00	197.47	42.98	198.00
HDL	35.00	7.42	35.00	36.75	4.81	35.00
LDL	91.00	43.40	81.50	94.50	34.44	90.00
VLDL	44.65	28.30	37.50	48.52	27.48	41.00
Triglycerides	158.95	104.86	116.00	185.08	186.63	135.00
Blood Urea	29.78	8.63	28.00	29.35	10.96	27.50
Serum Creatinine	1.01	.26	.90	.99	.34	.90
Serum uric acid	5.17	.93	4.90	5.32	1.59	5.10

Characteristics of the study population with respect to acute coronary syndrome and serum hs-CRP, OPG:

Table 2: Comparison of mean hs-CRP and Serum OPG in cases and controls

	Group					
	Control			Case		
	Mean	SD	Median	Mean	SD	Median
hsCRP mg/l	7.83	3.59	10.39	8.57	3.32	10.39
Serum OPG ng/ml	6.78	2.21	6.85	7.15	1.97	7.80

In this study, mean hsCRP in the control group is 7.83±3.59 mg/l and among the cases mean hsCRP is 8.57+3.32 mg/l.
P values = 0.3 indicating no significance.
But the mean difference in hsCRP between the two groups (controls and cases) after adjusting for variables like Hb, ESR and total cholesterol was statistically significant.
P=0.048 indicates major significance.



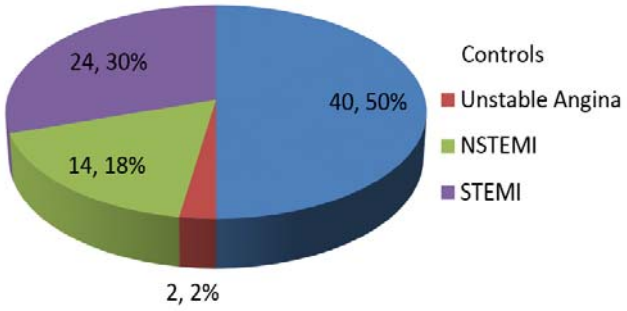
Graph 6: Distribution of hs-CRP levels among cases and controls

Table 3: Comparison of mean hs-CRP among two age groups in controls and cases

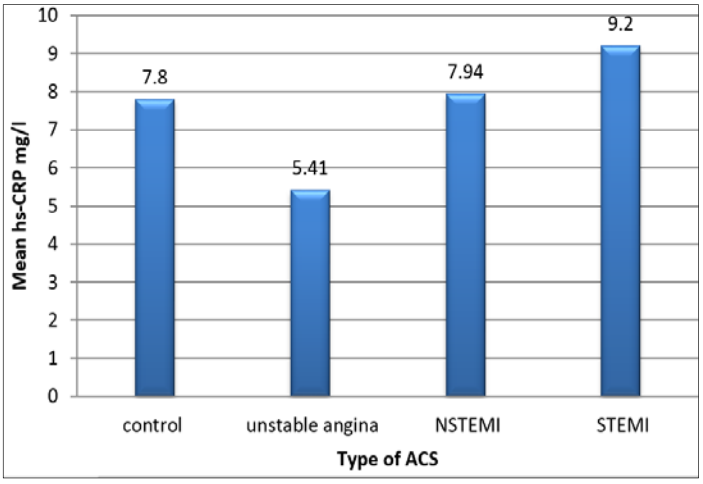
			Group						
			Control			Case			
			Mean	Median	SD	Mean	Median	SD	p
Age (yr)	40-59	hsCRP	7.66	10.39	3.85	8.20	10.39	3.49	0.7
	>60	hsCRP	7.97	10.39	3.45	8.94	10.39	3.19	0.3

Table 4: Comparison of mean serum OPG among two age groups in controls and cases

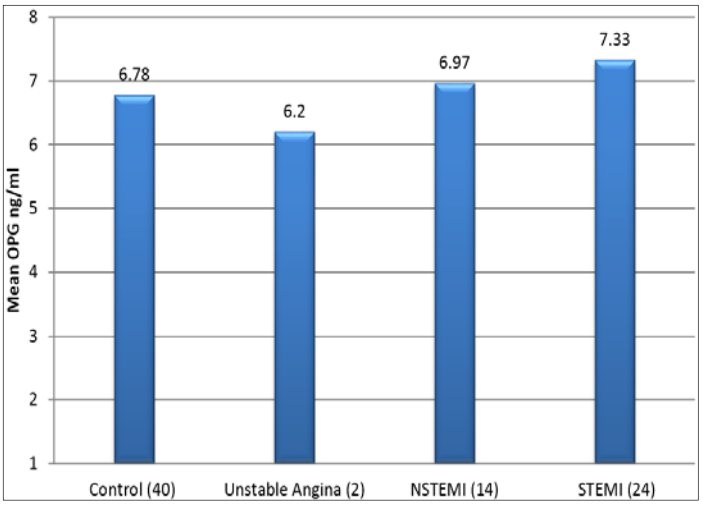
			Group						
			Control			Case			
			Mean	Median	SD	Mean	Median	SD	p
Age (yr)	40-59	Serum OPG	6.44	6.10	2.22	7.99	8.40	1.43	0.02
	>60 yr	Serum OPG	7.05	7.65	2.22	6.30	6.00	2.10	0.2



Graph 7: Distribution of type of ACS in the study group



Graph 8: Distribution of mean hs-CRP levels among cases



Graph 9: Distribution of mean serum OPG levels among cases

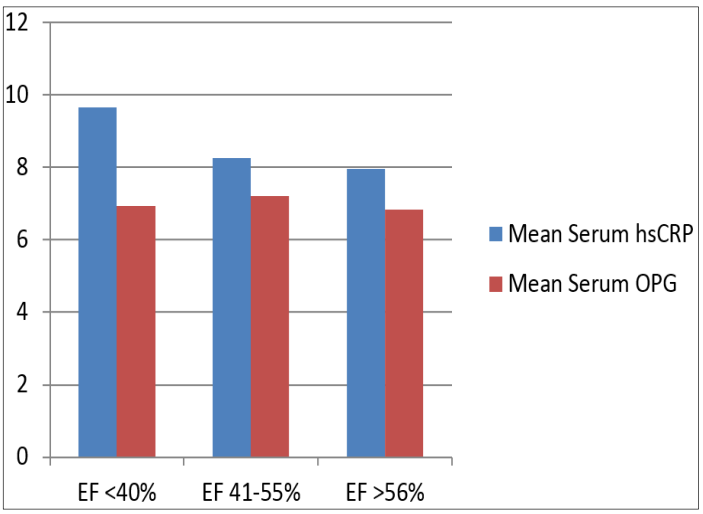
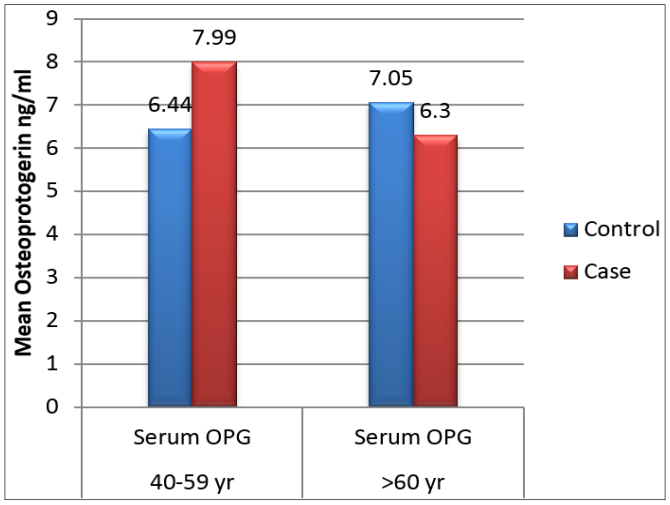


Table 5: Comparison of mean hsCRP and serum OPG to ejection fraction among cases.

Characteristics of the study population with respect to conventional risk factors and serum hs-CRP, OPG:



Graph 10: Comparison of mean serum OPG among two age groups in controls and cases

Table 6: Correlation between serum hsCRP and OPG levels with smoking index, alcohol intake, BMI and waist circumference.

Correlations					
		Smoking index	**Alcohol u year week**	**BMI kgm2**	**Waist circumference**
hS-CRP	R	-.133	.062	.157	.019
	P	.239	.586	.165	.864
	N	80	80	80	80
Serum OPG	R	.224*	.106	-.021	.061
	p	**0.046**	0.349	.854	.588
	N	80	80	80	80

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Table 7: Comparison of mean hs-CRP and OPG to duration of diabetes among the subjects.

	Duration Of Diabetes (yrs)					
	<5 yr		**6-10 yr**		**>11 yr**	
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**
Hs-CRP	7.99	3.76	7.69	3.56	8.71	3.06
Serum OPG	6.87	1.98	7.43	2.33	6.81	2.11

4. Discussion

According to a number of studies, serum OPG level is elevated in subjects with Coronary artery disease and in subjects with diabetes, independent of the conventional risk factors. We investigated hsCRP and Osteoprotegerin as risk factors in Acute Coronary Syndrome in patients of Type 2 Diabetes Mellitus(cases) n=40 and non ACS group(controls), n=40. In our study, Serum hsCRP and OPG in type 2 diabetic patients were not significantly correlating (p>0.05) with the conventional risk factors like alcohol, duration of diabetes, BMI, waist circumference, HbA1C and other relevant parameters. Mean total cholesterol was statistically significant (p=0.002) risk factor in case group (Type 2 DM with Acute coronary syndrome).

However, Serum OPG was significantly correlating with mean smoking index. In contrary to increased OPG levels with age, we found that there was a significant (p=0.02) increase in mean serum OPG among 40-59year age group compared to ≥60year age group. The mean difference in hs CRP between the two groups (controls and cases) after adjusting for variables like Hb, ESR and total cholesterol was statistically significant(p=0.048).

A study by Ahmed Abdul-hassan Abbas[142] showed no significant difference (p>0.05) in serum levels of OPG between patients among the three groups NSTEMI, STEMI and UA whereas we obtained marginally higher mean hsCRP and serum OPG levels in STEMI patients compared to other types of ACS. Mean hsCRP was marginally higher in low EF <40% (9.65 mg/l) compared to EF 41-55% (8.26 mg/l) and EF >56% (7.95 mg/l) in our study. We conclude that severe LV systolic dysfunction was observed in patients with high hsCRP levels and mild LV systolic dysfunction was observed in patients with high OPG levels.

5. Acknowledgments

I sincerely thank my guide and moderator, Dr. B.J. Subhash Chandra,
Dr. Basavana Gowdappa. H and Dr. K.A. Sudharshana Murthy for their constant support, my parents, husband and friends for their love and affection.

6. Conflicts of Interest

In our study, though there were higher values of hsCRP and serum OPG in case group compared to control group, it was statistically insignificant probably due to inadequate sample size.

7. References

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