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Correlation of Serum Soluble CD40 Ligand Level with Inflammatory Marker in Primary Hypertension

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Abstract

Background: Primary hypertension accounts for 90% cases of all hypertensions. Essential hypertension, which is considered to be one of the syndromes that include an increase in blood pressure (BP), systemic inflammation, abnormal lipid metabolism, abnormal sugar metabolism, abnormal blood coagulation, and left ventricular hypertrophy. Aim of the study. To measure serum sCD40 ligand and serum hs CRP in primary hypertensive cases and controls. To correlate serum sCD40L with both systolic and diastolic blood pressure and hs CRP in essential hypertension.**Methods:** The study was carried out in M.K.C.G. Medical College and Hospital Berhampur. Serum sCD40L and serum hs CRP has been measured by ELISHA methods. The comparision and correlation of result has been done. P value < 0.05 was considered as significant. **Results:** Maximum cases and controls are within the range of 41-50 yrs. Male to female ratio is 3:1. The Mean hs CRP and sCD40L levels were higher in hypertensive patients than control groups which is found to be statistically significant (p <0.001). sCD40L and hsCRP had significant positive correlation with both systolic and diastolic blood pressure. sCD40L and hsCRP had significant positive correlation with both systolic and diastolic blood pressure. **Conclusions:** Our study suggest that the estimation of Serum soluble CD40 ligand may be used as a pro thrombotic marker for early diagnosis. Soluble CD40L as a marker of platelet activation and hs-CRP as a inflammatory marker may have a prognostic value in hypertension. The timely therapeutic intervention may reduce morbidity and mortality in essential hypertensive individuals.

Keywords:-Hypertension, hs – CRP, inflammation, sCD40L – Soluble Cluster Differentiation 40 ligand.

INTRODUCTION

Primary hypertension accounts for 90% cases of all hypertensions.[1]The Seventh Report of the Joint National Committee classified hypertension as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or taking antihypertensive medication.

Worldwide hypertension is estimated to cause 7.5 million deaths which is almost 12.8% of total annual deaths.[2] In India prevalence of Hypertension varies from 17-20% with slight rural urban differences.

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Essential hypertension remains a major modifiable risk factor for cardiovascular disease (CVD) despite important advances in our understanding of its pathophysiology and the availability of effective treatment strategies.In primary hypertension there is evidence that platelets and the endothelium both get activated causing hypercoagulable state and thrombotic tendency.[3]High sensitive CRP is an inflammatory marker induces hypertension and endothelial dysfunction by inhibiting AMPK-eNOssignalling.[4]

Recently, studies have suggested that platelets also participate in inflammatory reactions. Platelets are known to produce inflammatory mediators including platelet-derived growth factor, platelet factor 4, and transforming growth factor. Platelets are also known to bind, via P-selectin(CD62P) expressed on the surface of activated platelets to the leukocyte receptor, P-selectin glycoprotein ligand-1 (PSGL-1). The relevance of this binding is supported by a study demonstrating that the infusion of recombinant soluble human form of P-selectin glycoprotein ligand-1 in an animal model of vascular injury reduced myocardial reperfusion injury and preserved vascular endothelial function.[5]Theclinical implications of heterotypic aggregates are shown by studies demonstrating that after acute myocardial infarction, circulating monocyte-platelet aggregates are both increased and are a more sensitive marker of in vivo platelet activation than platelet surface P-selectin.[6] Plaque rupture promotes activation of the inflammatory responses, and the consistent finding of heterotypic aggregates highlights the close interaction between inflammation and thrombosis in vascular disease.

Contributing to our understanding of the role of platelets inflammation are CD40-CD40 ligand (CD40L) interactions. The CD40 ligand (CD40L) is a transmembrane protein, structurally related to TNF-∝ that has been first identified on CD4 + T Cells.[7,8]Subsequently, CD40L has also been identified on the surface membrane of activated platelets,[9]fromwhere a soluble form (sCD40L)can be released into circulation.[10] Both membrane-bound and soluble CD40L interact with CD40 expressed on vascular cells, resulting inflammatory and prothrombotic responses.[9,11] Engagement of CD40L with CD40 on endothelial cells, in fact, results in phenotypic changes that are similar to those induced by TNF-α,i.e., increased expression of adhesion molecules and secretion of inflammatory cytokines.[12] In addition soluble CD40Lcan act as ligand of the platelet fibrinogen receptor glycoproteinIIb/IIIa and involved in thrombus stabilization and platelet activation.[13]Thus, sCD40L may represent a key molecule linking inflammation and prothrombotic state in human diseases.

Aims and Objectives

1. To measure serum sCD40 ligand and serum hs CRP in primary hypertensive cases and controls.
2. To correlate serum sCD40L with both systolic and diastolic blood pressure and hs CRP in essential hypertension.

MATERIALS AND METHODS

The study was carried out on 51 hypertensive patients and 51 normotensive controls who attended the outpatient department of medicine of M.K.C.G. Medical College and Hospital Berhampur.

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Exclusion Criteria

Cases with diabetes mellitus, thyroid disease, chronic kidney disease, smoking, autoimmune diseases and any other chronic diseases are excluded.

Inclusion Criteria

The study was approved by Institutional ethical committee. Informed consent was obtained from all cases.

Collection of Sample:Informed consent was taken from cases and controls. Four ml of venous blood was collected in a dry, sterile disposable syringe under aseptic conditions. one ml of blood was kept for fasting blood sugar estimation in vials containing fluoride as glycolytic inhibitor.Serum sample was analysed for soluble CD40 Ligand &,hs CRP. Details of different methods of estimation are described below.

Human soluble cluster of differentiation 40 ligand (sCD40L) estimation by elisa kit.

Serum soluble CD40 ligand was estimated using commercially available ELISA kit marketed by Sincere Biotech Catalog number: E13651623.

Principle: The kit assay Human sCD40L level in the Samples, use Purified Human sCD40Lantibody to coat microtiter plate wells, make solid-phase antibody, then add Samples(Containing Human sCD40L) to wells, combined Human sCD40L antibody which is HRP labelled, become antibody - antigen - enzyme-antibody complex, after washing completely, add TMB substrate solution, TMB substrate becomes blue color as HRP enzyme-catalyzed, reaction is terminated by the addition of a sulphuric acid solution and the color change (yellow) is measured spectrophotometrically at a wavelength of 450 nm. The concentration of Human sCD40L in the samples is then determined by comparing the O.D. of the samples to the standard curve.

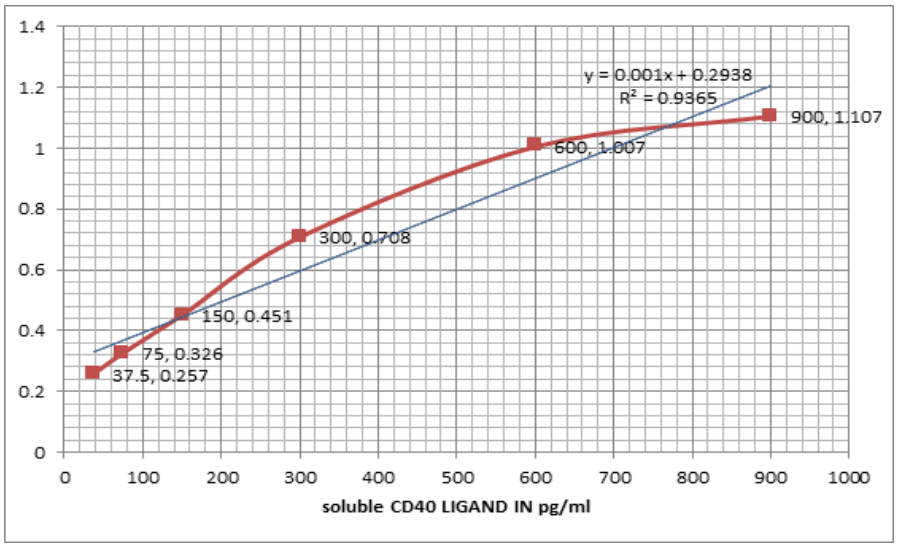

Figure 1: Standard graph for soluble CD40 ligand estimationX axis denotes sCD40L ligand level in pg/ml and Y axis denotesAbsorbance in OD at 450 nm wavelength.

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Estimation of hs CRP by elisa method

Serum hs CRP was estimated using commercially available ELISA kit marketed by XemaCo.LtdCatalog number: K250.

Principle of the test

This test is based on two-site sandwich enzyme immunoassay principle. Tested specimen is placed into the microwells coated by specific murine monoclonal antibodies to human CRP-antibodies. Antigen from the specimen is captured by the antibodies coated onto the microwell surface. Unbound material is removed by washing procedure. Second antibodies – murine monoclonal to human CRP, labelled with peroxidase enzyme, are then added into the microwells. After subsequent washing procedure, the remaining enzymatic activity bound to the microwell surface is detected and quantified by addition of chromogen-substrate mixture, stop solution and photometry at 450 nm. Optical density in the microwell is directly related to the quantity of the measured analyte in the specimen.

RESULTS

The study was carried out on 51 newly diagnosed primary hypertensive patients and 51 normotensive age and sex matched controls.

Maximum cases and controls are within the range of 41-50 yrs. Male to female ratio is 3:1 [Table 1].

The demographic and clinical data of cases and controls has been shown in [Table 2]. The mean and standard deviation of age, systolic blood pressure, diastolic blood pressure, of cases and controls has been tabulated.

The Mean hs CRP and sCD40L levels were higher in hypertensive patients than control groups which is found to be statistically significant ($p < 0.001$) [Table 3].

Bar diagram showing mean soluble CD40 ligand level in cases and controls. Mean soluble CD40L level in cases is 867.82pg/ml and in controls is 363.05pg/ml [Figure 2].

Bar diagram showing mean hs CRP level in cases and controls. Mean hs CRP level in cases is 4.9mg/1 and in controls is 0.97mg/1 [Figure 3].

[Table 4] shows that, sCD40L and hsCRP had significant positive correlation with both systolic and diastolic blood pressure This signifies that higher systolic and diastolic blood pressure associated with increase in these two variables (sCD40Land HSCRP).

In the above plot sCD40L and hsCRP had significant positive correlation with both systolic and diastolic blood pressure [Figure 4].

Table 1: Distribution of study population according to Age and Sex

Age (Years)	Case (n =51)		Control (n =51)	
	Male	Female	Male	Female
20-30	09	0	11	0
31-40	14	6	11	6
41-50	16	6	16	6
Total	39	12	39	12

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Table 2: Demographic and Clinical Data of Cases and Controls

Parameters	Cases (n =51)Mean ± SD	Controls (n =51)Mean ± SD	P Value
Age (years)	38.55 ± 6.99	38.23 ± 7.66	0.829
Systolic BP In mm of Hg	148.75 ± 7.43	117.44± 7.13	<0.05
Diastolic BP in mm of Hg	94.62±6.04	79.17 ± 4.14	<0.05

*p Value <0.05 is considered as significant

Table 3: Comparison of serum CD40 ligand and hs CRP level in Cases and Controls

Parameter	Cases (n=51)Mean ± SD	Control (n=51)Mean ± SD	t	p
sCD40L (pgm/ml)	867.82±289.57	363.05 ± 111.20	10.14	<0.001
hs CRP (mg/l)	4.9± 2.16	0.97 ± 0.34	11.55	<0.001

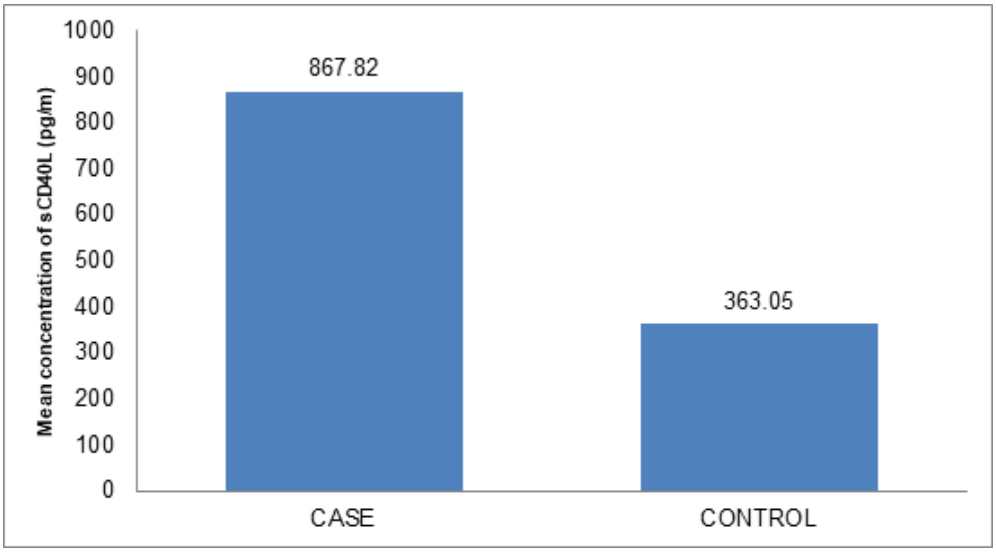

Figure 2: Bar diagram showing comparison of sCD40L Level (pg/ml) in cases and controls.

Table 4: Correlation matrix of SBP, DBP sCD40 and HSCRP: Correlations

		SBP	DBP	sCD40L	HS CRP
SBP	Pearson Correlation	1	.462**	.634**	.554**
	Sig. (2-tailed)		.001	.000	.000
	N	51	51	51	51
DBP	Pearson Correlation	.462**	1	.352*	.257
	Sig. (2-tailed)	.001		.011	.069
	N	51	51	51	51
sCD40L	Pearson Correlation	.634**	.352*	1	.845**
	Sig. (2-tailed)	.000	.011		.000
	N	51	51	51	51
HS CRP	Pearson Correlation	.554**	.257	.845**	1
	Sig. (2-tailed)	.000	.069	.000	
	N	51	51	51	51

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

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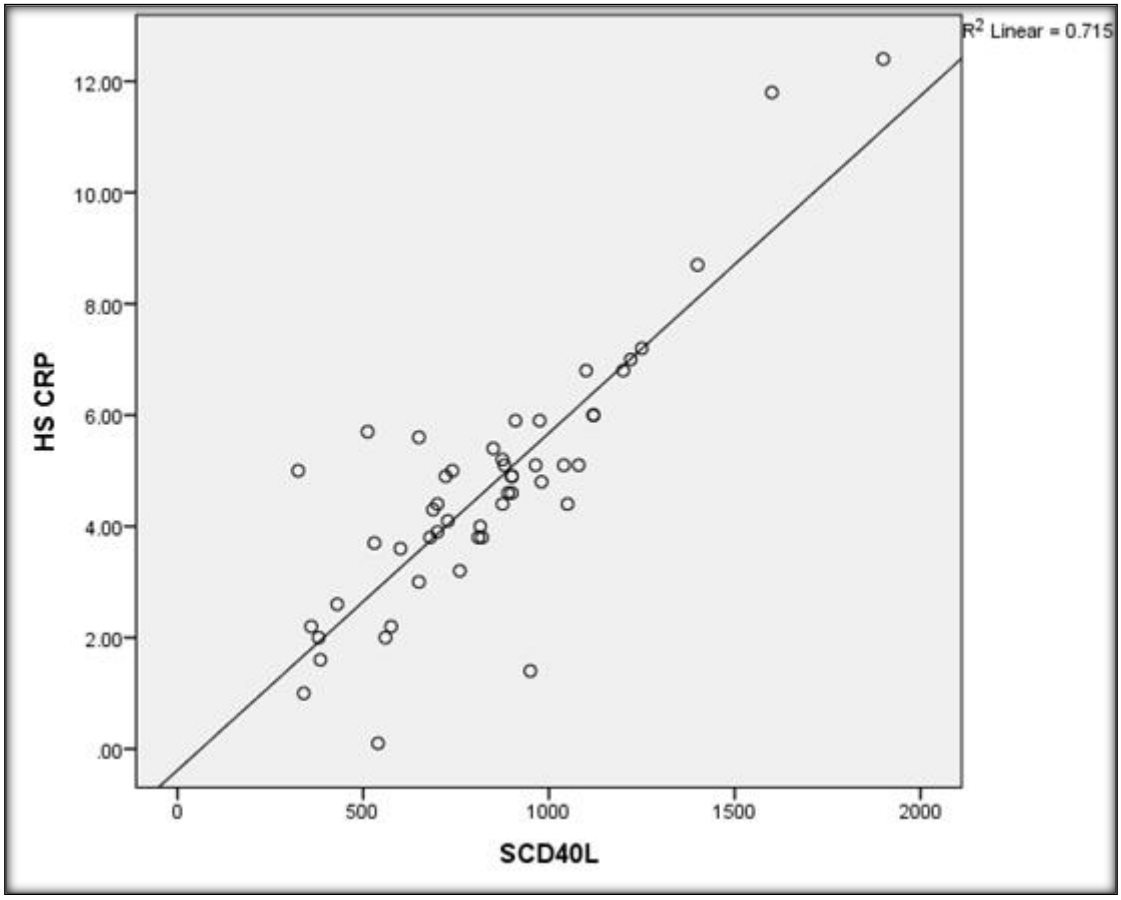

Figure 4: Scatter plot showing Correlation between hs CRP and sCD40L

DISCUSSION

High blood pressure is ranked as the third most important risk factor for attributable burden of disease in South Asia.[14] Hypertension exerts a substantial public health burden on cardiovascular health status and healthcare systems in India.[15,16]

The study was undertaken to analyze the relationship between platelet activation and inflammation in hypertensive patients.

In the present study shows that males are more prone to suffer from hypertension. [Table 1] It may be due to stress factor, hormonal activity, dietary habit, environmental and genetic predisposition. BethanyEverett,et al and Ghosh S, et al also found that male are more prone to suffer more than women in Hypertension.[17,18]

Clinical Parameters like SBP and DBP are significantly high in hypertensive cases in comparison to controls [Table 2].

In essential hypertension, which is considered to be one of the syndromes that include an increase in blood pressure (BP), abnormal lipid metabolism, abnormal sugar metabolism, abnormal blood coagulation, and left ventricular hypertrophy, other functional disorders of vascular endothelial cells are seen. Such functional disorders of vascular endothelial cells are considered to be risk

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factors for hypertension and prognostic factors for cardiovascular accidents.

This study explores that the primary hypertensive group showed higher serum soluble CD40 ligand values,(867.82±289.57)pg/ml compared to the normal control group (363.05±111.20)pg/ml, which was found to be statistically significant($p<0.001$). [Table 3, Figure 1] Serum soluble CD40 ligand value showed a significant degree of positive corelation with the systolic blood pressure($r=.634, p<.001$) and diastolic blood pressure($r=.352, p=.011$) [Table 4].

Many authors have worked over CD40-CD40 ligand system and soluble CD40 ligand in hypertension and cardiovascular diseases.

Jin-Chuan Yan et al,(2005) demonstrated patients with essential hypertension show increased expression of CD40 system, which suggests that hypertension is in part an inflammatory disorder.[19]

Surgit et al,(2015) demonstrated that soluble CD40 ligand level was obviously higher in hypertension patients compared with normotensive and that scd40l level was positively related to 24 hour systolic and diastolic BP and night time systolic and diastolic BP.[20]

Yu-quing Huang et al,(2017) provided evidence that scd40l levels in subjects with white coat hypertension and hypertension were significantly and consistently higher than those in healthy controls. Soluble CD40 ligand may represent a potential non-invasive atherosclerosis marker in white coat hypertension patients.[21]

Murat Guzel et al,(2019) provided evidence that novel platelet activation marker Soluble CD40 ligand levels increase in newly diagnosed hypertension patients, which was shown in both dipper and non dipper hypertension groups.[22]

So the result of our study is in accordance with the studies done by Surgit et al, Jin-Chuan Yan et al, Yu-quing Huang et al.

In the present study the healthy control group had the mean serum hs-CRP(0.97±0.34mg/l) and in hypertensive it was(4.9±2.16mg/l). The mean hs-CRP level in hypertensive patients was lower as compared to healthy controls which was statisticallysignificant ($p<0.001$). [Table 3, Figure 2]hs-CRP had positive correlation with both systolic($r=.554, p<0.001$) and diastolic blood pressure($r=.257, p=0.069$). [Table4]

Rogowski et al, (2007) Shafi M Dar et al, (2010) Satwika Sinha et al,Vibhanshu Gupta et al, (2011) (2014), YuttanaSudjaroen (2015) found hs CRP level is significantly increased in hypertensives than in normotensive controls.[22]

Oboh, H.A et al, (2013) also showed a positive correlation between hs CRP and systolic and diastolic blood pressure.[23]

So the results of our study was in consistent with the studies done by Shafi M Dar et al, YuttanaSudjaroen, Rogowski et al, Satwika Sinha et al, Vibhanshu Gupta et al, Oboh, H.A et al.

Soluble CD40 ligand correlates positively with hs CRP [Figure 3]. Activated platelets generate signals for the recruitment of leucocytes to the site of injury and thrombogenesis and can

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rapidly incite a cascade of inflammation by interacting with cells of vasculature.

CD40-CD40L interactions are central in immune responses and inflammation.sCD40L is currently being discussed as a prothrombotic marker.CD40L is rapidly upregulated during platelet activation and triggers an inflammatory response in cells. that constitutively express CD40 such as endothelial cells and monocytes/macrophages.[24] Thereby activated platelets generate signals for the recruitment of leukocytes to the site of injury and thrombogenesis and can rapidly initiate a cascade of inflammation by interacting with cells of the vasculature. These results support a link between circulating sCD40L and the underlying molecular mechanisms of inflammation in the formation of atherosclerosis, in patients with hypertension.[25]

CONCLUSIONS

Our study suggests that the estimation of Serum soluble CD40 ligand may be used as a pro thrombotic marker for early diagnosis of hypertension. Estimation of both soluble CD40L as a marker of platelet activation and hs-CRP as a inflammatory marker may have prognostic value in hypertension. Along with this the timely therapeutic intervention may reduce morbidity and mortality in essential hypertensive individuals

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