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High serum Matrix metalloproteinase- 9 level in patients with Essential hypertension

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Abstract: *Arterial hypertension causes changes in vascular wall structure, vascular remodeling which leads to several complications such as hypertensive heart disease, aortic aneurysm, peripheral arterial disease, chronic kidney disease and retinopathy. Matrix metalloproteinase-9 (MMP-9), a type IV gelatinase (Collagenase-B) plays a major role in extracellular matrix degradation and has been implicated as an important factor in atherosclerosis and vascular remodeling. They are also involved in numerous processes such as inflammation, fibrosis, angiogenesis and cell apoptosis. Increased activity of MMP-9 is related to the development and progression of cardiovascular complications. C-reactive protein (CRP) was believed to be a marker of vascular inflammation and recent research indicates that it plays an active role in atherogenesis. It is detectable in the early stages of plaque development and involved throughout the atherogenic process. Hence we measured the serum MMP-9 and hs-CRP in hypertensive patients. Fifty cases of essential hypertension without any complications and twenty five normotensive, healthy controls were selected for the study. Baseline investigations, serum MMP-9 and hs-CRP level were analyzed. We observed that hypertensive subjects showed significantly elevated MMP-9 level in comparison with normotensive control subjects. They also had significantly elevated hs-CRP levels indicating the presence of low grade inflammatory process. High serum MMP-9 and hsCRP levels indicate the inflammatory process in spite of antihypertensive drugs and so there is risk for cardiovascular complications in hypertensive subjects.*

Keywords: *Arterial hypertension, MMP-9, vascular remodeling, hsCRP.*

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I. Introduction

Arterial hypertension is a silent killer and major risk factor for atherosclerosis, coronary artery disease,stroke, kidney failure[1,2]. Chronic vascular inflammation plays a role in the development of essential hypertension either as pathogenic or secondary event. Inflammatory mediators such as CRP, IL-1β,IL-6,TNF –α and reactive oxygen species have been proposed to contribute essential hypertension through several mechanism including enhancement of arterial stiffness, endothelial dysfunction[3] and MMP-9 transcription through the activation of MAPK [4]. Hs-CRP is involved in vascular inflammation and plays a crucial role in the progression and development of atherosclerosis. Inflammation leads to additional inflammatory mediators such as MMP family of enzymes. The most commonly studied MMP in essential hypertension is MMP-9, a zinc dependent proteolytic enzymes. MMP-9 is secreted by several vascular cell types including endothelial cells,pericytes, podocytes, fibroblast, myofibroblast and monocyte derived macrophages [5].MMP-9 is involved in tissue repair, vascular remodeling , inflammation and atherosclerotic (AS) plaque rupture [6]. It is inhibited by TIMP1 and TIMP3. In early stage of hypertension, MMP-9 has a role in pressure induced vascular distensibility and increased fibrillar collagen deposited in vessel wall in compensated stage of hypertension [7]. It also plays divergent roles in formation and destabilization of AS plaques[8].Vascular remodeling contributes to the progression of vascular disease in pathological condition. Hence the serum level of MMP-9 and hsCRP were analyzed in essential hypertensive patients and normotensive healthy control subjects.

II. Methods

We enrolled 50 patients (male-17, female-33) with essential hypertension on medications without any complications in the age group of 40 to 60 years and 25 (male-8,female-17) normotensive , healthy subjects .Institutional Human ethics committee clearance and informed written consent were obtained. Fasting blood samples were collected from the hypertensive patients and controls and analyzed for baseline investigations by auto analyzer. Serum MMP-9 was assayed using ELISA kit and hs CRP by immunoturbidimetric method.

Statistical analysis:Statistical analysis was done by Mann-Whitney U test using SPSS software and the level of significance was fixed at < 0.05.

Table1: Physiological parameters in Hypertensive and control subjects.

Physiological parameters	Hypertension (N-50)	Control (N-25)	Mann-Whitney U-test z value	P value
AGE (Years)	52.34 ± 6.26	50.68 ± 3.95	1.91	N.S
BMI	24.7±3.53	24.75±3.2	0.87	N.S
BP(systolic)	148.08 ± 16.04	115.96 ± 7.68	6.54	< 0.001
BP (Diastolic)	89.84 ± 9.20	74.48 ± 6.46	6.18	< 0.001
pulse rate/min	81.84 ± 8.44	83 ± 6.59	0.53	N.S

Table 2: Biochemical parameters in Hypertensive and control subjects.

Biochemical parameters	Hypertension (N-50)	Control (N-25)	Mann-WhitneyU-test z value	P value
Plasma Glucose mg/dl	94.94 ± 31.14	100.80 ± 20.79	1.83	N.S
Serum Urea (mg/dl)	30.22 ± 9.49	28.36 ± 4.04	0.9	N.S
Serum Creatinine (mg/dl)	0.83 ± 0.11	0.81 ± 0.11	0.33	N.S

Table 3: Lipid profile in Hypertensive and control subjects.

Lipid profile	Hypertension (N-50)	Control (N-25)	Mann whitney U-test z value	P- value
Total Cholesterol (mg/dl)	197.24 ± 37.52	173.16 ± 20.18	2.74	<0.05
TGL (mg/dl)	162.1 ± 66.29	111.2 ± 39.73	3.58	<0.001
HDL –C(mg/dl)	42.08 ± 2.99	44.08 ± 5.52	1.17	N.S
LDL –C(mg/dl)	121.96 ± 38.32	96.12 ± 14.76	2.87	<0.05

Table 4: Liver function tests in Hypertensive and control subjects.

Liver function tests	Hypertension (N-50)	Control (N-25)	Mann-whitneyU-test z value	P value
AST(U/L)	24.1 ± 8.48	23.52 ± 6.35	0.53	N.S
ALT (U/L)	22.4 ± 9.09	20.16 ± 4.17	0.17	N.S
Total bilirubin (mg/dl)	0.77 ± 0.06	0.8 ± 0.11	1.19	N.S
Direct bilirubin(mg/dl)	0.18 ± 0.04	0.17 ± 0.06	1.23	N.S

Table5: Serum MMP-9, hsCRP and urinary albumin in study subjects

Parameters	Hypertension (N-50)	Control (N-25)	P value
MMP-9(pg/ml)	16.02 ±4.51	10.14 ±4.33	< 0.001
hsCRP(mg/L)	9.06 ± 3.67	3.74± 1.25	< 0.001
Urine Albumin (mg/L)	22.88 ± 9.88	15.84 ± 6.60	< 0.01

III. Results

There was no significant difference in BMI, plasma glucose, urea,creatinine and liver function tests in hypertensive subjects compared to controls.There was significant increase in total cholesterol ($p< 0.05$), Triglycerides ($p < 0.001$) and LDL-C (<0.05) in hypertensive subjects compared to controls.Serum MMP-9 level (16.02 ±4.51 vs 10.14 ±4.33) ($p< 0.001$)was significantly increased in hypertensive subjects when compared with controls.Serum hsCRP level (9.06 ± 3.67 vs 3.74± 1.25) ($p<0.001$) was significantly increased in hypertensive subjects compared to controls.Urine albumin was within the normal range in hypertensive subjects.

IV. Discussion

Matrix metalloproteinases are implicated in the pathology of vascular diseases and several studies suggest that MMPs play pathogenic roles in these disorders (9).We observed that MMP-9 was significantly higher in patients with hypertension than in controls which is consistent with previous studies (10,11). This could be due to inflammatory process as hsCRP was also elevated. Elevation of MMP-9 is important for vascular remodeling and abnormal MMP levels can stimulate vascular inflammation, a potential contributor in the pathogenesis and progression of essential hypertension (9,). Increased circulating levels of MMP-9 are not

only associated with increased incidence of recurrent cardiovascular events in the long term period.MMP-9 plays important role in extracellular matrix remodeling during all phases of atherosclerosis. MMP-9 also promotes local destruction of ECM in atheroma, leading to plaque destabilization and rupture (12). Studies have shown that various antihypertensive medications reduce the MMP-9 levels in hypertensive patients through various mechanism(13,14,15,16,). Serum hs-CRP was significantly increased in hypertensives in comparison with controls. CRP increases the blood pressure by several mechanism. CRP inhibits formation of nitric oxide by endothelial cells which in turn promote vasoconstriction, leukocyte adhesion, platelet activation, oxidation and thrombosis(17). High levels of CRP may up-regulate angiotensin receptors and enhance expression of plasminogen activator inhibitor-1 by endothelial cells (18). In the study, even though hypertensive subjects were on antihypertensive drugs, there was a significant elevation of serum MMP-9 and CRP levels suggesting the increased risk for cardiovascular complications.

V. Conclusion

Serum MMP-9 and hs-CRP was significantly high in hypertensive patients even with antihypertensive medication. Hence appropriate measures to control low grade inflammation would be required to prevent cardiovascular complications in hypertensive subjects.

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