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Role of homocysteine and cellular adhesion molecules in essential hypertensives without and with complications

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ABSTRACT:

High blood pressure (BP) increases the risk of CVD for people worldwide, essential hypertension remains a major modifiable risk factor despite advances in understanding of its pathophysiology and the availability of effective treatment strategies. Endothelial dysfunction a hallmark of essential hypertension causes changes in blood vessels, fibromuscular hyperplasia, and accelerated arteriosclerosis leading to microvascular as well as macrovascular complications. Of recent, it has been found that remodeling of the vascular wall is highly influenced by various inflammatory factors of which (CAMs), are primarily involved The primary aim was to assess the levels **of** the inflammatory molecules (ICAM-1 and VCAM-1 in essential hypertensives without and with complications. 525 individuals in the age group of 20-55 years , from both sexes attending the Hypertensive clinic in SRMC & RI were enrolled for the study .They were grouped as 3-group I being controls , group II being hypertensives without any complications and group III hypertensives with complications (175 each). The serum levels ICAM-1 & VCAM-1 were determined by ELISA Method. The mean values of ICAM-1 VCAM-1 showed a statistically highly significant difference between the 3 groups ($p<0.001$To conclude elevated levels of CAMs in essential hypertension, reflect enhanced leukocyte chemotaxis and adhesion, thereby increasing risk of atherosclerotic disease. In future asymptomatic individuals who are at increased risk for atherosclerosis can be identified with the help of these cell adhesion molecules serving as biochemical markers.

Keywords: Essential hypertension, cellular adhesion molecules, atherosclerosis

Introduction

Recently studies have revealed the role of inflammatory factors in enhancing remodeling of the vascular wall. The damaged vascular wall as well as cells infiltrating this wall, release the inflammatory factors [1]. The adherences of CAMS play a vital role in maintaining the vascular wall integrity [2]. The cellular adhesion molecules are involved in the risk of atherosclerosis, by causing alterations on vascular endothelial wall.

Homocysteine has an effect on multiple vascular responses. The production and bioactivity of

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vasoregulatory mediators are greatly influenced by the levels of homocysteine [3, 4].

Subjects & Methods

A total of 525 subjects between the age group of 20-55 years of age, from both sexes who were attending the Hypertensive clinic and Master health check up programme in Sri Ramachandra Medical College were enrolled for the study .They were grouped as three-Group I being controls (n=175), group II hypertensives without complications (n=175) and group III hypertensives with end organ damage (n=175). The anthropometric measurements were recorded. Blood was collected after overnight fasting blood along with urine samples .The biochemical parameters were estimated by standard protocols. The plasma homocysteine was determined by ELISA method (Axis Shield, UK), cellular adhesion molecules (ICAM-1, VCAM-1 by ELISA method (R & D Systems)

Exclusion criteria : Individuals and hypertensives with no other comorbidities , coffee consumption (>9 cups/day) smokers(> 20 cigarettes / day) ,chronic alcoholics(>10 Years) pregnant women , intake of oral contraceptive pills , fibric acid derivatives were excluded.

Results:

Comparing the mean values (**Table 2.0)** significant difference (p value <0.05) was observed in Waist/Hip ratio among the 3 groups while BMI SBP and DBP showed a statistically high significant difference indicating that blood pressure raises as the disease progresses.

A highly statistical difference was observed between the groups (**Table 5.0)** explicating the possible involvement of the above mentioned endothelial biomarkers in essential hypertension

All the p values showed a highly statistical significance of <0.001(**Table 6.0)**

Discussion:

The demographic data and Dietary pattern of the 3 study groups are represented in **Table 1.0**.

The mean age was found to be 40 ± 10, 49 ± 8 and 48 ± 7 in groups I, II and III respectively. The age did not show much difference between group II and III. Among the study population, females contributed a greater part when compared with the males. There is almost an equal distribution of males (n=89) and females (n=86) in group III.

Regarding the dietary pattern, it was observed that in group I, 24 were vegetarians while the remaining 151 were non-vegetarians. In group II, 38 were vegetarians and 137 were non vegetarians. In group III, 34 were vegetarians and 141 were non vegetarians. Thus the ratio of vegetarian to non-vegetarian participants in the groups ranges from 1:3 to 1:6.

Since coffee consumption is one of the secondary causes for hyperhomocysteinemia the questionnaires also include the coffee consumption status of the individuals included in this study. It was found that 139, 121 and 118 individuals consumed coffee less than nine cups per day in the 3 groups. It was thus observed that almost 80% of the study population consumed coffee in all the three groups. Caffeine plays a role in homocysteine metabolism thus it has an effect on homocysteine levels in essential hypertensives.

In group I, 14 were smokers, group II, 29 and in group III, 38 were smokers among the males. The ratio of smokers observed in the three groups was 1:2 to 1:3, with almost 50% in group III, indicating that smoking also contributes to end organ damage in essential hypertensives. Smoking exacerbates the effects of homocysteine in that it also acts independently from other vascular risk factors.

The clinical and physical characteristics are represented in T**able 2.0**. Data is expressed as mean ± SD. The mean values of Systolic blood pressure was found to be 114 ± 9,136 ± 15 and

141 ± 16 in groups I, II and III respectively. The mean levels of diastolic blood pressure was observed as 77 ± 6, 88 ± 11 and 90 ± 9 in groups I, II and III respectively. The mean level of both systolic and diastolic blood pressure was found to be higher in hypertensives with end organ damage when compared with controls as well as

hypertensives without end organ damage. The mean BMI was found to be 23.6 ± 3.4, 24.1 ± 3.38 and 25 ± 3.39 in groups I, II and III respectively.

Comparing the mean values a statistically significant difference (p value <0.05) was observed in BMI and Waist/Hip ratio among the 3 groups while SBP and DBP showed a statistically highly significant difference indicating that blood pressure raises as the disease progresses.

Since a statistical difference was observed further analysis was done **as s**hown in T**able 3.0**. Between the groups I & II a highly statistical difference was observed in SBP and DBP. Hypertension sets in even before the hypertensives go in for end organ damage as shown by the significant difference between groups I and II (P<0.0001) with minimal or no significant difference between groups II and III in the other parameters.

When control group was compared with hypertensives with end organ damage an observed in BMI and WHR (p<0.05). A significant change occurs in BMI and WHR when hypertensives developed end organ damage as shown by the statistically significant difference between groups I and III (p =0.022) and (p=0.008) for WHR. . A highly statistically significant difference (p<0.001) was observed in SBP and DBP.

SBP showed a statistically significant difference (p<0.05) when hypertensives without end organ damage were compared with hypertensives with end organ damage while the other parameters did not show any statistically significant difference between the two groups.

In groups I, II and III among the males 11, 25 and 30 individuals were alcoholics 1, 2 and 3 respectively. The distribution of alcoholics as observed in the table ranges from 1:3 to 1:4.

Comparing the mean values a statistically significant difference (p value <0.05) was observed in BMI and Waist/Hip ratio among the 3 groups while SBP and DBP showed a statistically highly significant difference indicating that blood pressure raises as the disease progresses.

Table 4.0 represents the mean levels of the various endothelial, inflammatory and oxidative stress biomarkers. The mean level of homocysteine was found to be 20.2 ± 13,

28.2 ± 13 and 43.7 ± 14 (in µmol/L) in groups I,II and III respectively . It is observed that the mean value of homocysteine was higher than the cut off value in our study population.

Previous studies reveal that hypertensives had significantly increasing values sICAM-1 (232.4 ± 16.5 *v* 189.8 ± 11.1 ng/mL) and sVCAM-1 (737.3 ± 65.6 *v* 565.7 6 46.8 ng/mL) compared to their normotensive counterparts [5]. Similar findings were observed in our study among 3 groups ICAM-1 (175 ± 129, 351 ± 89, 490 ± 139) respectively.

The matrix metalloproteinases play an important role in altering the collagen/elastin ratio. The MMP-9 mean levels were found to be 100 ± 99, 155 ± 29 and 219 ± 27 (in pg/mL) in groups I, II and III respectively.

Since various risk factors overlap for hypertension and other cardiovascular diseases it is thus a problem to deduce when one is a risk factor for the other. Yet the results of the in vitro studies reveal the roles of homocysteine in alterations of the vascular endothelium are consistent with known mechanisms for hypertension [6]. Hyperhomocysteinemia serves as an independent risk factor for primary hypertension [6, 7].

Homocysteine level were found to be elevated in hypertensives when compared with the controls [8].

A highly statistically significant difference (p <0.001) was observed in all the parameters also showing the same in post hoc test **Table 5.0.**

The cellular adhesion molecules are up regulated and probably influence the blood pressure hypertension as mentioned earlier. In our study the mean levels of ICAM-1 was observed as 175 ± 129, 351 ± 89 and 490 ± 139 (in pg/mL) respectively. Similarly the VCAM-1 the mean

values observed was 191 ± 80, 447 ± 97 and 660 ± 230 (in pg/mL) respectively. Leukocyte rolling across the sub endothelial space causes endothelial dysfunction which is mediated by the cellular adhesion molecules.

Various studies have reported that the levels of MMP-9 in hypertensives when compared with their normal counterparts are higher [9,10]. Supporting the above studies the mean levels of MMP-9 was (100 ± 22,155 ± 29, 219 ± 27) in the 3 groups.

The assessment of the relative risk for developing end organ damage in essential hypertension was analyzed statistically by stepwise logistic regression analysis with each of the newer and traditional risk factors in the hypertensive group.

The logistic regression analyses Table 6.0.showed that the risk odds ratio of each of the risk factors was significantly raised. Patients with high levels of homocysteine had almost six times increased risk of developing end organ damage. The high risk odds ratio (unadjusted OR= 14.7) associated with homocysteine could be due to exceptionally high levels of homocysteine were observed in the patient group with complications, which were almost twice that of the control group. Yet the increased risk leading to mortality has to be elucidated. The other conventional risk factors were independently associated with increased risk, coffee consumption, and obesity 1.4 times WHR 2.5 times. The low grade inflammatory marker hsCRP showed higher odds ratio of 18.1

Homocysteine showed an odds ratio of 5.9 when adjusted for other traditional risk factors while the unadjusted odds ratio was found to be 14.76 for the development of end organ damage. This confirms the role of homocysteine in the onset of end organ damage in essential hypertensives.

The cascade of events that occur initially in atherosclerosis is triggered by the attachment of circulating leukocytes followed by transendothelial migration into the intima is important [11,12,13].

The ability of their expression is usually very low exceptionally found to be higher in inflammatory conditions, when the endothelium is activated [14] and expression is triggered or is markedly increased [14,15,16]

Expression of cell surface adhesion molecules is well controlled [17,18,19] But when the endothelium is activated these levels are at a rise [17,20]

The imbalance in the ratio of vasodilators and constrictors leads to alterations in the endothelium wall leading to endothelial dysfunction in hypertensive individuals.

The glycoprotein adhesion molecules viz immunoglobulin group adhesion molecule-1 (ICAM-1) and vascular cell adhesion group are associated with enhancement of endothelial dysfunction mediated by their increased expression [21]. The mechanism involves adherence of leukocytes to endothelial surface and subsequent migration into the vessel wall. The migrated sources of inflammation enhance the initial process of atherosclerosis [22] human atherosclerotic plaques demonstrated over expression of adhesion molecules [23, 24]

In normal individuals the site of endothelial damage is quickly relieved and suppressed to prevent vascular issues from arising. One step in this process is to help reduce the chance of infection by increasing the injured area's affinity for monocytes. As previously mentioned, the blood is always circulating with each heartbeat and the injured site needs some way to stop these monocytes from simply rolling away- the answer is up regulation of the VCAM and ICAM receptors [25,26].

In hyperhomocysteinemia, the vessels are stressed from increased pressure, reactive oxidative species, and reduction of bioavailable NO, and increased cytokine concentrations which can mimic an inflamed injurious environment [26,27,28]. Due to this increased stress several studies have reported a drastic up-regulation in VCAM and ICAM and subsequently an increased binding of monocytes [27,29,30].

Upon binding to the up-regulated VCAM and ICAM receptors, the monocyte undergoes

diapedesis (intake during inflammation) into the sub-endothelial space where they convert into macrophages. During this process there is evidence that the binding of monocytes to VCAM and ICAM stimulates their NAPDH oxidases to undergo a "respiratory burst" which is intended to destroy any pathogens around [26, 27]

Normally this "burst" of reactive peroxidases and superoxides are kept in check by powerful antioxidants, but in a non-injured vessel who's antioxidant systems are already compromised by the unavailability of NO (nitrous oxide) and possibly GSH (gluthionine), along with the increased affinity and occurrence of monocyte adhesion could lead to a situation where reactive oxidative species are increasingly prevalent. Also the activation of these cells leads to a release cytokines, chemokines, and growth factors which give rise to an inflammatory environment [28]. This increase of reactive species would cause the activation of MMP-9 and MMP-2 to begin remodeling the endothelial extracellular matrix, basal membranes, and tight junction proteins which can cause increased permeability of LDL cholesterol to enter the sub- endothelial level forming a "bubble" in the intima.

In a culture of endothelial cells, the soluble ICAM-1 released into the circulation was found to be associated with their surface expression [31]. Up regulation of adhesion molecule genes plays a major role. It therefore implies that they may be expressed ***in*** *vivo* and serve as an early detector of vascular complications [32,33].

Intercellular adhesion molecule-1 member of the immunoglobulin (Ig) family functions vitally in adherence and transmigration of leukocytes. The endothelial expression of ICAM-1 is higher in atherosclerotic and transplant-associated atherosclerotic tissue. .

MMPs a group of endopeptidases [33,34,35] take part in hypertensive vasculature[36] by degrading ECM, enhancing vascular smooth muscle cells migration and proliferation, and monocyte penetration [37].

Derosa et al. [38] measured MMP-9 levels in hypertensives and were found to be high. Similar results have also been reported [39]

Table 1: Demographic data and Dietary Pattern of the 3 groups

Sr. No.	Parameters	Group-I (n=175)	Group-II (n=175)	Group-III (n=175)
1.	Age	40±10	49±8	48±7
2.	Sex male / Female	49/126	71 / 104	89 / 86
3.	Veg / Nonveg	24 /151	38/137	34/ 141
4.	Smoking	14 /49	23/71	38/89
5.	Alcohol	11/49	25/71	30/89
6.	Coffee consumption	139	121	118

Table 2: Clinical and Physical characteristics of the 3 groups

Sr. No.	Parameters	Group-I (n=175)	Group-II (n=175)	Group-III(n=175)	P value
1.	SBP(mm Hg)	114 ± 9	136 ± 15	141 ± 16	< 0.0001
2.	DBP(mm Hg)	77 ± 6	88 ± 11	90 ± 9	< 0.0001
3.	BMI	23.6 ± 3.4	24.1 ± 3.38	25 ± 3.39	< 0.0001
4.	Waist / Hip Ratio	0.87 ± 0.08	0.89 ± 0.08	0.90 ± 0.05	0.001

Table 3: Tukey –HSD Post-hoc test results of SBP, DBP, BMI and WHR

Sr. No.	Parameters	Group I & II (n= 175 , 175) P value	Group II & III (n= 175 , 175) P value	Group I & III (n= 175 ,175) P value
1.	SBP (mmHg)	< 0.001	0.035	< 0.001
2.	DBP (mmHg)	< 0.001	0.057	< 0.001
3.	BMI	0.307	0.482	0.022
4.	Waist / Hip ratio	0.039	0.846	0.008

Table 4: Levels of endothelial biomarkers

Sr. No.	Parameters	Group-I (n=175)	Group-II (n=175)	Group-III (n=175)	P value
1.	Homocysteine(µmol/L)	20 ± 13	28 ± 13	44 ± 14	< 0.0001
2.	ICAM-1 (pg/mL)	175 ± 129	351 ± 89	490 ± 139	< 0.0001
3.	VCAM-1 (pg/ mL)	191 ±80	447 ± 97	660 ± 230	< 0.0001
4.	MMP-9 (pg/mL)	100 ± 22	155 ± 29	219 ± 27	< 0.0001

Table 5: Tukey –HSD Post-hoc tests of endothelial biomarkers

Sr. No.	Parameters	Group I & II (n= 175 , 175) P value	Group II & III (n= 175 , 175) P value	Group I & III (n= 175 , 175) P value
1.	Homocysteine (µmol/L)	0.001	0.001	0.001
4.	ICAM-1(pg/mL)	0.001	0.001	0.001
5.	VCAM-1 (pg/mL)	0.001	0.001	0.001
6.	MMP-9 (pg/mL)	0.001	0.001	0.001

Table 6: Results of logistic regression analysis to assess end organ damage in essential hypertension

Sr. No.	Associated risk factors of end organ damage	Odds Ratio	95% CI
1.	Homocysteine (µmol/L)	5.9	1.12-31.7
2.	WHR	2.53	0.6-10.7
3.	BMI (kg/m^2)	1.44	0.82-2.5
4.	Coffee consumption	1.40	0.75-2.6
5.	Age	0.991	0.95-1.02
6.	Sex	1.05	0.56-1.95

Conclusion

The findings show that elevated levels of CAMs in essential hypertension, reflects the increased leukocyte chemotaxis and adhesion.
The CAMs may indicate subclinical atherogenesis and used clinically to identify end organ damage in essential hypertension since it is asymptomatic in nature.

References:

1. Ross R, Glomset J, Harker L: Response to injury and atherogenesis. Am J Pathol.1997; 86: 675–84.
2. Mulvihill N. T, Foley JB, Crean P, Walsh M. Prediction of cardiovascular risk using soluble cell adhesion molecules.Euro Heart J 2002; 23:1569-74.
3. Harker LA, Harlan JM, Ross R. Effect of sulfinpyrazone on homocysteine-induced endothelial injury and arteriosclerosis in baboons. Circ Res. 1983;53:731–9.
4. Quere I, Hillaire-Buys D, Brunschwig J, et al. Effects of homocysteine on acetylcholine- and adenosine-induced vasodilation of pancreatic vascular bed in rats. Br J Pharmacol. 1997;122:351–7
5. Christopher A. DeSouza, Donald R. Dengel, Richard F. Macko, Kim Cox, and Douglas R. Seals Elevated Levels of Circulating Cell Adhesion Molecules in Uncomplicated Essential Hypertension. AJH.December1997;10(12): PART 1.
6. Rodrigo R, Passalacqua W, Araya J, Orellana M, Rivera G.Implications of oxidative stress and homocysteine in the pathophysiology of essential hypertension. J Cardiovasc Pharmacol.2003;42(4):453-61.
7. Arroliga AC, Sandur S, Jacobsen DW, Tewari S, Mustafa M, Mascha EJ, Robinson K. Association between hyperhomocysteinemia and primary pulmonary hypertension.Respir Med.2003;97(7):825-29.
8. Jain S, Ram H, Kumari S, Khullar M. Plasma homocysteine levels in Indian patients with essential hypertension and their siblings. Ren Fail. 2003;25(2):195-201.
9. Tayebjee M.H., Nadar S.K., MacFadyen R.J.Tissue inhibitor of MMP-1 and MMP-9 levels in patients with hypertension. Relationship to tissue Doppler indices of diastolic relaxation. AJH. 2004; 17 :770–74.
10. Yasmin Wallace S., Mceniery C.M., Dakham, Z. Matrix Metalloproteinase-9 (MMP-9) , MMP-2, and Serum Elastase Activity are Associated with Systolic Hypertension and Arterial Stiffness. Arterioscler Thromb Vasc Biol. 2005;25:372-78.
11. Gimbrone MA, Kume N, Cybulsky MI: Vascular endothelial dysfunction and the pathogenesis of atherosclerosis.Atheroscler Rev 1993;25:1–9.
12. Ross R: The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;362:801– 809.
13. Munro JM, Cotran RS: The pathogenesis of atherosclerosis:atherogenesis and inflammation. Lab Invest 1988;58:249 –261.
14. Davies MJ, Gordon JL, Gearing AJH, et al: The expression of the adhesion molecules CAM-1, VCAM-1, PECAM,and E-selectin in human atherosclerosis. J Pathol 1993;171:223–229.
15. Poston RN, Haskard DO, Coucher JR, et al: Expression of intercellular adhesion molecule-1 in atherosclerotic plagues. Am J Pathol 1992;140:665– 673.
16. O'Brien KD, Allen MD, McDonald TO, et al: Vascular cell adhesion molecule-1 is expressed in human coronaryatherosclerotic plaques: implications for the mode of progression of advanced coronary atherosclerosis.J Clin Invest 1993;92:945–951
17. Gearing AJH, Hemingway I, Pigott R, et al: E-Selectin, ICAM-1, and VCAM-1: pathological significance. AnnNY Acad Sci 1992;667:324 –331.
18. Newman W, Beall LD, Carson CW, et al: Soluble Eselectin is found in supernatants of activated endothelial cells and is elevated in the serum of patients with septic shock. J Immunol 1993;150:644 –654

19. Hackman A, Abe Y, Insull W, et al: Levels of soluble cell adhesion molecules in patients with dyslipidemia.Circulation 1996;93:1334 –1338

20. Adams DH, Mainolfi E, Elias E, et al: Detection of circulating intercellular adhesion molecule-1 after liver transplantation-evidence of local release within the liver during graft rejection. Transplantation 1993;55:83–87.

21. Bevilacqua MP, Nelson RM. Selectins. J Clin Invest.1993; 91**:**379-87.

22. Ross R**.** The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature.1993; 362:801-09.

23. Davies MJ, Gordon JL, Gearing AJH**.** The expression of the adhesion molecules ICAM-1, VCAM-1 and E-selectin in human atherosclerosis. J Pathol.1993;171: 223-29.

24. O'Brien KD, McDonald TO, Chait A, Allen MD, Alpers CE. Neovascular expression of E- selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in human atherosclerosis and their relation to intimal leucocyte content. Circulation 1996; 93: 672-82.

25. Carmel, Ralph, comp. ―Homocysteine in Health and Disease.‖ 1st. Cambridge, MA:Cambridge University Press, (2001). . pg 431-438.

26. Silverman MD, Ramapogal JT, Davis M, Lopez G,Rosenbaum JT, Lelkes PI. Homocysteine Upregulates Vascular Cell Adhesion Molecule1 Expression in Cultured Human Aortic Endothelial Cells and Enhances Monocyte Adhesion. Arteriosclerosis Thromb Vasc Biol.2002;22:587–92.

27. Ross, Russell. Atherosclerosis: An Inflammatory Disease. New England Journal of Medicine.1999; 340:2115-126.

28. Deem TL**,** Cook-Mills JM.Vascular Cell Adhesion Molecule-1 (VCAM-1) Activation of Endothelial Cell Matrix Metalloproteinases. Blood.2004;104:2385–393.

29. Kim, Cuk-Seong . Homocysteine Promotes Human Endothelial Cell Dysfunction Via Site- Specific Epigenetic Regulation Of P66shc. Cardiovascular Research. (2011)92.3: 466-75.

30. Leeuwenberg JF, Smeets E. F., Neefjes J. J., Shaffer M. A., Cinek T., Jeunhomme T. M, et al. E-selectin and intercellular adhesion molecule-1 are released by activated human endothelial cells *in vitro*. Immunology. 1992;77: 543-49.

31. Gearing AJH, Newman W**.** Circulating adhesion molecules in disease. Immunol Today. 1993; 14: 506-12.

32. Ferri C,Desideri G, Valenti M, Bellini C, Pasin M, Santucci A, et al. Early upregulation of endothelial adhesion molecules in obese hypertensive men. Hypertension 1999; 34: 568-73.

33. Bayramoglu A, Gunes HV, Metintas M, The association of MMP-9 enzyme activity, MMP-9 C1562T polymorphism, and MMP-2 and -9 and TIMP-1, -2, -3, and -4 gene expression in lung cancer. Genet Test Mol Biomarkers.2009;13: 671–78.

34. Humphrey, D. Mechanisms of arterial remodelling in hypertension: coupled roles of wall shear an intramural stress. Hypertension.2008;52: 195–200.

35. Berg G, Miksztowicz V, Schreier L, Metalloproteinases in metabolic syndrome, Clinica Chimica Acta.2011; 412: 1731–39.

36. Li-Saw-Hee E., Edmunds, A.D. Blann, D.G. Matrix metalloproteinase-9 and tissue inhibitor metalloproteinase - 1 levels in essential hypertension. Relationship to left ventricular massand anti-hypertensive therapy. Int J Cardiol. 2000; 75: 43–47.

37. Tayebjee M.H., Nadar S.K., MacFadyen R.J.Tissue inhibitor of MMP-1 and MMP-9 levels in patients with hypertension. Relationship to tissue Doppler indices of diastolic relaxation. AJH. 2004; 17:770–74.

38. Derosa G., D'Angelo A., Ciccarelli L. Matrix Metalloproteinase-2, -9, and Tissue Inhibitor of Metalloproteinase-1 in Patients with Hypertension. Endothelium. 2006;13: 227–31.

39. Yasmin Wallace S., Mceniery C.M., Dakham, Z. Matrix Metalloproteinase-9 (MMP-9), MMP-2, and Serum Elastase Activity are Associated with Systolic Hypertension and Arterial Stiffness. Arterioscler Thromb Vasc Biol. 2005;25:372-78.

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