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Evaluation of Homocysteine, hsCRP and Microalbuminuria in Hypertensives without and with end Organ Damage-A Case Control Study

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Abstract

Background: *Homocysteine considered to be a marker of endothelial dysfunction is formed from a sulfur-containing amino acid, methionine. The total plasma homocysteine levels are between 5-15 µmol / L in healthy individuals. As reported by various prevalence studies, the rate is found to be comparitively higher in Indians with a mean level of 19.5-23.2 µmol / L. Hyperhomocysteinemia is the most common risk factor for stroke and cardiovascular diseases by causing vascular dysfunction. Elevated levels of homocysteine could also lead to alterations in mediators of endothelial vasodilatation.*

Methods: *A total of 496 individuals 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 & Research Institute were enrolled for the study. They were grouped as three-Group I being controls, group II being hypertensives without complications and group III being hypertensives with end organ damage. After overnight fasting, blood and spot urine samples were collected. All the biochemical parameters were estimated by standard methodologies. The plasma homocysteine was determined by ELISA method (Axis Shield, UK), urinary microalbumin and hsCRP was determined by Immunoturbidimetric method. Albumin Creatinine Ratio (ACR) was also calculated.*

Results: *The results are expressed as Mean ± SD. The mean values of SBP, DBP and BMI showed a statistically highly significant difference between the 3 groups ($p<0.001$). Regarding the biochemical parameters LDL c, Chol /HDL ratio , the renal parameters microalbumin, ACR and the markers plasma homocysteine and the hsCRP levels showed a statistically highly significant A strong positive correlation was detected between hsCRP and DBP between the group 2 & 3.*

Conclusion: *The inflammatory marker hsCRP was found to show a strong positive association with DBP among hypertensives with and without end organ damage indicating that the process of inflammation starts early in the disease. Homocysteine correlates with urinary microalbumin and albumin /creatinine ratio indicating that renal dysfunction could be due to hyperhomocysteinemia*

A significant increase in microalbumin, hsCRP and homocysteine in essential hypertensives suggests that monitoring the levels of these parameters would be of great value in assessing the onset of end organ damage in essential hypertensives. Hyperhomocysteinemia plays a role in the setting of endothelial morphology and function.

Keywords: *Cardiovascular risk, Endothelial dysfunction, Essential hypertension, Homocysteine, hsCRP, Microalbuminuria.*

Introduction

Cardiovascular disease is a major contributor of mortality worldwide; the precipitating factor being essential hypertension. It is usually asymptomatic and manifests as severe organ damage. Homocysteine plays a prominent role in the pathogenesis of vascular diseases presenting as increase in blood pressure. Hyperhomocyst-einemia (HHcy) is found to be a causative factor in the pathogenesis of vascular lesions in patients with hypertension especially in Indians with a different genetic variations compared to other populations. Microalbuminuria is a marker of renal injury that can often be detected earlier than any tangible decline in glomerular filtration rate. Micro albuminuria is now widely accepted as an independent risk factor for cardiovascular morbidity and mortality [1]. Homocysteine causes endothelial dysfunction by increasing oxidation of endothelium, altering balance of vasomotor dilatation and constriction, and also increasing the coagulability of blood [2]. Studies regarding homocysteine causing renal damage in hyperten-sives is lacking. The aim of this study was to assess the influence of Hcy on microalbuminuria in essential hypertensives with and without end organ damage.

Many risk factors have been identified leading to an increased blood pressure. Thus emphasis has been given to the early diagnosis at prehypert-ension stage itself. There is lot of research indicating the role of vascular inflammation in the setting and progression of hypertension.[3]. Tumor Necrosis Factor-a (TNF-a), Interleukin-6 (IL6) and C-Reactive Protein (CRP) are markedly elevated in people with hypertension [4].

Materials & Methods

Type of study: Case-Control Study.

Group I consists of healthy individuals with normal blood pressure without any history of any illness or disease.

Group II consists of newly diagnosed hypertensives as well as known hypertensives under control without any evidence of end organ damage viz renal , cardiac , retinal changes and serum creatinine level < 1.2 mg/dl.

Group III consists of hypertensives with clinical or laboratory evidence of end organ damage viz renal cardiac , retinal changes and serum creatinine level > 1.2 mg/dl.

People taking steroids, oral contraceptive pills and fibric acid derivatives and subjects having diabetes mellitus, smokers and chronic alcoholics were excluded from the study.

This study was conducted in hypertensive clinic of General Medicine Department in Sri Ramachandra Medical College. The study was been approved by the Institutional Ethics Committee. Out of 296 samples, 173 belonged to Group I , 161 to Group II and 162 to Group III. The fasting blood and spot urine samples were collected from the subjects after informed consent. The anthropometric measurements were recorded. The plasma homocysteine was determined by ELISA method (Axis Shield, UK), urinary microalbumin and hsCRP was determined by Immunoturbidimetric method. Albumin Creatinine Ratio (ACR) was also calculated as urinary albumin concentration (mg)/ mmol of creatinine.

The obtained data were analysed by ANOVA and post hoc test. SPSS Software Version 19.0 was used. P value <0.05 was considered significant.

Results

The values are expressed as Mean ± SD

A statistically significant difference was observed in waist hip ratio (p value <0.05) . A highly statistical difference was observed in SBP, DBP and BMI (p value <0.001).(Table 1)

There is no statistical significant difference in plasma glucose values between the groups. The total cholesterol, triglyceride, HDL cholesterol showed a significant difference (p value <0.05) between the groups. There is statistically highly significant difference (P value <0.001) between the groups with respect to other biochemical parameters. (Table 2)

The plasma homocysteine levels showed a highly statistical difference indicating that homocysteine levels show a marked increase as disease progresses. The mean hsCRP levels are higher in hypertensives with end organ damage.

There is statistically highly significant difference (p value <0.001) between the groups in SBP, DBP, Homocysteine and hsCRP. There is significant difference in Total cholesterol , HDL c, LDL c, Chol /HDL ratio, urinary microalbumin and ACR between groups 2 & 3 between 1 & 3, except HDL c which shows significant difference between 1 & 2. Regarding the anthropometric measurements, Waist /hip ratio shows a statistical difference between group 1 & 2 and a highly statistical difference between group 1 & 3. (Table 3)

Correlation analysis of homocysteine with other variables of the 3 different groups

When homocysteine was compared against routine biochemical parameters, microalbuminuria and albumin /creatinine ratio in group 2 showed correlation with p value <0.05.Other biochemical parameters in group 1,2 as well as 3 did not show significant difference in correlation with homocysteine.(Fig 1 & 2)

Correlation analysis of hsCRP with DBP in Group 2 & 3

In the same way , when hsCRP was compared against routine biochemical parameters , Diastolic blood pressure in group 2&3 showed correlation with p value <0.05.Other biochemical parameters in groups 1,2 as well as 3 did not show significant correlation with hsCRP (Fig 3 & 4).

Table 1 : Showing anthropometric data and blood pressure measurements

S.No	Parameters	Group-1 (n=173)	Group-2 (n=161)	Group-3 (n=162)	P value
1.	Age (years)	40 ± 10	49 ± 8	48 ± 7	
2.	SBP(mmHg)	114 ± 9	136 ± 15	141 ± 16	< 0.001
3.	DBP(mmHg)	77 ± 6	88 ± 11	90 ± 9	< 0.001
4.	BMI(kg/m^2)	23.6 ± 3.4	24.1 ± 3.38	25 ± 3.39	<0.001
5.	Waist / Hip Ratio	0.87 ± 0.08	0.89 ± 0.08	0.89 ± 0.05	0.013

Table 2 : Biochemical parameters of the 3 groups

S.No	Parameters	Group-1 (n=173)	Group-2 (n=161)	Group-3 (n=162)	p value
1.	Plasma glucose (F)(mg/dl)	84.9 ± 19.11	88 ± 12.4	86 ± 15.0	0.197
2.	Plasma glucose (PP) (mg/dl)	103.21 ± 31.0	106 ± 19.0	107± 29.2	0.411
3.	Total chol (mg/dl)	156.86 ± 26.15	157.03 ± 39.0	166.2 ± 31.0	0.012
4.	Triglyceride (mg/dl)	111.01 ± 58.43	119.34 ± 45.04	128 ± 48.0	0.010
5.	HDL-C (mg/dl)	44.63 ± 8.31	47 ± 8.0	44.5 ± 8.1	0.008
6.	LDL c (mg/dl)	108.78 ± 25.11	113.09 ± 26.30	125.2 ± 31	< 0.001
7.	Chol /HDL ratio	3.59 ± 0.83	3.37 ± 0.96	3.8 ± 0.98	< 0.001
8.	Urinary microalbumin mg /L	10.71 ± 8.28	16 ± 20	53.1 ± 93	< 0.001
9.	ACR(mg/ mmol)	1.2 ± 1.44	1.75 ± 1.84	4.6 ± 10. 38	< 0.001
10.	Homocysteine (µmol/L)	20.28 ± 12.8	28.63 ± 13.51	43.8 ± 14.5	< 0.001
11.	hsCRP(mg/dl)	0.97 ± 0.75	2.01 ± 1.46	3.93 ± 1.29	< 0.001

*P value <0.05 is considered statistically significant.

**P value <0.001 is considered statistically highly significant

Table 3 : Multiple comparative study between the 3 groups

S.No	Parameters	Group 1 & 2 p value	Group 2 & 3 p value	Group 1 & 3 p value
1.	SBP (mm Hg)	< 0.001 **	0.035 *	< 0.001 **
2.	DBP (mm Hg)	< 0.001 **	0.057	< 0.001 **
3.	BMI (kg/m ^{2})	0.307	0.482	0.022 *
4.	Waist / Hip ratio	0.039 *	0.846	< 0.001 **
5.	Total chol (mg/dl)	0.899	0.028 *	0.021 *
6.	Triglyceride (mg/dl)	0.296	0.253	<0.001 **
7.	HDL-Chol (mg/dl)	<0.001 **	<0.001 **	0.899
8.	LDL c (mg/dl)	0.324	<0.001 **	<0.001 **
9.	Chol /HDL ratio	0.081	<0.001 **	0.030 *
10.	Urinary Microalbumin mg/L	0.652	<0.001 **	<0.001 **
11.	A/C Ratio (mg)/ mmol	0.661	<0.001 **	<0.001 **
12.	Homocysteine (µmol/L)	<0.001 **	<0.001 **	<0.001 **
13.	hsCRP (mg/dl)	<0.001 **	<0.001 **	<0.001 **

*P value <0.05 is considered statistically significant.
**P value <0.001 is considered statistically highly significant

Fig 1 : Correlation of Homocysteine with urinary microalbumin in Group 2 (n=161)

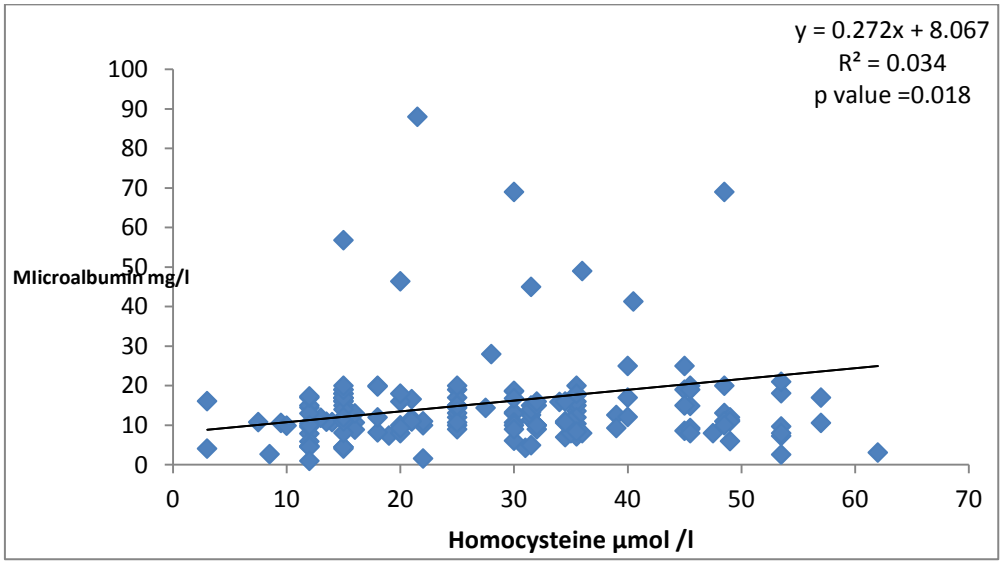


Fig 2: Correlation of Homocysteine with ACR in Group 2 (n=161)

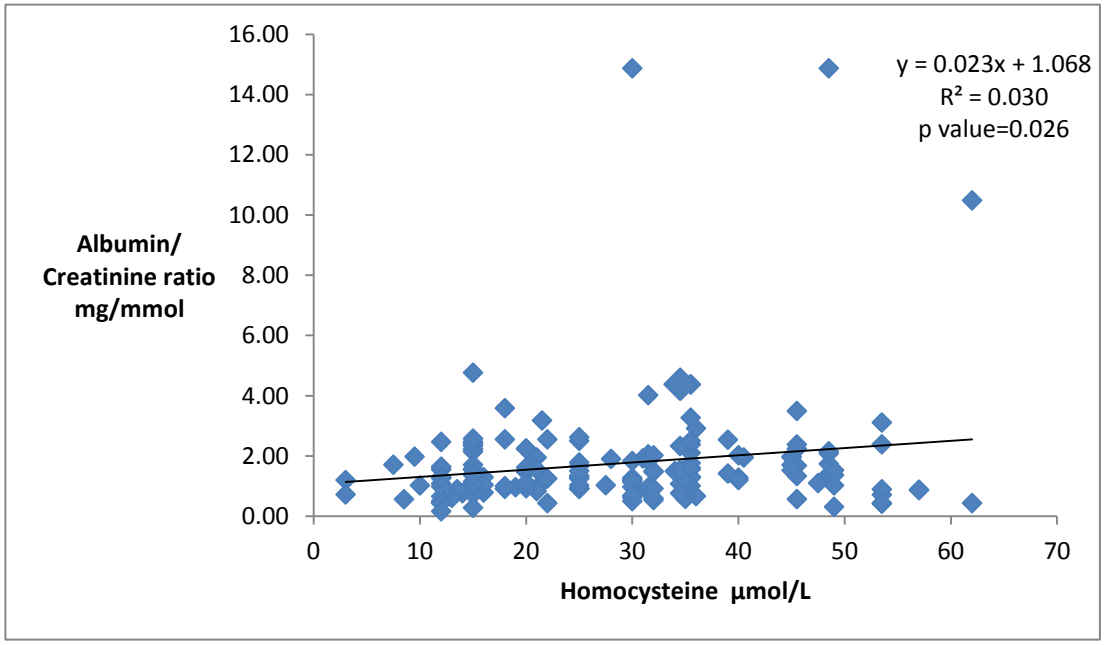


Fig 3: Correlation of hsCRP with DBP in Group 2 (n=161)

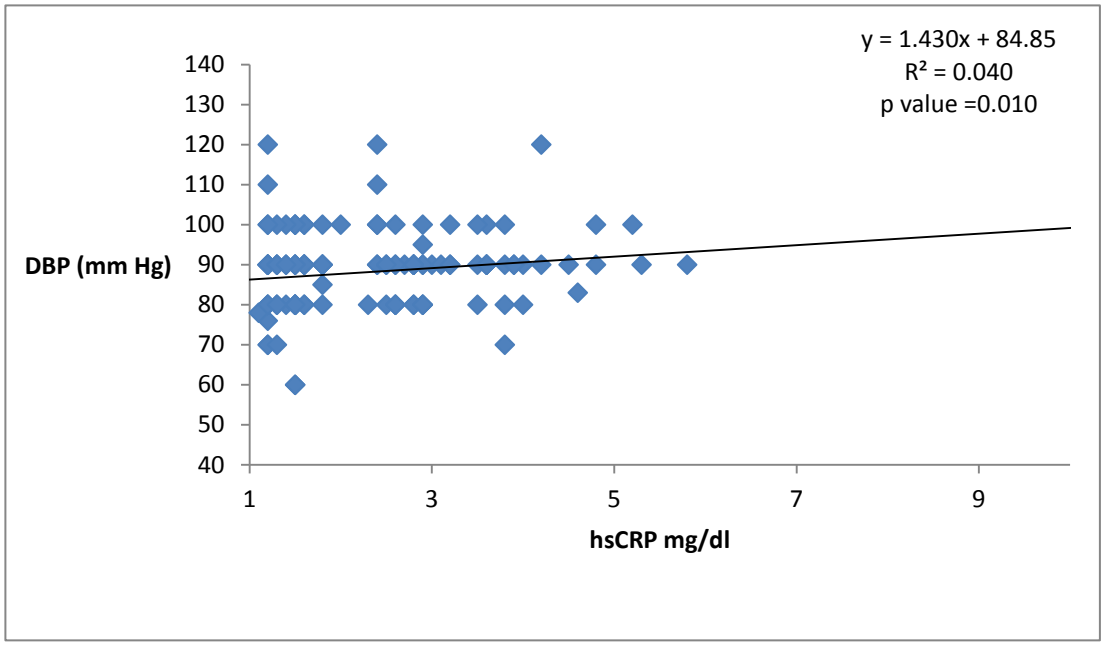
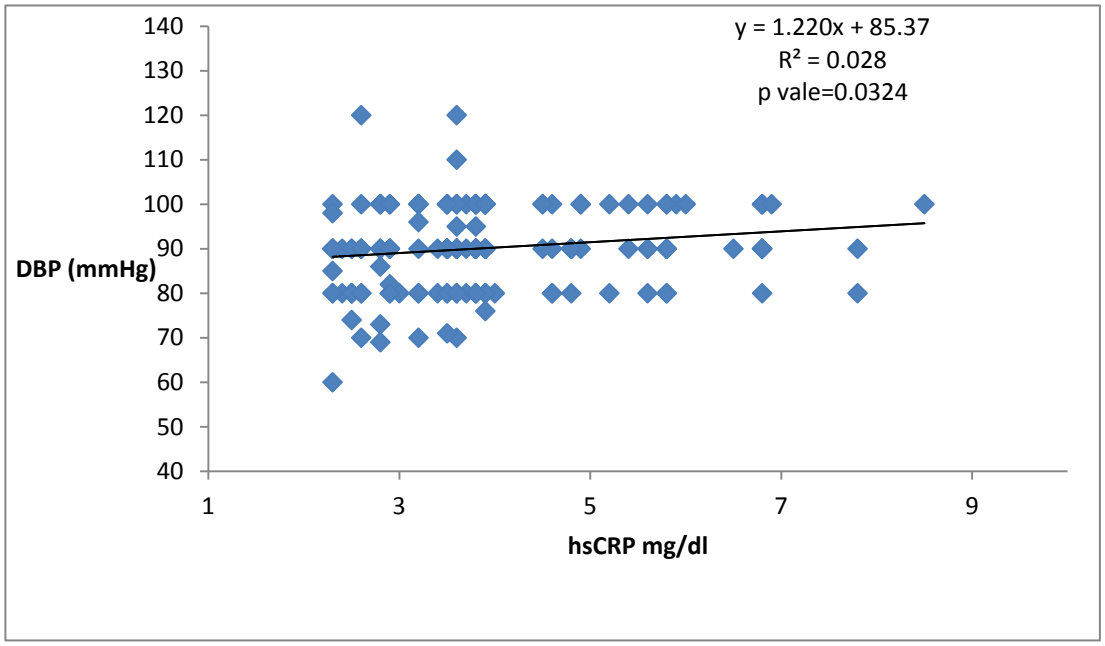


Fig 4: Correlation of hsCRP with DBP in Group 3 (n=162)



Discussion

It has already been known that Hyperhomocyst-einemia (Hhcy) has a major role in hypertension. Patients with slightly higher blood levels of homocysteine compared to normal are found to be predisposed to endothelial diseases, in the absence of other risk factors of endothelial dysfunction. Hyperhomocysteinemia causes impaired functioning and endothelial and smooth muscle cells of vessels [5,6].

It is found that Hhcy contributes to elevation in the blood pressure by diminishing vasodilatation by specific vasodilators like nitric oxide, causing the increased release of reactive oxygen species and leads to alterations in the elasticity of the vascular wall [7].

Studies by [8,9]. have shown that impaired vasodilatation correlates with high levels of Hcy in essential hypertension. The mechanism involves a possible interaction between Hcy and endothelium by increasing thrombogenesis thus precipitating angina or myocardial infarction.

Recent studies have demonstrated the deleterious effects of increased plasma Hcy levels on the

vital organs. Diet induced chronic Hhcy also leads to alterations in cardiac and renal function [10,11].

Leakage of small amounts of proteins in urine has been considered since 1980s a crucial sign of early kidney disease, especially in hypertensive patients. In hypertension, microalbuminuria was shown to associated with altered metabolism [12,13,14] Essential hypertension causes renal ischemia and nephrosclerosis, leading to renal impairment [15].

Correlation analysis showed that the levels of plasma Hcy had positive relationship with micro albuminuria (r=0.946, P<0.01) [16] . In our study also levels of plasma Hcy showed a positive relationship with micro albuminuria and ACR in group 2 (r=0.187, P=0.01) and r=0.1752, p=0.026) respectively.

Various studies [17,18,19,20], have shown that Hhcy leads to endothelial damage in all the organs in hypertension patients which is manifested in the kidneys as microalbuminuria.

Hcy is shown to induce oxidative stress in endoplasmic reticulum of meningeal cells through the activation of MAP kinase pathway [21]. Hhcy alters the cell signaling pathway mediated by ceramide leading to an increased expression of monocyte chemo attractant protein-1 [22,23]. Thus kidneys can be affected at pre-hypertension state indicating the involvement of Hcy leading to renal dysfunction [24,25].

Homocysteine acts as a prooxidant resulting in renal cell injury [26]. This leads defective functioning of glomerular basement membrane and raised intraglomerular pressure. Decreased nutritional status in the form of inadequate blood levels of pyridoxine, cobalamine and folate can lead to hyperhomocysteinemia. But studies have shown that prophylactic supplementation of the above mentioned vitamins does not bring about good outcome in all cases.

Various studies [27,28,29] found linkage between homocysteinemia and renal failure. Homocysteine is degraded almost completely in kidney tissue[30]. In patients with hyperhomocysteinemia there is decreased renal clearance of homocysteine resulting in increased levels in blood [31,32,33]

It is a well established fact that CRP being an acute phase protein gets increased to varying high levels during acute or chronic inflammation. Many studies have proven that CRP levels are increased in hypertensive people [34,35]. According to our study, a significant association exists between DBP and hs CRP in hypertensives (groups II & III) (r= 0.2003, p=0.010 for group II; r=0.1681, p=0.0324 for Group III) but not in control group(r=0.0287, p=0.707).

Many studies [36,37,38] do find the same kind of result as ours. Sesso et al [39] found that individuals with prehypertension especially with increased DBP have increased hsCRP.

Inflammation also contributes to the development of hypertension. CRP increases blood pressure by various pathways –decreased vasodilation by interfering with production of nitric oxide, increased leukocyte adhesion, platelet activation, oxidation, thrombosis and upregulation of angiotensin type-1 receptor [40,41]. Recently many circulating inflammatory markers are found to be associated with indices of arterial stiffening suggesting the possible role of inflammation [42,43,44]. According to Ki Chul Sung, studies showed elevated hsCRP in hypertensives [45]. Several mechanism have been elucidated for the possible role of hsCRP in the setting and progression of hypertension; salient ones being oxidative stress, increased level of adhesion molecules, plasminogen activator inhibitor-1 and oxidized LDL [46]

Studies suggest that the levels of hsCRP increases with the increase in the blood pressure [47]. more so with the duration of hypertension. However [48,49]. did not find any association between hsCRP and the duration of hypertension [50,51] has reported that hsCRP levels in pre-hypertension leads to adverse cardiovascular events in addition to hypertension.

Inflammatory processes lead to increased collagen deposition and fibrosis resulting in decreased myocardial function [52,53,54.55,56].

In patients with diastolic cardiac decompensation, collagen in the extracellular matrix is found to be anatomically and physiologically defective [57,58]. Inflammatory marker CRP alters the collagen/elastin ratio of the blood vessels [59,60]

Conclusion

Hyperhomocysteinemia in essential hypertension increases the risk of complications of hypertension resulting in damage to organs such as kiney, retina, heart etc. Early screening in hypertensive patients for microalbuminuria, hyperhomocysteinemia and increased hsCRP levels may reduce risk of further complications like chronic renal and cardiac diseases.

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Conflicts of Interests: None

References

1. Agrawal V, Marinescu V, Agarwal M . Cardiovascular implications proteinuria: an indicator of chronic kidney disease. Nat Rev Cardiol 2009 ; 6: 301-31
2. Stanger O, Weger M .. Interactions of homocysteine, nitric oxide, folate and radicals in the progressively damaged endothelium. Clin Chem Lab Med 2003 ;41: 1444-1454.
3. LI Jian-jun. Inflammation in hypertension: primary evidence. Chin Med J. 2006;119:1215-21.
4. Pauleto P, Rattazzi M. Inflammation and Hypertension: the search for a link. Nephrol Dial Transplant 2006;21:850-3
5. Jakubowski H . The pathophysiological hypothesis of homocysteine thiolactone-mediated vascular disease JPP 2008; 59: 155–167.
6. Niittynen L, Nurminen ML, Korpela R. Role of arginine, taurine and homocysteine in cardiovascular diseases. Ann Med 1999; 31: 318-326.
7. Rodrigo R, Passalacqua W, Araya J . Homocysteine and essential hypertension. J Clin Pharmacol 2003 ;43: 1299-1306
8. Lip GY, Edmunds E, Martin SC .A pilot study of homocysteine levels in essential hypertension: relationship to von Willebrand factor, an index of endothelial damage. Am J Hypertens 2001 ;14: 627-631.
9. Sainani GS, Sainani R . Homocysteine and its role in the pathogenesis of atherosclerotic vascular disease. J Assoc Physicians India 2002 ; 50: 5-8.
10. Kumagai H, Katoh S, Hirosawa K. Renal tubulointerstitial injury in weanling rats with hyperhomocysteinemia. Kidney Int 2002 ;62: 1219–1228.
11. Yi F, Dos Santos EA, Xia M. Podocyte injury and glomerulosclerosis in Hyperhomocysteinemia rats. Am J Nephrol 2007 ;27: 262–268.
12. Yun L, Xu R, Zhang L. The role of micro albuminuria in arterial endothelial dysfunction in hypertensive patients with carotid plaques. Int Heart 2014 ;J 55: 153159.
13. Färbom P, Wahlstrand B, Almgren P . Interaction Between Renal Function and Micro albuminuria for Cardiovascular Risk in Hypertension: The Nordic Diltiazem Study. Hypertension 2008 ;52: 115-122.
14. Polonla J, Carmona J, Mendes E, Pisco L .Prevalence of Microalbuminuria in Non-Diabetic Hypertensive Patients Attended by Portuguese GPs. Rev Port Cardiol 2007; .26: 637-644.
15. Rodriguez-Iturbe, B., Vaziri, N.D., Herrara-Acosta, J. and Johnson, R.J. Oxidative stress, renal infilteration of immune cells and salt-sensitive hypertension: All for one and one for all.

Am. J. Physiol. Renal Physiol 2004 ; 286: F606-F616.

16. Wenlin MA, Ruhui LIU, Lin LI, Weiqi SHI, Liang DENG, Yan JIN and Ming LUO J The Relationship between Micro Albuminuria and Plasma Homocysteine Level in Chinese Patients with Hypertension. J Hypertens 2014;, 3:5
17. Joseph J, Loscalzo J. Methoxistasis: integrating the roles of homocysteine and folic acid in cardiovascular pathobiology. Nutrients,2013 ;15: 3235-3256
18. Woo KS, Chook P, Lolin YI (1997) Hyperhomocyst(e) inemia is a risk factor for arterial endothelial dysfunction in humans. Circulation 96: 2542-2544.
19. Castro R, Rivera I, Blom HJ . Homocysteine metabolism,hyperhomocysteinemia and vascular disease: an overview. J Inherit Metab Dis 2006 ; 29: 3-20.
20. Marti F .Hyperhomocysteinemia is independently associated with albuminuria in the population-based CoLaus study. BMC Public Health 2011 ; 26:11:733.
21. Ingram AJ, Krepinsky JC, James L Activation of mesangial cell mapk in response to homocysteine. Kidney Int 2004 ; 66: 733-745.
22. Yi F, Zhang AY, Li N .Inhibition of ceramide-redox signaling pathway blocks glomerular injury in hyperhomocysteinemia rats. Kidney Int 2006 ;70: 88–96.
23. Hwang SY, Woo CW, Au-Yeung KK .Homocysteine stimulates monocyte chemo attractant protein-1 expression in the kidney via nuclear factor-kappaB activation. Am J Physiol Renal Physiol 2008 ; 294: F236–F244.
24. Wollesen F, Brattstrom L, Refsum H .Plasma total homocysteine and cysteine in relation to glomerular filtration rate in diabetes mellitus. Kidney Int 1999 ; 55: 1028–1035.
25. Davies L, Wilmshurst EG, McElduff A (2001) The relationship among homocysteine, creatinine clearance, and albuminuria in patients with type 2 diabetes. Diabetes Care 24: 1805–1809.
26. Tsai JC, Perrella MA, Yoshizumi M, Hsieh CM, Haber E, Schlegel R,Lee ME. Promotion of vascular smooth muscle cell growth by homocysteine:a link to atherosclerosis. Proc Natl Acad Sci U S A. 1994;91:6369–6373.
27. Chico A, Perez A, Cordoba A, Arcelus R, CarrerasG, de Leiva A, Gonzales-Sastre F, Blanco-Vaca F.Plasma homocysteine is related to albumin excretionrate in patients with diabetes mellitus: a new link between diabetic nephropathy and cardiovascular disease? Diabetologia 1998;41:684-693.
28. Emoto M, Kanda H, Shoji T, Kawagishi T, Komatsu M, Mori K, Tahara H, Ishimura E, Inaba M, Okuno Y, Nishizawa Y. Impact of insulin resistance andnephropathy on homocysteine in type 2 diabetes Diabetes Care 2001;24:533-538.
29. Lanfredini M, Fiorina P, Peca MG, Veronelli A,Mello A, Astorri E, Dall'Aglio P, Craveri A. Fasting and post-methionine load homocyst(e)ine values are correlated with microalbuminuria and could contribute to worsening vascular damage in noninsulin-dependent diabetes mellitus. Metabolism 1998;47:915-921
30. Dudman NP, Guo XV, Gordon RB, Dawson PA,Wilcken DE. Human homocysteine catabolism:Three major pathways and their relevance to development of arterial occlusive disease. J Nutr 1996;126 :1295S-3000S.
31. House JD, Brosnan ME, Brosnan JT. Character-ization of homocysteine metabolism in the rat kidney. Biochem J 1997;328:287-292.
32. Brattström L, Lindgren A, Israelsson B, Andersson A, Hultberg B. Homocysteine

and cysteine:determinants of plasma levels in middle-aged and elderly subjects. J Intern Med 1994;236:631-641.
33. Bostom A, Brosnan JT, Hall B, Nadeau MR, Selhub J. Net uptake of plasma homocysteine by the rat kidney in vivo. Atherosclerosis 1995;116:59-62.
34. Rohde LE, Hennekens CH, Ridker PM. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. Am J Cardiol. 1999;84:1018-22.
35. Bermudez EA, Rifai N, Buring J, Manson JE,Ridker PM. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. Arterioscler Thromb Vasc Biol. 2002;22:1668-73.
36. Dawri S, Padwal MK, Melinkeri R. Evaluation of high sensitivity C-reactive protein and serum lipid profile in prehypertension and essential hypertension. NJIRM. 2014 Jan-Feb;5(1):1-5.
37. Ryu SY, Lee YS, Park J, Kang MG, Kim KS.Relations of plasma high-sensitivity C-reactive protein to various cardiovascular risk factors. J Korean Med Sci. 2005;20:379-83.
38. M. Shafi Dar, A. A. Pandith, A. S. Sameer, M. Sultan, A. Yousuf, S. Mudassar. hs-CRP: a potential marker for hypertension in Kashmiri population.Indian J Clin iochem.2010;25(2):208-12.
39. Sesso HD, Bruing JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. JAMA. 2003;290:294551.
40. Devaraj S, Xu DY, Jialal I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells; implications for the metabolic syndrome and atherothrombosis. Circulation. 2003;107:398-404.
41. Wang CH, Li SH, Weisel RD, Fedak PW, Dumont AS, Szmitko P, et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. Circulation. 2003;107:1783-90.
42. Pauleto P, Rattazzi M. Inflammation and Hypertension: the search for a link. Nephrol Dial Transplant. 2006;21:850-3.
43. Bautista LE, Lopez- Jaramillo, Vera LM, Casas JP,Otero AP, Guaracao AI. Is C-Reactive Protein an independent risk factor for essential hypertension? J Hypertens. 2001;19(5):857-61.
44. Mendall MA, Patel P, Ballam L, Strachan D,Northfield TC. C-reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. BMJ. 1996;312:1061-5.
45. Sung KC, Suh JY, Kim BS, Kang JH, Kim H, Lee MH, et al. High sensitivity C-reactive protein as an independent risk factor for essential hypertension.Am J Hypertens. 2003;16:429-33.
46. King DE, Egan BM, Mainous AG 3rd, Geesey ME. Elevation of C-reactive protein in people with prehypertension. J Clin Hypertens. 2004;6:562-8.
47. Gupta AK, Johnson WD. Prediabetes and prehypertension in disease free obese adults correlate with an exacerbated systemic proinflammatory milieu. J Inflammation. 2010;7:36.
48. Bautista LE, Lopez- Jaramillo, Vera LM, Casas JP, Otero AP, Guaracao AI. Is C-Reactive Protein an independent risk factor for essential hypertension? J Hypertens. 2001;19(5):857-61.
49. Dawri S, Padwal MK, Melinkeri R. Evaluation of high sensitivity C-reactive protein and serum lipid profile in prehypertension and essential hypertension. NJIRM. 2014 Jan-Feb;5(1):1-5.

50. A. I. Qureshi, M. F. Suri, J. F. Kirmani, A. A.Divani, Y. Mohammad. Is prehypertension a risk factor for cardiovascular diseases? Stroke.2005;36(9):1859-63.
51. Nicoletti A, Michel JB. Cardiac fibrosis and inflammation: interaction with hemodynamic and hormonal factors. Cardiovasc Res. 1999;41:532–43. [PubMed]
52. Siwik DA, Colucci WS. Regulation of matrix metalloproteinases by cytokines and reactive oxygen/nitrogen species in the myocardium. Heart Fail Rev. 2004;9:43–51. [PubMed]
53. Yambe M, Tomiyama H, Hirayama Y, et al. Arterial stiffening as a possible risk factor for both atherosclerosis and diastolic heart failure. Hypertens Res. 2004;27:625–31. [PubMed]
54. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation. 2003;107:714–20. [PubMed]
55. Pirro M, Schillaci G, Savarese G, et al. Low-grade systemic inflammation impairs arterial stiffness in newly diagnosed hyper-cholesterolaemia. Eur J Clin Invest. 2004;34:335–41. [PubMed]
56. Kass DA. Ventricular arterial stiffening: integrating the pathophysiology. Hypertension. 2005;46:185–93.[PubMed]
57. Kuwahara F, Kai H, Tokuda K, et al. Hypertensive myocardial fibrosis and diastolic dysfunction: another model of inflammation? Hypertension. 2004;43:739–45. [PubMed]
58. Li YY, McTiernan CF, Feldman AM. Interplay of matrix metalloproteinases, tissue inhibitors of metalloproteinases and their regulators in cardiac matrix remodeling. Cardiovasc Res. 2000;46:214–24.[PubMed]
59. Lin R, Liu J, Gan W, Yang G. C-reactive protein-induced expression of CD40-CD40L and the effect of lovastatin and fenofibrate on it in human vascular endothelial cells. Biol Pharm Bull. 2004;27:1537–43.[PubMed]
60. Lee SW, Song KE, Shin DS, et al. Alterations in peripheral blood levels of TIMP-1, MMP-2, and MMP-9 in patients with type-2 diabetes. Diabetes Res Clin Pract. 2005;69:175–9. [PubMed]

Abbreviations

ACR = Albumin Creatinine Ratio
ANOVA = Analysis of Variance
BMI = Body Mass Index
DBP = Diastolic Blood Pressure
ELISA = Enzyme Linked Immunosorbent Assay
HDL chol = High Density Lipoprotein cholesterol
Hhcy = Hyperhomocysteinemia
hsCRP = High sensitivity C-reactive protein
LDL c = Low Density Lipoprotein cholesterol
MAP kinase = mitogen-activated protein kinase
mg / dl = Milligram per deciliter
mg/ L = Milligram per liter
mm Hg = Millimeter of Mercury
mg/ mmol = Milligram per millimole
µmol /L = Micromole per liter
SBP = Systolic Blood Pressure
SD = Standard deviation