ejpmr, 2022,9(8), 65-69

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

SERUM CALPROTECTIN AND CRP: A POSITIVE PROGNOSTIC DETERMINANT IN NEWLY DIAGNOSED PRIMARY HYPERTENSION

[1]*Dr. Kanwal, [2]Dr. Vishal, [3]Dr. FNU Sahrish, [4]Dr. Sumeet Kumar, [5]Dr. Meena Kumari, [6]Dr. Berkha, [7]Dr. Vijay

[1]MBBS, General Practitioner (Babal Sain Medical Center Thul Pakistan).
[2]MBBS, General Practitioner (Baniyas Alahli Medical Center Abu Dhabi UAE).
[3]MBBS, Lecturer (Chandka Medical College Larkana).
[4,5]MBBS, Department of Internal Medicine (Dow University of Health Sciences, Pakistan).
[6]MBBS, Department of Internal Medicine (Peoples University of Medical and Health Sciences, Nawabshah).
[7] MBBS, Medical Officer (Liaquat University of Medical and Health Sciences Jamshoro).

***Corresponding Author: Dr. Kanwal**

MBBS, General Practitioner (Babal Sain Medical Center Thul Pakistan).

Article Received on 03/06/2022 **Article Revised on 24/06/2022** **Article Accepted on 14/07/2022**

ABSTRACT

Background: The most common cause of cardiovascular death is hypertension. Endothelial damage and inflammation are two hallmarks of the illness, which is still not completely understood. Systemic inflammatory disorders, infection, and atherosclerosis all increase the level of calprotectin in the bloodstream. **Aim:** Serum calprotectin levels were measured to assess inflammation in individuals with newly diagnosed primary hypertension. **Design:** Cross sectional study. **Methodology:** A cross-sectional study was conducted involving fifty newly diagnosed hypertensive patients and fifty healthy adults after following inclusion criterion. Each patient's blood pressure, metabolic data, and demographic information were collected. Calprotectin levels in the blood were measured using an ELISA KIT. Assessment of the variables that influence serum calprotectin levels as well as the risk factors for hypertension was performed. Analysis was performed using SPSS version 25. A Chi-square test with a significance level of less than or equal to 0.05 was carried out. **Results:** Out of 100 patients enrolled, the difference between the control group's serum calprotectin levels of 239.8 ng/mL and the hypertensive patient group's levels of 97.6 ng/mL was statistically significant. The control group's levels were higher. (p =0.001). There is no association between serum calprotectin levels and age, gender, or BMI in the group of people who have hypertension. A decreased blood calprotectin level was shown to be independently associated to mean systolic blood pressure (r value=-.485**) (p = 0.001). Serum calprotectin at 131.9 ng/mL differentiated hypertensives from healthy controls with 71.2% sensitivity and 81.1% specificity. (AUC= 0.767). **Conclusion:** The findings of this investigation contradicted our hypothesis that an elevated calprotectin level in newly diagnosed hypertension individuals indicates inflammatory processes at the cellular level. Studies on individuals at varying stages of hypertension may provide light on the association between hypertension and calprotectin. Calprotectin's role in hypertension-related inflammation is a complicated one, and molecular research is needed to comprehend it.

KEYWORDS: Primary hypertension, Calprotectin, inflammation.

INTRODUCTION

Hypertension is among the most significant risk factors for cardiovascular disease that can be modified.[1] The hunt for inflammatory markers implicated in the etiology of primary hypertension and related end organ damage is constantly rising. Although this has still not been completely understood, multiple earlier investigations have demonstrated the existence of inflammatory response and oxidative stress-mediated endothelium injury underlying hypertension.[2] Hypertensive cardiovascular damage has been linked to several inflammatory regulating molecules such angiotensin II, (TNF-α), (MCP-1), and Interleukins, however it is not apparent which of these and comparable indicators really triggers inflammation in the early stage of disease.[3,4] End organ damage may be detected noninvasively, and therapies aiming at lowering hypertension-related morbidity and death are expected to be developed using possible indicators.[5,6]

Calprotectin is a calcium-binding protein with immunomodulatory, anti-proliferative, and proinflammatory properties that is present in the cytoplasm of monocytes, macrophages, and dendritic cells, notably neutrophilic granules.[7,8] Conditions that progress with acute endothelial damage, such as acute coronary ischemia, preeclampsia, and, in particular,+1 lymphocyte-mediated immune response, as well as acute

exacerbations of chronic inflammatory diseases, such as inflammatory arthritis and inflammatory bowel diseases, are associated with dramatic increases in calprotectin levels in body fluids.[9–12]

Calprotectin levels also were linked to an increase in chronic disorders such cystic fibrosis, soft tissue disorders, malignancy, and cardiovascular disease.[13–15] Several studies have examined calprotectin levels in essential hypertension patients, however the link between high blood pressure and end organ damage is unclear.[16-18] It is true that calprotectin is typically referred to as a marker of acute inflammation; however, in considerationof the role that endothelial damage plays in the pathogenesis of hypertension, it has also been suggested that serum calprotectin levels may be a marker of the inflammatory process in hypertension, in that regards This research evaluated blood calprotectin levels in newly diagnosed primary hypertension patients as an early inflammatory marker.

METHODOLOGY

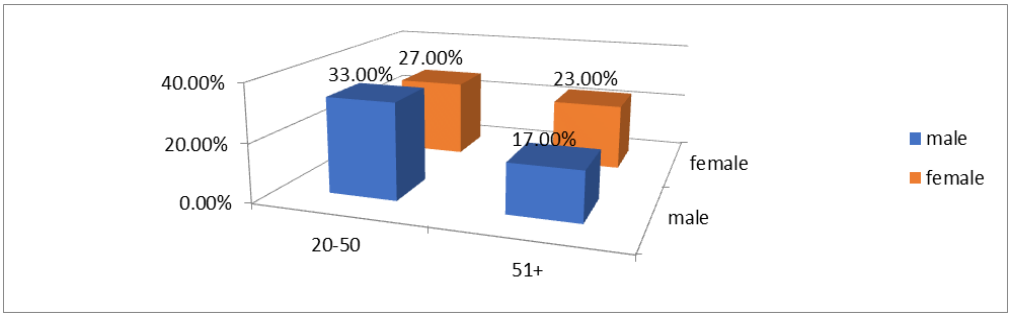
Study Setting: Cross-sectional study was conducted at Medicine ward, Lumhs from January 3rd, 2022, to May 30th, 2019. A total of 100 patients were enrolled for study, out of which two groups were formed, group 1 comprises of newly diagnosed primary Hypertensive patients and group two comprise of Control patients Participants who met the inclusion criteria participated sequentially. Data collection by using non-convenience probability sampling. A questionnaire collected socio-demographic information. Exclusion criteria were age under 18 and chronic drug use, active infection, acute renal damage, and chronic systemic illness, such as cardiovascular disease or cancer. All participants gave written informed consent. All patients were instructed to rest for 5 minutes in a quiet, comfortable room before the treatment. They were asked whether they'd taken coffee, alcohol, or cigarettes in the last 30–60 min. Morning blood samples were taken after an 8-hour fast to assess metabolic parameters and calprotectin. Serum calprotectin levels were measured using a Bioassay Technology Laboratory.

A clinician used ABP monitoring to diagnose hypertension, and readings were interpreted according to ESC/ESH 2018 guidelines. The mean of two BP readings was reported. Systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg characterize hypertension. ABG monitoring confirmed diagnosis (ABPM). Analysis covered subjects with at least 70% 24 h ABPM measurements. 130/80 mmHg throughout 24 h, 135/85 mmHg for daytime average, and 120/70 mmHg for nighttime average were diagnostic for hypertension.[19]

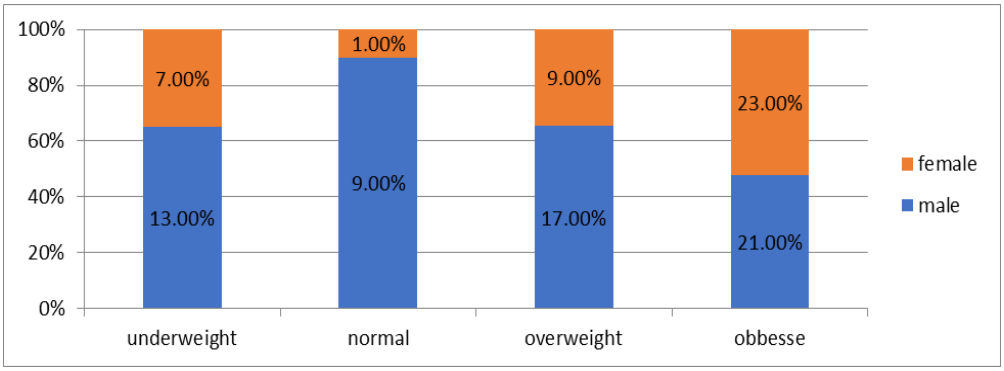
Statistical Analysis: The collected data was analyzed by using SPSS version 26. Data outputs were also presented with charts, tables, and figures accordingly. Chi square ware applied with P-value< 0.05 as significant.

Ethical Approval: Ethical clearance was obtained from the ERC LUMHS. Permission to conduct the study was obtained from DR LAB LUMHS. Written informed consent was obtained from each patient before data collection.

RESULTS



Graph 1: Showing Age wise distribution of sample population (n=100).



Graph 2: Showing BMI wise distribution of sample population (n=100).

Graph: 3 represents Pearson correlation of Serum Calpoprectin and mean systolic Pressure (n=100).

Pearson Correlation between Serum Calpoprectin and mean systolic Pressure		
Serum Calprotectin (pg/mL)	r -value	-.485**
	p value	.0001

Graph 4: One-Sample Statistics of serum Calpoprectin and Mean Sys BP: (n=100).

Variables	Mean	Std. Deviation	Std. Error Mean	T	P
Serum Calpoprectin (pg/mL)	11.946	9.7903	.8992	11.956	0.001
Mean systolic Pr:	9.26	6.789	.793	13.808	

Graph 5: Showing classification of mean Blood pressures, group wise (n=100).

Blood Pressure Groups	Mean Values	P value
Mean Systolic in group A	149	0.001
Mean Systolic in group B	118	
Mean diastolic in group A	98	
Mean diastolic in group B	79	

Table 01: Showing pearson correlation between serum calprotectin and CRP levels, where (r = -.0471) with p value (p=0.0001) shows significant relationship.

Variables	Pearson correlation	Serum CRP
Serum calprotectin	R value	-.471**
	P value	0.0001

DISCUSSIONS

In our region, this is the novel research assessing levels of blood calprotectin in newly diagnosed patients with Primary hypertension. Serum calprotectin levels were considerably elevated in the control group than other group comprising hypertensive patients. This conclusion is not in line with the prior studies testing calprotectin in inflammatory disoreders.[9,17,20–22] Throughout the whole patient group, serum uric acid and SBP adversely influenced serum calprotectin levels. These results, which are consistent yet not with earlier investigations, cannot be a coincidence and demand explanation. As, during acute inflammation, serum calprotectin levels rise. Endothelial and inflammatory cells cooperate to increase calprotectin release. Several investigations on inflammation and pathogenetic processes in hypertension found greater CRP, uric acid, and calcium levels.[23–28] Serum uric acid and calcium levels found to be lowering serum calprotectin levels. Low calprotectin levels are probably associated to hypertension-related inflammation. The first hypothesis includes a fast rise in neutrophil-derived calprotectin in hypertensive tissue and serum, followed by a quick fall to normal limits. this is likely due to short neutrophil half-life. One previous study role of Angiotensin II in initial-stage inflammatory induced hypertension and cardiac ischemia, more than 280 genes were activated, including neutrophil-derived calprotectin. This research found that calprotectin caused RAGE-mediated cytotoxicity in cardiac cells, that calprotectin-associated neutrophil levels surged unexpectedly after Angiotensin II administration, and that serum and tissue levels dropped progressively on the third and seventh days. This abrupt drop was ascribed to short neutrophil half-life.[29] Another variable which has to be taken into account is whether or not the technique that was employed to assess the levels of calprotectin serum was applicable to the research group. From this vantage point, the development of this idea would benefit from a more in-depth investigation of the molecular properties of calprotectin. Calprotectin is found in the form of a stable noncovalent heterodimer of S100A8 and S100A9, which is capable of undergoing a rapid conversion into a heterotetrameric form in response to an increase in calcium levels in the neutrophilic cytosol of approximately 100-fold as a direct result of neutrophil activation.[30–32] The neutrophil-exiting calprotectin molecule is protein-complexed. It's been suggested that neutrophil-derived oxidative stress alters the molecular structure of calprotectin in the ECF, making it more susceptible to proteolysis. Low blood calprotectin levels may be due to molecular degradation in the inflammatory zone or during test specimen freezer.[32]

In a prior study that investigated the association between the lipid profile and serum calprotectin level in patients with axial spondylo-arthropathy, the researchers found that healthy people had greater calprotectin levels. Our findings are quite similar to those of the previous study. Because of its diminutive dimensions, one of the hypotheses put out by those authors in relation to this surprising result involves the local concentration of calprotectin in synovial fluid.[33] It is probable that the serum calprotectin levels in our hypertension group are inadequate to represent the current subclinical inflammation for the reasons that were explained above.

The levels of uric acid in the blood were shown to have an inverse relationship with the levels of calprotectin in the serum, with uric acid levels having an effect on calprotectin levels. It has been suggested that uric acid contributes to the development and progression of cardiovascular disease in a number of different ways, one of which is inflammation.[23,34,35] There were no studies that we could find that investigated the connection between calprotectin and uric acid in hypertensive patients; however, the connection between calprotectin and uric acid in the inflammatory process has been the topic of study in the past. According to the findings of a number of investigations, a rise in calprotectin levels is

brought about by synovial-derived monosodium urate crystals via the activation of neutrophils.[36–38] The S100 protein family and uric acid are tissue-damaging alarmin molecules.[39] The research that has been done up to this point suggests that there is, in fact, a positive association between calprotectin and uric acid in the course of the inflammatory process. It is possible that the vulnerability of the calprotectin heterotetramers to fast proteolysis is the root cause of the negative association that was discovered in this investigation. When all of these data from the current research are taken into consideration, we believe that the role of calprotectin in hypertension is one that merits further investigation and should be investigated in more depth.

The study's limits include the small number of participants and the use of blood samples that had been held for some time, as well as the inability to compare the various calprotectin assessment procedures. It's also possible that additional endothelium indicators may have helped us understand our results.

CONCLUSIONS AND RECOMMENDATIONS

Minimal studies have evaluated calprotectin levels in newly diagnosed primary hypertension patients without clearly explaining endothelial damage. In this research, calprotectin levels were significantly lower in newly diagnosed primary hypertensive patients. Further comparative investigations with larger population size and hypertensive patients at various phases, with or without comorbidities, are required to understand calprotectin's role in the inflammatory process. Developing novel techniques with high clinical relevance for measuring calprotectin or reviewing existing methods, particularly for stored samples, can benefit clinical practise.

REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC), "Worldwidetrends in blood pressure from 1975 to 2015: a pooled analysisof 1479 population-based measurement studies with 19·1 million participants,") e Lancet, 2017; 389(10064): 37–55.
2. R. Khaddaj Mallat, C. Mathew John, D. J. Kendrick, and A. P. Braun, "+e vascular endothelium: a regulator of arterialtone and interface for the immune system," Critical Reviews inClinical Laboratory Sciences, 2017; 54(7-8): 458–470.
3. E. Gkaliagkousi, S. Douma, C. Zamboulis, and A. Ferro,"Nitric oxide dysfunction in vascular endothelium andplatelets: role in essential hypertension," Journal of Hypertension, 2009; 27(12): 2310–2320.
4. L. Xiao and D. G. Harrison, "Inflammation in hypertension,"Canadian Journal of Cardiology, vol. 36,no. 5, pp. 635–647,2020.
5. E. H. C. Tang and P. M. Vanhoutte, "Endothelial dysfunction:a strategic target in the treatment of hypertension?" PfluegersArchiv European Journal of Physiology, 2010; 459(6): 995–1004.
6. A. C. Montezano, M. Dulak-Lis, S. Tsiropoulou, A. Harvey, A. M. Briones, and R. M. Touyz, "Oxidative stress and humanhypertension: vascular mechanisms, biomarkers, and noveltherapies," Canadian Journal of Cardiology, 2015; 31(5): 631–641.
7. B. Johne, M. K. Fagerhol, T. Lyberg et al., "Functional andclinical aspects of the myelomonocyte protein calprotectin,"Molecular Pathology, 1997; 50(3): 113–123.
8. J. Yang, J. Anholts, U. Kolbe, J. Stegehuis-Kamp, F. Claas, andM. Eikmans, "Calcium-binding proteins S100A8 and S100A9: investigation of their immune regulatory effect in myeloid cells," International Journal of Molecular Sciences, 2018; 19(7): 1833.
9. S. Miyamoto, M. Ueda, M. Ikemoto et al., "Increased serum levels and expression of S100A8/A9 complex in infiltrated neutrophils in atherosclerotic plaque of unstable angina," Heart, 2008; 94(8): 1002–1007.
10. J. Li, L. Huang, S. Wang, and Z. Zhang, "Increased serum levels of high mobility group protein B1 and calprotectin in pre-eclampsia," International Journal of Gynecology & Obstetrics, 2018; 142(1): 37–41.
11. M.-A. Meuwis, G. Vernier-Massouille, J. C. Grimaud et al., "Serum calprotectin as a biomarker for Crohn's disease,"Journal of Crohn's and Colitis, 2013; 7(12): e678–e683.
12. M. Jarlborg, D. S. Courvoisier, D. S. Courvoisier et al., "Serum calprotectin: a promising biomarker in rheumatoid arthritis and axial spondyloarthritis," Arthritis Research and) erapy, 2020; 22(1): 105.
13. L.-P. Ma, E. Haugen, M. Ikemoto, M. Fujita, F. Terasaki, and M. Fu, "S100A8/A9 complex as a new biomarker in prediction of mortality in elderly patients with severe heart failure,"International Journal of Cardiology, 2012; 155(1): 26–32.
14. F. Shabani, A. Farasat, M. Mahdavi, and N. Gheibi, "Calprotectin (S100A8/S100A9): a key protein between inflammation and cancer," Inflammation Research, 2018; 67(10): 801–812.
15. I. Str´ız and I. Trebichavsk´y, "Calprotectin - a pleiotropic molecule in acute and chronic inflammation," Physiological Research, 2004; 53(3): 245–253.
16. C. Feng, Y. Tao, T. Shang, and M. Yu, "Calprotectin, RAGE and TNF-α in hypertensive disorders in pregnancy: expression and significance," Archives of Gynecology and Obstetrics, 2011; 283(2): 161–166.
17. S. Trabulus, M. Oruc, S. Yavuzer et al., "Myeloid-related protein complex 8/14 increases in hypertensive patients with excessive renal damage," Clinical Nephrology, 2020; 93(5): 234–242.
18. S. K. Kunutsor, J. L. Flores-Guerrero, L. M. Kieneker et al., "Plasma calprotectin and risk of cardiovascular disease: findings from the PREVEND prospective cohort study," Atherosclerosis, 2018; 275: 205–213.

19. B. Williams, G. Mancia, W. Spiering et al., "2018 practice guidelines for the management of arterial hypertension of the European society of cardiology and the European society of hypertension," Blood Pressure, 2018; 27(6): 314–340.
20. K. Croce, H. Gao, Y. Wang et al., "Myeloid-related protein-8/ 14 is critical for the biological response to vascular injury," Circulation, 2009; 120(5): 427–436.
21. M. M. McCormick, F. Rahimi, Y. V. Bobryshev et al., "S100A8 and S100A9 in human arterial wall," Journal of Biological Chemistry, 2005; 280(50): 41521–41529.
22. M. J. Robinson, P. Tessier, R. Poulsom, and N. Hogg, "+e S100 family heterodimer, MRP-8/14, binds with high affinity to heparin and heparan sulfate glycosaminoglycans on endothelial cells," Journal of Biological Chemistry, 2002; 277(5): 3658–3665.
23. M. Jin, F. Yang, I. Yang et al., "Uric acid, hyperuricemia and vascular diseases," Frontiers in Bioscience, 2012; 17(1): 656–669.
24. Y. Wang, J.-W. Hu, Y.-B. Lv et al., "+e role of uric acid in hypertension of adolescents, prehypertension and salt sensitivity of blood pressure," Medical Science Monitor, 2017; 23: 790–795.
25. C. Sabanayagam and A. Shankar, "Serum calcium levels and hypertension among US adults," Journal of Clinical Hypertension, 2011; 13(10): 716–721.
26. H. Sun, J. Shi, H. Wang et al., "Association of serum calcium and hypertension among adolescents aged 12-17 years in the rural area of Northeast China," Biological Trace Element Research, 2013; 155(3): 344–351.
27. F. G. Hage, "C-reactive protein and hypertension," Journal of Human Hypertension, 2014; 28(7): 410–415.
28. Y. Kansui, K. Matsumura, Y. Morinaga et al., "C-reactive protein and incident hypertension in a worksite population of Japanese men," Journal of Clinical Hypertension, 2019; 21(4): 524–532.
29. Y. Wu, Y. Li, C. Zhang et al., "S100a8/a9 released by CD11b +Gr1 + neutrophils activates cardiac fibroblasts to initiate 6 International Journal of Hypertension angiotensin II-induced cardiac inflammation and injury," Hypertension, 2014; 63(6): 1241–1250.
30. N. Leukert, T. Vogl, K. Strupat, R. Reichelt, C. Sorg, and J. Roth, "Calcium-dependent tetramer formation of S100A8 and S100A9 is essential for biological activity," Journal of Molecular Biology, 2006; 359(4): 961–972.
31. C. Propper, X. Huang, J. Roth, C. Sorg, and W. Nacken, "Analysis of the MRP8-MRP14 protein protein interaction by the two-hybrid system suggests a prominent role of the C-terminal domain of S100 proteins in dimer formation," Journal of Biological Chemistry, 1999; 274(1): 183–188.
32. T. S. Hoskin, J. M. Crowther, J. Cheung et al., "Oxidative cross-linking of calprotectin occurs in vivo, altering its structure and susceptibility to proteolysis," Redox Biology, 2019; 24: 101202.
33. F. Genre, J. Rueda-Gotor, S. Remuzgo-Martınez et al., "Association of circulating calprotectin with lipid profile in axial spondyloarthritis," Scientific Reports, 2018; 8(1): 13728.
34. G. Ndrepepa, "Uric acid and cardiovascular disease," Clinica Chimica Acta, 2018; 484: 150–163.
35. R. J. Johnson, D.-H. Kang, D. Feig et al., "Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease?" Hypertension, 2003; 41(6): 1183–1190.
36. C. Ryckman, C. Gilbert, R. de M´edicis, A. Lussier, K. Vandal, and P. A. Tessier, "Monosodium urate monohydrate crystals induce the release of the proinflammatory protein S100A8/A9 from neutrophils," Journal of Leukocyte Biology, 2004; 76(2): 433–440.
37. C. Ryckman, S. R. McColl, K. Vandal et al., "Role of S100A8 and S100A9 in neutrophil recruitment in response to monosodium urate monohydrate crystals in the air-pouch model of acute gouty arthritis," Arthritis & Rheumatism, 2003; 48(8): 2310–2320.
38. D. Vedder, M. Gerritsen, M. T. Nurmohamed, R. F. van Vollenhoven, and C. Lood, "A neutrophil signature is strongly associated with increased cardiovascular risk in gout," Rheumatology, 2020.
39. M. E. Bianchi, "DAMPs, PAMPs and alarmins: all we need to know about danger," Journal of Leukocyte Biology, 2007; 81(1): 1–5.