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ORIGINAL ARTICLE

EVALUATION OF HSP-70, TNF- A AND HS CRP LEVELS IN PATIENTS WITH HYPERTENSION

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ABSTRACT

Background: Hypertension significantly increases the risk of cardiovascular disease, kidney failure, and stroke. Hypertension is a multifaceted and has multifactorial causation. Hypertension can be caused by several factors such as excessive salt or alcohol consumption, stress, age, and genetics, family history, obesity, and physical condition. Objective of the study was evaluation of HSP-70, TNF-α and HS CRP levels and their relationship with hypertensive Patients.

Materials & Methods: This study included 50 patients with hypertension and 40 individuals from a healthy control group of 50 patients, 28 males and 22 females, aged between 40 and 70 years. They were compared with the healthy group. The factors measured in these groups were, (HSP-70), (TNF-α), (HS CRP).

Result: The result of this study showed a significant difference when comparing the data of high blood pressure patients with the group of healthy people. We noted that most of the tests were higher than the normal limit, which included (HSP-70, CRP) in patients with high blood pressure. The P value was ≥ (0.0001)

Conclusions: Immunological cells and inflammation are major contributors to hypertension, which is a risk factor for cardiovascular disease. The results showed a significant difference (P value = ≤ 0.0001) in HSP-70 and HS CRP but there was no significant difference in TNF-alpha in patients of hypertension.

KEY WORDS: Hypertension; High sensitivity C reactive protein (HS CRP); heat shock protein 70(HSP-70); tumor necrosis factor alpha (TNF-α).

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INTRODUCTION

One of the main risk factors for cardiovascular disease, hypertension has grown to be a substantial worldwide health burden.[1] Hypertension is defined as having a blood pressure reading more than 140/90 mmHg, and it affects around 41.5% and 33.3% of men and women in England, respectively, with the percentage rising sharply in those over 60.[2] Despite the availability of many antihypertensive drug classes, hypertension management is frequently inadequate.[3] Furthermore, the prevalence of uncontrolled hypertension continues to increase internationally.[4] As a result, the major purpose of antihypertensive treatment is to reduce the risk of stroke. The risk factors for hypertension are only partially understood, which explains some of the gaps in existing primary preventive measures and the development of novel medications for the treatment of this widespread ailment. It has recently been determined that persistent low-grade inflammation plays a significant role in the development of vascular disease. For instance, results from studies using models of atherosclerosis have demonstrated the importance of chronic low-grade inflammation in the development and advancement of the condition.[5] Even after controlling for possible confounding variables.[6] Moreover, it has been shown that elevated HS CRP levels might predict the onset of hypertension in both normotensive and pre-hypertensive people.[7] In reaction to injury, systemic inflammation, and other inflammatory stimuli, the usual acute-phase blood protein known as C-reactive protein is raised, which suggests that it is an infection marker. Most of the time, the liver produces C-reactive protein in response to pro-inflammatory cytokines such

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TNF-α, IL-1, IL-6, and IL-17. Mature adipocytes and leukocytes generate C-reactive protein in response to lipopolysaccharides, whereas inflammation stimulates the generation of TNF-α. The synthesis of C-reactive protein can be increased. Endothelial cells generate many chemoattractant and adhesion molecules, including soluble intercellular adhesion molecule and monocyte chemokine protein. Elevations of C-reactive protein can be a sign of poor vascular outcomes and can also directly prevent the production of nitric oxide. This is because endothelial nitric oxide synthase mRNA stability is influenced by post-transcriptional factors, which lowers nitric oxide production and accelerates the onset of several cardiovascular diseases.[8] Indicators of inflammation that are reliable and sensitive include C-reactive protein levels. Vascular tone regulation by endothelial cells is hampered by elevated C-reactive protein levels.[9] Pro-inflammatory cytokine TNF-α is secreted by a variety of cell types, such as mast cells, endothelial cells, fibroblasts, neutrophils, eosinophils, activated macrophages, lymphocytes (T and NK cells), and neurons. TNF-α controls the growth, proliferation, differentiation, apoptosis, autoimmunity and inflammation of cells.[10] It influences the immune system, controls the acute phase and early inflammatory reactions, and supports the body's defense against viral infections by synthesizing more cytokines and adhesion molecules, such as endothelial adhesion molecules.[11] Heat, poisons, injuries, surgeries, and even behavioral or psychological stress can all activate the heat shock proteins (HSP-70) protein family.[12].It is evident from the widespread occurrence of the so-called heat shock response and its evolutionary conservation that HSP-70 is necessary for cell survival.[13].There is evidence that several HSPs interact with other cellular proteins to aid in their production, disassembly, stabilization, and transport, even if the specific roles of the numerous HSP members are yet unknown. The majority of our understanding of HSP-70 regulation and function is based on investigations of cultured cells .Little is known about their in vivo expression, although it is apparent that HSP-70 is activated in the healthy animal in response to a number of stressors.[14]

MATERIAL AND METHODS

2.1 Study design: Case control study

2.2 Sampling Technique: The sampling technique used in this study is purposive sampling. Purposive sampling is a non-probability sampling method where the researcher selects individuals based on specific characteristics or criteria relevant to the study. In this case, patients with high blood pressure and healthy controls were specifically chosen to form the case and control groups, respectively.

2.3 Inclusion & Exclusion Criteria: Inclusion criteria included Cases & controls

Cases: Individuals aged 40-70 years diagnosed with high blood pressure, attending the Internal Medicine Department at Imam Hussein Teaching Hospital in Karbala, during the study period (October 2023 to February 2024).

Controls: Healthy individuals aged 40-70 years, without a history of high blood pressure or related chronic illnesses.

Exclusion Criteria was individuals with coronary arterial or cerebrovascular disease, fever, malignancy, haematological disease. Patients with acute or chronic respiratory diseases including hypoventilation syndrome and sleep apnea syndrome.

2.4 Sample collections: This study was conducted in the consulting clinic of the Internal Medicine Department at Imam Hussein Teaching Hospital in Karbala Governorate. The study included 50 patients (28 males and 22 females) suffering from high blood pressure and aged between 40 and 70 years & 40 healthy people.The sample size was calculated through Rao soft calculator. The study spanned from October 2023 to February 2024 and included information (name, age, gender, height, weight, duration of illness and other illnesses as well as the treatment used). This study measured heat shock protein-70, tumor necrosis factor alpha, and high sensitivity C reactive protein. 5 ml of blood was drawn using a 5 ml medical syringe from all participants. Blood samples were placed in gelatin tubes (often referred to as gel tubes) that are free of anticoagulants, As these tubes contain a gelatinous component that helps in the process of separating serum after centrifugation. After 15 minutes of standing at room temperature, samples were centrifuged for 10 min at speed of 3000 rounds per minute to separate the serum which was stored in - 20°C until needed. Samples were collected after taking the patient's verbal consent, drawing 5 ml of venous blood, and analyzed.

2.5 Statistical Analysis: The data was analyzed using SAS software and the results were compared using the least significant difference (LSD) value at the probability level of 0.05 and 0.0001.[15]

RESULTS

The results showed that there was a significant difference in HSP-70 and HS CRP in hypertensive patients compared to the control group, but there was no significant difference in TNF-alpha, as shown in Table 1.

The results showed that there was a significant difference in HSP-70 but there was no significant difference in HS CRP, TNF-alpha in hypertensive patients across gender, as shown in Table 2.

Table 1: Comparison of the TNF- α, HSP-70 and HS CRP between patients and the control group.

Parameter	Subject	Means ±S.D	P value
TNF – α (pg/ml)	Patient	1.83±0.17	Not Significant
	Control	1.38 ±0.11	
HSP-70 (ng/ml)	Patient	3.21 ±1.72	0.0001
	Control	1.76 ±0.20	
HS CRP (mg/l)	Patient	1.79 ±0.24	0.0001
	Control	1.37 ±0.21	

Table 2: Comparison of the TNF- α, HSP-70and HS CRP between male patients and female patients.

Parameter	Subject	Means ± S.D	P value
TNF - α (pg/ml)	Man	1.87 ±0.33	Not Significant
	Woman	1.62 ±0.40	
HSP-70 (ng/ml)	Man	3.64 ±1.73	0.0001
	Woman	1.74 ±0.31	
HS CRP (mg/l)	Man	1.65 ±0.14	Not Significant
	Woman	1.40 ±0.21	

No.of man=28
No.of woman=22

The results showed that there was no significant difference in HSP-70, HS CRP, TNF-alpha in hypertensive patients across age groups, as shown in Table 3.

Table 3: Comparison of the TNF- α, HSP-70and HS CRP between patients aged 40-55 and patients aged 56-70.

Parameter	Subject	Means ±S.D	P value
TNF – α (pg/ml)	40 - 55	2.85 ±1.30	Not Significant
	56 - 70	1.91 ±0.22	
HSP-70 (ng/ml)	40 - 55	3.28 ±1.81	Not Significant
	56 - 70	3.13 ±1.63	
HS CRP (mg/l)	40 - 55	1.88 ±0.43	Not Significant
	56 - 70	1.41 ±0.36	

The result relationship between HSP-70, HS CRP, and TNF-alpha in hypertensive patients and the duration of their disease, which was classified as 1-3 years, 4-6 years, or more than 7 years. The evaluation revealed an increase in the rate over a period of 4-6 years in individuals with high blood pressure, there ration between duration of hypertension and the level of HSP-70, HS CRP and TNF-alpha as shown in Figure 1, 2 and 3.

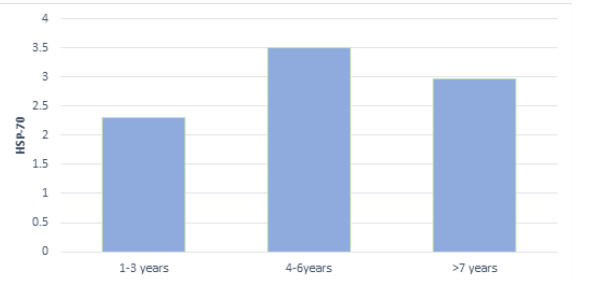

Figure 1: Ration between duration of hypertension and the level of HSP-70.

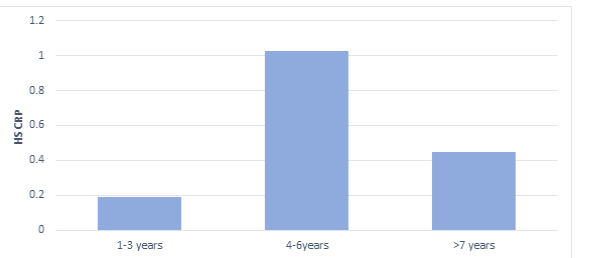

Figure 2: Ration between duration of hypertension and the level of HS CRP.

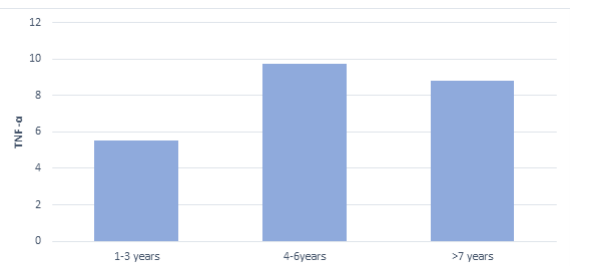

Figure 3: Ration between duration of hypertension and the level of TNF- α.

The results showed that there was sensitivity between TNF-alpha and hypertension when compared with the control group as shown in figure 4.

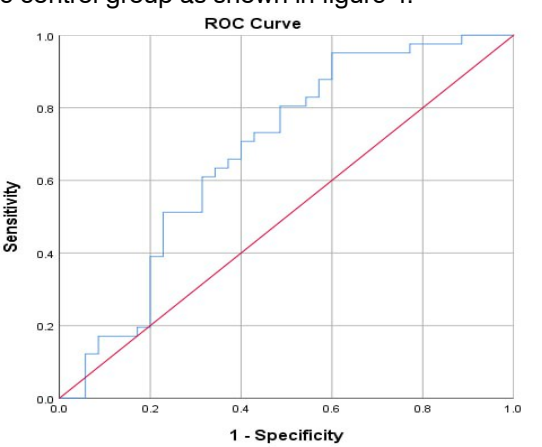

Figure 4: ROC curve of TNF- α in hypertensives compared to control group.

The results showed that there was sensitivity between HSP-70 and hypertension when compared with the control group as shown in figure 5.

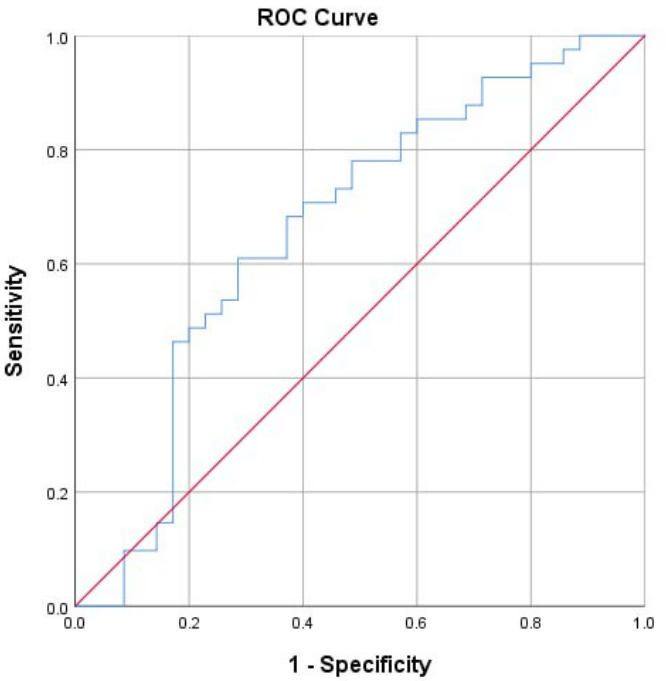

Figure 5: ROC curve of HSP-70 in patients hypertensive compared to control group.

DISCUSSION

Heat shock protein 70 has been linked to hypertension in a number of epidemiological and clinical studies.[16]. Essential hypertension is a common medical disease whose etiology is unclear. Research has revealed a connection between cardiovascular diseases, specifically essential hypertension, and the HSP-70 gene.[17] Some cross-sectional studies found that patients with essential hypertension have higher plasma levels of inflammatory markers such as (CRP), (TNF-alpha), and adhesion molecules than healthy people, indicating that inflammation plays a role in the pathogenesis of hypertension, as in table 1. The results can be explained HSP-70 levels were significantly inversely correlated with age, but not with sex. The function and potential involvement of HSP-70, notably in cytoprotection against various stressors, might account for these observations.[18] Our findings from Kunming participants suggest that HSP-70 levels in lymphocytes decline with aging. Other studies have found that HSP-70 levels in human lymphocytes fluctuate with aging.[19] Tanno-Sobetsu, a prospective cohort research done in Japan, revealed no connection between raised HS-CRP alone with increased risk of developing hypertension in both men and women.[17] According to our research, individuals with hypertension had elevated TNF-α levels in comparison to those with normal blood pressure at comparable ages. This implies that TNF-α may contribute to the development of hypertension via inflammatory responses and cellular immunity, among other pathways[20] as in table 2,3. The relationship between HSP-70, HS CRP, and TNF-alpha in hypertensive patients and the duration of their disease, which was classified as 1-3 years, 4-6 years, or more than 7 years as in Figure 1, 2 and 3. High blood HSP-70 levels have been linked to improved survival in individuals who have had severe trauma.[21] It has been shown that older people with acute heat illness have lower HSP-70 levels than younger people.[22] Human serum HSP-70 (inducible) levels rise after exercise, indicating a possible systemic function for HSP-70 from other tissues or organs.[17] The links between the several inflammatory markers in hypertension have been studied in some detail. For example, after controlling for other risk factors, Bautista et al.'s cross-sectional study of the connection between IL-6, TNF-alpha, and HS CRP and hypertension in a random sample of 196 apparently healthy people revealed no significant link between the three variables and hypertension. Even with its small sample size of 79 hypertensive people, this brief research is the first one to investigate the potentially misleading relationship between several inflammatory markers and hypertension.[23] Figure (4) showed a sensitivity between TNF-alpha and hypertension when compared with the control group. Real-time PCR was used to analyze TNFα and receptor expression in the renal medulla of rats. Which have lower blood pressure salt-sensitivity than rats, were employed as salt-insensitive controls.[24] Figure (5) showed a sensitivity between HSP-70 in hypertension when compared with the control group, Different kinds of

inflammation in human's lead phagocytes to produce more ROS, and alter the activities of anti-stress genes. Environmental influences can also alter the action of anti-stress genes.[25] Microenvironment can induce oxidative stress . Individual susceptibility to stress may represent the organism's immunological response. In humans, traumatic tissue injuries cause changes in HSP expression and cytokine production, and HSPs may reflect trauma-associated immunomodulation. Mathematical study supports the concept that short-term stress reveals individual neutrophils' susceptibility to stress during the first minute following exposure. Long heat shocks, such as those lasting more than three minutes, do not reveal individual neutrophil susceptibility to stress. Individual sensitivity can be realized at the mRNA level of anti-stress neutrophils.[26]

CONCLUSION

Inflammation and immune cells contribute significantly to hypertension, which is a risk factor for cardiovascular disease. Moreover, inflammation has a role in hypertension. Increased blood and inflammatory marker levels have an early prognostic influence on the occurrence of hypertension and a corresponding predictive value for the condition's consequences and prognosis. The results showed a significant difference (P value = ≤ 0.0001) in HSP-70 and HS CRP but there was no significant difference in TNF-alpha in cases & controls.

REFERENCES

1. He FJ, MacGregor GA. Cost of poor blood pressure control in the UK: 62,000 unnecessary deaths per year. J Hum Hypertens. 2003;17:455–7. https://doi.org/10.1038/sj.jhh.1001581
2. T.M. Misleading measurements: modeling the effects of blood pressure misclassification in a United States population. Med Decis Making. 2006;26:624–32. https://doi.org/10.1177/0272989X06295356
3. Hasan AH, Abdulzahra MA, Hashim AM, Al-Mawlah YH. Biochemical markers of liver function test (ALT, AST, ALP) in thyroid dysfunction (hyperthyroidism and hypothyroidism). J Biotech Res. 2024;16:167–74.
4. Chobanian AV. The hypertension paradox - More uncontrolled disease despite improved therapy. New Armen Med J. 2009;3(4):60–70. https://doi.org/10.1056/NEJMsa0903829
5. Sanz J, Moreno PR, Fuster V. The year in atherothrombosis. J Am Coll Cardiol. 2010;55:1487–98. https://doi.org/10.1016/j.jacc.2009.12.027
6. Al-Hawwas M, Tanguay JF. The role of inflammation in atherosclerosis: what we have learned from clinical trials. Hear Metab. 2013;(60):9–13.
7. Chrysohoou C, Pitsavos C, Panagiotakos DB, Skoumas J, Stefanadis C. Association between prehypertension status and inflammatory markers related to atherosclerotic disease: the ATTICA study. Am J Hypertens. 2004;17(7):568–73. https://doi.org/10.1016/j.amjhyper.2004.03.675
8. Iaccarino G, Ciccarelli M, Sorriento D, Galasso G, Campanile A, Santulli G, et al. Ischemic neoangiogenesis enhanced by β2-adrenergic receptor overexpression: a novel role for the endothelial adrenergic system. Circ Res. 2005;97(11):1182–9. https://doi.org/10.1161/01.RES.0000191541.06788.bb
9. FichtIscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. Circulation. 2000;102(9):1000–6. https://doi.org/10.1161/01.CIR.102.9.1000
10. Aggarwal BB, Gupta SC, Kim JH. Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. Blood. 2012;119:651–65. https://doi.org/10.1182/blood-2011-04-325225
11. Seo SH, Webster RG. Tumor necrosis factor alpha exerts powerful anti-influenza virus effects in lung epithelial cells. J Virol. 2002;76(3):1071–6. https://doi.org/10.1128/JVI.76.3.1071-1076.2002
12. Lindquist S, Craig EA. The heat-shock proteins. Annu Rev Genet. 1988;22:631–77. https://doi.org/10.1146/annurev.ge.22.120188.003215
13. I.J. B, D.R. M. Stress (heat shock) proteins molecular chaperones in cardiovascular biology and disease. Circ Res. 1998;83(2):117–32. https://doi.org/10.1161/01.RES.83.2.117
14. Khademi A. Complex survey data analysis with SAS. J Stat Softw. 2018;84. https://doi.org/10.18637/jss.v084.b02
15. Pockley AG, Georgiades A, Thulin T, De Faire U, Frostegård J. Serum heat shock protein 70 levels predict the development of atherosclerosis in subjects with established hypertension. Hypertension. 2003;42(3):235–8. https://doi.org/10.1161/01.HYP.0000086522.13672.23
16. Evans A, Arveiler D, Yellon DM, Latchman DS, Cambien F, Luc G, et al. Analysis of the association of a heat shock protein70-1 gene promoter polymorphism with myocardial infarction and coronary risk traits. Dis Markers. 1998;13(4):227–35. https://doi.org/10.1155/1998/235151
17. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-α) and essential hypertension. J Hum Hypertens. 2005;19(2):149–54. https://doi.org/10.1038/sj.jhh.1001785
18. Rao DV, Watson K, Jones GL. Age-related attenuation in the expression of the major heat shock proteins in human peripheral lymphocytes. Mech Ageing Dev. 1999;107(1):105–18. https://doi.org/10.1016/S0047-6374(98)00143-2
19. M.F., H.O., S.S., H.A., T.M., M.M. The combination of abdominal obesity and high-sensitivity C-reactive protein predicts new-onset hypertension in the general Japanese population: the Tanno-So-

betsu study. Hypertens Res. 2015;38(6):426–32. https://doi.org/10.1038/hr.2015.27

20. Woodward M, Rumley A, Tunstall-Pedoe H, Lowe GDO. Associations of blood rheology and interleukin-6 with cardiovascular risk factors and prevalent cardiovascular disease. Br J Haematol. 1999;104:246–57. https://doi.org/10.1046/j.1365-2141.1999.01158.x
21. Wang ZZ, Wang CL, Wu TC, Pan HN, Wang SK, Jiang JD. Autoantibody response to heat shock protein 70 in patients with heatstroke. Am J Med. 2001;111:654–7. https://doi.org/10.1016/S0002-9343(01)00974-3
22. Welch WJ. Mammalian stress response: cell physiology, structure/function of stress proteins, and implications for medicine and disease. Physiol Rev. 1992;72(4):1063–81. https://doi.org/10.1152/physrev.1992.72.4.1063
23. Ogawa K, Suzuki K, Mitsuharu O, Yamazaki K, Shinkai S. The association of elevated reactive oxygen species levels from neutrophils with low-grade inflammation in the elderly. Immun Ageing. 2008;5. https://doi.org/10.1186/1742-4933-5-13
24. Singh R, Kolvraa S. Genetics of human longevity with emphasis on the relevance of HSP-70 as candidate genes. Front Biosci. 2007;12:4504–13. https://doi.org/10.2741/2405
25. Semenkov VF, Michalski AI, Sapozhnikov AM. Heating and ultraviolet light activate anti-stress gene functions in humans. Front Genet. 2015;6. https://doi.org/10.3389/fgene.2015.00245
26. Guisasola MC, Alonso B, Bravo B, Vaquero J, Chana F. An overview of cytokines and heat shock response in polytraumatized patients. Cell Stress Chaperones. 2018;23:483–9. https://doi.org/10.1007/s12192-017-0859-9

CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	RAAH, RJM
Acquisition, Analysis or Interpretation of Data:	RAAH, RJM, LAAD
Manuscript Writing & Approval:	RAAH, RJM, LAAD

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.