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The role of some oxidative stress and inflammatory factors in essential hypertension

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Abstract

Background and Objective: Oxidative stress and inflammation are cooperative events involved in essential hypertension development. This study aimed to evaluate the association of N-terminal pro-Brain natriuretic peptide, matrix-metalloprotinase-9 and 8-oxo2-deoxyguanosine with the essential hypertension, detect the effect of other confounding factors like the stage of the disease and gender, and estimate the correlation between the selected parameters.

Methods: This case-control study was performed at College of Pharmacy, Hawler Medical University on 50 hypertensive patients of both genders with essential hypertension as well as 45 matched age–gender adults were also enrolled in this study as a control group. The selected parameters were analyzed using ELISA technique.

Results: There was a significant elevation in the serum levels of N-terminal pro-Brain natriuretic peptide, matrix-metalloprotinase-9 and 8-oxo2-deoxyguanosine in patients with essential hypertension as compared with the controls. The mean serum levels N-terminal pro-Brain natriuretic peptide, matrix-metalloprotinase-9 and 8-oxo2-deoxyguanosine were increased significantly according to the stage progression of the disease P <0.001. No gender effects could be found.

Conclusion: Data suggested an association between circulating biomarkers (NT-proBNP, MMP -9, 8-oxo-2-dG) with the development of essential hypertension, there was a significant elevations in the serum selected parameters level in patients as compared with the control group.

Keywords: EHT; NT-proBNP; MMP -9; 8-oxo-2-dG.

Introduction

Essential hypertension (EHT) is considered as one of the most important risk factors for chronic cardiovascular remodeling and dysfunction.[1] It has become a major cause of morbidity and mortality worldwide.[2] Oxidative stress (OS) and inflammatory process are cooperative events involve in the pathogenesis of EHT. Mounting evidence indicates that OS plays an important role in the development of EHT. In hypertension, increased reactive oxygen species (ROS) production leads to endothelial dysfunction, enhanced contractility, inflammation, and increased deposition of extracellular matrix proteins (ECM). Matrix metalloproteinases (MMPs) are a group of zinc-dependent proteolytic enzymes able to degrade various extracellular matrix components under both physiological and pathological conditions.[3] Enhanced MMP activity is often found in clinical hypertension.[4] As an important member of this family MMP-9, increased MMP-9 levels have been reported in hypertensive patients. Matrix metalloproteinases (MMPs) are believed to be responsible for the destruction of connective tissue at sites of chronic inflammation. N-terminal pro B-type natriuretic peptide (NT-proBNP) is a 76-amino acid polypeptide that is released by cardiac myocytes, in response to increased ventricular wall stress, as

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typically occurs with volume overload and ventricular contractile dysfunction.[5] The production of NT-proBNP is stimulated by heart volume overload secondary to systolic dysfunction. N-terminal-Pro-BNP is used in the diagnosis, prognosis of congestive cardiac failure,[6] diagnose and manage heart failure. NT-proBNP is used as a candidate biomarker that may enable the early detection of hypertension, hypervolemia, where increased levels of NT-proBNP indicate cardiac dysfunction, as an indicator for follow-up, therapy and prognosis.[7] Evidence that OS byproduct 8-oxo-2deoxy guanosine (8-oxo-2dG) increased in patients with EHT. 8-oxo-2dG is generated by the oxidation of DNA under physiopathological conditions or environmental stress; it has been linked to several biological processes and diseases among them is hypertension.[8] This study aimed to assess the association between NT-proBNP, MMP-9, 8-oxo-2dG with the EHT. In addition, to find out the effect of other confounding factors like the stage of the disease and gender on serum levels of these biomarkers and finally detect the correlation between all studied parameters.

Methods

This case-control study was performed at Hawler Medical University, College of Pharmacy on 50 patients with EHT of both genders who were selected and diagnosed by a specialist physician using clinical examination at Erbil Teaching Hospital and after exclusion of other diseases by clinical history, laboratory investigations and clinical examination. Patients group classified into stage I ,stage II and stage III of EHT according to the Eighth Joint National Committee (JNC 8) report[9] in order to study the effect of staging on the serum levels of studied parameters, and for the comparing purpose 46 apparently healthy adults matched age –gender were also enrolled in this study as a control group and completed the baseline questionnaire concerning several risk factors. This study was done in the period between November 2013 to December 2014. The control group was confirmed to be normal by clinical, biochemical and hematological examinations. Biochemical, hematological, all clinico-pathological data of the patients were collected from the clinical files of the patients. A case sheet had been prepared for each patient including the following information: age, gender, occupation, social history, chief complains, other diseases, and medications. All procedures were in accordance with the established ethical standards. The protocol for the research has been approved by Ethics Committee of Medical Research at the College of Pharmacy, Hawler Medical University. Verbal informed consents were taken from all the participants before participation.

Sample Collection: Ten ml of the fasting blood samples were collected and left for 30 minutes for coagulation, centrifuged for 15 minutes at 2500-3500 rpm. The sera were separated and divided into several parts and put them into several plastic plain tubes to do the biochemical tests. The sera were stored at (-80 C º) until the day of the analysis. The sera were prepared for measurement by warming the frozen sera at room temperature. The focused parameters were measured using ELISA technique at Medical Research Center, Hawler Medical University. The hypothesis suggests that oxidation and inflammatory processes influence the risk of adverse clinical outcomes are worth for investigating.

Statistical Study: The data were analyzed using the statistical package for the social sciences (version 18). The results of biochemical tests were expressed as the mean ± standard deviation (SD). Furthermore, student's t-test was used to compare means of two groups; it can be used to determine if two sets of data are significantly different from each other. A *P* value of ≤0.05 was considered statistically significant. The Analysis of Variance (ANOVA) was used to compare three or more means. Estimate the (LSD)

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or the minimum difference between a pair of means which is necessary for statistical significance. Correlations between laboratory findings and continuous variables were evaluated using linear regression analysis.

Results

Subjects Characteristics: This study included 96 participants of both genders, 50 of them were newly diagnosed with EHT with the mean age of 50.9± 9.2 years. The reminders 46 were apparently healthy adults with the mean age of 49.1± 9.4 years.

Essential Hypertension Effect: There was a significant elevation in the serum levels of the NT-proBNP, MMP -9, 8-oxo-2-dG as compared with the control group (*P* <0.001) as shown in Table 1.

Table 1: Comparison between patients and control groups regarding the mean levels of NT-proBNP, MMP -9 and 8-oxo-2-dG.

Variables	Group	N	Mean	±SD	SE	*P* value
Age	Patients	50	50.9000	9.27857	1.31219	0.376
	Control	46	49.1957	9.49999	1.40070	
Systolic	Patients	50	16.7000	1.61940	0.22902	< 0.001
	Control	46	11.7609	0.84155	0.12408	
Diastolic	Patients	50	9.6300	0.77466	0.10955	< 0.001
	Control	46	7.5543	0.67682	0.09979	
MMP-9 (ng/ml)	Patients	50	2.3638	1.18680	0.16784	< 0.001
	Control	46	1.4226	0.87738	0.12936	
NT-proBNP(pg/ml)	Patients	50	304.3340	204.19890	28.87809	< 0.001
	Control	46	76.5261	20.98343	3.09384	
8 oxo2dG(mg/ml)	Patients	50	170.4020	41.95269	5.93301	< 0.001
	Control	46	84.1196	34.07789	5.02451	

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Stage Effect: Table 2 shows the effect of stages of hypertension on ages, systolic blood pressure, diastolic blood pressure and mean blood pressure while Table 3 shows that the mean serum levels of NT-proBNP, MMP -9, 8-oxo-2-dG were increased significantly according to the stage progression of the disease (*P* <0.001).

Table 2: The effect of stages of hypertension on ages, systolic blood pressure, diastolic blood pressure and mean blood pressure.

Dependent Variable	Group	N	Mean	±SD	LSD	*P* value
Age	Control	46	49.19	9.50	0.87	
	Stage I	14	49.64	9.15	0.49	
	Stage II	21	51.85	8.26	0.72	0.743
	Stage III	15	50.73	11.09		
	Total	96	50.08	9.37		
Systolic	Control	46	11.76	.84	.000	
	Stage 1	14	14.78	.42	.000	
	Stage II	21	16.52	.51	.000	<0.001
	Stage III	15	18.73	.70		
	Total	96	14.33	2.80		
Diastolic	Control	46	7.55	.67	.000	
	Stage 1	14	9.35	.41	.000	
	Stage II	21	9.57	.42	.000	<0.001
	Stage III	15	9.96	1.21		
	Total	96	8.63	1.27		
Mean -BP	Control	46	8.95	.61	.000	
	Stage 1	14	11.16	.34	.000	
	Stage II	21	11.88	.37	.000	<0.001
	Stage III	15	12.88	.92		
	Total	96	10.53	1.70		

The mean difference is significant at the 0.05 level.

Table 3: The effect of stages of hypertension on serum levels of NT-proBNP, MMP -9 and 8-oxo-2-dG.

Dependent Variable	Group	N	Mean	±SD	LSD	*P* value
MMP-9 (ng/ml)	Control	46	1.42	.87	0.28	
	Stage I	14	1.16	.22	0.000	
	Stage II	21	2.20	.39	0.000	< 0.001
	Stage III	15	3.70	1.12		
	Total	96	1.91	1.14		
NT-proBNP	Control	46	76.52	20.98	0.009	
	Stage 1	14	137.67	16.18	0.001	
	Stage II	21	228.26	61.39	0.000	< 0.001
	Stage III	15	566.38	174.02		
	Total	96	195.17	186.55		
8oxo-2dG	Control	46	84.12	34.07	0.000	
	Stage 1	14	124.88	38.24	0.000	
	Stage II	21	170.77	14.08	0.000	< 0.001
	Stage III	15	212.36	23.67		
	Total	96	129.05	57.75		

The mean difference is significant at the 0.05 level.

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Gender –Effect: Statistical study revealed that there were no significant differences between men and women regarding mean serum levels of NT-proBNP, MMP -9, 8-oxo-2-dG in patient and control groups (Table 4 and Table 5) respectively, so there was no gender effect.

Table 4: Comparison between men and women regarding the mean serum levels of NT-proBNP, MMP -9 and 8-oxo-2-dG in patients group.

	Gender	N	Mean	±SD	SE	*P* value
Age	Men	26	51.654	10.024	1.966	0.555
	Women	24	50.083	8.536	1.742	
Systolic	Men	26	16.885	1.657	0.325	0.407
	Women	24	16.500	1.588	0.324	
Diastolic	Men	26	9.654	0.704	0.138	0.823
	Women	24	9.604	0.859	0.175	
MMP-9 (ng/ml)	Men	26	2.539	1.393	0.273	0.282
	Women	24	2.174	0.906	0.185	
NT-proBNP (pg/ml)	Men	26	317.235	209.041	40.996	0.647
	Women	24	290.358	202.345	41.303	
8-oxo-2dG (mg/ml)	Men	26	173.485	43.557	8.542	0.594
	Women	24	167.063	40.805	8.329	

Table 5: Comparison between men and women regarding the mean serum levels of NT-proBNP, MMP -9 and 8-oxo-2-dG in control group.

	Gender	N	Mean	±SD	SE	*P* value
Age	Men	23	47.08	9.59	2.00	0.13
	Women	23	51.30	9.12	1.90	
Systolic	Men	23	11.97	0.57	0.12	0.08
	Women	23	11.54	1.01	0.21	
Diastolic	Men	23	7.56	0.62	0.13	0.91
	Female	23	7.54	0.73	0.15	
MMP-9 (ng/ml)	Men	23	1.34	0.82	0.17	0.536
	Women	23	1.50	0.93	0.19	
NT-proBNP (pg/ml)	Men	23	80.74	20.51	4.27	0.175
	Women	23	72.30	21.03	4.38	
8-oxo-2dG (mg/ml)	Men	23	77.65	23.98	5.00	0.201
	Women	23	90.58	41.38	8.62	

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The Correlation Coefficient: There was a non significant weak correlation between age and MMP-9, non significant weak correlation between age and NT-pro BNP, non significant weak correlation between age and 8-oxo-2dG, significant strong correlation between SBP and MMP-9, significant strong correlation between SBP and NT-pro BNP, significant strong correlation between SBP and 8-oxo-2dG, significant moderate correlation between DBP and MMP-9, significant weak correlation between DBP and NT-pro BNP, significant moderate correlation between DBP and 8-oxodG, significant strong correlation between MMP-9 and NT-pro BNP, significant strong correlation between MMP-9 and 8-oxodG, significant strong correlation between NT-pro BNP and 8-oxodG (Table 6).

Table 6: The correlation coefficient between the NT-proBNP, MMP -9 and 8-oxo-2-dG in patients group.

X Variable	Y Variable	R	P	N
Age	MMP-9	0.1	0.2	50
Age	NT-pro BNP	0.05	0.6	50
Age	8-oxodG	0.05	0.7	50
SBP	MMP-9	0.9	<0.001	50
SBP	NT-proBNP	0.9	<0.001	50
SBP	8-oxodG	0.8	<0.001	50
DBP	MMP-9	0.4	0.001	50
DBP	NT-pro BNP	0.3	0.005	50
DBP	8-oxodG	0.4	0.003	50
MMP-9	NT-pro BNP	0.9	<0.001	50
MMP-9	8-oxodG	0.8	<0.001	50
NT-proBNP	8-oxodG	0.7	<0.001	50

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Discussion

Effect of Essential Hypertension on the Serum Levels of Studied Biomarkers (NT-proBNP): This study revealed a significant elevation in the serum levels of NT-proBNP as compared with the control group and this finding was consistent with the previous findings.[10-13] So this finding could indicate that there was a significant relationship between serum NT-proBNP level as an inflammatory marker with the development of EHT. Accordingly, inflammatory marker NT-proBNP is considered as contributor marker in EHT development. The present data supported the hypothesis of the current study and others[13] who published that NT-proBNP levels could be associated with inflammatory status and there was a link between NT-Pro-BNP and inflammatory process. This finding could be intended to address the prognostic value of NT-proBNP in EHT, which was confirmed by the previous findings[11] who reported that plasma NT-proBNP had a significant prognostic value in hypertensive patients. The explanation for the significant elevation of NT-proBNP in EHT was that the secretion of NT-proBNP by ventricular myocytes is a landmark of cardiac remodeling and is of particular interest in hypertension.[12] It's secretion as a consequence of pressure overload and wall stretch.[14] Natriuretic peptides also depend strongly on ventricular afterload, particularly BP.[15] This study showed that serum NT-proBNP was a powerful circulating diagnostic marker, a non invasive indicator associated with the development of EHT and might act as early predictors of EHT and it was considered as a potential candidate marker for diagnosis and follow up.

Matrix Metalloproteinase-9: Since EHT may be a part of an inflammatory disease, circulatory factors related to inflammation could be a predictor of EHT development. It was hypothesized that the MMP-9 might play an independent role in modulating BP in patients with EHT. This study aimed to elucidate whether the serum level of MMP-9 was associated with EHT. The study has demonstrated that there was a significant elevation in the serum level of MMP-9 in patients as compared with the control group. Accordingly, Inflammatory marker MMP-9 is considered as a contributor marker to BP in EHT. This finding provided an important link between risk factor inflammation and the development of EHT. In addition, another study supported the current finding and published that, elevation of plasma MMP-9 has been associated with increased arterial stiffness and elevated BP in EHT.[16] Elevation of MMP-9 is important because abnormal MMP levels can stimulate vascular inflammation, a potential contributor in the pathogenesis and progression of EHT.[17] This result was consistent with the many previous findings.[17-20] The explanation of this significant elevation was that it is well known that there was a contribution of inflammation with the development of hypertension and target organ damage. MMP-9 is an inflammatory mediator that may contribute to hypertension and its target organ consequences. MMPs are implicated in the development of chronic vascular diseases, but the key effectors and mechanism of action remain unknown.[21] This study was shown available evidence supporting the link between inflammation and EHT development and discuss the implications for the therapy of EHT in future.

8-Oxo-2 Deoxy Guanosine: The present study was designed to simultaneously assess the OS levels by measuring 8-oxo-2dG in the patients and control groups. It was aimed to test the OS as a potential early risk factor for EHT initiation in Erbil population by examining 8-oxo-2dG as a byproduct of ROS-induced DNA damage. 8-oxo-2dG was significantly increased in patients as compared to the control group. The result of the current study was concordant with previous findings.[22,23] The present study was designed to assess

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the serum 8-oxo-2dG level to express the degree of OS in patients with EHT. Therefore, it is of interest to test the idea that OS serves as a risk factor for EHT development. Therefore, this study has offered the opportunity to test whether OS could be a potential early risk factor for developing EHT.

Staging Effects: In the patients' group, the level of NT-proBNP, MMP -9, 8-oxo-2-dG were increased significantly according to the stage progression. Accordingly, elevated serum NT-proBNP, MMP -9, 8-oxo-2-dG levels serve as a simple, non-invasive tool and an independent parameter for assessing disease severity. The analysis of NT-proBNP, MMP -9, 8-oxo-2-dG was based upon an evaluation of the utility of serum NT-proBNP, MMP -9, 8-oxo-2-dG levels in the development of the disease and detecting the severity of EHT. Similarly, a study has reported that MMPs have been implicated in the development and progression of EHT.[17] The present study was designed to assess the serum levels of 8-oxo-2dG to express the degree of OS in hypertensive patients and to clarify the severity of disease by investigating the staging of EHT.

Gender Factor: Statistical study revealed that there was no gender effect. The explanation for this finding might be that women who enrolled in this study were elderly, so there was no hormonal effect. In contrast, another study reported that plasma NT-pro-BNP levels increase with age and are higher in women than men after adjustment for age.[24] In addition, another study reported that NT-proBNP was significantly higher in women than in men.[25] The factors that contribute to OS are also involved with inflammation; this information was supported by the current study that, there was significant strong correlation between SBP and MMP-9, a significant strong correlation between SBP and NT-pro BNP significant strong correlation between SBP and 8-oxo-2dG, a significant moderate correlation between DBP and MMP-9. To the best of our knowledge, this is the first report in Iraq /Kurdistan Governorate population, to evaluate the association between the selected parameters with the development of EHT which have not been fully investigated before. This study offers the opportunity to test whether the inflammatory status and OS could be a potential early risk factor for the development of EHT. NT-proBNP, MMP -9, 8-oxo-2-dG may be helpful as part of the evaluation of treatment in patients with EHT or as a guide to the selection and timing of alternative therapies. Selected parameters have also been proposed as an indicator for follow-up, therapy and prognosis as well as may serve as a surrogate marker in the clinical evaluation and management of EHT.

Conclusion

Available data suggested a strong association between the serum levels of NT-proBNP, MMP -9, 8-oxo-2-dG with the risk of EHT. These parameters could provide a relatively simple, noninvasive method for investigating EHT. OS and the inflammatory process may serve as a risk factor for the development of EHT in Hawler population. Future studies should focus on whether anti-inflammatory, antioxidant drugs are beneficial in reversing.

Competing interests

The authors declare that they have no competing interests.

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