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The potential role of malondialdehyde, glutathione peroxidase, and interleukin-18 in the development of essential hypertension

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Abstract

Background and objectives: The oxidative stress and inflammatory process are cooperative events involved in the development of essential hypertension. This study was as a step for elucidating the contribution of the malondialdehyde, glutathione peroxidase, interleukin -18 and lipid profile with the development of essential hypertension. This study aimed to assess whether the variation in serum malondialdehyde, glutathione peroxidase, interleukin-18 and lipid profile levels were associated with the development of essential hypertension, moreover, find out the effect of age, gender and stage on the serum focused parameters levels and finally detect the correlation coefficient.

Methods: This case-control study was performed at the College of Pharmacy, Hawler Medical University in newly diagnosed and untreated patients with essential hypertension of both genders, and 50 of the matched age–gender healthy adults as a control group in the period between 2013-2014.

Results: Patients exhibited a significant elevation in the serum malondialdehyde, glutathione peroxidase, interleukin-18 and lipid profile levels.

Conclusion: This investigation provided for the first evidence the ability of selected parameters in combination patterns as factors involved in essential hypertension pathophysiology and are regarded as markers of diagnostic significance. The demonstration of these parameters provided new insights into understanding the independence of antioxidant status and inflammatory pathways in essential hypertension development.

Keywords: Essential Hypertension; Malondialdehyde; Glutathione Peroxidase; Interleukine -18.

Introduction

Oxidative Stress (OS) is caused by an imbalance between the production of reactive oxygen species (ROS) and a biological system's ability to readily detoxify the reactive intermediates, reduction of the blood pressure (BP) to the normotensive state in hypertensive subjects led to a definite reduction in the free radicals (FRs) generation and that this could help in preventing the long term complications of hypertension which was mediated by the FRs.[1] The evidence suggests that inflammation can lead to the development of hypertension and that OS and endothelial dysfunction are involved in the inflammatory cascade.[2] There was a strong association of OS with high BP, and there was a positive correlation between a marker of OS and systolic and diastolic BP.[3]Therefore it is well known that OS is increased during hypertension Evidence has indicated that the OS byproduct malondialdehyde (MDA) increased in patients with EHT. Several studies have involved hypertensive patients and demonstrated that MDA could be a biomarker of OS.[1] MDA is released from the lipoperoxidation of polyunsaturated fatty acids in the cell membrane. The exposure to ROS increases the production of antioxidant enzymes.[4] Glutathione

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peroxidase (GPX) can be rapidly expressed when cells or organisms are exposed to OS, and increased activity of glutathione peroxidase has been reported in patients with newly diagnosed essential hypertension.[5] Clinical and population studies have consistently found increased circulating levels of interleukin 18 (IL-18) in patients with hypertension.[6] Experimental evidence indicates that the expression of IL -18 and/or its receptor can be induced by catecholamines or angiotensin, two factors that are involved in the pathophysiology of hypertension.[6] The measurement of serum MDA, GPX, L-18 and lipid profile levels may be considered medically necessary for hypertensive patients concomitant with other risk factors. Limited information is available on the utility of the serum levels of these markers in the assessment of BP in patients with essential hypertension (EHT). The study aimed to determine the levels of oxidant byproduct MDA, antioxidant enzyme GPX, and inflammatory marker IL-18 in patients with EHT. The specific objectives were to assess the lipid profile in EHT patients as compared with the control group, as well as to assess the association between these parameters and other risk factors in hypertensive patients.

Methods

Study Design

This case-control study was conducted at the College of Pharmacy, Hawler Medical University, Kurdistan Region, Iraq, in the period between June 2013- May 2014 in 50 patients with EHT and 50 of matched age –gender apparently healthy adults as a control group with no history of hypertension or antihypertensive drugs. The patients were randomly selected from the adult patients routinely attending the Internal Medicine Out-Patient Clinic at Erbil Teaching Hospital for follow-up and management. Healthy individuals were also randomly selected from the staff and sub-staff of the same hospital. The participants were interviewed and informed about the nature of the study, and all participants provided their verbal consent. All procedures were in accordance with the established ethical standards. The protocol for the research has been approved by the Ethics Committee of Medical Research at the College of Pharmacy /Hawler Medical University. Patients with the chronic liver disease, renal disease, endocrine dysfunction, and coronary heart disease were excluded from the study. Both groups completed the baseline questionnaire, including the self-reported questions concerning several risk factors for EHT, such as a history of diabetes, smoking, physical activity, alcohol consumption, and hormone replacement therapy, as well as anthropometric and hypertension record.

Grouping of patients

The patient group was classified into stage I and stage II. EHT according to the guidelines of Joint National Committee 7 [7]to study the effect of staging on the levels of the focused parameters.

Collection of Sample

Ten ml of the fasting blood samples were collected and left for 30 minutes, 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. Oxidative stress/antioxidant status imbalance were analyzed through the quantification of MDA via a spectrophotometric method using thiobarbituric and trichloroacetic acids as reagents, MDA reacts with thiobarbituric acid under acidic conditions at 95°C, forming a pink complex with the maximum absorbance of 532 nm.[8] The GPX and IL-18 levels were measured using enzyme linked immunosorbent assay (ELISA). The total serum cholesterol (TC) and high-density lipoprotein cholesterol (HDLc) triglyceride (TG)levels were determined using commercial enzymatic kits. The low-density lipoprotein-cholesterol (LDLc) level

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was calculated through Friedewald's formula: LDLc (mg/dL) =TC (mg/dL) − HDLc (mg/dL) − triglycerides / 5 (mg/dL). The hypothesis suggesting that oxidation/ antioxidant status and inflammatory processes influence the risk of adverse clinical outcomes are worth for investigating.

Statistical analysis

The data were analyzed using the statistical package for the social sciences (version 18). Student's t-test was used to compare the means of two groups. It can be used to determine if two sets of data are significantly different from each other. The one-way analysis of variance (ANOVA) was used to determine whether there were any statistically significant differences between the means of two or more independent (unrelated) groups (although you tend only to see it used when there are a minimum of three, rather than two groups). Post hoc tests are designed for situations in which the researcher has already obtained a significant omnibus F-test with a factor that consists of three or more means, and additional exploration of the differences among means is needed to provide specific information on which means are significantly different from each other. A *P* value of <0.05 was considered statistically significant.

Results

This study included 100 individuals (42 men and 58 women) aged between 40 and 65 years. Among the participants, 50 were essential hypertensive patients with a mean age of 50.0 ± 9.4years. The remaining 50 participants were apparently healthy adults with a mean age of 48.3 ± 9.6years.

Effect of Essential Hypertension on the Serum Levels of Focused Parameters

Patients with EHT had significantly higher serum MDA,GPX, and IL-18 levels than the control group p<0.001. In addition, the TG, TC, LDLc, and HDLc levels were significantly higher in patients than in the control group *P* <0.001. The mean BMI values were not significantly different (Table 1).

Table 1: The characteristics of the studied participants.

Parameters	Patients N= 50	Healthy N= 50	*P* value
Age (years)	50.0 ± 9.4	48.3 ± 9.6	0.375
SBP (mmHg)	160 ± 14	116 ± 4.6	<0.001
DBP (mmHg)	93 ± 5.4	74 ± 4.8	<0.001
MABP (mmHg)	115 ± 7.6	88.5 ± 3.6	<0.001
BMI (KG/m2)	23.8 ± 1.2	24.0 ± 1.0	0.328
MDA (nmol/L)	0.09 ± 0.027	0.04 ± 0.02	<0.001
GPX (ng/ml)	1.58 ± 0.39	1.22 ± 0.16	<0.001
IL18 (pg/ml)	31.18 ± 1.27	30.24 ± 1.09	<0.001
TG (mg/dl)	96.76 ± 35.1	80.97 ± 13.2	0.004
TC (mg/dl)	175 ± 32.6	151 ± 24.4	<0.001
LDLc (mg/dl)	93.8 ± 30.0	75 ± 12.29	<0.001
HDLc (mg/dl)	38.5 ± 4.1	41.5 ± 5.3	0.002

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Age Effect

The effect of age on the levels of the selected parameters in the patient group was shown in Table 2.

Table 2: The effects of ages on the serum levels of the studied parameters in patient group.

Parameters		N	Mean	±SD	*P value*	Significant by LSD test
MDA nmol/L	A- < 40	10	.08300	.022201		A X D
	B- 40-49	10	.08720	.013637		B X D
	C- 50-59	19	.09042	.027943	< 0.001	C X D
	D- 60+	11	.12464	.020839		
	Total	50	.09582	.027323		
GPX ng/ml	A- < 40	10	1.440	.0966		A X D
	B- 40-49	10	1.470	.0949		B X D
	C- 50-59	19	1.511	.0994	0.005	C X D
	D- 60+	11	1.936	.7284		
	Total	50	1.582	.3900		
IL18 pg /ml	A- < 40	10	30.40	1.075		
	B- 40-49	10	31.00	1.633	0.011	
	C- 50-59	19	31.32	1.157		A X D
	D- 60+	11	31.82	.982		
	Total	50	31.18	1.273		
TG mg/ dl	< 40	10	96.380	43.2412		
	40-49	10	81.500	10.7212		
	50-59	19	91.658	24.4996	0.036	B X D
	60+	11	119.818	48.0433		C X D
	Total	50	96.766	35.1154		
TC mg/dl	< 40	10	164.170	27.4153		
	40-49	10	153.770	26.6074		B X C
	50-59	19	185.116	29.3301	0.019	B X D
	60+	11	189.845	36.8475		
	Total	50	175.698	32.6459		
LDLc mg/dl	< 40	10	73.900	18.7169		A X D
	40-49	10	88.500	24.0335		B X D
	50-59	19	88.847	19.8743	< 0.001	C X D
	60+	11	125.418	36.3517		
	Total	50	93.834	30.0949		
HDLc mg/dl	< 40	10	40.90	3.725		A X D
	40-49	10	40.70	4.084		B X D
	50-59	19	38.05	3.358	0.02	C X D
	60+	11	35.09	3.754		
	Total	50	38.50	4.181		

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In this study, age was classified into four groups (A< 40, B 40–49, C 50–59, and D 60+). The results of the statistical analysis showed significant differences among age groups (< 40 and 60+, 40–49 and 60+, and 50–59 and 60+) in terms of MDA and GPX levels. However, in terms of IL-18 level, significant differences were found between the age groups < 40 and 60+, whereas in terms of the TG level, significant differences were found between the age groups 40–49 and 60+and 50–59 and 60+. In terms of the TC level, significant differences were observed between the age groups 40–49 and 50–59 and 40–49 and 60, whereas in terms of LDLc and HDLc levels, significant differences were observed between the age groups 40–49 and 60+, 40–49 and 60+, and 50–59 and 60+.

Gender effect

The effect of gender on the levels of the selected parameters in the patient group was presented in (Table 3). Men and women exhibited a significant difference in serum MDA levels *P* value <0.05, GPX *P* = 0.048, LDLc *P* <0.001, HDLc *P* = 0.059 (near the significant level), while, in case of IL-18 there was a difference, but this difference reach near the significant level *P* = 0.064.

Table 3: The effect of gender on the serum levels of the studied parameters in patient group.

Parameters	Men N= 21	Women N= 29	*P* value
Age (years)	50.0 ± 9.4	48.3 ± 9.6	0.128
SBP (mmHg)	160 ± 14	116 ± 4.6	0.924
DBP (mmHg)	93 ± 5.4	74 ± 4.8	0.787
MABP (mmHg)	115 ± 7.6	88.5 ± 3.6	0.967
BMI (KG/m2)	23.8 ± 1.2	24.0 ± 1.0	0.338
MDA (nmol/L)	0.1 ± 0.26	0.08 ± 0.02	0.031
GPX (ng/ml)	1.71 ± 0.57	1.49 ± 0.11	0.048
IL18 (pg/ml)	31.57 ± 1.43	30.9 ± 1.08	0.064
TG (mg/dl)	104.38 ± 43.19	91.25 ± 27.39	0.195
TC (mg/dl)	184.27 ± 32.38	169.47 ± 31.95	0.11
LDLc (mg/dl)	116.79 ± 30.96	77.2 ± 14.77	< 0.001
HDLc (mg/dl)	37.19 ± 3.01	39.45 ± 3.43	0.059

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Staging Effect

The serum MDA level was significantly higher *P* value <0.05 in stage II hypertensive patients than in stage I. Overall, the levels of the other parameters were not significantly different, except for TG and HDLc *P* = 0.013, *P* <0.001 respectively (Table 4).

Correlation Coefficient

The correlation between systolic and diastolic blood pressures with the selected parameters was represented in Tables 5 and 6. There are a significant strong correlations between SBP and MDA ,GPX , IL-18 and LDLc (*P* <0.001, r = 0.68, 0.65, 0.63, 0.61 respectively). While there are significant weak correlations between SBP and TG, TC (*P* <0.001, r = 0.39, 0.51 respectively), and there is a significant negative very weak correlation between SBP and HDLc (*P* <0.001, r = - 0.057). There are a significant strong correlations between DBP and MDA, GPX, IL-18 and LDLc (*P* <0.001, r = 0.68, 0.65, 0.63, 0.61, respectively). While there are significant weak correlations between DBP and TG, TC (*P* <0.001, r = 0.39, 0.51) respectively, and there is a significant negative very weak correlation between DBP and HDLc (*P* <0.001, r = - 0.057).

Table 4: Comparison between stage I and stage II hypertensive patients regarding the serum levels of studied parameters.

Parameters	Stage I N= 22	Stage II N= 28	*P* value
Age (years)	50.0 ± 9.4	48.3 ± 9.6	0.375
SBP (mmHg)	160 ± 14	116 ± 4.6	< 0.001
DBP (mmHg)	93 ± 5.4	74 ± 4.8	< 0.001
MABP (mmHg)	115 ± 7.6	88.5 ± 3.6	< 0.001
BMI (KG/m2)	23.8 ± 1.2	24.0 ± 1.0	0.328
MDA (nmol/L)	0.08 ± 0.02	0.10 ± 0.02	0.014
GPX (ng/ml)	1.47 ± 0.12	1.66 ± 0.49	0.07
IL18 (pg/ml)	30.64 ± 0.95	31.61 ± 1.34	0.06
TG (mg/dl)	83.07 ± 22.72	107.19 ± 39.5	0.013
TC (mg/dl)	172 ± 39.54	178 ± 32.0	0.5
LDLc (mg/dl)	84.9 ± 17.87	100. 8 ± 35.7	0.062
HDLc (mg/dl)	41.36 ± 3.2	36.25 ± 3.43	< 0.001

Table 5: Relationship Between Systolic Blood Pressure and the Parameters in Hypertensive Patients.

Parameters	r-value	*P* value
MDA	0.68	< 0.001
GPX	0.65	< 0.001
IL-18	0.63	< 0.001
TG	0.39	< 0.001
TC	0.51	< 0.001
LDLc	0.61	< 0.001
HDLc	-0.057	< 0.001

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Discussion

General View

OS/antioxidant status and inflammation are considered as a significant and novel risk factor for coronary diseases, such as hypertension.[9] The actual functions of these processes in the development and progression of EHT remain unclear.

The Effect of Essential Hypertension on the Serum Levels of Studied Parameters

OS biomarker MDA level was significantly higher in patients with EHT *P* <0.001 (Table 1) which was agreeable with that of previous studies.[1,3,10] There was a strong association of OS with high BP, and there was a positive correlation between the marker of OS and systolic and diastolic BP.[3] Accordingly, OS has been implicated in EHT pathogenesis. In addition, there was a significant increase in GPX levels in patients with EHT as compared with the control group *P* <0.001 (Table 1). This result was concordant with the previous studies,[1,5] in which a significant increase in the GPX levels was reported. This result may be partially explained by the increased OS caused by the overproduction of ROS in patients with EHT and is paralleled by a significant increase in the levels of relevant enzymes, particularly GPX. Several researchers have reported contradictory findings on the antioxidant status of patients with EHT. These contradicting findings might be explained by the continuous exposure to FRs to overwhelm the activity of the GPX. This inconsistency might generally be understood on the basis of methodological variations. Data may be obtained from other demographic groups, thus giving rise to variations related to patient lifestyles. Moreover, the present study revealed a significant increase in the serum IL-18 level as compared with the control group *P* <0.001 (Table1). Elevated serum IL-18 levels have been shown to be a predictive parameter for the development of EHT. The result of the present study was concordant with the finding of the previous study.[11] IL -18 is apparently an attractive candidate biomarker for the diagnosis of patients with EHT. In this study, IL-18 was evaluated as a serum marker for inflammation and has been evaluated as a potential tool for EHT risk prediction. Thus far, the presented data support the association between inflammation and EHT development. The data also support the hypothesis suggesting that the IL-18 levels might serve a key function in the inflammatory response, which contributes to the EHT development. Therefore, IL-18 is a pro-inflammatory cytokine possibly implicated in EHT pathogenesis. The results of the statistical analysis revealed that highly significant differences existed in

Table 6: Relationship between diastolic blood pressure and the parameters in hypertensive patients.

Parameters	r-value	*P* value
MDA	0.68	<0.001
GPX	0.65	<0.001
IL-18	0.63	<0.001
TG	0.39	<0.001
TC	0.51	<0.001
LDLc	0.61	<0.001
HDLc	-0.057	<0.001

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the TG, TC, LDLc, and HDLc levels in patients with EHT as compared with the control group *P* = 0.004, 0.001, 0.001, and 0.002, respectively (Table 1). Essential hypertension was associated with lipoperoxidation, and an imbalance in the antioxidant status suggested that OS is important in EHT pathogenesis.

Age Effect

The effects of age on the levels of the selected parameters in the patients' group was shown in Table 2. The results of the statistical analysis showed that significant differences existed between age groups < 40 and 60+, 40–49 and 60+, and 50–59 and 60+ in terms of MDA and GPX levels. In terms of IL-18 level, significant differences were found between the age groups < 40 and 60+, whereas in terms of TG levels, significant differences were found between the age groups 40–49 and 60+and 50–59 and 60+. In terms of TC levels, significant differences were found between the age groups 40–49 and 50-59 and 40–49 and 60+. Finally, in terms of LDLc and HDLc levels, significant differences were found between the age groups 40–49 and 60+, 40–49 and 60+, and 50–59 and 60+. The result of the current study was agreeable with the concept that advanced age is considered as a risk factor for getting EHT, the mean age at diagnosis was 50.0 ± 9.4 (Table 1), so this finding was in harmony with[12] who published that hypertension can be age related, a decrease in glomerular filtration rate is related to aging, and this results in decreasing efficiency of sodium excretion. This study was designed to investigate the age effect on the relationship between oxidative stress/anti-oxidative status and the inflammatory process with EHT. The increased prevalence of hypertension with advanced age[13] was also evident. Blood pressure tends to increase with age, such that a higher prevalence of hypertension could be expected as a consequence of the growing elderly population.[14] In healthy individuals and hypertensive patients, increasing age was associated with the progressive and specific decrease in vasodilation related to acetylcholine. These results support the concept suggesting that advancing age is an independent factor leading to the progressive impairment of endothelium-dependent vasodilation in humans.[15] They were shown that GPX level was significantly higher *P*< 0.05 in elderly hypertensive patients than in the control group.[16] These results were consistent with those of the present study (Table 2). The observed GPX activities were contradictory, and whether GPX activity decreases[17] or increases[18] with age remains unclear. Studies have already established that aging is associated with a disruption of glutathione metabolism.[19] The decrease in GPX activity with age could be caused by the selenium deficiency, which may be associated with the poor diet of older adults or with the oxidative modifications in enzymatic proteins. Researchers have emphasized that ROS-induced protein damage may be associated with increasing age.[20] It was reported the function of the variations in IL-18 level and function in older adults.[21] IL-18 levels are related to physical function in 65- to 80-year old individuals. IL -18 may serve an important function in age-related functional impairment.

Gender Effect

The serum GPX levels in women with EHT were significantly lower than those in men (Table 3). In another study, no difference in enzyme activity was observed between men and women with EHT.[22] In addition, (Table 3) shows no significant difference between men and women with EHT in terms of IL-18 level *P* = 0.064. By contrast,[23] reported that women with EHT exhibited reduced IL-18 levels because of the small population size or because of methodological, demographical and lifestyle variations. Studies reported that the prevalence of hypertension is higher in men than in women at younger ages.[24] This finding can be attributed to the fact that women are more protected from OS because of estrogen effect.[25] Thus, the

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differences in the susceptibility to OS between men and women have been emphasized. Although numerous studies have been conducted on the oxidant-antioxidant imbalance in hypertension, supporting data for men at the early stages of hypertension remains limited.

Staging Effect

There was a significant difference between stages I and II in terms of the MDA level P = 0.05 (Table 4). Meanwhile, it was reported that MDA levels significantly increased in stage I and II hypertension groups as compared with the control group P< 0.05 (3). No significant differences were observed between stages I and II in terms of the GPX and IL-18 levels P = 0.07 and 0.06 respectively (Table 4). These findings might be attributed to the small number of participants. The activity of the Se-dependent enzyme GPX has been reported to increase in patients with different stages of EHT.[26] By contrast, it was demonstrated that GPX level significantly decreased P <0.05 in the prehypertension, stage I and stage II hypertension groups compared with the control group.[3]It was hypothesized that the body tends to combat stress through the overexpression of the GPX gene, which serves as the first line of defense in EHT. As the severity of hypertension advances to stages I and II, even the defensive mechanism via GPX may deteriorate because of the enhanced production of free radicals, which may be the reason for the reduced GPX levels.[27] In terms of IL-18 level, previous studies were carefully reviewed and detected that no results that supported this finding were found. Thus, no data concerning the effect of staging level on serum IL-18 level were present. Accordingly, the present study is the first attempt to investigate the effect of staging on the IL-18 levels in patients with EHT.

Correlation Coefficient

The associations between the selected parameters and EHT were shown in (Tables 5, 6). Moderately positive correlations were observed among MDA, GPX, and IL-18 levels, as well as the lipid profile in hypertensive patients, except for HDLc, which had a moderately negative correlation. This finding demonstrated a moderately linear correlation between the studied parameters and EHT. The results of the present study were consistent with previous studies[24] in which IL-18 level has been reported to be positively correlated with TGs but negatively correlated with HDLc. Previous studies were carefully reviewed, but no previous data were found to support this finding. A positive correlation was found between OS and BP by measuring MDA as a marker of OS; this finding was concordant with the results of a previous study.[3] Clinical Implications: The present study supported the increasing evidence suggesting that the MDA, GPX, and IL-18 levels, as well as the lipid profile, may serve as alternative markers for the clinical evaluation and management of EHT. According to the results of the previous studies and of the present study, OS may be considered as a novel therapeutic target for EHT. This study speculated that inflammation mediated by the elevated serum IL-18 level represents a mechanism that accelerates the development of EHT. Thus, the clinical implication of the present study is that the suppression or antagonism of IL-18 might be clinically beneficial. In this work, the potential function of OS in the development of EHT was examined by estimating the MDA level as a marker of lipid peroxidation. In addition, the relationship of oxidant/antioxidant balance and inflammatory process with EHT incidence was investigated. For this purpose, the serum MDA level was measured as an index of lipids and as a marker of OS, whereas serum GPX activity was determined as an antioxidant enzyme, and the IL-18 level was investigated as an inflammatory marker. Enhanced OS mediates the endothelial dysfunction associated with hypertension. The present study aimed to investigate the relative

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contributions of the oxidant/anti-oxidant enzymes and inflammatory processes to the pathogenesis of endothelial dysfunction in EHT. Increasing evidence of the importance of ROS highlights the need for reliable and reproducible markers of OS, the assessment of which can be used to monitor treatment-induced changes. Given the relationship between OS and hypertension, drugs with antioxidant effects can be expected to lower the BP. The inflammatory state in hypertension may provide a new therapeutic target for future drug design. Thus, the inhibition of IL-18 may provide a new therapeutic strategy for EHT. The pharmacologic targeting of IL-18 may supply an effective strategy to control EHT. The observed increase in inflammatory parameters in subjects who subsequently developed EHT is particularly relevant and confers options for potential primary prevention strategies.

Conclusion

Patients with EHT exhibited higher serum MDA, GPX, IL-18 levels and lipid profile, the coexistence of OS, antioxidant imbalance and inflammation with EHT was significantly correlated with serum MDA and IL-18levels. Therefore these results suggested that increased GPX can be one of the detrimental factors in contributing antioxidant status in patients with EHT. The progression of hypertension (stage II) demonstrated by increased BP which was associated with increased serum MDA, GPX, and IL-18 levels. Further elaborated studies including a larger sample size are needed to verify the role of antioxidant status and inflammatory process.

Competing interests

The authors declare that they have no competing interests.

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