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The Impact of the Oxidative Stress and Inflammatory Process on the Serum Levels of Malonaldialdehyde, Glutathione Peroxidase, and Interlukine-18 in Patients with Essential Hypertension

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Abstract: Background and objectives: The oxidative stress, antioxidant status and inflammatory process are cooperative events involved in development and progression of essential hypertension. This study was as a step for elucidating the contribution of the malondialdehyde, glutathione peroxidase, interlukine -18 and lipid profile with the incidence, development, and progression of essential hypertension. Aims: The aims of this study were, to assess the change in serum malondialdehyde, glutathione peroxidase, interlukine-18 and lipid profile levels in patients with essential hypertension, moreover, find out the effect of other confounding factors age, gender and stage of the disease on the serum levels of focused parameters and finally detect the correlation between all interested parameters. Patients and Methods: This study was designed to examine the associations between the serum interested parameters levels with the incidence of essential hypertension in 50 patients of both genders, and for the comparing purpose an equal number of the matched age–gender healthy adults also enrolled in this study as a control group. The hypothesis that oxidant /antioxidant status and inflammatory process influence the risk of adverse clinical outcomes are worthy for investigating. Accordingly, malondialdehyde was measured using coloremetric method, while, glutathione peroxidase and interlukine -18 were measured using enzyme linked immmunosorbent assay and lipid profile was estimated using commercial kit. Results: Patients exhibited a significant elevation in the serum malondialdehyde, glutathione peroxidase, interleukin-18 and lipid profile levels as compared with the control group. Conclusion: The data of the present study indicated that an alteration in oxidant / antioxidant status and inflammatory process in patients with essential hypertension. This investigation provided the first evidence of the ability of malondialdehyde, glutathione peroxidase, interlukine -18 and lipid profile in combination patterns as a factors involved in essential hypertension pathophysiology, etiology and are regarded as a markers of prognostic significance and potential therapeutic targets for future. The demonstration of these parameters provided a new insights into understanding the independence of oxidative stress /antioxidant status and inflammatory pathways in essential hypertension incidence, development and progression.

Keywords: Essential Hypertension, Malondialdehyde, Glutathione Peroxidase, Interleukine -18

1. Introduction

Essential hypertension (EHT) or hypertension of unknown cause, accounts for more than 90% of hypertension cases [1,2]. Oxidative stress/antioxidant status imbalance and inflammation are considered as significant and novel risk factors for hypertension [3,4]. Oxidative stress (OS), which results from either free radical (FR) overproduction or antioxidant exhaustion, has been implicated in the development and progression of hypertension [5].

Evidence has indicated that the OS byproduct malondialdehyde (MDA) increased in patients with EHT [6]. Several studies have involved hypertensive patients and demonstrated that MDA can be a biomarker of oxidative damage [7]. Malondialdehyde is released from the lipoperoxidation of polyunsaturated fatty acids in the cell

membrane [8]. The exposure to reactive oxygen species (ROS) increases the production of antioxidant enzymes [9].

Glutathione peroxidase (GPX) can be rapidly expressed when cells or organisms are exposed to OS [10]. Chronic low-grade inflammation has been implicated as an integral part of the pathogenesis of vascular diseases [11]. Essential hypertension may contribute to inflammatory diseases [12].

Circulating interleukine-18 (IL-18), as an inflammatory marker, has been found to be a strong predictor of systemic inflammatory processes [13]. Inflammation may be implicated in the development of hypertension, either as a primary or secondary event [14]. The measurement of serum MDA, GPX, IL-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 blood pressure in patients with EHT.

The main aim of this study was 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 of essential hypertensive patients as compared with the control group, as well as to assess the association between these parameters and other risk factors in hypertensive patients.

2. Patients and Methods

2.1. Study Design

This case control study was conducted at the College of Pharmacy, Hawler Medical University, Kurdistan Region, Iraq, from April 2013 to January 2014 and involved 50 patients with EHT and an equal number of matched age –gender apparently healthy adults was also enrolled in this study as a control group for comparing purposes with no history of hypertension or antihypertensive drugs. The participants were selected from the adult patients routinely attending at the Internal Medicine Out Patient Clinic at Erbil Teaching Hospital for follow-up and management. Healthy individuals were 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. The study protocol was approved by the Ethical Committee of the General Director of Health in Erbil Governorate.

Patients with 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 history of diabetes, smoking, physical activity, alcohol consumption, and hormone replacement therapy, as well as anthropometric and hypertension record.

2.2. Grouping of Patients

The patient group was classified into stage I and stage II EHT according to the guidelines of Joint National Committee 7 [15] to study the effect of staging on the levels of the focused parameters.

2.3. Methods

2.3.1. Collection of Sample

Fasting blood samples (10 mL) were collected from the veins of the participants (healthy adults and patients with EHT) of both genders. The blood samples were left to stand for 30 min to coagulate and then centrifuged for 15 min at 2500 rpm to 3500 rpm. The sera were separated and divided into several portions, after which they were placed into several plastic plain tubes for biochemical tests. The sera were stored at −20 °C until analysis (within one to two months). The frozen sera were prepared for measurement by warming at room temperature.

2.3.2. Biochemical Determinations

Oxidative stress/antioxidant status imbalance was analyzed through the quantification of MDA via a spectrophotometric method using thiobarbituric and trichlorocetic 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 [16]. The GPX and IL-18 levels were measured using enzyme linked immuno sorbent assay (ELISA). The serum total cholesterol (TC) and high-density lipoprotein-cholesterol (HDLc) triglyceride (TG) levels were determined using commercial enzymatic kits. The low-density lipoprotein-cholesterol (LDLc) level was calculated through Friedewald's formula: LDLc (mg/dL) = TC (mg/dL) − HDLc (mg/dL) − triglycerides / 5 (mg/dL).

2.4. Statistical Analyses

The data were analyzed using the Statistical Patch for Social Sciences v18. The results of the biochemical tests were expressed as mean ± standard deviation. Furthermore, student t-test was performed to compare two means. Post-hoc test was used to show the significant difference between two of the three variables. Multiple regression was used to reveal the association between each biomarker (as a dependent variable) and several independent variables. $p \leq 0.05$ was considered statistically significant. The correlations between laboratory findings and continuous variables were evaluated using linear regression analysis.

3. 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, who had a mean age of 50.0 ± 9.4 years. The remaining 50 participants were apparently healthy adults with mean age of 48.3 ± 9.6 years.

3.1. Effect of Essential Hypertension on the Serum Levels of Focused Parameters

Hypertensive patients 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 subjects 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/m^2)	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

3.2. Age Effect

The effect of age on the levels of the focused parameters in the patient group was shown in (Table 2). 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 50–59and 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+. While the effect of age on the levels of the studied parameters in the control group was shown in (Table 3). The results of the statistical analysis showed a significant differences among the groups (< 40 and 50–59, < 40 and 60+, 40–49 and 60+ , and 40–49 and 50–59) in terms of MDA, GPX, and IL18 levels. Moreover, significant differences were found among age groups (< 40 and 50–59 and < 40 and 60+) in terms of the TG, TC, and HDLc levels. Meanwhile, no significant differences were found among the age groups in terms of LDLc level.

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

Parameters		N	Mean	±SD	p	Significance by LSD test
	A- < 40	10	.08300	.022201		A X D
	B- 40-49	10	.08720	.013637		B X D
MDA	C- 50-59	19	.09042	.027943	< 0.001	C X D
	D- 60+	11	.12464	.020839		
	Total	50	.09582	.027323		
	A- < 40	10	1.440	.0966		A X D
	B- 40-49	10	1.470	.0949		B X D
GPX ng/ml	C- 50-59	19	1.511	.0994	0.005	C X D
	D- 60+	11	1.936	.7284		
	Total	50	1.582	.3900		
	A- < 40	10	30.40	1.075		
	B- 40-49	10	31.00	1.633	0.011	
IL18pg /ml	C- 50-59	19	31.32	1.157		A X D
	D- 60+	11	31.82	.982		
	Total	50	31.18	1.273		
	< 40	10	96.380	43.2412		
	40-49	10	81.500	10.7212		
TG mg/ dl	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		
	< 40	10	164.170	27.4153		
	40-49	10	153.770	26.6074		B X C
Total cholestrol	50-59	19	185.116	29.3301	0.019	B X D
	60+	11	189.845	36.8475		
	Total	50	175.698	32.6459		
	< 40	10	73.900	18.7169		A X D
	40-49	10	88.500	24.0335		B X D
LDLc	50-59	19	88.847	19.8743	< 0.001	C X D
	60+	11	125.418	36.3517		
	Total	50	93.834	30.0949		
	< 40	10	40.90	3.725		A X D
	40-49	10	40.70	4.084		B X D
HDLc	50-59	19	38.05	3.358	0.02	C X D
	60+	11	35.09	3.754		
	Total	50	38.50	4.181		

Table 3. *The effects of ages on the mean serum levels of studied parameters in controls groups.*

Parameters		N	Mean	SD	p	Significance by LSD test
	A- < 40	12	.0354	.0126		
	B- 40-49	10	.0438	.0192		A X C
MDA	C- 50-59	21	.0525	.0194	0.006	A X D
	D- 60+	7	.0654	.0207		B X C
	Total	50	.0485	.0201		B X D
	A- < 40	12	1.067	.1614		
	B- 40-49	10	1.160	.1506		A X C
GPXng/ml	C- 50-59	21	1.295	.1117	< 0.001	A X D
	D- 60+	7	1.343	.0787		B X C
	Total	50	1.220	.1641		B X D
	A- < 40	12	29.58	.793		
	B- 40-49	10	29.80	1.229	0.001	A X C
IL18 pg/ml	C- 50-59	21	30.62	1.024		A X D
	D- 60+	7	30.86	.900		B X C
	Total	50	30.24	1.098		B X D
	< 40	12	72.100	12.4213		
	40-49	10	81.750	8.7631		A X C
TG mg/dl	50-59	21	83.295	13.1628	0.04	A X D
	60+	7	88.114	15.2260		
	Total	50	80.974	13.2984		
	< 40	12	135.808	9.821		
	40-49	10	151.360	28.135	0.05	A X C
Total cholesterol mg/dl	50-59	21	155.105	26.135		A X D
	60+	7	165.286	22.171		
	Total	50	151.150	24.473		
	< 40	12	70.425	13.853		
	40-49	10	72.300	11.106		
LDLc mg/dl	50-59	21	76.829	10.820	0.194	Non Sig.
	60+	7	81.771	13.712		
	Total	50	75.078	12.2941		
	< 40	12	45.42	5.838		
	40-49	10	41.40	6.059	0.019	A X C
HDLc mg/dl	50-59	21	40.24	4.206		A X D
	60+	7	38.71	3.498		
	Total	50	41.50	5.354		

3.3. Gender Effect

The effect of gender on the levels of the focused parameters in the patient group was presented in (Table 4). 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 other parameters, while, in case of IL-18 there was a difference ,but this difference reach near the significant level p= 0.064. While, the effect of gender on the levels of the focused parameters in the control group was shown in (Table 5). There were significant differences between men and women in term of all parameters except for age and BMI.

Table 4. *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/m^2)	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

Table 5. *The effect of gender on the serum levels of the studied parameters in controls group.*

Parameters	Men N= 21	Women N= 29	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/m^2)	23.8 ± 1.2	24.0 ± 1.0	0.328
MDA (nmol/L)	0.06 ± 0.01	0.03 ± 0.01	< 0.001
GPX (ng/ml)	1.30 ± 0.14	1.15 ± 0.15	0.001
IL18 (pg/ml)	31.05 ± 0.95	29.66 ± 0.76	< 0.001
TG (mg/dl)	85.88 ± 13.01	77.47 ± 12.58	0.027
TC (mg/dl)	167.53 ± 19.99	139.28 ± 20.38	< 0.001
LDLc (mg/dl)	80.83 ± 12.11	70. 9 ± 10.8	0.004
HDLc (mg/dl)	38.67 ± 3.2	43.55 ± 3.43	0.001

3.4. 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 6).

Table 6. *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/m^2)	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

3.5. Correlation Coefficient

The correlation between systolic and diastolic blood pressures with the focused parameters were represented in (Tables 7,8).

Table 7. *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

Table 8. *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

4. Discussion

4.1. General View

Oxidative stress and inflammation are considered as a significant and novel risk factors for coronary diseases, such as hypertension [3,4]. The actual functions of these processes in the development and progression of EHT remain unclear.

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

4.2.1. The Effect of Essential Hypertension on the Serum Levels of Malondialdehyde

This study revealed that the OS biomarker MDA level was significantly higher in patients with EHT than in the control group p<0.001 (Table 1).

This finding is supported by the results of previous studies that reported increased MDA levels in patients with EHT. Therefore, the result of the present study was agreeable with that of previous studies [17–24]. Accordingly, Os has been implicated in EHT pathogenesis.

4.2.2. The Effect of Essential Hypertension on the Serum Levels of Glutathione Peroxidase

The results of the statistical analysis revealed 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 findings of previous studies [25–27], in which a significant increase in the GPX levels was reported. It was published that the GPX levels in prehypertensive individuals significantly increased as compared with that in control individuals [28]. This result may be partially explained by the increased OS caused by the overproduction of ROS radicals in patients with EHT and is paralleled by a significant increase in the levels of relevant enzymes, particularly GPX. Glutathione peroxidase has been observed to be rapidly expressed when organisms or cells are exposed to OS [29]. Several researchers have reported contradictory findings on the antioxidant status of patients with EHT. The result of the present study was not consistent with the findings of previous studies [19,20,23,30–32]. These contradicting findings might be explained by the recent diagnosis of patients in the current study and by the absence of continuous exposure to hydrogen peroxide, hydrogen peroxynitrite, and other free radicals to overwhelm the activity of the antioxidant enzyme 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.

4.2.3. The Effect of Essential Hypertension on the Serum Levels of Interlukine-18

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 and progression of EHT. The result of the present study was concordant with the finding of previous study [33]. Interlukine -18 is apparently an attractive candidate biomarker for the diagnosis and prognosis of patients with EHT. Indeed, IL-18 provides a significant prognostic information as opposed to the classic lipid profile and inflammatory markers [34]. 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 incidence. The data also support the hypothesis suggesting that the IL-18 levels might serve a key function in inflammatory response, which contributes to the EHT incidence. Therefore, IL-18 is pro-inflammatory cytokine possibly implicated in EHT pathogenesis.

4.2.4. The Effect of Essential Hypertension on the Serum Levels of Lipid Profile

The results of the statistical analysis revealed that highly

significant differences existed in the TG, TC, LDLc, and HDLc levels in patients with EHTas 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.

4.3. Age Effect

The effects of age on the levels of the focused parameters in the patient 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 50-59and 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+.

In the control group, the results of the statistical analysis showed significant differences between the age groups < 40 and 50–59, < 40 and 60+, 40–49 and 60+, and 40–49 and 50=59 in terms of the MDA, GPX and IL18 levels. Moreover, significant differences were observed between the age groups < 40 and 50–59and < 40 and 60+ in terms of TG, TC, and HDLc levels. Meanwhile, no significant difference was observed between the age groups in terms of LDLc level (Table 3).

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 [35] who published that, the most important risk factor for hypertension in large populations is the age effect.

This study was designed to investigate the age effect on the relationship between oxidative stress/anti-oxidative status and the inflammatory process with EHT. Hypertension can also be age-related, it is not a chronic disease, but it is independently associated with cardiovascular diseases in the elderly, which is why aging and hypertension are well-documented cardiovascular risk factors [36]. Most structural vascular and function alterations result in cardiovascular complications, such as in aging and hypertension [37,38]. Moreover, the vascular changes associated with EHT are generally considered to be related to the aging process [39]. The increased prevalence of hypertension with advanced age [40] 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 [41]. 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 [42,43]. They were shown that GPX level was significantly higher P < 0.05 in elderly hypertensive patients than in the control group [44,45]. These results were consistent with those of the present study (Table 2). The observed GPX activities were contradictory, and whether GPX activity decreases [46] or increases [47] with age remains unclear. Moreover, no alteration in the GPX level was observed with aging [48,49]. Studies have already established that aging is associated with a disruption of glutathione metabolism [50,51]. The decrease in GPX activity with age could be caused by selenium deficiency, which may be associated with the poor diet of elderly people or with the oxidative modifications in enzymatic proteins. Researchers have emphasized that ROS-induced protein damage may be associated with increasing age [52]. It was reported the function of the variations in IL-18 level and function in elderly people [53]. Interlukine-18 levels are related to physical function in 65- to 80-year old individuals. Interlukine -18 may serve an important function in age-related functional impairment.

4.4. Gender Effect

The serum GPX levels in women with EHT were significantly lower than those in men (Table 4). In other study, no difference in enzyme activity was observed between men and women with EHT [54]. In addition, (Table 4) shows no significant difference between men and women with EHT in terms of IL-18 level p= 0.064. By contrast, [55] reported that women with EHT exhibited reduced IL-18 levels because of the small population size or because of methodological, demographical and life style variations. Studies reported that the prevalence of hypertension is higher in men than in women at younger ages [56]. This finding can be attributed to the fact that women are more protected from OS because of estrogen effect [57]. Thus, the differences in the susceptibility to OS between men and women have been emphasized. They were reported that the level of oxidative damage in the DNA is higher in men than in women [58,59]. Other studies demonstrated that oxidative damage to mitochondrial DNA is significantly lower in female rats than in male rats [60,61]. Although numerous studies have been conducted on the oxidant-antioxidant imbalance in hypertension, supporting data for men at the early stages of hypertension remain limited.

The healthy men had higher MDA, GPX, and IL-18 levels, as well as lipid profile p <0.05, than the healthy women (Table 5). The findings of the present study were concordant with those of previous studies [35], which reported that GPX activity decreased in women with similar ages and from a healthy population compared with healthy men.

4.5. Staging Effect

There were a significant differences between stages I and II in terms of the MDA level p = 0.05 (Table 6). Meanwhile, it was reported that MDA levels significantly increased in the stage I and II hypertension groups as compared with the

control group $p<0.05$ [23].

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 6). 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 [62,63]. 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 [23].

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 [64].

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.

4.6. Correlation Coefficient

Tables 7 and 8 show the association between the focused parameters and hypertension were shown in (Tables 7, 8). 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 moderately negative correlation. This finding demonstrated a moderately linear correlation between the studied parameters and hypertension. The results of the present study were consistent with those of previous studies [55], 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 oxidative stress and blood pressure by measuring MDA as a marker of oxidative stress, this finding was concordant with the results of a previous study [23].

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 and progression 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 aim of the present study was to investigate the relative 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 oxidative stress, 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.

5. Conclusion

Compared with healthy participants, patients with EHT exhibited higher serum MDA, GPX, IL-18 levels and lipid profile. The coexistence of OS and inflammation with EHT was significantly correlated with serum MDA $r = 0.68$, $p <0.05$ and IL-18 $r = 0.63$, $p <0.05$ levels. The progression of hypertension (stage II) demonstrated by increased blood pressure was associated with increased serum MDA, GPX, and IL-18 levels.

Further elaborated studies including larger sample size are needed to verify the role of oxidative stress / antioxidant status and proinflammatory cytokine activation in essential hypertension. Further studies are warranted in order to assess their utility as a predictors of the presence of essential hypertension.

Abbreviations

BMI: Body mass index, BP: Blood pressure, DBP: Diastolic blood pressure, ELISA: Enzyme linked immuno sorbent assay, EHT: Essential hypertension, FR: Free radical, GPX: Glutathione peroxidase, HDLc: High density lipoprotein, IL-18: Interlukine-18, LDLc: Low density lipoprotein, MRBP: Mean arterial blood pressure, MDA: Malondialdehyde, OS: Oxidative stress, ROS: Reactive oxygen species, SBP: Systolic blood pressure, Se :Selenium, SOD: Superoxide dismutase, TC: Total cholesterol, TG: Triglyceride.

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