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The Relation of Serum High-Sensitive C- reactive Protein to Serum Lipid Profile, Vitamin D and other Variables in a Group of Hypertensive Patients in Erbil-Iraq

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Abstract: ***Background and objectives: Hypertension is an established risk factor for atherosclerosis. Elevated levels of high-sensitive C-reactive protein (hs-CRP) were detected in hypertensive patients. Recent studies suggest a link between high-sensitive C-reactive protein (hs-CRP) and atherosclerosis in hypertension. Growing evidence suggests that vitamin D affects the cardiovascular system The objective of this study was to assess the relationship of hs-CRP to lipid profile, vitamin D and other variables in hypertensive patients in Erbil-Iraq. Subjects and Methods: This cross-sectional study was conducted on two-hundred adults (130 hypertensives and 70 normotensives). The participants were classified into three groups according to their BP measurements as normotensive (group I), stage I hypertension (group II) and stage II hypertension (group III). Serum hs-CRP, lipid profile, vitamin D levels, and other variables were evaluated in all studied groups. Results: Hs-CRP level was significantly higher in hypertensives as compared to normotensives (P <0.001). The means of total cholesterol (TC), triglyceride (TG) and low-density lipoprotein (LDL) were significantly higher, while the mean of high-density lipoprotein (HDL) was significantly lower in hypertensives than in normotensives (P <0.001). The mean of vitamin D was significantly lower in hypertensives than in normotensives (P<0.001). Hs-CRP was positively correlated with TC, TG, and LDL but inversely correlated with HDL and vitamin D. Conclusions: Higher levels of hs-CRP were detected in hypertensive patients than normotensives. The higher hs-CRP levels were significantly correlated with higher grades of hypertension. Hs-CRP was positively correlated with lipid profile and inversely correlated with vitamin D .Increased levels of hs-CRP in hypertension may suggest a role of inflammation in hypertension. Hs-CRP estimation may be recommended in evaluation of all hypertensive patients.***

Keywords: Hs-CRP, Hypertension, Lipid profile, Vitamin D

1. Introduction

Hypertension is an established major independent risk factor for development of atherosclerosis and multiple cardiovascular diseases worldwide. [1]According to the 2006 Iraqi national survey for chronic disease risk factors, 40.4% of the Iraqi adult populations have elevated blood pressure.[2] Many recent studies correlate between hypertension and inflammation.[3] New proof indicates that vascular inflammation may have a role in the initiation and /or development of hypertension.[4] Several researchers have noticed higher high-sensitive C-reactive protein (hs-CRP) levels in patients with hypertension.[5] Vitamin D deficiency or insufficiency is a common condition that affects up to one-half of otherwise healthy middle aged to elderly population.[6] Although vitamin D deficiency involves mainly musculoskeletal system, growing evidence suggests that vitamin D affects the cardiovascular system also.[7]

High concentrations of CRP might reduce nitric oxide production in endothelial cells, leading to vasoconcentration and increase blood pressure. Endothelial dysfunction and inflammation were associated with arterial stiffness .[8] Hs-CRP ,an acute phase reactant protein, is a proinflammatory atherogenic marker which can be an early cardiac risk predictor.[9] A hs-CRP test measures low levels of CRP using laser nephelometry. The test gives a sensitivity results down to 0.04 mg/L. The American Heart Association and U.S. Centers for Disease Control and Prevention have defined risk groups as follows: low: hs-CRP level under 1.0 mg/L, average: between 1.0 and 3.0 mg/L, and high: above 3.0 mg/L.[10,11]

To date, and up to our knowledge, there was no previous study done regarding the same subject in Erbil city . The objective of this study was to assess the correlation between hs-CRP levels to serum lipid profile and other variables in a group of hypertensive patients in Erbil city-Iraq.

2. Patients and Methods

This cross-sectional study was conducted in Rizgary teaching hospital between July 2015 and July 2016 .A total of 200 participants (130 participants with essential hypertension and additional 70 normotensives, as control group) were enrolled in the study. According to blood pressure (BP) measurements, The participants were classified into three groups; Group I (normotensive participants, SBP≤120 mmHg, and /or DBP ≤80 mmHg, n=70), group II (stage 1 hypertension, SBP 140-159 mmHg, and /or BDP 90-99 mmHg , n=67) and group III (stage 2 hypertension , SBP≥160 mmHg, and /or DBP≥ 100 mmHg, n= 63). All participants were assessed by a detailed history, physical examination, echocardiographic evaluation and other investigational tools. Blood samples were drawn to measure the hs-CRP ,serum lipid profile and vitamin D level for each participant.

The inclusion criteria were patients with essential hypertension, age ≥ 18 years and of both genders.

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The exclusion criteria were patients with secondary hypertension (diabetic nephropathy, polycystic kidney disease, renovascular hypertension) ,Cushing syndrome ,thyroid disease , chronic renal failure , patients with primary hyperparathyroidism, , malabsorption, osteomalcia or osteoporosis, patients on medications like anticonvulsants , glucocorticoids and vitamin D supplements.

BMI (Body Mass Index, weight/height^2) was calculated according to a standard definition.[12]

Based on recommendations of the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) [13], hypertension was defined as systolic blood pressure ≥140 mmhg and diastolic blood pressure ≥ 90 mmhg for adults aged 18 years and less than 60 years, and systolic blood pressure ≥ 150 or diastolic ≥ 90 in general population ≥ 60 years. Blood pressure measurements used in this study were taken with a mercury sphygmomanometer. Measurements were made to the nearest 2mmhg, in the sitting position with the arm supported, and repeated after 5 minutes' rest if the first recording is high. We will take 2 measurements at each visit.

Transthoracic echocardiographic examinations were performed in the left lateral position. Standard M-mode, 2-Dimensional and Doppler echocardiographies were performed using (Brand GE Vivid E9 -2009) echocardiography machine.LV end-diastolic diameter (LVDd), LV end-systolic diameter(LVSd), left atrial(LA) and all other diameters were measured according to established standards of the American Society of Echocardiography. [14] LV mass (LVM) were calculated according to the Devereux formula [15] : LVM=1.04[(LVDd + IVSth +PWT) ^{3} –(LVDd) ^{3}]-13.6.Thereafter, LV mass index(LVMI) was obtained by the following formula: LVM/body surface area (g/m^2) [16] . In the presence of LVH, the LVM exceeds 134 grams in men and 110 grams in women per meter square body surface area (m^2 BSA).

Although a consensus regarding the optimal level of serum 25(OH) D has not yet been established , most experts define vitamin D deficiency as a 25(OH) D level of <20 ng/ml , vitamin D insufficiency as 21 to 29 ng/ml and the optimal concentration of 25(OH) D is at least 30 ng/ml.[17]

Estimation of serum lipid profile was done by using automated biochemistry analyzer and according to standard methods.[18]
Pulse pressure (PP) is the difference between the systolic and diastolic pressure readings (PP= SBP-DBP). It is measured in millimeters of mercury (mmHg). It represents the force that the heart generates each time it contracts.[19]

The mean arterial pressure (MAP) is a term used to describe an average blood pressure in an individual. It is defined as the average arterial pressure during a single cardiac cycle.[19] MAP=DBP+1/3 PP.

The data were collected by interviewing the patients using a questionnaire designed by the researchers. The questionnaire included information about socio-demographic data (age, gender, marital status, …), hypertension, risk factors like hyperlipidemia, IHD, obesity, family history, others), and history of smoking and alcoholism.

3. Ethical Considerations

The study protocol was approved by the ethics committee of the College of Medicine of Hawler Medical University. This study was conducted by using an informed verbal consent from the patients prior to participation in the study. The purpose of the study was carefully explained to each patient.

4. Statistical Analysis of Data

Data were analyzed using the statistical package for social sciences (SPSS, version 19). Student's t test for two independent samples was used to compare means. Correlation coefficient (r) was obtained to demonstrate the correlations between variables . A 'P' value of ≤ 0.05 was considered as statistically significant.

5. Results

The age and BMI were matched in all three groups of the study (P =0.49 and 0.98, respectively). As expected, SBP, DBP, PP and MAP values were significantly higher in hypertensive groups as compared to normotensive group (P<0.001, for each). Statistically higher levels of TC, TG, LDL (P<0.001, for each) and lower level of HDL (P<0.001) were found in hypertensives than in normotensives. IVS, PW, LVM, LVMI and RWT levels were significantly higher (P <0.001, for each) in hypertensives as compared to normotensives. We found also that the mean of vitamin D level was significantly lower (7.61 ng/dl) and the mean of hs-CRP level was significantly higher (2.75 mg/dl) in hypertensives than normotensives (17.3 ng/dl and 0.74 mg/dl respectively) (P<0.001, for each), as shown in Table 1.

In Table 2 , which compares between the two hypertensive groups and as expected, SBP , DBP , PP and MAP values were significantly higher (P<0.001, for each) in group III as compared to group II. There were no differences in both groups regarding serum lipid profile values (P=0.91, 0.87, 0.74 and 0.8 respectively), the same applies to EF (P=0.85). IVS, PW, LVM, LVMI , RWT and left atrium values were significantly higher in group III patients than in group II patients. Group III patients had significantly higher hs-CRP values (3.67 mg/dl) than group II patients (1.83 mg/dl) (P<0.001). Although the mean value of vitamin D was lower (6.9 ng/dl)in group III patients than in group II patients (8.32 ng/dl), but it was not statistically significant (P=0.5).

Hs-CRP correlated positively with SBP, DBP, PP, MAP, TC, TG, LDL ,LVM, LVMI, and correlated negatively with HDL and vitamin D, as shown in Table 3.

6. Discussion

In the present study, hypertensive patients had higher hs-CRP levels than normotensives. This indicates that inflammation might be associated with hypertension. This is

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compatible with other studies. Ki Chul Sung et al[20] and Sesso et al[21] found a positive relation between increasing levels of hs-CRP and risk of developing hypertension. But Bautista et al[22] in 2003 didn't find such association.

CRP has been reported to decrease nitric oxide production[8] and increases endothelin-1 and plasminogen activator inhibitor-1 activity in endothelial cells[23] to induce vasoconstriction, platelet activation, and thrombosis. In addition, CRP has shown to up regulate angiotensin receptor-1 and thus enhancing angiotensin-II activity and this leads to rise in blood pressure.[24]

In our study, hypertensive patients had abnormal lipid profile and that was evident by the presence of high TC, TG and LDL levels and low HDL level. This is compatible with other studies. Rasouli M et al[25] found higher cholesterol and TG levels in hypertension. In the Strong Heart Study (2006) [26] , an abnormal lipid profile was found in hypertensive American Indian population. Marco et al[27] found that participants who were prehypertensives and later developed hypertension had higher levels of TG and lower HDL levels. All these data suggest that vascular inflammation plays a role in pathophysiology of hypertension and may exacerbate the pro-atherogenic effects of hypertension.

In our study, elevated hs-CRP levels were associated with high PP. This result is compatible with Abramson et al[28] study which found such a positive association. Recent studies emphasize the possibility that arterial stiffening may precede the development of hypertension. Arterial stiffening was associated with many circulating inflammatory markers suggesting that inflammation may play a role in arterial stiffness.[29] If the blood vessel becomes rigid in conditions such as arteriosclerosis or atherosclerosis, the pulse pressure would be very high. Some evidence suggests that pulse pressure is a better predictor of clinical outcome than the systolic or diastolic blood pressure alone. Several studies have identified that high pulse pressure causes more artery damage compared to high blood pressure with normal pulse pressure.[30] Recent work suggests that a high pulse pressure is an important risk factor for heart disease. A meta-analysis in 2000, which combined the results of several studies of 8,000 elderly patients in all, found that a 10 mm Hg increase in pulse pressure increased the risk of major cardiovascular complications and mortality by nearly 20%.[31]

A positive association between high hs-CRP level and high MAP was also found in the present study. Many other studies found the same relationship.[32,33]

In the present study, hs-CRP was positively related to LVM and LVMI, an echocardiographic marker of left ventricular hypertrophy (LVH). This result is compatible with other previous studies[34], which found that patients with different involved target organ had different inflammatory degree, which hypertensive patients with LVH had the highest hs-CRP levels.

Finally, in the present study, hs-CRP was negatively related to vitamin D level. Although vitamin D deficiency involves mainly musculoskeletal system, growing evidence suggests that vitamin D affects the cardiovascular system also. [7] Recent clinical studies showed that low levels of vitamin D are associated with a higher prevalence of hypertension and LVH.[35] Elevated hs-CRP and vitamin D deficiency are associated with inflammatory changes that have been associated with cardiovascular events.[36]

7. Conclusions

Higher levels of hs-CRP were seen in hypertensive patients than normotensives. The higher hs-CRP levels were significantly correlated with higher grades of hypertension. Hs-CRP was positively correlated to lipid profile and inversely correlated to vitamin D .Increased levels of hs-CRP in hypertension implies a role of inflammation in hypertension. Hs-CRP estimation may be recommended in evaluation of all hypertensive patients.

8. Conflicts of Interest

The authors report no conflicts of interest

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Table 1: Comparison of baseline, biochemical and echocardiographic characteristics between hypertensives and normotensive participants

Variables	Group I **Normotensive N=70**		Group II and III **hypertensive** N=130		p
	Mean	**SD**	**Mean**	**SD**	
Age	49.9	9.3	52.24	9.15	0.49
BMI	26.77	6.8	27.60	7	0.98
SBP	118	8.8	157.26	7.39	<0.001
DBP	78	4.7	95.49	4.2	<0.001
PP	40	4.1	61.77	2.3	<0.001
MAP	91.3	5.6	116.04	4.1	<0.001
Cholesterol	145.1	29.3	200.83	19.5	<0.001
TG	99.75	32	180.29	19.3	<0.001
LDL	71.52	17.9	113.56	20.1	<0.001
HDL	41.5	4.6	37.05	3.6	<0.001
EF	61.7	3.6	62.1	3.7	0.58
IVS	8.25	0.5	12.46	0.7	<0.001
PW	7.86	0.3	11.86	0.6	<0.001
Left atrium	25.12	1.25	33.17	2.1	<0.001
LVM	102	9.18	223.79	15.6	<0.001
LVMI	60.66	5.3	121.14	7.5	<0.001
RWT	0.38	0.01	0.50	0.03	<0.001
Vit D	17.3	7.4	7.61	5.6	<0.001
Hs-CRP	0.74	0.8	2.75	1.5	<0.001

Table 2: Comparison of baseline, biochemical and echocardiographic characteristics between two hypertensive groups

Variables	Hypertensive group (II and III), N=130				p
	Stage I Group II (n=67)		Stage II Group III (n=63)		
	Mean	SD	Mean	SD	
Age	51.74	8.4	52.75	9.9	0.89
BMI	27.4	9	27.8	5	0.57
SBP	142.92	8.29	171.6	6.5	<0.001
DBP	90.22	2.8	100.75	5.6	<0.001
Cholesterol	199.44	20.5	202.22	18.6	0.91
TG	179.78	19.1	180.8	29.5	0.87
LDL	111.52	19.2	115.61	21.1	0.74
HDL	36.6	1.8	37.5	6.1	0.8
PP	52.7	3.5	70.85	1.1	<000.1
MAP	107.2	3	124	5.3	<000.1
EF	62.4	3.5	61.8	3.9	0.85
IVS	11.65	0.6	13.28	0.9	<0.001
PW	11.07	0.5	12.66	0.7	<0.001
Left atrium	32.2	2	34.15	2.2	0.066
LVM	203.89	11.2	242.69	20.4	<0.001
LVMI	111.35	6.1	130.93	9.4	<0.001
RWT	0.47	0.02	0.54	0.04	0.001
Vit D	8.32	7.22	6.9	6.5	0.5
Hs-CRP	1.83	1.1	3.67	2.1	<0.001

Table 3: Correlation of hs-CRP with serum lipid profile and other variables in hypertensive patients

Variables	*r value*	*P value*
SBP	0.75	<0.001
DBP	0.68	<0.001
PP	0.7	<0.001
MAP	0.72	<0.001
Cholesterol	0.63	<0.001
TG	0.32	0.001
LDL	0.6	<0.001
HDL	-0.35	0.001
LVM	0.58	<0.001
LVMI	0.58	<0.001
Vit D	-0.32	0.044

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