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High Sensitive C-reactive protein as Prognostic Marker for Cardiovascular Disease among Sudanese Hypertensive Patients.

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Abstract:

Background: Highly sensitive C-reactive protein, hs-CRP, is an acute phase protein which represents a sensitive systemic marker of inflammation and tissue damage especially in cardiovascular disease. Hypertension is a common health problem throughout the world and one of the major risk factors for Cardiovascular Disease, CVD, therefore this study aims at the evaluation of this highly sensitive C-reactive protein, hs-CRP, as a prognostic marker for CVD in hypertensive patients. **Materials and Methods**: A case control study was carried out in Abuda center during the period from January to February 2016. In this study 50 hypertensive patients were enrolled (13 males and 37 females) and 50 normotensive as a control group. Serum hs-CRP levels, TG and cholesterol were measured by Cobas, 311 automated analyzer. The data were, then, analyzed by using SPSS® software computer program**.** **Results**: The mean serum level of hs-CRP, cholesterol and triglyceride showed a significant increase in hypertensive patients compared to the control groups, assuming p-values of (0.002, 0.000 and 0.000) respectively. In case of the gender, age, BMI and duration of disease categories, the results indicated an insignificant increase in hs-CRP among females, overweight subjects and those of more than 5 years duration of HTN, with p-values of (0.382, 0.387and 0.166), respectively. Females, overweight group, more than 60 years and more than 5 years duration of HTN showed insignificant increase in diastolic and systolic BP. The mean TG level showed insignificant increase in males, normal weight group and more than a 5 year duration of HTN with p-values of (0.862, 0.509 and 0.921), respectively, and insignificant decrease in patients more than 60 years with a p-value of (0.959). **Conclusion:** the study concluded that the hypertensive patients have increased hs-CRP, cholesterol and triglyceride compared to control HTN group with p-values of (0.862, 0.509 and 0.921), respectively, and an insignificant decrease in patients more than 60 years with a p-value of (0.959).

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Keywords: hs-CRP, HTN, BMI, CVD, triglyceride, cholesterol

Introduction:

Hypertension is defined as blood pressure, BP, equal or above 140/90 mmHg [1]. High blood pressure is the leading cause of cardiovascular disease and death globally. It is associated with at least 7.6 million deaths per year worldwide, (13.5% of all deaths), making it the major risk of CVD. The importance of BP as a modifiable risk factor for CVD is well recognized and many effective and inexpensive BP lowering treatments are available, therefore hypertension control and prevention of subsequent morbidity and mortality clearly should be achievable [2]. Sudan is considered one of leading countries in Africa for prevalence of HTN. However, a proper national registry on HTN is not available in Sudan. Nevertheless, a recent study showed an increasing incidence of HTN [3].There is a compelling experimental and clinical evidence suggesting crucial role for inflammation in initiation and progression of atherosclerosis. Among all blood biomarkers C-reactive protein, the classical acute phase reactant that can be measured with high sensitivity assays seems to be the most promising candidate [4]. CRP is a member of the pentraxin family of protein and is synthesized by liver and also produced by cells in vascular wall such as endothelial cells, smooth muscle cells and adipose tissue [5]. Its plasma half-life is 19 hours and it catabolized by hepatocytes [6]. The possible mechanistic role of CRP in plaque deposition is highly complex, exerting proatherogenic effects in atherosclerosis. CRP may facilitate monocyte adhesion and transmigration into the vessel wall, a critical early step in the atherosclerotic process [7]. CRP, an

inducible protein secreted in response to inflammatory stimulus, binds to pathogens and activates the complement to enhance opsonisation and clearance, even before the production of specific IgM or IgG. CRP bound to multivalent ligand initiates the assembly of C3 convertase through the classical pathway, which leads presentation of ligand with opsonic complement fragments [8]. Atherosclerosis is a chronic inflammatory disease process that occurs over a number of years and contributes to approximately 50% of all deaths in modern western societies [9]. A high level of plasma lipids, particularly low-density lipoproteins (LDL), is a major cause of vascular damage. Mechanistic studies suggest that they play a role in relevant feature for initiation and progression of lesions, such as endothelial dysfunction, intimal disorganization and thickening [10]. Triglyceride lipolysis by LPL on endothelial cell surface elaborates high concentration of lipolysis products along the blood endothelial interface; contribute to atherosclerosis through mechanisms encompassing pro inflammatory, pro-coagulant, and pro-apoptotic gene activation. TG lipolysis releases neutral and oxidized free fatty acids that induce endothelial inflammation, vascular apoptosis, and reactive oxygen species production in endothelial cells and altered lipid raft physiology [11].

Materials and methods:

In this case control study, 100 subjects were included. Fifty were diagnosed with hypertension and 50 normotensive as control. Exclusion criteria involved patients with hepatitis and

systemic illness.. Our sampling was performed from January to February 2016. After overnight fasting, 5ml of venous blood was withdrawn. Blood samples were centrifuged at 1500 rpm for 10 min and stored until analyzed.

Ethical Considerations

This study protocol was formally approved by the Ethical Committee of Omdurman Islamic University. Permission of hospitals mangers were taken before beginning. Informed consent was taken from every participant before enrolling.

Measurement of BMI:

Anthropometric data including weight and height were measured. Body mass index (BMI) was defined as weight (in kilograms) divided by the square of the height in meters.

Estimation of highly sensitive C-reactive protein:

According to the procedure provided, serum levels of hs-CRP were measured, using Cobas 311 automated analyzer. Particles enhanced immune-turbidimetric assay. Human CRP agglutinates with latex particles were coated with monoclonal anti-CRP antibodies. The precipitate is determined turbidimetrically.

Estimation of cholesterol:

Cholesterol esters were cleaved by the action of cholesterol esterase to free cholesterol and fatty acids. Cholesterol oxidase then catalyzed the oxidation of cholesterol to cholest-4-en-3-one and hydrogen peroxide. In the presence of peroxidase, the hydrogen peroxide

triggered the coupling of phenol and 4-aminophenazone to form red quinone-imine dye. The absorption was directly proportional to concentration of cholesterol and was measured, using Cobas 311 (autoanalyzer).

Triglyceride Estimation

Triglyceride was catalyzed by glycerol kinase peroxidase method through sequences of enzymatic catalysis step by lipases, triglyceride catalyzed to yield H_2O_2, which on oxidation gives color dye quinonimine. The absorbance directly was proportional to concentration of triglyceride and was measured by cobas 311.

Statistical analysis:

Statistical analysis was performed using the statistical package for social science (SPSS). The data was displayed as (mean ± SD) for variables of analyzed concentration. The independent t-test was employed to compare the difference between continuous variables. P-values less than 0.05 were considered statistically significant.

Results: In our study, 50 individuals with hypertension were (26% men and 74%woman) participated. The mean serum levels of cholesterol, triglyceride and hs-CRP were 195.1± 49.1mg/dL, 171.5± 77.7mg/dL, and 5.93± 9.96mg/L respectively.

According to hypertension group, the mean level of hs-CRP and triglyceride show highly significant increase results and cholesterol level also show highly significant

increase results compared with normal individuals as show in table (3-1).

Table (3-1) the mean of parameters level in study group classified as hypertensive patients and normal individuals.

Variable	Case	Control	P. Value
hs-CRP	5.93± 9.9	1.41± 1.2	0.002
Cholesterol	195.1± 49.1	151.6± 30.4	0.000
Triglyceride	171.5± 77.7	110.2± 50.2	0.000

Our study showed insignificant increase in mean triglyceride levels in males compared to females, while showed insignificant increase in mean levels of diastolic BP, systolic BP, hs-CRP and cholesterol in females compared to males as shown in table (3-2).

Table (3-2) the mean parameters level in study group classified as male and female.

Variable	Male	Female	P. Value
hs-CRP mg/L	3.3± 3.6	6.67± 11.3	0.382
Cholesterol mg/dL	187.3± 48.7	197.8± 49.4	0.511
Triglyceride mg/dL	174.8± 65.4	170.4± 82.4	0.286
Systolic BP mmHg	136.9± 15.5	141.9± 46.0	0.706
Diastolic BP mmHg	82.7± 8.8	84.5± 8.3	0.519

Our study revealed that there was insignificant increase in mean levels of cholesterol and triglyceride in normal weight group in comparison to overweight and insignificant

increase in mean levels of systolic BP, diastolic BP and hs-CRP level in overweight group in comparison to normal weight group as showed in table (3-3).

Table (3-3) the mean levels of parameters in study classified as normal weight and overweight.

Variables	Normal weight(BMI≤26.5 Kg/m^2)	Over weight (BMI>26.5 Kg/m^2)	P-value
hs-CRP mg/L	4.59± 6.2	7.07± 12.31	0.387
Cholesterol mg/dL	204.5± 44.9	187.1± 51.8	0.213
Triglyceride mg/dL	179.5± 99.5	164.0± 53.9	0.367
Systolic BP mmHg	132.2± 16.3	147.8± 52.1	0.174
Diastolic BP mmHg	82.8± 9.0	85.0± 7.9	0.367

According to age of patients the results showed slightly insignificant increase in mean levels of diastolic BP, systolic BP and cholesterol and insignificant decrease of hs-CRP and triglyceride in patients more than 60 years compared with less than 60 years as showed in table (3-4).

Table (3-4) the effect of age patients on hs-CRP, triglyceride, cholesterol, diastolic BP and systolic BP.

Variable	**Less than 60 years**	**More than 60 years**	**P. value**
hs-CRP mg/L	**7.62± 13.68**	**4.71± 6.03**	**0.312**
Cholesterol mg/dL	**194.3± 45.8**	**195.7±52.1**	**0.922**

Triglyceride mg/dL	**172.2± 96.9**	**171.0± 62.2**	**0.959**
Systolic BP mmHg	**133.8± 14.8**	**145.6± 52.1**	**0.311**
Diastolic BP mmHg	**83.3± 7.1**	**84.5± 9.3**	**0.637**

Also our study revealed that there was significant increase in the mean cholesterol level in patients have duration less than 5 year of hypertension compared with more than 5 years, we have observed that long history of disease (more than 5 years) have an insignificant increase in hs-CRP and triglyceride levels and insignificant decrease in systolic BP and diastolic BP compared to those (less than 5 years) group showed in table (3-5).

Table (3-5): the effect of duration of disease on hs-CRP, cholesterol, triglyceride, diastolic BP, systolic BP.

Variable	Less than 5 years	More than 5 years	P. Value
hs-CRP mg/L	**3.81± 2.93**	**7.74± 13.13**	**0.166**
Cholesterol mg/dL	**209.9± 40.0**	**182.5± 53.2**	**0.048**
Triglyceride mg/dL	**170.3± 94.8**	**172.5± 61.4**	**0.921**
Sytolic BP mmHg	**144.6± 57.6**	**137.2± 14.9**	**0.521**
DiastolicBP mmHg	**84.1± 8.2**	**83.9± 8.7**	**0.920**

Discussion:

Hypertension is most important public health problem in developing countries and one of major risk factors for cardiovascular disease.

In this study, 50 patients with hypertension were studied to evaluate serum hs-CRP, total cholesterol and triglyceride as predictor marker for CVD.

The results of independent t-test showed that, there was a highly significant increase in hs-CRP level of the case in comparison with the control group of (p-value 0.002). This result agreed with the previous study that reported that HTN is a part of an inflammation, therefore observed elevated levels of hs-CRP in hypertensive individuals, which may be due to CRP, induce a decrease in endothelium-dependent relaxation and thus a potential risk factor for HTN, reverse causation might also be implicated, whereby high blood pressure might induce inflammation and raise CRP levels. Our results indicate that high sensitive CRP could be a useful predictor marker for cardiovascular disease in hypertensive patients [12].

The results of this study clearly showed that the total cholesterol and triglyceride were significantly higher in hypertensive patients in comparison to normotensive individuals with (p-value 0.000) for both parameters. These findings were completely in agreement with the result of previous studies [13]. There is a close relationship between HTN and lipid abnormalities. This gives evidence that cholesterol induces endothelial dysfunction even at normal or high to normal by reducing the bioavailability of endothelium-derived nitric oxide. Endothelium vasodilation, in fact correlates inversely with total cholesterol levels [14]. These results indicate the routine investigation of lipid profile in

hypertensive patients may help to prevent further aggravation and risk of CVD.

The results showed the mean serum hs-CRP has an insignificant difference in females compared to males with p-value of (0.387). These results agree with [15].

In this study the mean TG and cholesterol levels showed insignificant difference when compared males with females with p-values of (0.86 and 0.511) respectively. These finding agree with [16].

Our results revealed that there was an insignificant difference in mean hs-CRP in overweight hypertensive patients in comparison to normal weight with a p-value of (0.387).These finding agree with [17].

In addition the results showed that there was an insignificant difference in mean triglyceride levels between normal weight and overweight patients with p-value of (0.509). This agreed with previous study [12].

*The results denoted that there was an insignificant increase in systo*lic and diastolic BP in overweight compared to normal weight with p-values of (0.174 and 0.367) respectively. These results are in accord with [18]. The possible justification that obesity characterized by the activation of the sympathetic nervous system, which leads to the activation of the renin angiotensin system and sodium retention might hold true [19].

As far as age is concerned the results found no significant increase in cholesterol in patients elder than 60 years compared to younger individuals with a (p-value 0.922), yet an insignificant decrease in hs-CRP and TG, with p- values (0.312 and 0.959) respectively, was observed.

The results also elucidated that there was no significant difference in systolic and diastolic BP between individuals below 60 years of age and

those above with p-values (0.311 and 0.637) respectively. This was in controversy with [20].

On the other hand concerning the duration of disease there was no significant difference in TG, hs-CRP, diastolic BP and diastolic BP with p-values of (0.921, 0.166, 0.920 and 0.521) respectively. In contrast there was a significant increase in the mean cholesterol level in those, who spent less than 5 years duration of disease compared to those who suffered more than 5 years of disease duration with a p-value of (0.048). This finding agreed with the previous study that reported the deleterious effects of antihypertensive drugs, like thiazide on lipid profile, observed mainly in the short term and almost disappear in long term studies that last for 5 or more years [21].

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