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Original Article

An Assessment of the Relationship Between Essential Hypertension, Nf-Kb Transcription Factor and Oxidative Stress

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ABSTRACT

Background and aims. *The mechanisms that are associated with the development and progression of hypertension or high blood pressure have not been totally demystified. As a result of hypertension being associated or linked with the inflammation cascades, this research was designed to determine BMI (body mass index), Systolic and diastolic blood pressure (SBP and DBP), Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB p65), gluthathione peroxidase (GPx) and 8-hydroxy-2'-deoxyguanosine (8OHdG) in hypertensive subject's relative to control.* ***Methods.*** *A total of one hundred and (185) subjects, of which, sixty-five (65) and sixty (60) subjects were treated and newly diagnosed essential hypertensive subjects respectively while the remaining sixty (60) subjects were apparently healthy subjects without hypertension were used as control samples. Statistical analysis was done using SPSS, ANOVA was the tool of choice in comparing means, and all values were significant at p< 0.05.* ***Results.*** *In this research, DBP, SBP, NF-κB P65 and 8OHdG were significantly higher while GPx was lower in both treated and newly diagnosed hypertensive subjects compared with control. A significant higher variation in DBP, SBP, NF-κB P65, 8OHdG and GPx was observed in newly diagnosed hypertensive subjects when compared with treated hypertensives.* ***Conclusion.*** *It appears activation of the inflammation Cascades through the NF-κB pathway together with oxidative stress and oxidative DNA are associated with essential hypertension. Furthermore, the beneficial effect of treatment in the form of Diet, Lifestyle modifications and antihypertensive drugs can be described as incontrovertible. These findings could help in designing better testing and treatment strategies to get better clinical outcomes.*

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INTRODUCTION

Hypertension (or HTN) or high blood pressure is an abnormally persistent high arterial blood pressure. The Joint National Committee 7 (JNC7) pegs normal blood pressure at a systolic BP < 120 mmHg and diastolic BP < 80 mm Hg. Hypertension is defined as systolic BP level of ≥140 mmHg and/or diastolic BP level ≥ 90 mmHg [1]. Essential hypertension is defined as a form of hypertension in which secondary causes such as Reno vascular disease, renal failure, pheochromocytoma, aldosteronism, or other causes are ruled. Essential hypertension is a heterogeneous disorder, with different patients having different underlying factors that lead to the development of high blood pressure. Essential

hypertension stands on its own because the causes of high BP in most patients presently classified as having essential hypertension can be recognized [2].

Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells is a complex that regulates : transcription of DNA, c production of cytokines and the survival of the cell as a living entity .The gene that controls ;the transcription factor NF-κB is a very important regulator of immunological and inflammatory responses. The NF-κB /Rel family of proteins in mammals consists of five members: p50, p52, p65 (Rel-A), c-Rel, and Rel-B proteins, which form homo- or heterodimers and stay inactive in resting cells as a complex with inhibitory molecules known as IB proteins. The heterodimer of p50 and p65 is the most common form of NF-κB activated by the canonical route. If subjected to traditional view, hypertension acts as a major associate of endothelial dysfunction and vascular damage, promoting activation of endothelial cells, recruitment of inflammatory cells in the arterial wall and activation of vascular resident elements. It has therefore been shown that as a result of the aforementioned, an inflammatory response can ensue in the arteries of animal models of hypertension. This phenomenon is characterized and mediated by the production and release of cytokines and adhesion molecules [3]. Mechanisms leading to this inflammatory response are complex and can include both mechanical stress of the wall of the arteries and pro-inflammatory effects of humoural factors, such as Angiotensin II (AngII). Evidences from basic science researches and clinical studies showed that AngII, besides regulating the vascular tone, may exert some pro-inflammatory effects on the arterial wall, in the process eliciting vasodilatation and reducing nitric oxide (NO) generation [4]. It has been concluded from experimental research that inflammation contributes to the development of hypertension by inducing vascular damage, renal damage, and/or abnormal central neural regulation [5]. The prevalence of risk factors for cardiovascular disease such as obesity, diabetes mellitus, and dyslipidemia has also been reported to increase with the development of hypertension. Therefore, the paradigm shift inflammation may influence the development of van array of systemic pathophysiological processes or conditions involved in the development of hypertension [6].

Antioxidants are molecules stable enough to donate an electron to a rampaging free radical and neutralize I its deleterious effectt, as a rule, these antioxidants delay or inhibit cellular damage mainly through their free radical scavenging property. Such antioxidants, including glutathione, ubiquinol, and uric acid, are produced during normal metabolism in the body [7]. Antioxidants are of two types; Endogenous and Exogenous antioxidants. Endogenous antioxidants are enzymes, like superoxide dismutase, catalase, glutathione peroxidase or non-enzymatic compounds, such as uric acid, bilirubin and albumin. Exogenous antioxidants include; vitamin E, vitamin C, β-carotene, vitamin E, flavonoid [8] and must be taken therapeutically or through diet.

Normal cellular metabolism is well established as the source of endogenous reactive oxygen species (ROS), and it is these (normally nonpathogenic) cellular processes that account for the background levels of oxidative DNA damage detected in normal tissue. Electron transport chains all possess the potential to “leak” electrons to oxygen resulting in superoxide formation. Whereas there is growing evidence for the involvement of ROS in atherosclerotic plaque development, the role of DNA damage in this chronic inflammatory disease is less clear, one of the most striking results of it cardiovascular manifestations were reported by [9], postulating a strong correlation between premature coronary heart disease in men and high lymphocyte 8-OHdG levels. [10]. In an experimental model of atherosclerosis, increased levels of 8-OH-dG were reduced consequently to a reduction of dietary lipid [11]. Humans who do not have *GSTM1* have been known to possess higher levels of 8-OHdG in the smooth muscle cell DNA from atherosclerotic lesions [12]. These reports are further evidence for the presence of DNA damage in cardiovascular disease, but fail to determine whether or not this is an epiphenomenon. Countless experiments have provided evidences that DNA and RNA are susceptible to oxidative damage. Oxidative nucleotide as glycol and 8-hydroxy-2-deoxyguanosine is found to be increased during oxidative damage to DNA under UV radiation or damage due to free radical interactions. Maybe because of being charged with the responsibility of being the cell’s power house, there is documented evidence that mitochondrial DNA is more vulnerable to oxidative damage that have role in many diseases including cancer [13].

The Haptoglobins (Hp) are plasma Alpha-glycoprotein which binds free hemoglobin,summarily preventing oxidative stress and other damages. Haptoglobin is an acute phase reactant that binds free hemoglobin and removes it from the circulation to prevent kidney injury and iron loss following hemolysis [14]. Also, by binding free hemoglobin, haptoglobulin performs the functions of an antioxidant. In addition, haptaoglobin has been known as a potent suppressor of lymphocyte function. the end point of this is the modulation of type 1 and type 2 helper T cell(Th1/Th2) so that a balance within the body can be achieved. Three major haptoglobulin phenotypes are known to exist (Hp 1-1, Hp 2-2, and Hp 2-2). Hp 1-1 is bio chemically the most effecient in mopping up free hemoglobulin while Hp 2-2 is adjudged to be the least active, Hp 2-1 being the intermediate [15]. Haptoglobin binds to free hemoglobin, forming hemoglobin-haptoglobin (Hb-Hp) complex, which is then degraded by the monocyte macrophage system. It can therefore be deduced that amain function of haptoglobin is to prevent tissue damage caused by free hemoglobin and reduce iron loss in hemolytic conditions. Haptoglobin, formed as a result of the expression of the *Hp* gene, is a scavenger of free

hemoglobin. Haptoglobin levels increase or decrease in response to various acquired conditions. They are inherited in a co-dominant manner and result in the 3 phenotypes, that is, Hp 1-1, Hp 2-1, and Hp 2-2. Unlike Hp 1 proteins which exist in dimer forms, Hp 2 proteins can polymerize to form multimers resulting in a higher molecular mass. This unique property is applied in haptoglobin phenotyping [16]. It also affects determination of the reference interval of haptoglobin levels in serum resulting in higher ranges being observed when the $Hp1$ allele is present and lower ranges when the $Hp2$ allele is present [16]. As essential hypertension has been linked to accelerated inflammation, oxidative stress and plasma protein abnormalities, this research was designed to evaluate the likely influence that the haptoglobin types will have on the inflammatory cascades and, perhaps blood pressure.

METHODS

Study Design

A case control design was used; a stratified sampling method was used. Stratification was by age, therapy and complication. Ethical Clearance was obtained from Federal Medical Centre, Ido Ekiti, Ekiti State. The nature and purpose of research was explained to each participant using an informed consent for illiterate participants and verbal explanation for illiterate participant. Participants were not being forced to answer questions, but at their free will. The participants were assured of confidentiality and voluntary participation and there were told no financial benefits whatsoever.

Study area and sample size

Study area was Federal Teaching Hospital, Ido-Ekiti and its immediate environs. A total of 190 subjects were investigated, 60 of these were apparently healthy subjects who served as control subjects. 65 were newly diagnosed hypertensive subjects, the remaining 65 subjects were hypertensive subjects on therapy. An informed consent in written form was obtained from the subjects after due explanation before they partook in the study. Stratification was by based on age, gender and therapy.

Inclusion and exclusion criteria

Men and women who are hypertensive whether on therapy or not partook in the study. Inclusion was based on the cut-off of at least 140mmHg systolic or 90mmHg diastolic blood pressure. Subjects below the age of 21 years, pregnant women, nursing mothers, diabetes mellitus subject, chronic kidney disease, and sufferers of other disease conditions were excluded.

Sample Collection

Venous Blood sample of about 5ml was collected from the cubical Fossa using 22G needle and syringe, out of which 5mlsinto plain bottle. The blood in the non-anticoagulant bottle was be allowed to clot first and centrifuged at 12000rpm for 5minutes to separate serum from cells. The serum sample was stored at a temperature of -20 degree Celsius for maximum of 21 days before assays for NF-κB p65 and oxidative DNA damage.

Methods of Determination of Parameters

Body mass index, expressed in kg/m^2.was calculated for each individual by using the formula:
Formula used; BMI = Weight (kg)/Height (m)^{2}It is expressed in kg/m^2 [17].
Systolic and diastolic blood pressure of the participants was measured using a blood pressure monitor.
Principle: the oscillations of pressure in a sphygmomanometer cuff are recorded during gradual deflation; the point of maximal oscillation corresponds to the mean intra-arterial pressure. The oscillations begin at approximately systolic pressure and continue below diastolic, so that systolic and diastolic pressure can only be estimated indirectly according to some empirically derived algorithm.
Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells P65 was estimated using ELISA technique.
Principle: NF-κB ELISA kit is high sensitive and specific assay with a simple and optimized procedure. The 96 – well (8 ×12 strips) clear plate is pre immobilized with NF-κB consensus sequencing oligo. The activated NF-κB (nuclear extract) in sample portion was added into the well and binds to the oligo. The activated NF-κB was detected with a specific antibody against p65 subunit and a HRP conjugate. The assay utilizes colorimetric detection method, which can be easily measured by spectrophotometry at 405nm.
8OHdG as a marker of Oxidative DNA Damage (8OHdG) was estimated using Sandwich ELISA technique.
Principle: The Principle is based on standard sandwich enzymes linked immunosorbent assay (ELISA) technology. Human specific polyclonal antibodies precoated onto the micro well plates and the enzymes labeled antibody and a serum contain naïve antigen is mixed, resulting between the native antigen and the antibodies to form a sandwich

complex. After equilibrium is attained, the antibody bound fraction is separated form unbound antigen by decantation. The density of color produced is proportional to the concentration of analytic present in the sample captured in the plate.

Statistical Analysis

Results obtained were subjected to statistical analysis using SPSS (version 17 software, SPSS Inc. Chicago, Illinois, USA). All parameters were expressed as mean + S.D. The ANOVA was the tool of choice in comparing means. Correlation was also done. Values are to be statistically significant or otherwise $p<0.05$.

RESULTS

Distribution of all Subjects under examination

A combined total of one hundred and ninety subjects (190) subjects were included in this study. One hundred and thirty (130) subjects had history of hypertension and sixty (60) subjects that do not have hypertension disease were used as control. Out of the 130 essential hypertensive subjects, 65 were on treatment while the remaining 65 were newly diagnosed.

When comparing all estimated parameters across groups, BMI, SBP, DBP, 8OHdG and NF-κB Levels was significantly higher in both treated and newly diagnosed hypertensive subjects when compared with control($p=0.001$). However, GPx Levels was significantly lower in both treated and newly diagnosed hypertensive subjects relative to control. With the exception of BMI, there was a significant variation in the levels of the above parameters between the treated and the newly diagnosed group.

Figures 1 to 4 presents and conpared the values of all assessed parameters in different haptoglobin phenotypes. Hp 1-1 appears to be the optimum as the most favourable level of these parameters was seen in hypertensives belonging to this group. Hp 2-2 appears to be associated with the highest values of DBP, SBP, NF-κB P65 and 8OHdG but lower GPx. Hp 2-1 appears to be the intermediate

Table 1. Estimated parameters in treated and newly diagnosed hypertensive subjects compared to control

Variables	Treated HTN n=65	Newly diagnosed HTN n=65	Control n=60
Gender(male/female)	31/34	30/35	28/32
BMI	23.65±2.04^{A}	24.44±2.21^{EA}	22.67±1.57
SBP(mmHg)	136.76±4.75^{CF}	152.8±5.06^{F}	122.58±4.2
DBP(mmHg)	89.23±3.38^{CF}	95.65±5.75^{F}	78.83±3.38
8OHdG (ng/ml)	6.62±2.89^{C}	5.38±5.^{19FA}	2.90±1.96
NF-κB (u/ml)	7.38±1.34^{CF}	9.89±1.11^{F}	2.97±0.70
GPx	90.78±14.25	86.11 ±5.17	133.76±22.03
HP polymorphisms			
1-1 (%)	10(15.4)	5(7.7)	29(48.3)
2-1 (%)	34(52.3)	26(40)	24(40)
2-2 (%)	21(32.3)	34(52.3)	7(11.7)

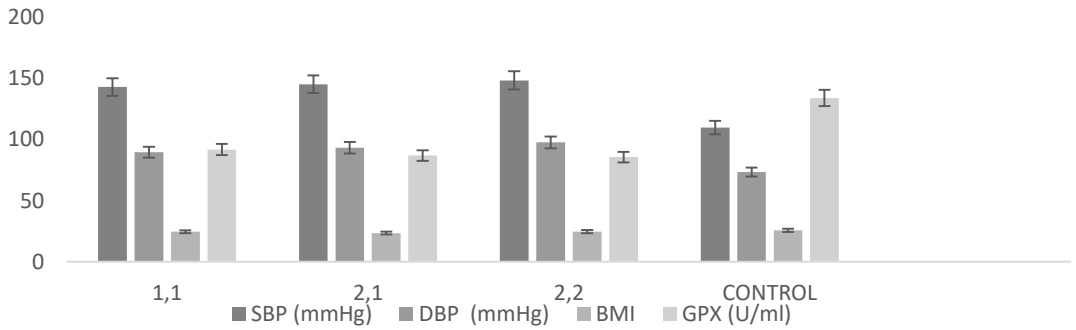

Fig 1: comparing SBP: DBP: BMI: GPX: according to haptoglobin phenotypes in all subjects

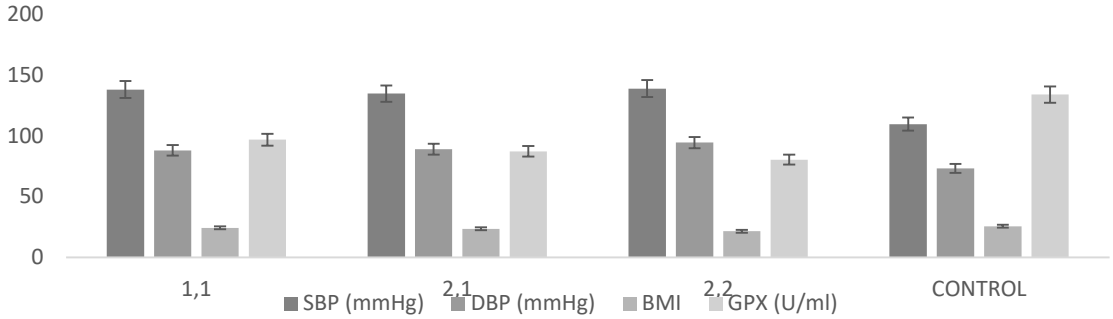

Fig 2: comparing SBP: DBP: BMI: GPX: according to haptoglobin phenotypes in treated hypertensive subjects

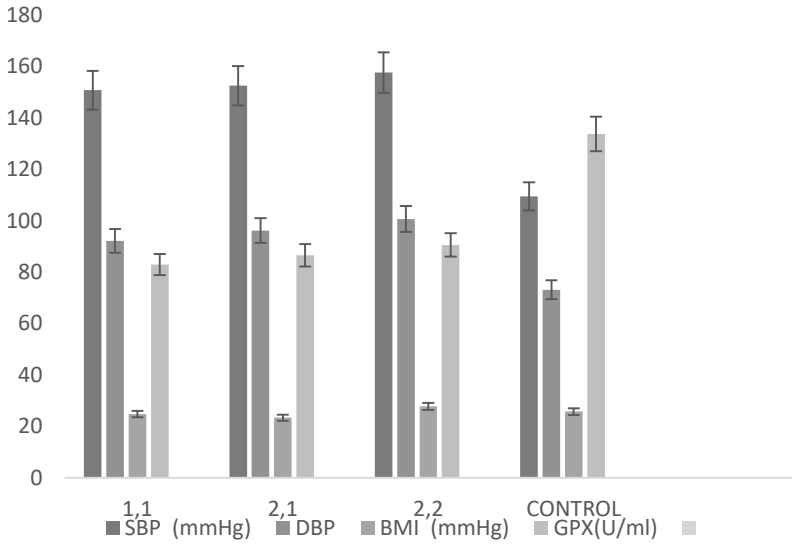

Fig 3: Comparing SBP: DBP: BMI: GPX according to haptoglobin phenotypes in untreated hypertensive subjects

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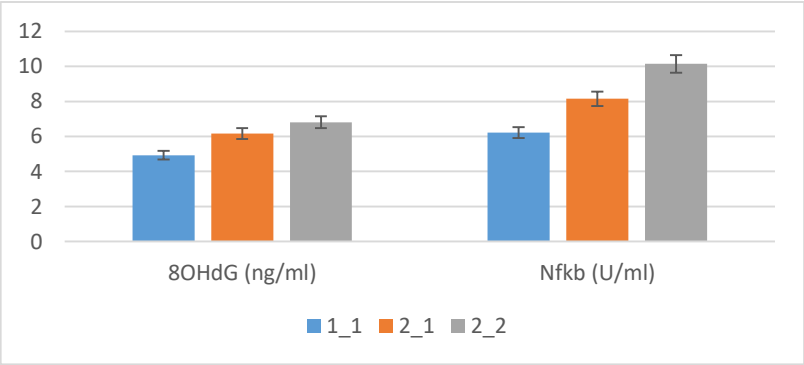

Figure 4: comparing 8OHdG and NFKB according to haptoglobin phenotypes in hypertensive subjects

DISCUSSION

Hypertension (HTN) Hypertension is usually defined by the presence of a chronic elevation of systemic arterial pressure above a certain threshold value. Hypertension can be defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg [18]. Common symptoms of hypertension include: Severe headache, irregular heartbeat and difficulty breathing, blood in urine, pounding in the chest or ears and neck, vision problem and nose bleed. There are two types of

hypertension: Primary hypertension and secondary hypertension. Essential or primary hypertension is defined as high BP whose etiology cannot be adduced to any specific condition or ailment [2]. As hypertension has been thought to be a manifestation of an interplay between the inflammation cascades and antioxidant status/ ROS accumulation, this study was designed primarily to assess body mass index, (BMI), systolic and diastolic blood pressure (SBP and DBP) , Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells NF-κBP65(NF-κBP65 and oxidative DNA damage(8OHdG). Secondly, it was also designed to assess the effect of treatment, gender and age on all estimated parameter.

BMI (Body mass index) is a person's weight in kilograms divided by the square of height in meter (kg/m^2).It ranges from as follows <18.5kgm^2 indicates underweight. 18.5kg/m^2 to 25kg/m^2 indicates normal; 25.kg/m^2 to <30kg/m^2 indicates obesity [17]. In this research, BMI was significantly higher in untreated (p=0.0035) hypertensive subjects when compared with control. This finding partially agrees with the works of [19] where body mass index was seen to be insignificantly higher in hypertensive, whether treated or untreated, when compared to control. These findings are however not surprising as obesity have been known to be a risk factor for the development of hypertension [20]. So have earlier postulated that accumulation of fats predisposes to inflammation which in turn brings about an increase in blood pressure [21]. However, the bidirectional relationship between hypertension and obesity is still subject to confirmation Also BMI appears to normalize upon classical treatment as seen when treated were compared with untreated hypertensive subjects. Treatment with Diuretic drugs appears to be the best drugs in keeping BMI in check. BMI in both treated and untreated hypertensive subjects appears to be directly proportional with advancement with age. The highest pressure within the major arteries as the heart muscle contracts to pump blood through the body is known as systolic pressure while the diastolic pressure is the lowest pressure found within the major arteries when the heart muscle relaxes between beats [22]. Systolic and Diastolic blood pressure were found to be significantly higher when compared with control (p=0.001). This finding is in agreement with the work of Flint *et al*. [23] which shows that Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) were higher in hypertensive subjects compared to control. These findings are however not surprising as increased pulse pressure have been known to be a risk factor for the development of hypertension. The use of diuretic appears to be the best drugs in returning Diastolic and Systolic blood pressure back towards normal. There was no significance difference in blood pressure across the gender lines, but according to age, it was observed that blood pressure not only increases with advancement in age but that response to treatment reduces with advancement in age a finding that agrees with an earlier report [24]

Nuclear factor kappa-light-chain-enhancer of activated b cells (NF-κB) represents a family of inducible transcription factors, which regulates a large array of genes involved in different processes of the immune and inflammatory responses [25]. p65, also known as RelA, is one of the five components that form the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) transcription factor family. NF-κB p65 level was significantly higher in both treated and untreated hypertensive compared to control (p=0.001). This finding is line with Price *et al*. [26] where NF-κB p65 was seen to be significantly higher in hypertensive subjects compared to control. As hypertension have been theorized to be an inflammatory disease Solak *et al*. [27], the finding that NF-κB p65- a known mediator of the inflammation cascades being higher in hypertensive subjects is showing a direction towards which the management of hypertension should be directed. However, NF-κB p65 seen to be lower in treated compared to untreated hypertensive subjects further confirms the efficacy or indispensability of treatment or management, the management of hypertension have been known to give better clinical outcomes the moment its multifactorial nature was taken into consideration [28]. When hypertension is to occur, the wall of the blood vessels will be inflamed, infiltration of the immune mediator and cells will occur, the laying down of non-cellular matrix will reduce the volume of inner space of blood vessels, hypertension will then occur as a result of vascular remodeling [29]. As a result of this finding a likely research question of whether NF-κB p65 level is associated with hypertension can be answered in the affirmative.

8-hydroxy-2′-deoxyguanosine (8OHdG) is an indicator of oxidative stress, impaired metabolism, and mitochondrial dysfunction, 8OHdGis a compound formed through hydroxylation of the guanine base by radical oxygen species (ROS) [30]. 8OHdGis thus, a dual parameter in assessing both antioxidant status and DNA damage [31]. In this research, there was a significant variation when treated was compared with control (p=0.001) and when untreated hypertensive was compared with control (p=0.0360) and also when both treated and untreated hypertensive subjects were compared (p=0.3466). This finding is line with Di Minno *et al.* [32] which shows that 8OHdG level has a significant variation when treated hypertensive was compared with control, when untreated hypertensive was compared with control and when untreated and treated were compared with control. As 8OHdG has been seen to be higher in this research in hypertensive patients even much more when the hypertensive is untreated, buildup of ROS when hypertension is

untreated could be the likely reason why NF-κB inflammation is about [33]. It has been known that oxidative DNA damage results in macromolecular damage and is implicated in various disease states such as cardiovascular diseases, diabetes, cancer, neurodegeneration, and aging [34]. These findings look interesting and may be the link and solution where altered aging, some metabolic diseases and high incidence of cancer is associated with hypertensive patients, also when there is an increased body mass index (BMI), among hypertensive subjects it can cause an increased risk of DNA damage which could lead to oxidative stress [35].

The Haptoglobins (Hp) are plasma Alpha-glycoproteins which binds free hemoglobin, thus preventing oxidative damage [36]. Three major haptoglobin phenotypes are known to exist (Hp 1-1, Hp 2-1, and Hp 2-2). Hp 1-1 is biologically the most effective in binding free hemoglobin and suppressing inflammatory responses associated with free hemoglobin. Hp 2-2 is biologically the least active, and Hp 2-1 is moderately active [15]. In this study, Hp 2-2 (46.34%) has the highest frequency in essential hypertensive subjects compared to Hp 2-1 (14.63%) and Hp 1-1(39.03%) in all subjects. These findings go along with previous works where the relationship between haptoglobin and development of hypertension was recorded. The reason for the higher incidence of Hp 2 allele in hypertension and much more in untreated hypertension could be as a result of BMI (body mass index), lack of this allele's ability to scavenge ROS, which could lead to the development of hypertension. As a result of the findings above, the question that asked whether some haptoglobin phenotypes affect antioxidant status in essential hypertension relative to control, with reference to this work, the Hp phenotype 2(Hp 2-1 and Hp2-2) can be said to be a determinant of higher blood pressure in hypertensive subjects

An antioxidant enzyme class that has the ability to scavenge free radicals is glutathione peroxidase (GPX). The exposure of ROS increases the production of antioxidant enzymes. Glutathione peroxidase can be rapidly expressed when cells or organisms are exposed to oxidative stress [37]. In this study, GPX in treated and untreated hypertensive subjects, respectively was insignificantly higher when compared to control. GPX was significantly higher in treated subjects when compared with untreated subjects. This finding goes along with the works of [38]. Glutathione forms a part of the antioxidant system that plays a vital role in preventing oxidative stress, and an imbalance in the oxidant/antioxidant system has been linked to the pathogenesis of hypertension. Oxidative stress has been implicated in the pathogenesis of hypertension and patients with hypertension or animal models of hypertension have been found to have higher levels of plasma free radicals, markers of oxidative stress, and decreased antioxidant capacity when compared with normotensive controls [39]. Hypertension has been linked to generation of ROS and the antioxidant system has been known to be lower. Hypertension is considered to be the most important risk factor in the development of CVD. An increasing body of evidence suggests that oxidative stress, which results in an excessive generation of reactive oxygen species (ROS), has a key role in the pathogenesis of hypertension.

CONCLUSION

This research showed that inflammation and oxidative DNA damage is linked to essential hypertension, it was discovered that NF-κB P65 and 8OHdG level was high in treated hypertensive and much higher in untreated hypertensive when compared with control. These findings could help in determining better management of essential hypertension cases which will give a better outcome.

Recommendation

There is need to explore various possible forms of action to help in the management of essential hypertension, as much the effect of drugs in form of lifestyle modification, diet and antihypertensive drugs is undeniable, NF-κB p65 and 8OHdG levels should be included as routine laboratory tests for hypertensive subjects. It should be recommended for better clinical outcome.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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