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Neutrophil-to-lymphocyte ratio in patients with white-coat hypertension

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ABSTRACT

Introduction: White coat hypertension (WCH), a distinct phenotype of hypertension, is defined as elevated office blood pressure (BP) measurements during repeat visits with normal out-of-office BP measurements. The association of WCH with cardiovascular risk remains unclear; however, current data support an association between untreated WCH and the risk for cardiovascular events, cardiovascular mortality, and all-cause mortality. Increased inflammatory processes may explain the underlying pathophysiology of the increased risk for cardiovascular events in WCH; therefore, we evaluated the neutrophil-to-lymphocyte ratio (NLR) of patients with WCH compared with matched normotensive controls.

Material and Method: Forty-five eligible subjects with WCH and 45 age, sex, and BMI matched healthy and normotensive subjects were included in the study. The subjects were assessed by office arterial BP and 24-hour ambulatory BP measurements. An automated blood count analyzer measured the NLR values.

Results: The mean NLR in the patients-with-WCH group was significantly higher than that in the control group (2.67±0.27 vs. 2.46±0.34, p<0.001, Student's t-test); however, NLR was not correlated with BP measurements in either the WCH or control group.

Conclusion: NLR, a marker of inflammation, was increased in patients with WCH compared to the controls. Inflammation is a triggering mechanism for various cardiovascular and cerebrovascular events. Therefore, NLR has value as a potential independent risk factor that deserves further study, particularly in patients with WCH.

Keywords: High blood pressure, systemic hypertension, inflammation, neutrophil-to-lymphocyte ratio, white coat hypertension

INTRODUCTION

Hypertension is a major preventable cause of morbidity and mortality worldwide. Due to the increasing use of out-of-office blood pressure (BP) measurements, several distinct hypertension phenotypes have become apparent. One of these is white coat hypertension (WCH), defined as elevated office BP measurements during repeated visits with normal out-of-office BP measurements as assessed by home and/or 24-hour ambulatory BP monitoring measurements. Therefore, current guidelines recommend using out-of-office BP measurements to diagnose phenotypes, such as WCH (1). A systematic review demonstrated that the overall prevalence of WCH, defined by 24-hour ambulatory BP measurements (ABPM), in the general population ranges from 5% to 65%, and the prevalence increases with age (2-5).

Although hypertension is a well-established risk factor for morbidity and mortality, the association of WCH with cardiovascular risk remains unclear (5, 6). Several previous meta-analyses have reported weak to no associations of WCH with cardiovascular and all-cause mortality (7), especially for treated WCH (4); however, a recent meta-analysis revealed untreated WCH, but not treated WCH, as a risk factor for cardiovascular events, cardiovascular mortality, and all-cause mortality (8). An increase in atherosclerosis possibly causes this increase. Inflammatory processes are increasingly being recognized as playing a central role in the pathogenesis of atherosclerotic diseases and their complications (9). Elevated levels of systemic inflammatory markers have been found to be associated with cardiovascular diseases (10-12), and increased inflammatory processes may explain the underlying pathophysiology of the increased risk for cardiovascular events in WCH. Several previous studies have demonstrated an increase in novel inflammatory markers in WCH and sustained hypertension, such as high-sensitivity c-reactive protein (CRP), soluble CD40 ligand, procalcitonin, and pentraxin-3 (13-16).

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The neutrophil-to-lymphocyte ratio (NLR), routinely determined by complete blood count analysis, has emerged as a novel inflammation marker. It has been documented that NLR may predict inflammatory status for various cardiovascular risk factors, such as hypertension, diabetes mellitus, obesity, and smoking (17-19). Increased NLR is also associated with a poor prognosis of various cancers and ischemic heart disease (20-22). Although it has previously been shown that increased NLR is associated with essential hypertension and its complications, the relationship between NLR and WCH has not been previously studied (23-26). This study aimed to evaluate the NLR in patients with WCH compared with age-, sex-, and body mass index (BMI)-matched normotensive controls.

MATERIAL AND METHOD

Study Setting

This cross-sectional case-control study was conducted in the internal medicine outpatient clinics of the local University Hospital per the Declaration of Helsinki. Approval for this study was obtained from Akdeniz University Medical School Non-Interventional Clinical Researchs Ethics Committee (Date: 08.07.2020, Decision No: 488). All patients provided written informed consent.

Study Design and Participants

This study aimed to evaluate patients with WCH compared to age-, sex-, and body mass index (BMI)-matched normotensive controls. WCH was defined and diagnosed as a measured office BP of greater than 140/90 mmHg with an ambulatory measurement of less than 135/85 mmHg (2). Healthy subjects, recruited from the routine check-up program of the local University Hospital, were used as a control group. Patients with sustained hypertension; diabetes mellitus (fasting glucose >126 mg/dL or hemoglobin A1c >6.5%); a history of smoking or alcohol intake of more than 30 g/day; hyperlipidemia; obesity (BMI ≥30 kg/m^2); cardiac, renal, cerebral, and other systemic diseases; and recent major surgery or illness were excluded from the study. Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, as recommended by the 2013 ESH/ESC guidelines for the management of arterial hypertension (27). Hyperlipidemia was defined as the presence of at least one of the following conditions: increased plasma triglycerides (>200 mg/dL), total cholesterol (>200 mg/dL), low-density lipoprotein cholesterol (>130 mg/dL), or decreased high-density lipoprotein cholesterol (<40 mg/dL for men and <50 mg/dL for women) (28). Forty-five eligible subjects with WCH and 45 age-, sex-, and BMI-matched healthy and normotensive subjects were included in the final analysis.

Assessment Instruments

The subjects underwent a comprehensive assessment, including medical history, physical examination, and measurement of laboratory variables. Body weight and height were measured with the subjects wearing light clothes without shoes. BMI was calculated as the weight (kg)/height squared (m)^2. All the subjects' resting electrocardiograms were normal. A mercury sphygmomanometer was used to measure arterial BP after the patient had remained in a sitting position for 5 min. For each subject, the average of three readings obtained within 5 min was recorded. For ABPM, a portable non-invasive recorder (SpaceLabs Medical Devices, Inc., Redmond, WA, USA) programed to record BP every 30 min for 24 hours was used for all measurements. This information was then used to calculate the average ambulatory BP over 24 hours for each subject. For laboratory evaluations, blood samples were collected from the antecubital vein without a tourniquet between 08:30 a.m. and 09:00 a.m. after overnight fasting. An automated blood count analyzer measured the total and differential blood cell counts. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Fasting plasma glucose, creatinine, alanine aminotransferase levels, c-reactive protein and lipid profiles were measured by enzymatic-colorimetric assays (Roche Diagnostic GmbH, Mannheim, Germany).

Statistical Analyses

SPSS statistical software (SPSS for Windows 16.0, Chicago, IL, USA) was used for the analyses. For a type 1 (α) error of 0.05 and a power of 80%, a sample size per group of at least 36 subjects was needed to detect an actual difference. The normality of the distribution was determined by Shapiro–Wilk tests. NLR values between the groups were compared by Student's t-tests and Pearson's correlation coefficients. Data for categorical variables were presented as frequency and percentage, and continuous variables were expressed as mean±SD. Statistical significance was defined as $p<0.05$.

RESULTS

Age, gender distribution, and BMI were similar between the WCH and control groups. Office systolic and diastolic BP measurements were significantly higher in patients with WCH ($p<0.001$, Student's t-test). The metabolic parameters in the study groups were similar as a result of the participant selection process. The mean NLR in the patients-with-WCH group was significantly higher than that in the control group (2.67±0.27 vs. 2.46±0.34, $p<0.001$, Student's t-test). However, NLR was not correlated with BP measurements in the WCH and control groups (Spearman's rho correlation coefficient 0.16 and 0.09, p value 0.14 and 0.42, respectively) (**Table**).

Table. Study group characteristics and laboratory results

Parameters	WCH group (n=45)	Control group (n=45)
Gender (men/women)	45 (21/24)	45 (22/23)
Age (years)	55±3	55±2
BMI (kg/m^2)	23.7±3.1	23.6±3.2
Office systolic BP measurement (mmHg)	146±4.7**	127±5.1
Office diastolic BP measurement (mmHg)	94±5.3***	81±4.6
Fasting plasma glucose (mg/dL)	86.8±9.7	87.1±9.6
Creatinine (mg/dL)	0.9±0.2	0.9±0.2
Alanine aminotransferase (U/L)	25.7±3.5	25.5±3.4
C-reactive protein (mg/dL)	0.23±0.11	0.17±0.07
Total cholesterol (mg/dL)	169.4±21.9	169.9±22.1
LDL cholesterol (mg/dL)	88.3±12.1	88.9±11.6
HDL cholesterol (mg/dL)	48.7±5.4	48.4±5.3
Triglyceride (mg/dL)	129.6±15.8	128.9±16.3
White blood cell (×10^3/mm^3)	6.76±1.72	6.69±1.74
Neutrophil (×10^3/mm^3)	4.74±1.55	4.66±1.62
Lymphocyte (×10^3/mm^3)	1.81±0.19*	1.90±0.21
Neutrophil to lymphocyte ratio	2.67±0.27***	2.46±0.34

WCH: White coat hypertension, BMI: Body mass index, BP: Blood pressure, LDL: low-density lipoprotein; HDL: high-density lipoprotein. *p<0.05, **p<0.01, and ***p<0.001, Student's t-test, WCH group vs. control group.

DISCUSSION

Hypertension is a well-established risk factor for morbidity and mortality, possibly due to its' relation with atherosclerosis. Atherosclerosis is characterized by a complex multifactorial pathophysiology. Inflammatory processes in vessel walls are increasingly recognized as playing a central role in the initiation, progression, and final steps of atherosclerosis (9,29). WCH, a distinct phenotype of hypertension, was recently demonstrated as a risk factor for cardiovascular events, cardiovascular mortality, and all-cause mortality, especially if left untreated (4,8). Several inflammatory markers have been shown to be increased in WCH (14-16), but the relationship between NLR and WCH has not been previously studied. In this matched case-control study, we aimed to evaluate the NLR in patients with WCH compared to age-, sex-, and body mass index (BMI)-matched normotensive controls. We excluded patients with several confounding factors such as sustained hypertension, diabetes mellitus, smoking or alcohol intake, hyperlipidemia, obesity, cardiac, renal, cerebral, and other systemic diseases, and recent major surgery or illness. In this study population, we have demonstrated that NLR was increased in patients with WCH, compared to age-, sex-, and body mass index (BMI)-matched normotensive controls.

There are several studies in the literature on the relationship between inflammation, including NLR, and essential hypertension (23-26). However, there are limited studies about the relationship between systemic inflammation markers and WCH. Ozdogan et al. (14) reported that in patients with WCH, high-sensitivity CRP, a marker of low-grade inflammation, is higher than normotensive patients, whereas in patients with essential hypertension, high-sensitivity CRP levels were even higher than in patients with WCH. Andrikou et al. (30) confirmed higher high-sensitivity CRP levels and demonstrated that WCH is also associated with arterial stiffening compared with normotensive patients. Similarly, several studies have also reported increased soluble CD40 ligand, procalcitonin, and pentraxin-3 levels in WCH compared to normotensive groups (14-16).

Neutrophil-to-lymphocyte ratio is a novel, non-invasive, easily-calculable, and easily obtained marker as a surrogate for inflammation. NLR has been previously studies and in many hemato-oncologic, immunologic and infectious diseases as well as cardiologic disorders, and the increase has been associated with increased morbidity and mortality. It has been well documented that NLR is associated with increased inflammatory status for various cardiovascular risk factors and essential hypertension and its complications (17-19,23-26). Herein, we add to the literature that an increase in NLR is seen in patients with in WCH, compared to controls, as a novel marker of inflammation. Although WCH as a risk factor for cardiovascular events, cardiovascular mortality, and all-cause mortality is still of debate, an increase in NLR as a surrogate for increased inflammation may suggest that patients with WCH are also at risk for cardiological disorders such as ischemic heart disease.

This study has certain limitations. First, the sample size was small, although higher than the calculated sample size; nevertheless, both groups were homogeneous in terms of age, gender, BMI, and laboratory results. Second, due to the case-control study design, the results may not reflect long-term effects. Third, these findings are limited to a homogeneous group of patients, so the results may not apply to all patients with WCH.

CONCLUSION

We have demonstrated that NLR, a marker of systemic inflammation, was increased in patients with WCH compared to controls. Inflammation is a triggering mechanism for various cardiovascular and cerebrovascular events; therefore, NLR has value as a potential independent risk factor that deserves further study, particularly in patients with WCH.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for this study was obtained from Akdeniz University Medical School Non-Interventional Clinical Researchs Ethics Committee (Date: 08.07.2020, Decision No: 488).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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