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Biomarker Differences between Controlled and Uncontrolled Hypertension among US Adults: National Health and Nutrition Examination Survey 2005-2010

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ABSTRACT: This study aims to determine biomarker differences between controlled and uncontrolled hypertension using nationally representative samples.
Those in the uncontrolled hypertension group were more likely to have CVD (p=0.0258) and diabetes (p=0.0004), less likely to meet the recommended waist circumference (p=0.0039) and BMI (p=0.0209), and less likely to drink alcohol (p=0.0002) than those in the controlled hypertension group, after controlling for demographic variables. Upon controlling for demographic variables, risk factors and diseases related to hypertension, those in the uncontrolled hypertension group had higher total cholesterol (p<.0001), HDL (p=0.0702, marginally significant), LDL (p<.0001), triglycerides (p=0.0702, marginally significant), apolipoprotein B (p<.0001), transferrin receptor (p=0.0692, marginally significant), and ACR (p<.0001) than those in the controlled hypertension group.
Conclusion: Our study found that ACR, total cholesterol, HDL, LDL, triglycerides, apolipoprotein B, and transferrin receptor are biomarkers associated with the risk of uncontrolled hypertension compared to controlled hypertension. Since uncontrolled hypertension is linked to very high risks of cardiovascular disease and chronic kidney disease, our findings may provide a partial answer to why antihypertensive treatment is ineffective for certain groups of patients. Further studies are warranted to examine the cause of uncontrolled hypertension.

KEYWORDS: Biomarker, Uncontrolled Hypertension, Transferrin receptor, ACR

I.INTRODUCTION

Hypertension is an important risk factor for cardiovascular disease, stroke, chronic kidney disease, and other health conditions [1,2] and it remains a public health problem in the United States (U.S.) due to its high prevalence and poor control rates[3]. According to the Centers for Disease Control and Prevention (CDC) [4], while the prevalence rate of hypertension in the U.S. increased from 25.5% in 1988-1994 to 30.4% in 2011-2014, uncontrolled hypertension rates decreased from 77.2% to 51.3% in the same time frame. This decrease in the uncontrolled hypertension rate may have been driven by a significant increase in the proportion of hypertensive patients who take multiple antihypertensive agents. These polytherapy regimens have been shown to be effective for patients to meet their blood pressure (BP) goals[5-8]. Despite this decrease in uncontrolled hypertension rates, uncontrolled hypertension is still a powerful risk factor for future fatal and nonfatal cardiovascular disease events[9]. Failure to treat uncontrolled hypertension can result in permanent neurological, cardiovascular and renal damage[9].

Biomarkers have been widely employed in clinical practice for the diagnosis and assessment of the severity of hypertension [10, 11]. Previous studies have described that several biomarkers, such as C-reactive protein (CRP), plasminogen activator inhibitor 1.(PAI-1), B-type natriuretic peptide(BNP), homocysteine, urinary albumin/creatinine ratio, serum ferritin, Apolipoprotein B , Transferrin Receptor 1, etc., were significantly related to hypertension. [11-17]

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Vol. 5, Issue 9 , September 2018

However, limited studies have been conducted to investigate biomarkers to distinguish between uncontrolled and controlled hypertensive patients. Therefore, this study aimed to determine biomarker differences between controlled and uncontrolled hypertension using nationally representative samples from National Health and Nutrition Examination Survey (NHANES) data from 2005-2010.

II. METHODS

A. Study Population

The NHANES program has been conducted every other year by the National Center for Health Statistics in the CDC since 1999 [18]. Designed to assess the health and nutrition status of adults and children in the U.S., NHANES is a biennial comprehensive survey that combines interviews and physical examinations. More information about measurement procedures and protocols can be found in the NHANES website available at http://www.cdc.gov/nchs/about/major/nhanes/datalink.htm.
Three cycles of NHANES surveys, 2005-2006, 2007-2008, and 2009–2010, were combined for this study. After excluding those who were aged less than 20 years or normotensive, a total of 4,565 remaining participants were included in the analyses.

B.Measures

Main Predictor: Uncontrolled Hypertension
Uncontrolled hypertension was defined as those who had systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg among those taking antihypertensive medications. Controlled hypertension was defined as systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg among hypertensive subjects taking antihypertensive medication.

Potential Covariates
For this study, we evaluated the following hypertension risk factors reported in the literature to be associated with hypertension risk: waist circumference, body mass index (BMI), current smoking status, alcohol consumption, and physical activity. Alcohol consumption was defined as having at least 12 drinks of any type of alcoholic beverage in the past year. Physical activity was defined as engaging in physical activity of moderate-intensity for at least 10 minutes continuously. Demographic variables included age, gender, race, education, and marital status.

Cardiovascular disease (CVD), diabetes and chronic kidney disease (CKD) were included in this study. CVD was defined as having any of five major CVD outcomes, including congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack, and stroke. Diabetes and CKD were defined as being told by a doctor to currently have diabetes and CKD, respectively.

Outcome variables: Biomarkers
The following biomarkers were selected based on evidence of association from previous clinical studies and availability in the NHANES data: total cholesterol, HDL- cholesterol (HDL), LDL-cholesterol (LDL), triglyceride, albumin to creatinine ratio (ACR), parathyroid hormone, apolipoprotein B, C-reactive protein (CRP), serum folate, Insulin, fasting glucose, homocysteine, ferritin, and transferrin receptor. Most of these biomarkers have been reported to be associated with hypertension either individually or as part of a multi-marker risk score.[11-18]

In short, biomarkers were measured on baseline blood samples collected in the mornings. Lipids, including total cholesterol, HDL, LDL, triglyceride, and apolipoprotein B were measured enzymatically in serum or plasma using Roche Hitachi 717 and Hitachi 912**.** Glucose concentration was determined by a hexokinase method using Roche Hitachi 911. Insulin was determined by a ELISA method using Merocodia Insulin. CRP was measured on a Behring Nephelometer with latex-enhanced nephelometry. Serum folate was measured using the Bio-Rad Laboratories Quantaphase II Folate radioassay kit. Ferritin was measured with the Roche/Hitachi 912 clinical analyzer. Total homocysteine in plasma is measured by the Abbott Homocysteine assay. Transferrin receptor was measured via immuno-turbidimetry using Roche kits on the Hitachi 912 clinical analyzer. Parathyroid hormone was measured with the Elecsys 1010 analyzer. Urine albumin and urine creatinine were used for the calculation of ACR. Urine creatinine was measured by a variation of the Jaffe method on the Beckman CX3 analyzer. Urine albumin concentration was

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Vol. 5, Issue 9 , September 2018

measured by the fluorescent immunoassay. A more detailed description of the method used can be found on the NHANES web site. [19]

Statistical Analyses

Descriptive statistics of the demographic variables, risk factors of hypertension, chronic diseases related to hypertension, and biomarkers were analyzed using a combination of a weighting factor in the NHANES and PROC SURVEYREG, PROC SURVEYLOGISTIC, and PROC SURVEYFREQ in SAS. Rao–Scott $\chi 2$ tests, which adjusted for the complex sampling design using PROC SURVERYFREQ, were conducted to assess any differences in demographic characteristics between controlled and uncontrolled hypertension groups. Because the distributions of all biomarkers were skewed, logarithmically transformed biomarkers were used in the analyses. Moreover, due to non-normality, geometric means were measured to assess differences in biomarkers between controlled and uncontrolled hypertension groups using multiple regression analyses after controlling for age, gender, race, education, marital status, alcohol consumption, waist circumference, BMI, CVD, diabetes, and CKD. These controlled variables were selected using $p<0.20$ in bivariate analyses as a screening criterion by Mickey and Greenland (1989)[20]. Standard errors of the multiple regression analyses were estimated using Taylor series linearization (TSL), implemented within the SURVEYREG procedure, to incorporate complex sampling design and post-standardization. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc).

III.RESULTS

Table 1 provides the descriptive statistics for the demographic characteristics of the controlled and uncontrolled hypertension groups in this study sample. Those in the uncontrolled hypertension group were more likely to be older ($p<.0001$), less educated ($p<.0001$), and not married ($p=0.0437$) than their controlled hypertension group counterparts. While a higher proportion of black was observed among uncontrolled hypertension group than controlled hypertension group (18.5% vs. 13.5%), a lower proportion of white (69.1% vs. 75.4%) was observed among uncontrolled hypertension group ($p<.0001$). However, no gender difference was found between groups. Although frequency was not weighted, percentage and Rao–Scott $\chi 2$ tests accounted for the sampling design and weights.

Table 1. Demographic differences between controlled and uncontrolled hypertension

	Controlled Hypertension (n=3117)	Uncontrolled Hypertension (n=1448)	
	Mean ± SE or N(%)	Mean ± SE or N(%)	p-value
Age (years)	60.4 ± 0.48	64.0 ± 0.43	<.0001
Gender			
Female	1666 (54.8)	802 (57.7)	0.0998
Male	1451 (45.2)	646 (42.3)	
Race			
Hispanic	569 (6.3)	284 (7.7)	<.0001
White	1650 (75.4)	675 (69.1)	
Black	782 (13.5)	438 (18.5)	
Others	116 (4.7)	51 (4.7)	
Education			
Less than High school	981 (21.0)	521 (27.2)	<.0001
High school graduate	789 (27.6)	385 (28.4)	
Some college	767 (27.2)	353 (27.9)	
College graduate or above	571 (24.2)	187 (16.4)	
Marital status			
Not married	1379 (37.1)	690 (41.9)	0.0437
Married	1733 (62.9)	757 (58.1)	

Frequency was not weighted.
Percentage and Rao–Scott $\chi 2$ tests accounted for sampling design and weights.

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Vol. 5, Issue 9 , September 2018

Table 2 presents the unadjusted and demographic adjusted differences in risk factors and hypertension-related chronic diseases between the controlled and uncontrolled hypertension groups. In unadjusted differences, those in the uncontrolled hypertension group were more likely to have CVD (p=0.0258) and diabetes (p=0.0004), less likely to meet the recommended waist circumference (p=0.0039) and BMI (p=0.0209), and less likely to drink alcohol (p=0.0002) than those in the controlled hypertension group. No significant difference existed in smoking status between the two hypertension groups. After controlling for demographic variables, those in the uncontrolled hypertension group were less likely to drink alcohol (p=0.0298) and less likely to meet the recommended waist circumference (p=0.0745, marginally significant) than those in the controlled hypertension group.

Table 3 presents the unadjusted and adjusted mean differences in biomarkers between the controlled and uncontrolled hypertension groups. In the unadjusted mean differences in biomarkers, those in the uncontrolled hypertension group had higher total cholesterol (p<.0001), HDL (p=0.0022), LDL (p=0.0013), apolipoprotein B (p=0.0002), transferrin receptor (p=0.0577), ACR (p<.0001), parathyroid hormone (p=0.0338), and homocysteine (p=0.082, marginally significant) than those in the controlled hypertension group. No difference in triglycerides, glucose, insulin, CRP, folate, and ferritin existed between the two hypertension groups.
After controlling for demographic variables, risk factors and diseases related to hypertension, those in the uncontrolled hypertension group were found to have higher total cholesterol (p<.0001), HDL (p=0.0702, marginally significant), LDL (p<.0001), triglycerides (p=0.0702, marginally significant), apolipoprotein B (p<.0001), transferrin receptor (p=0.0692, marginally significant), ACR (p<.0001) than those in the controlled hypertension group. No difference in glucose, insulin, CRP, folate, parathyroid hormone, homocysteine, and ferritin existed between the two hypertension groups.

Table 2. Differences in major risk factors and hypertension-related diseases between controlled and uncontrolled hypertension

	Controlled Hypertension (n=3117)	Uncontrolled Hypertension (n=1448)	
	Mean ± SE or N(%)	Mean ± SE or N(%)	p-value*
Unadjusted differences			
Alcohol consumption, n(%)	1766 (69.9)	789 (61.8)	0.0002
Smoking, n(%)	487 (30.1)	211 (29.7)	0.8977
Physical activity, n(%)	1067 (40.9)	484 (38.2)	0.1895
Waist circumference (cm)	106.8 ± 0.36	105.0 ± 0.49	0.0039
BMI, (kg/m^2)	31.6 ± 0.16	30.93 ± 0.25	0.0209
CVD, n(%)	845 (22.1)	413 (25.7)	0.0258
Diabetes, n(%)	838 (22.3)	432 (26.5)	0.0004
CKD, n(%)	172 (4.3)	103 (5.4)	0.1141
Adjusted differences			
Alcohol consumption, n(%)	1766 (63.4)	789 (57.9)	0.0298
Smoking, n(%)	487 (23.2)	211 (24.3)	0.6244
Physical activity, n(%)	1067 (32.8)	484 (32.9)	0.9546
Waist circumference (cm)	104.6 ± 0.40	103.5 ± 0.56	0.0745
BMI, (kg/m^2)	30.8 ± 0.19	30.5 ± 0.26	0.3534
CVD, n(%)	845 (24.3)	413 (24.5)	0.9420
Diabetes, n(%)	838 (28.0)	432 (30.2)	0.1222
CKD, n(%)	172 (4.5)	103 (5.0)	0.4667

*Survey regression procedure was performed.
Adjusted for age, gender, race, education, and marital status

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Vol. 5, Issue 9 , September 2018

Table 3. Differences in biomarkers between controlled and uncontrolled hypertension

	Controlled Hypertension (n=3117)	Uncontrolled Hypertension (n=1448)	p-value*
	Geometric mean ± SE	Geometric mean ± SE	
Unadjusted differences			
Total Cholesterol (mg/dL)	187.8 ± 1.01	196.7 ± 1.01	<.0001
HDL-Cholesterol (mg/dL)	48.9 ± 1.01	50.9 ± 1.01	0.0053
LDL-Cholesterol (mg/dL)	103.1 ± 1.01	109.3 ± 1.01	0.0021
Triglycerides (mg/dL)	147.3 ± 1.02	152.1 ± 1.02	0.2530
Apolipoprotein B (mg/dL)	91.2 ± 1.01	96.8 ± 1.01	0.0002
Glucose (mg/dL)	112.8 ± 1.01	115.5 ± 1.01	0.1518
Insulin (uU/mL)	12.8 ± 1.03	11.7 ± 1.03	0.0356
C-reactive protein(mg/dL)	0.3 ± 1.03	0.2 ± 1.05	0.6709
Folate (ng/mL)	17.1 ± 1.02	16.9 ± 1.03	0.6414
Ferritin (ng/mL)	52.6 ± 1.07	54 ± 1.18	0.8816
Transferrin receptor (mg/L)	3.6 ± 1.03	4.0 ± 1.04	0.0231
Albumin to Creatinine Ratio (mg/g)	0.1 ± 1.04	0.2 ± 1.05	<.0001
Parathyroid Hormone (pg/Ml)	45.6 ± 1.02	49.9 ± 1.03	0.007
Homocysteine (umol/L)	9.0 ± 1.02	9.5 ± 1.02	0.0383
Adjusted differences			
Total Cholesterol (mg/dL)	180.7 ± 1.01	191.5 ± 1.02	<.0001
HDL-Cholesterol (mg/dL)	49.2 ± 1.02	50.5 ± 1.02	0.0702
LDL-Cholesterol (mg/dL)	94.8 ± 1.03	102.1 ± 1.04	<.0001
Triglycerides (mg/dL)	148.5 ± 1.04	156.9 ± 1.03	0.0692
Apolipoprotein B (mg/dL)	87.5 ± 1.02	93.7 ± 1.02	<.0001
Glucose (mg/dL)	119.6 ± 1.02	121.8 ± 1.02	0.2174
Insulin (uU/mL)	11.8 ± 1.06	11.4 ± 1.06	0.2760
C-reactive protein(mg/dL)	0.3 ± 1.06	0.3 ± 1.07	0.7854
Folate (ng/mL)	18.8 ± 1.05	17.8 ± 1.05	0.1105
Ferritin (ng/mL)	79.3 ± 1.32	74.7 ± 1.31	0.6938
Transferrin receptor (mg/L)	3.8 ± 1.13	4.3 ± 1.12	0.0152
Albumin to Creatinine Ratio (mg/g)	0.2 ± 1.08	0.4 ± 1.10	<.0001
Parathyroid Hormone (pg/Ml)	57.7 ± 1.08	59.9 ± 1.07	0.2299
Homocysteine (umol/L)	10.9 ± 1.05	10.8 ± 1.04	0.6875

*Survey regression procedure was performed.

IV. DISCUSSION

To our knowledge, our study is the first to examine biomarker differences between controlled and uncontrolled hypertension. Overall, our study found that ACR, transferrin receptor, and lipid profile including total cholesterol, HDL, LDL, triglycerides, and apolipoprotein B were associated with the risk of uncontrolled hypertension compared to that of controlled hypertension.

A. Lipids and Uncontrolled hypertension

It has been well known that dyslipidemia is associated with hypertension, such that blood pressure becomes abnormally high due to the heart's increased strain to pump blood through hardened and narrowed arteries from cholesterol plaque and calcium buildup[21]. Our study had partially different findings with previous studies on uncontrolled hypertension. For instance, Prejbisz et al. found that while total cholesterol, LDL cholesterol, and triglyceride levels were higher in patients with uncontrolled hypertension compared to patients with controlled hypertension, HDL was not different between two groups[22]. Further, Jafa et al. reported that while total cholesterol and LDL were higher in patients with

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International Journal of AdvancedResearch in Science, Engineering and Technology
Vol. 5, Issue 9 , September 2018

uncontrolled hypertension than in those with controlled hypertension, triglycerides and HDL were not different between two groups[23]. However, our study showed that all lipids, including total cholesterol, HDL, LDL, triglycerides, and apolipoprotein B were higher in uncontrolled hypertension than in controlled hypertension.
One possible reason for the contrasting results in HDL and triglycerides between previous studies and our study may be related to racial/ethnic differences. Prejbisz et al. included Polish patients in Poland in their study whereas Jafa et al. included Southern Asians in rural Bangladesh, Pakistan, and Sri Lanka in their study. Several studies have described that HDL and triglycerides differentially affect racial/ethnic groups in chronic diseases including metabolic syndrome and myocardial infarction [24-26]. Therefore, the relationship between HDL or triglycerides and uncontrolled hypertension may be different among racial/ethnic groups. Although we controlled racial/ethnic groups in the analyses to assess the relationship between HDL or triglycerides and uncontrolled hypertension, further studies are needed regarding racial/ethnic differences in these relationships.

B. Glomerular endothelial function and uncontrolled hypertension
Urine albumin excretion or ACR, which reflects glomerular endothelial dysfunction,is used to screen people with chronic conditions including hypertension and diabetes that put them at an increased risk of developing CKD and/or CVD [27]. Previous studies have also shown an association between the urine albumin excretionor ACR and incidence of hypertension[12, 28, 29], and recent studies have examined the association of ACR with uncontrolled hypertension, specifically [30,31]. For example, Agarwal found that uncontrolled hypertension was strongly related to ACR in CKD, and Verdalles et al. found that the prevalence of resistant hypertension increased significantly with albuminuria measured with ACR. While both studies examined these associations among CKD patients, our study demonstrated that ACR was higher in patients with uncontrolled hypertension than in those with controlled hypertension even after controlling for CVD and CKD. Because ACR is an important biomarker to diagnose for CKD, CKD may be a confounder of the relationship between ACR and uncontrolled hypertension. However, our study found a strong association between ACR and uncontrolled hypertension without CKD participants ($p<0.0001$, not shown).

C. Transferrinreceptor and uncontrolled hypertension
Transferrinreceptor plays an important role in cellular iron transport and may be elevated in persons with iron deficiency [15]. Recent studies have shown that iron deficiency or elevated transferrin receptors is related to several cardiovascular diseases including chronic left heart failure and pulmonary hypertension.[15, 32-35]. Our study is, to our knowledge, the first to examine that transferrin receptor is associated with uncontrolled hypertension. We found that transferrin receptor was higher in patients with uncontrolled hypertension than in those with controlled hypertension even upon controlling for demographic variables, risk factors, CVD, CKD, and diabetes. This finding has important clinical and public health implications

D. Limitations
Our study has several limitations related to data. First, controlled and uncontrolled hypertension were defined by blood pressure on a single visit, which may have incorrectly assigned some participants to uncontrolled hypertension. Second, medication for hypertension was determined by self-reports, which may have been inaccurate. Further, adherence to antihypertensive medication was not assessed although adherence issues are common in antihypertensive therapy.

E. Conclusions
Despite these limitations, our study is the first to examine biomarker differences between controlled and uncontrolled hypertension using nationally representative hypertensive patients from three NHANES periods. Our findings suggest that ACR, total cholesterol, HDL, LDL, triglycerides, apolipoprotein B, and transferrin receptor are associated with the risk of uncontrolled hypertension compared to that of controlled hypertension. Further, uncontrolled hypertension is linked to very high risks of CVD and/or CKD. Therefore, our findings may provide a partial answer to why antihypertensive treatment is not effective for certain groups of patients. Further studies are needed to examine the causal biomarker pathways of uncontrolled hypertension.

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Vol. 5, Issue 9 , September 2018

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