RESEARCH ARTICLE

Association of adipokines and endothelial dysfunction with ambulatory, central, and peripheral blood pressures in healthy young adults

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ABSTRACT
Early identification of individuals at risk for the development of hypertension would provide the opportunity to target such patients with individualized preventive therapy. Emerging evidence strongly suggests that both ambulatory and central blood pressures (BP) are better predictors of future cardiovascular events compared to peripheral office brachial pressures. Accordingly, the purpose of this study was to investigate predictors (adipokines, insulin sensitivity, and endothelial dysfunction) of higher ambulatory, central, and peripheral blood pressures in a mixed ethnicity cohort of 299 non-hypertensive, young-middle aged adults.
After adjustment for BMI and QUICKI (Quantitative Insulin Sensitivity Check Index: insulin sensitivity measure), multiple linear regression showed that both PAI-1 (Plasminogen activator inhibitor-1) and adiponectin were significantly associated with central SBP ($p = 0.034$ and 0.045, respectively). PAI-1 also had a significant association with 24-hour DBP and a marginally significant association with central DBP ($p = 0.016$ and 0.066, respectively). Higher QUICKI was significantly associated with lower peripheral SBP ($p = 0.023$), as well as lower peripheral and ambulatory DBP. Endothelial dysfunction (lower % FBF (forearm blood flow) increase) was significantly associated with higher peripheral, ambulatory, and central SBP and DBP measures ($p < 0.01$ for all). In conclusion, the study findings suggest the possible future utility of PAI-1, adiponectin, QUICKI, and endothelial function as early predictors of BP-associated cardiovascular risk in young asymptomatic individuals.

Key terms: adipokines, insulin resistance, endothelial dysfunction, ambulatory blood pressure, central blood pressure, prehypertension

INTRODUCTION

Elevation in systolic blood pressure (SBP) is the leading risk factor worldwide for cardiovascular mortality [1]. Therefore, identification and prevention of the progression from prehypertension to sustained arterial hypertension (HTN) is of critical importance [2]. Substantial differences in BP are observed when measured outside versus in the office. Therefore, ambulatory BP monitoring is considered the reference gold standard for out-of-office BP assessment [3].

Peripheral blood pressure measured in the brachial artery is accepted as an important predictor of future cardiovascular risk. However, systolic pressure in the aorta (central) systolic pressure is typically lower than corresponding brachial values [4]. Central blood pressure have been reported to be a stronger determinant of cardiovascular events than are peripheral blood pressures.[5]

Accordingly, current evidence strongly suggests that both ambulatory and central blood pressures (BP) are better predictors of future cardiovascular events compared to peripheral office brachial pressures.[6] Studies to date comparing ambulatory and central blood pressures with peripheral pressures have naturally focused on older hypertensive individuals at relatively high risk for cardiovascular morbidity and mortality.[7,8] However, earlier identification of individuals at risk for cardiovascular disease would provide the opportunity to target such patients with individualized preventive therapy.

The purpose of this study was to identify predictors of higher ambulatory, central, and peripheral blood pressures in non-hypertensive individuals. Higher levels of inflammation, insulin resistance, and endothelial dysfunction are thought to be involved in the pathogenesis of elevated BP.[9] Correspondingly, we investigated the association of inflammatory markers (adipokines and CRP), insulin sensitivity/resistance (quantitative insulin sensitivity check index, QUICKI), and endothelial function (forearm blood flow, FBF) with mean peripheral (office), ambulatory (24-hour), and central pressures in young, non-hypertensive, non-diabetic individuals.

METHODS

Study design and population. The study was designed to assess the role of inflammatory markers and microvascular dysfunction in the development and progression of insulin resistance and prehypertension. The study protocol was approved by the Thomas Jefferson University Institutional Review Board and written informed consent was obtained from all subjects. Study participants were recruited from the patient population of a large urban academic family medicine outpatient practice serving 40,000 individuals in Philadelphia, Pennsylvania, and from a cohort of 500 young adult African American men and women enrolled in prior investigations of cardiovascular risk. Recruitment took place between July 2011 and February 2014. The main eligibility criteria were: (i) age between 18 and 45; (ii) no clinically diagnosed hypertension, i.e.,

systolic blood pressure (SBP) <140 mm Hg and diastolic blood pressure (DBP) <90 mm Hg; (iii) no clinically diagnosed diabetes. In this paper, we report on the evaluation of the association of inflammatory markers, insulin sensitivity/resistance and endothelial function with blood pressures, using data collected during baseline assessments.

Data collection and study measures. Information was collected on subject sociodemographics, family history of diabetes and cardiovascular disease, and anthropometric measures (height and weight, waist circumference). Body Mass Index (BMI) was computed as weight divided by height squared (kg/m^2). Finally, both serum and urine samples were obtained and analyzed.

Adipokine (adiponectin, IL-6, PAI-1,TNF□) and CRP measurement. The adipokine and CRP assays were performed using commercially available ELISA kits following the manufacturers' instructions.

Glucose and insulin measurement. Glucose was analyzed by the glucose oxidase technique with the Glucostat analyzer (YSI, Model 27), which was calibrated routinely. Insulin was assayed using a solid phase radioimmunoassay, "Coat-A-Count" (Diagnostic Products Corporation). The quantitative insulin sensitivity check index (QUICKI) was computed as the reciprocal of the sum of the log fasting glucose (mg/dL) and the log fasting insulin (uU/ml), in measured units without SI conversion, following the method of Katz et al: QUICKI = 1 / { log fasting glucose (mM/l) + log fasting insulin (uU/ml) }.[10] Higher (more positive) QUICKI values indicate greater insulin sensitivity.

Endothelial function. We followed a well standardized, non-invasive method of post-ischemic flow mediated vasodilation.[11] This approach assesses the entire forearm vasculature rather than a single large artery. Forearm blood flow (FBF) was measured at rested baseline (FBF_{base}) and again at hyperemic induced maximal vasodilation (FBF_{max}). FBF_{max} and the ratio of FBF_{max}/FBF_{base} are accepted non-invasive measures of endothelial function.[12] We analyzed a variation of the FBF ratio, the percent increase between the FBF_{base} and FBF_{max}, computed as $(FBF_{max}-FBF_{base})/FBF_{base}$ x 100. Greater increases in FBF indicate better endothelial function.

Office blood pressure was assessed after 10 minutes rest. Two successive BP readings, with a one-minute interval between measurements, were obtained from subjects in the seated position, using a Dinamap ProCare 100 automatic BP monitor (GE Healthcare, Piscataway, NJ), with the appropriate size cuff on the left arm for all subjects.

Ambulatory blood pressure monitoring. Using a validated oscillometric device (Spacelabs model 90217, Issaquah, WA), automated readings were taken at 20-minute intervals during waking hours, and at 30-minute intervals during sleep. Ambulatory BP was assessed during a normal weekday, including normal recreational activities.

Central pressure measurement. The SphygmoCor XCEL system (AtCor Medical Inc (UASA), Itasca, IL) uses a brachial general transfer function to assess central SBP and DBP.

Data analyses. The primary aims of these analyses were to assess the association of

inflammatory markers (CRP, IL6, TNF□, PAI-1, and adiponectin) with blood pressure, specifically: (i) peripheral (office) SBP and DBP; (ii) ambulatory (24-hour) SBP and DBP; and (iii) central SBP and DBP. Higher levels of CRP, IL6, TNF□, and PAI-1 were hypothesized to be associated with higher BP values, while the reverse was hypothesized for adiponectin. Additional study aims included the assessment of the association between insulin resistance and endothelial dysfunction with the peripheral, ambulatory, and central pressures.

Continuous variables were summarized with means and standard deviations (or with geometric means and interquartile ranges, if skewed), while categorical variables were summarized with frequency counts and percentages. We used multiple linear regression to analyze each BP outcome, with the final model including all 5 inflammation measures as predictors, as well as age, sex, race, marital status, employment status, smoking, drinking, body mass index (BMI), insulin sensitivity/resistance (QUICKI), and endothelial function (% FBF increase from baseline to maximal vasodilation). The analyses were conducted in SAS 9.4 and Stata 13.1.

The study was powered for the association between inflammatory markers and peripheral and ambulatory blood pressure. It had 90% power to detect effect sizes equal to about a quarter of a standard deviation in blood pressure per standard deviation of a marker (e.g., 2-3 mm Hg higher SBP per 2 mg/L in CRP, or 2 mm Hg lower DBP per 4 □g/mL in adiponectin), which correspond to correlations of about 0.20-0.25. These are small-to-modest targeted associations, but they are realistic given that the study population was young and without clinical signs of disease. Power was more limited for central blood pressure, since pulse wave measurements were available only for a subset of study participants.

RESULTS

The study enrolled a total of 312 subjects. After the exclusion of 13 subjects (1 older than 45 years, 1 hypertensive, and 11 with missing data on inflammation measures), the study population for these analyses included 299 subjects. Table 1 presents a summary of basic subject characteristics. The study included relatively young subjects (18 to 45 years old), primarily women, and sizable numbers of both African Americans and Asians.

Table 1. Summary of study subject characteristics (N = 299 except where noted).

Age (years), mean [sd]	27 [7]
Sex, n (%)	
Female	191 (64)
Male	108 (36)
Race, n (%)	
White*	162 (54)
African American	74 (25)
Asian	63 (21)
Marital status, n (%)	
Not married	245 (82)
Married	54 (18)
Employment status, n (%)	
Student	183 (61)
Unemployed	22 (7)
Employed	94 (31)
Smoking, n (%)	17 (6)
Alcohol, n (%)	228 (76)
Weight (kg),** mean [sd]	72 [17]
Body Mass Index (BMI, kg/m^2),** mean [sd]	25.4 [5.5]
BMI status,** n (%)	
Normal weight***	149 (58)
Overweight	68 (27)
Obese	38 (15)

sd: standard deviation.
(*) Includes 14 Hispanics/Latinos.
(**) Total N = 255 because of missing data.
(***) Includes 6 underweight subjects.

Table 2 summarizes the inflammation measures (CRP and four adipokines), as well as clinical variables. For SBP, ambulatory measurements tended to be higher than both peripheral and central values. For DBP, ambulatory and central measurements were higher than peripheral values. The three types of BP were strongly correlated (all correlations > 0.65, both for SBP and DBP measures). About 84% of the study subjects were normotensive by either their peripheral or ambulatory blood pressure, although the two measures did not always agree. Of 268 subjects who had measurements for both office BP and 24-hour BP, 204 (76%) were normotensive on both and 10 (4%) were pre-hypertensive on both. But 41 (15%) subjects were normotensive on one and pre-hypertensive on the other, 5 (2%) subjects were normotensive on their office BP and hypertensive on their 24-hour BP, and 8 (3%) subjects were pre-hypertensive on their office BP and hypertensive on their 24-hour BP.

Table 2. Summary of inflammation measures, insulin sensitivity/resistance, endothelial measures, blood pressure, and vascular stiffness.

INFLAMMATION MEASURES (N = 299)		
CRP (mg/L), geometric mean [iqr]	1.1	[2.1]
IL6 (pg/mL), geometric mean [iqr]	1.9	[1.5]
TNFα (pg/mL), mean [sd]	9.0	[2.9]
PAI-1 (mg/mL), mean [sd]	47	[27]
Adiponectin (µg/mL), geometric mean [iqr]	8.5	[7.8]
INSULIN SENSITIVITY/RESISTANCE (N = 297)		
Glucose (mg/dL), mean [sd]	95	[8]
Diabetes status, n (%)		
Normal (glucose <100 mg/dL)	223	(75)
Pre-diabetic (glucose 100-125 mg/dL)	74	(25)
QUICKI, mean [sd]	0.37	[0.03]
ENDOTHELIAL MEASURES (N = 271)		
FBF baseline, mean [sd]	3	[1]
FBF post-ischemic, mean [sd]	27	[9]
FBF increase (baseline to post-ischemic) (%), mean [sd]	795	[330]
BLOOD PRESSURE (N = 299 for peripheral, 268 for ambulatory, and 79 for central)		
SBP: peripheral (office) (mm Hg), mean [sd]	108	[11]
SBP: ambulatory (24-hr) (mm Hg), mean [sd]	117	[10]
SBP: central aortic (mm Hg), mean [sd]	105	[10]
DBP: peripheral (office) (mm Hg), mean [sd]	66	[8]
DBP: ambulatory (24-hr) (mm Hg), mean [sd]	72	[6]
DBP: central aortic (mm Hg), mean [sd]	75	[8]
Blood pressure status: peripheral, n (%)		
Normotensive	252	(84)
Pre-hypertensive (120-139/80-89)	47	(16)
Blood pressure status: ambulatory, n (%)		
Normotensive	225	(84)
Pre-hypertensive (130-134/80-84)	30	(11)
Hypertensive	13	(5)

iqr: interquartile range. sd: standard deviation.
FBF: forearm blood flow. SBP: systolic blood pressure. DBP: diastolic blood pressure. PP: pulse pressure.

In unadjusted analyses (results not shown), higher PAI-1 levels were significantly associated with higher peripheral, ambulatory, and central SBP values, and ambulatory and central DBP values. Similarly, higher adiponectin was significantly associated with lower values on all three SBP measures and on peripheral and central DBP measures. Finally, higher CRP was significantly associated with

higher office SBP and DBP, as well as 24-hour DBP.

Tables 3 and 4 summarize the results of the final multivariable linear regression models for SBP and DBP outcomes, respectively. The results are expressed as the average mean difference in blood pressure associated with a difference of about 1 standard deviation in each marker's levels (e.g., for each additional increment of 2 mg/L in CRP, office SBP was estimated to be higher by 0.9 mm Hg, Table 3).

Table 3. Association of the inflammation, insulin sensitivity/resistance, and endothelial measures with systolic blood pressure (SBP).

Predictor*		**Office SBP** (mm Hg)			**24-hour SBP** (mm Hg)			**Central SBP** (mm Hg)		
	increment	*D*	*(95% CI)*	*P*	*D*	*(95% CI)*	*P*	*D*	*(95% CI)*	*P*
CRP (mg/L)	2	0.9	(-0.4, 2.1)	0.181	1.0	(-0.3, 2.3)	0.115	-0.3	(-2.1, 1.5)	0.758
IL6 (pg/mL)	2	-1.0	(-2.7, 0.7)	0.263	-0.7	(-2.5, 1.0)	0.433	-2.3	(-5.9, 1.3)	0.211
TNFα (pg/mL)	3	-0.6	(-2.1, 0.8)	0.371	-0.5	(-1.9, 1.0)	0.524	-1.1	(-5.7, 3.4)	0.623
PAI-1 (mg/mL)	25	-0.5	(-1.6, 0.7)	0.423	0.8	(-0.3, 2.0)	0.162	2.3	(0.2, 4.5)	0.034
Adiponectin (μg/mL)	8	-0.5	(-2.4, 1.4)	0.612	0.4	(-1.6, 2.3)	0.721	-4.8	(-9.4, -0.1)	0.045
QUICKI	0.03	-1.6	(-3.1, -0.2)	0.023	-0.7	(-2.1, 0.7)	0.325	-1.6	(-4.2, 1.0)	0.218
FBF increase (%)	300	-2.3	(-3.3, -1.3)	0.001	-2.5	(-3.5, -1.4)	0.001	-4.0	(-5.8, -2.3)	0.001

(*) All models also controlled for age, sex, race, marital status, employment status, smoking, drinking, and body mass index (BMI).
D: mean SBP difference (in mm Hg), corresponding to the increment shown (~1 standard deviation) for each predictor. CI: confidence interval. FBF: forearm blood flow.

Compared to the unadjusted results, the adjusted results regarding the inflammation measures were substantially attenuated, particularly after adjustment for BMI and QUICKI. Therefore, in the final analyses, none of the 5 inflammatory markers were significant predictors of office or 24-hour SBP (Table 3). However, both PAI-1 and adiponectin were significantly associated with central SBP ($p = 0.034$ and 0.045, respectively, Table 3). PAI-1 also had a significant association with 24-hour DBP and a marginally significant association with

central DBP (p = 0.016 and 0.066, respectively, Table 4).

Higher QUICKI was significantly associated with lower peripheral SBP (p = 0.023, Table 3), as well as lower peripheral and ambulatory DBP (p = 0.049 and 0.015, Table 4). Finally, bigger % FBF increases from baseline to maximal vasodilation were significantly associated with lower values on all 3 SBP and all 3 DBP measures (p < 0.01 for all, Tables 3 and 4).

With respect to other subject characteristics, older participants within our young cohort tended to have significantly higher SBP and DBP than younger ones (p = 0.040, 0.012, and 0.009, for the 3 SBP measures; p = 0.001, 0.001, and 0.019, for the 3 DBP measures). Males had higher office and 24-hour SBP than females (p = 0.001 for both), but gender differences were smaller and non-significant for DBP. Higher BMI was significantly associated with higher peripheral and central SBP (p = 0.001 and 0.017, respectively), but its association with DBP was weaker.

Table 4. Association of the inflammation, insulin sensitivity/resistance, and endothelial measures with diastolic blood pressure (DBP).

Predictor*		**Office DBP** (mm Hg)			**24-hour DBP** (mm Hg)			**Central DBP** (mm Hg)		
	increment	*D*	*(95% CI)*	*P*	*D*	*(95% CI)*	*P*	*D*	*(95% CI)*	*P*
CRP (mg/L)	2	0.1	(-0.9, 1.1)	0.850	0.6	(-0.3, 1.5)	0.176	0.6	(-1.2, 2.5)	0.502
IL6 (pg/mL)	2	-0.6	(-2.0, 0.9)	0.435	-0.5	(-1.7, 0.8)	0.443	-2.6	(-6.2, 1.1)	0.166
TNFα (pg/mL)	3	-0.6	(-1.8, 0.6)	0.318	-0.2	(-1.2, 0.8)	0.694	-1.5	(-6.2, 3.1)	0.513
PAI-1 (mg/mL)	25	0.6	(-0.4, 1.5)	0.237	1.0	(0.2, 1.8)	0.016	2.1	(-0.1, 4.3)	0.066
Adiponectin (μg/mL)	8	-1.0	(-2.6, 0.6)	0.238	1.1	(-0.2, 2.4)	0.110	-3.8	(-8.6, 0.9)	0.112
QUICKI	0.03	-1.2	(-2.3, 0.0)	0.049	-1.2	(-2.2, -0.2)	0.015	-0.2	(-2.8, 2.5)	0.891
FBF increase (%)	300	-1.3	(-2.2, -0.4)	0.003	-1.2	(-2.0, -0.5)	0.001	-2.4	(-4.2, -0.6)	0.009

(*) All models also controlled for age, sex, race, marital status, employment status, smoking, drinking, and body mass index (BMI).
D: mean DBP difference (in mm Hg), corresponding to the increment shown (~1 standard deviation) for each predictor. CI: confidence interval. FBF: forearm blood flow.

DISCUSSION

Both ambulatory and central blood pressures (BP) are better predictors of cardiovascular mortality compared to peripheral office brachial pressures.[6] Ambulatory BP monitoring is a better predictor of clinical outcomes than conventional office BP measurements, and uniquely affords the opportunity to identify white-coat

hypertension and masked hypertension, and to assess nighttime blood pressure.[13] Central BP has been found to be an independent and superior predictor of vascular damage and cardiovascular prognosis compared to peripheral pressures.[14,15] Central BP may better represent the load imposed on the coronary and cerebral arteries compared with peripheral pressures.[14] Previous studies comparing ambulatory and central BP with peripheral pressures have largely enrolled older hypertensive individuals.[7,8] We specifically studied young non-hypertensive individuals in an effort to identify predictors of higher peripheral, ambulatory, and central BP, which could potentially facilitate earlier identification of individuals at risk for cardiovascular disease before development of overt symptoms.

In most, but not all previous studies, ambulatory pressures are typically lower than casual office pressures.[16] In our study, mean ambulatory SBP and DBP were 9 and 6 mm Hg higher, respectively. This may be due in part to inclusion of masked hypertensives in our study (13 subjects: 5% of study cohort), along with the fact that our study population was younger than in most previously reported studies comparing ambulatory pressures to casual pressures. In a previous study specifically comparing ambulatory pressures compared to casual pressures, patients with higher ambulatory pressures were younger.[17]

Inflammatory adipokines, insulin resistance, and endothelial dysfunction have previously been identified as likely contributors to the pathogenesis of elevated BP.[9] Of the adipokines evaluated in this study, PAI-1 and adiponectin associations with BP remained significant after adjustment for insulin resistance, endothelial dysfunction, and a number of other subject characteristics. Both PAI-1 and adiponectin were significantly positively and negatively associated with central SBP respectively, while PAI-1 also had a significant association with 24-hour DBP and a marginally significant association with central DBP. The fact that associations were found between PAI-1 and adiponectin primarily with central pressures, and not peripheral and ambulatory pressures, is even more remarkable given that central BP measurements were available for only a subset of our study population and resulting power to detect associations between inflammatory markers and central BP was limited. Our results suggest that central pressures may be more reflective and/or sensitive to early signs of cardiovascular risk in younger patients, which is highly consistent with the recent expert panel recommendation that central pressures be used in clinical cardiovascular risk assessment when deciding whether to initiate, intensify or change therapy in younger patients.[18]

Adiponectin has both antidiabetic and antiatherogenic properties.[19] While the exact mechanism underlying the association between hypoadiponectinemia and cardiovascular disease in humans remains unknown, anti-inflammatory[20] and vasodilatory[21] properties of adiponectin have also been reported and could contribute to the inverse association between adiponectin and central SBP found in this study.

Hypertension has been associated with and may exert its detrimental effects in part by promotion of a prothrombotic state.[22] PAI-1 is the principal regulator of fibrinolysis.[23] Since fibrinolysis maintains blood vessel patency via clot breakdown, decreased fibrinolysis is associated with increased cardiovascular risk.[24] PAI-1 levels have previously been correlated with both SBP and DBP in 2600 individuals within the Framingham cohort, with an average age of 53.[25] Our study findings demonstrate a similar association in healthy young individuals with an average age of 27.

PAI-1 is also an acute phase reactant, with elevated levels found in inflammation.[23] Fibrinolysis is also associated with endothelial function. Since PAI-1 is synthesized in several sites including endothelium,[23] vascular endothelial injury results in lower PAI-1 levels.[26] Therefore, endothelial dysfunction is accompanied by abnormal fibrinolysis. Endothelial function is an independent predictor of cardiovascular morbidity and mortality, and is thought to be a key mediator of the progression of hypertension and atherosclerosis.[27] Endothelial dysfunction has previously been associated with central and peripheral pressures in healthy individuals ages 41-48.[28] In this study, endothelial dysfunction (lower % FBF increases) was significantly associated with higher peripheral, ambulatory, and central SBP and DBP measures in an even younger, healthy cohort.

Our findings are based on a large cohort of healthy young adults, including a sizable fraction of both African Americans and Asians. The availability of peripheral, ambulatory, and central pressures is another strength of the study, as is the measurement of (and control for) a number of relevant factors, including BMI, insulin resistance, and endothelial dysfunction. Although we assessed four specific adipokines and CRP, there are many other inflammatory markers that we did not measure which could be potentially valuable predictors of BP in a young population. Finally, our analyses and results are based on cross-sectional data from which it is difficult to infer causality. However, we are currently analyzing longitudinal follow-up findings from our study cohort. We anticipate that those prospective findings observed over time will add further information to our understanding of the development of cardiovascular risk in young asymptomatic adults.

CONCLUSIONS

We report the clustering of known cardiovascular risk factors (inflammatory adipokines, endothelial dysfunction, and blood pressure) in healthy young individuals. The study findings suggest the possible future utility of PAI-1, adiponectin, and endothelial function as early predictors of BP-associated cardiovascular risk in young asymptomatic individuals. Further longitudinal study of healthy young individuals is needed to establish whether inflammatory adipokines and endothelial dysfunction predict the future development of clinical hypertension and its associated complications.

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