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THE ASSOCIATION OF PLASMA RESISTIN WITH DIETARY SODIUM MANIPULATION, THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM, AND 25-HYDROXYVITAMIN D_3 IN HUMAN HYPERTENSION

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Abstract

Objective—Both resistin and vitamin D have been associated with the renin-angiotensin-aldosterone system (RAAS). We investigated the association between resistin and the RAAS, and resistin and vitamin D under controlled dietary sodium conditions.

Design—Retrospective cross-sectional study of subjects from the HyperPATH Consortium, who were maintained in high dietary sodium (HS) and low dietary sodium (LS) balance for one week each.

Patients—Caucasian subjects with hypertension (n=177).

Measurements—25-hydroxyvitamin D (25[OH]D) levels were used to assess vitamin D status. Plasma resistin and RAAS measures were evaluated on each dietary intervention.

Results—Resistin levels were significantly higher in LS, where RAAS activity was high, when compared to HS balance, where RAAS activity was suppressed (6.36 vs. 5.86 μg/L, $p<0.0001$); however, resistin concentrations were not associated with plasma renin activity or serum aldosterone on either diet. 25(OH)D levels were positively and independently associated with resistin in both dietary conditions (HS: $\beta=0.400$, p-trend=0.027; LS: $\beta=0.540$, p-trend=0.014).

Conclusions—Dietary sodium loading reduced resistin levels, possibly by suppressing the RAAS; however, circulating RAAS components were not related to resistin concentrations within each specific dietary sodium condition. 25(OH)D was positively associated with resistin and may be involved in resistin regulation through an unknown mechanism. Further studies to better understand resistin regulation in human hypertension are warranted.

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KEY TERMS

resistin; renin; angiotensin; sodium; vitamin D

INTRODUCTION

Adipose tissue is an endocrine organ that produces peptides with paracrine and endocrine functions termed adipokines [1]. In animal models, resistin is an adipokine whose initial importance was underscored by its association with obesity and insulin resistance [2, 3]. Subsequent human studies, however, have failed to consistently support these links [4–9]. One potential explanation for these conflicting observations may relate to the fact that resistin, while generated by adipocytes in mice, is produced by inflammatory cells within adipose tissue in humans [10–13]. While the role of resistin in human obesity and insulin pathobiology remains controversial, other studies have associated resistin concentrations with blood pressure [13–16], heart failure [17], and activity of the renin-angiotensin-aldosterone system (RAAS) [18, 19].

Experiments in transgenic mice have associated increased activity of the local adipose tissue RAAS with higher resistin levels [18]. In humans, one study described higher resistin levels in patients with primary hyperaldosteronism when compared to essential hypertensives and normotensives [19]. To our knowledge, further studies focused on elucidating the specific role of the RAAS in human resistin regulation are lacking.

Separate lines of evidence support vitamin D as a negative regulator of the RAAS [20]; vitamin D has been shown to lower renin expression in mice [21, 22], and is inversely associated with plasma renin activity (PRA) in humans [23–26]. 25-hydroxyvitamin D (25[OH]D) has been positively associated with the adipokine adiponectin [27–29], but to our knowledge has never been reported in association with resistin.

We sought to evaluate the relationship between resistin and the RAAS by studying hypertensive humans undergoing dietary sodium manipulation. We further explored the association between 25(OH)D and resistin given both their prior connections to RAAS activity.

METHODS

Study Population

This cross-sectional analysis was performed on data gathered from subjects studied in the International Hypertensive Pathotype (HyperPATH) Consortium. The HyperPATH study has been an on-going, multi-site study, aimed at investigating the pathophysiologic and genotypic mechanisms involved in hypertension and cardiovascular diseases. Participants were studied at four collaborating centers: Brigham and Women's Hospital (Boston, MA), University of Utah Medical Center (Salt Lake City, UT), Vanderbilt University Hospital (Nashville, TN), and Hôpital Européen Georges Pompidou (Paris, France).

Subjects with chronic kidney disease, coronary heart disease, heart failure, suggested or known causes of secondary hypertension, and active malignancy were not enrolled in the HyperPATH study. All enrolled subjects had a glomerular filtration rate of > 60 mL/min. Enrolled subjects were classified as having hypertension if they had an untreated seated diastolic blood pressure (DBP) > 100 mmHg, a DBP > 90 mmHg with one or more antihypertensive medications, measured as the average of three readings with standard manual sphygmomanometer, or the use of two or more antihypertensive medications. Study

procedures included dietary sodium modulation to maintain high-sodium (HS) and low-sodium balance (LS) in sequence.

Following the original study, 25(OH)D measurements were performed on all the available frozen plasma of subjects with hypertension (n=345). Since race is known to influence 25(OH)D concentrations and RAAS activity [30, 31], the final study population for this analysis was restricted to Caucasian subjects with 25(OH)D measurements who were successfully maintained in sodium balance per study protocols (below) and with available frozen plasma in both HS and LS balance to measure resistin (n=177).

The HyperPATH Study Protocol

A particular strength of the HyperPATH study design was its rigorous study protocol, conducted in Clinical Research Centers, and designed to minimize notable confounders of the RAAS (dietary sodium intake, body posture, diurnal variation, and medications). To avoid interference with RAAS assessment, participants taking angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or mineralocorticoid receptor antagonists, were withdrawn from these medications three months before study initiation. Beta-blockers were withdrawn one month before study initiation. If needed for blood pressure control, subjects were treated with amlodipine and/or hydrochlorothiazide; however, these medications were stopped three weeks prior to laboratory evaluation.

Subjects were maintained in HS (≥200 mmol Na/24h) and then LS (≤10 mmol Na/24h), for 7 days each. Both study diets also included fixed quantities of potassium (80 mmol/day) and calcium (1000mg/day); vitamin D intake was not specifically controlled. After each diet phase, participants were admitted to the institutional Clinical Research Center and maintained in a supine position overnight. For each diet phase, baseline blood sampling was obtained in the morning, frozen without preservatives until assayed, and used to measure components of the RAAS and resistin. Baseline blood pressure was determined while supine between the hours of 8:00 AM and 10:00 AM, following 10 hours of overnight rest using the average of five readings from a Dinamap automated device (Critikon, Tampa, FL). External sodium balance and diet compliance were confirmed on admission to the Clinical Research Center with a 24-hr urine creatinine and sodium excretion of ≥ 150 mmol for HS, and ≤ 30 mmol for LS. Study protocols were approved by the Human Subjects Committees/ Institutional Review Boards of each location, and informed written consent was obtained from each subject.

Biochemical Assessments

Plasma 25(OH)D levels were measured using the Diasorin assay (Stillwater, MN). Plasma renin activity (PRA) (Diasorin, Inc., Stillwater, MN), serum aldosterone (Siemens, Los Angeles, CA), plasma resistin (R&D Systems, Minneapolis, MN), and plasma glucose and insulin, were measured from the morning baseline blood sampling of both LS and HS phases. The intra-assay variation of the plasma resistin assay was 1.8–7.7% with an inter-assay variation of 3.4–9.3%, and a dynamic range of 0.21–50 μg/L. The homeostasis model assessment index (HOMA-IR) was calculated from plasma glucose and insulin values ([glucose] × [insulin] / 22.5), and used as a general representation of insulin resistance. All blood samples from the four participating study centers were processed and stored at a central laboratory (Brigham and Women's Hospital, Boston, MA).

Statistical Methods

Analyses were performed to first evaluate the relationship between resistin, dietary sodium balance, and the RAAS, and subsequently the relationship between 25(OH)D and resistin.

Paired t-tests were used to compare data between HS and LS for normally distributed variables, which are presented as mean values with standard deviations (SD). Non-normally distributed variables (HOMA-IR, PRA, and aldosterone) are presented with median values and interquartile ranges and compared using the non-parametric Wilcoxon Ranks test. Vitamin D status was categorized based on clinically relevant definitions for 25(OH)D deficiency (<49.9 nmol/L, n=70), insufficiency (49.9–74.9 nmol/L, n=81), and sufficiency (≥74.9 nmol/L, n=26) [32].

Linear regression was employed to test the associations between resistin and demographic characteristics. Multivariable adjustment for age, gender, body-mass index (BMI), HOMA-IR, and systolic blood pressure (SBP) was applied when evaluating the relationship between resistin and 25(OH)D status. Linear regression results are reported with effect estimates (β), the 95% confidence intervals for β, and the corresponding p-value. HOMA-IR, PRA, and aldosterone were transformed to their natural logarithm when used in linear regression models. The level for significance for all tests conducted was set at α=0.05 and reported p-values are two-tailed. Data analyses were performed using SAS v9.1 (Cary, NC) and SPSS v15.0 (Chicago, Il) statistical software.

RESULTS

Characteristics of the Study Population

The study population had a mean age of 49.4 years (SD=7.8, range 25–71), a mean BMI of 27.9 kg/m^2 (SD=3.5, range 19.8–37.3), and a mean 25(OH)D of 56.0 nmol/L (SD=21.5, range 15.7–148.9). As expected, HS balance was associated with a suppression of RAAS activity, an elevation of blood pressure, and a lower HOMA-IR when compared to LS balance [33] (Table 1). Furthermore, in LS balance where RAAS activity was high, plasma resistin concentrations were significantly higher when compared to HS balance (Table 1).

The Association between Components of the RAAS and Resistin

To further investigate the changes in resistin levels seen with manipulation of dietary sodium, we evaluated the relationship between resistin and individual components of the RAAS. Plasma resistin did not significantly associate with PRA or serum aldosterone concentrations under either dietary condition; although a non-significant positive trend between aldosterone and resistin was seen (Table 2). Additionally, consistent with on-going controversies in prior human studies [4–9], we observed no association between plasma resistin with BMI, insulin resistance, or blood pressure (Table 2).

The Association between 25(OH)D and Resistin

We explored the relationship between 25(OH)D and plasma resistin levels in both HS and LS balance. Increasing 25(OH)D status was associated with higher resistin concentrations in both HS (β=0.345, 95% C.I.=[0.005, 0.685], p-trend=0.047) and LS (β=0.502, 95% C.I.=[0.112, 0.892], p-trend=0.012) balance. Following multivariable adjustment for age, gender, BMI, HOMA-IR, and systolic blood pressure (SBP), 25(OH)D status remained independently associated with plasma resistin levels in both HS (β=0.400, 95% C.I.=[0.046, 0.754], p-trend=0.027) and LS (β=0.540, 95% C.I.=[0.112, 0.967], p-trend=0.014) balance (Figure 1).

DISCUSSION

Resistin is an adipokine whose role in human physiology continues to be explored; in addition to its implications in obesity and metabolism, it has been associated with hypertension [13–16] and the RAAS [18, 19]. We investigated the relationship between resistin,

the RAAS, and vitamin D in Caucasians strictly phenotyped as hypertensive, studied under meticulous dietary conditions, and observed three notable findings. First, one week of dietary sodium loading resulted in suppression of RAAS activity and decreased resistin concentrations. However, within each specific dietary intervention, resistin levels were not associated with PRA or aldosterone; this suggests that either dietary sodium manipulation may affect resistin independently of circulating RAAS activity, or possibly that the variability in RAAS activity within each dietary intervention was too small to observe an association with resistin. Second, higher 25(OH)D levels were associated with higher resistin concentrations; this novel positive relationship parallels that seen previously between 25(OH)D and adiponectin [27–29] and raises new questions regarding the role of vitamin D in adipokine regulation in humans. Third, we observed no relationship between resistin and BMI or HOMA-IR, supporting several human studies that also failed to see these relationships [4–9].

Understanding a potential relationship between the RAAS and resistin may provide a mechanistic basis for associations between resistin and blood pressure. Like adiponectin, components of the RAAS, except for aldosterone, are produced by adipocytes [34]. Activity of the RAAS is known to be inversely related to circulating adiponectin [18, 35]; however, the effect of the RAAS on resistin is not well established. Kim et al. showed that increased activity of the adipose tissue RAAS resulted in higher resistin concentrations in transgenic mice [18]. The only human study to analyze the association between the RAAS and resistin demonstrated that individuals with primary hyperaldosteronism had more circulating resistin than those with essential hypertension or normotension [19]. Since patients with primary hyperaldosteronism have suppression of other RAAS components, the observation in transgenic mice that adipose-tissue specific RAAS activity (which is not known to include aldosterone) raised resistin levels is not necessarily consistent with human findings demonstrating a positive association between aldosterone and resistin. On the other hand, correlating murine findings to human physiology may not be straightforward since human resistin is produced by inflammatory cells within adipose tissue rather than adipocytes [10–13].

Our findings extend the work of these prior investigations; we observed significantly higher resistin levels during LS conditions, when RAAS activity was several fold higher than in HS balance. However, when each diet was analyzed separately, neither PRA nor aldosterone were associated with resistin. Within each dietary condition, RAAS neared the extremes of its spectrum; the inter-individual variability in PRA and aldosterone were much smaller than the variability when comparing LS to HS balance. Thus, we may have lacked sufficient power to observe significant associations between individual RAAS components and resistin in our effort to meticulously control dietary sodium. On the other hand, our results may implicate sodium balance, independent of the circulating RAAS, as a determinant of resistin concentrations. It is also possible that local adipose tissue RAAS activity (not directly evaluated in our study) is related to resistin regulation in humans, as previously seen in mice [18].

Vitamin D has been implicated as an inhibitor of the RAAS via antagonism of renin gene expression [20–26], and positively associated with adiponectin levels[27–29]; however, to our knowledge, the relationship between vitamin D and resistin has never been reported. Based on the inverse relationship between vitamin D and the RAAS [20], and the proposed positive relationship between the RAAS and resistin [18, 19], an inverse association between 25(OH)D and human resistin concentrations could be hypothesized. In contrast, we observed that higher 25(OH)D status independently predicted higher resistin levels. Though the lack of any other corroborative or ancillary data preclude us from making further conclusions, we speculate that the relationship between vitamin D and resistin in humans may not involve the RAAS, or may be more complicated than our current state of understanding. This may

again be underscored by the fact that the majority of human resistin is not produced by adipocytes, as is the case with adiponectin [10–13].

Our results must be interpreted within the context of our study design. This analysis was cross-sectional, and thus cannot prove causality or directionality of associations. We studied a population of Caucasians with hypertension, thus the generalizability of our results to other races and blood pressure status remains uncertain. On the other hand, a major strength of our study was that subjects underwent a paired intervention design with meticulous control for race, sodium/RAAS status, and hypertension phenotype; all of these could otherwise confound measures of the RAAS and result in unreliable observations [30, 31]. Our study design controlled dietary sodium and calcium intake, but because calcium and parathyroid hormone were not directly measured, we cannot comment on whether associations between 25(OH)D and resistin were independent of these factors. Vitamin D intake was not controlled in the HyperPATH study design, but we speculate that the vast majority of the study population was not taking vitamin D supplements given that the mean 25(OH)D level was only 56.0 nmol/L (22.4 ng/mL); thus, it is unlikely that many subjects had significant vitamin D intake during the one week of HS and LS diet phases. Though our study population had normal renal function on enrollment, the majority of them did not have assessments of their glomerular filtration rate under each dietary condition. Since renal function has been inversely associated with resistin[36, 37], it is possible that the change in resistin we observed with dietary sodium manipulation could have been influenced by changes in glomerular filtration rate. Both resistin and the RAAS have been implicated in the inflammatory response [38–41]; because we did not assess inflammatory markers in our study population, our study does not address the potential role inflammation may play in our observations. Our findings do not exclude a relationship between the adipose tissue RAAS and resistin; since we did not directly investigate adipose RAAS activity, we are unable to comment on the role it may play. Future studies focused on further characterizing these associations are required.

Resistin remains an interesting molecule; although its putative role in human obesity and insulin resistance is yet to be determined, it continues to be implicated in both hypertension and cardiovascular disease [13, 17]. We observed increased resistin concentrations with sodium restriction and higher resistin levels with higher 25(OH)D status; whether these phenomena were related directly to dietary sodium manipulation, modulation of local or circulating RAAS activity, or other mechanisms, remains unresolved. Our findings raise new interest into the role dietary sodium, the adipose tissue RAAS, and/or vitamin D may play in human resistin physiology; future studies to investigate these relationships are warranted.

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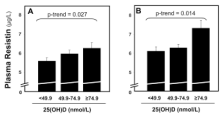

Figure 1. The relationship between 25(OH)D and plasma resistin concentrations in high-dietary sodium balance (A) and low-dietary sodium balance (B)

Bars represent the mean resistin concentration in each 25(OH)D category while whiskers represent the standard error of means. P-values represent the test statistic for multivarvariate linear regression trends.

Table 1

Study population characteristics in HS and LS balance.

	HS	LS	p
n	177		-
Age (y)	49.4 (7.8)		-
Gender (% female)	43.5		
BMI (kg/m^2)	27.9 (3.7)		-
25(OH)D (nmol/L)	56.0 (21.5)		-
24h Urine Sodium (mmol)	231.1 (62.4)	12.4 (7.6)	<0.0001
Systolic Blood Pressure (mmHg)	146.5 (20.8)	131.4 (19.3)	<0.0001
Diastolic Blood Pressure (mmHg)	86.7 (11.1)	78.9 (10.5)	<0.0001
PRA (μg/L/h)	0.40 (0.20, 0.80)	1.80 (0.90, 3.35)	<0.0001
Aldosterone (nmol/L)	0.108 (0.069, 0.188)	0.387 (0.268, 0.591)	<0.0001
Glucose (mmol/L)	5.20 (1.26)	5.50 (1.46)	0.02
Insulin (pmol/L)	67.4 (49.2)	76.0 (46.9)	0.001
HOMA-IR	11.7 (8.2, 19.2)	15.2 (9.6, 23.5)	<0.0001
Plasma resistin (μg/L)	5.86 (1.60)	6.36 (1.85)	<0.0001

Results reported as mean (SD) for normally distributed variables and median (interquartile range) for non-normally distributed variables. (LS=low dietary sodium; HS=high dietary sodium; HOMA-IR=homeostatic model assessment; PRA=plasma renin activity; BMI=body-mass index; 25(OH)D=25-hydroxyvitamin D).

Table 2

The univariate association between plasma resistin and other study variables in HS and LS balance.

Variable	HS		LS	
	β	p	β	p
BMI (kg/m^2)	0.011	0.76	0.022	0.59
24h Urine Sodium (mmol)	0.002	0.36	−0.001	0.96
SBP (mmHg)	−0.004	0.53	−0.011	0.14
DBP (mmHg)	−0.013	0.25	−0.008	0.57
PRA (μg/L/h)	−0.132	0.31	0.138	0.33
Aldosterone (nmol/L)	0.312	0.16	0.252	0.27
Glucose (mmol/L)	−0.23	0.08	−0.08	0.53
Insulin (pmol/L)	0.0001	0.74	0.001	0.72
HOMA-IR	−0.226	0.21	0.003	0.99

(HS=high dietary sodium balance; LS=low dietary sodium balance; β=univariate effect estimate; BMI=body-mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; PRA=plasma renin activity; HOMA-IR=homeostatic model assessment).