Clinial Study

The influence of body mass index and renin–angiotensin–aldosterone system activity on the relationship between 25-hydroxyvitamin D and adiponectin in Caucasian men

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Abstract

Objective: Previous studies have suggested that circulating adiponectin concentrations are associated positively with vitamin D and negatively with body mass index (BMI) but have not accounted for the influence of the renin–angiotensin–aldosterone system (RAAS) in this relationship. This is particularly relevant because increased RAAS activity is associated with obesity and is known to lower adiponectin levels. We evaluated the association between adiponectin and 25-hydroxyvitamin D (25(OH)D) after controlling RAAS activity with dietary sodium equilibration and also evaluated whether this relationship was influenced by BMI.

Design: Cross-sectional study of 115 hypertensive Caucasian men from the Hypertensive Pathotype Consortium.

Methods: To manipulate RAAS activity, all subjects underwent 1 week of high dietary sodium (HS) diet to suppress RAAS and 1 week of low dietary sodium (LS) diet to stimulate RAAS. Linear regression was used to evaluate the association between adiponectin and 25(OH)D, and the effect of BMI on this relationship, in each dietary condition.

Results: Adiponectin was higher on HS, where circulating RAAS activity was low, when compared with LS (25(OH)D levels were positively associated with adiponectin, and BMI was a statistically significant effect modifier of the relationship between 25(OH)D and adiponectin on both diets (P interaction < 0.01 between BMI and 25(OH)D).

Conclusions: Higher 25(OH)D concentrations were independently associated with higher adiponectin levels, particularly when BMI was high. Dietary sodium balance and circulating RAAS activity did not appear to affect this relationship. Future studies should explore whether vitamin D supplementation increases adiponectin levels in obesity.

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Introduction

Adiponectin is a peptide hormone secreted almost exclusively by adipose tissue, yet paradoxically obesity is a state of hypoadiponectinemia (1, 2). Because higher adiponectin concentrations are associated with improved cardiovascular profiles, identifying etiologies for adiponectin deficiency and methods to raise circulating adiponectin in obesity may have clinical importance (1, 3–6).

In addition to adiponectin deficiency, obesity has consistently been shown to be a condition of relative vitamin D deficiency (7, 8) and excess tissue renin–angiotensin–aldosterone system (RAAS) activity (9–13); adipocytes produce all of the components of the RAAS, generating a local adipose tissue RAAS that is distinctly regulated from the circulating RAAS (12–18). This may be relevant since increased RAAS activity lowers adiponectin, while inhibiting the RAAS increases it (19–24); whether increased adipose tissue RAAS activity in obesity contributes to adiponectin deficiency is not known. Prior cross-sectional studies suggested a positive association between 25-hydroxyvitamin D (25(OH)D) and adiponectin; however, they were not designed to study the role of the RAAS in this relationship (25–27). As age, gender, race, body mass index (BMI), hypertension status, dietary sodium balance, and RAAS activity are all known to affect adiponectin measurements (1, 22, 23, 28–31), the independent association of vitamin D and
adiponectin is best evaluated after controlling or adjusting for these elements. Vitamin D is an inhibitor of renin expression in animals (32–34), and accruing evidence in humans has associated vitamin D deficiency with augmented RAAS activity, particularly in obesity (11, 35–38). Recent evidence suggests that the association between metabolic disturbances and both 25(OH)D and adiponectin strengthens with obesity, where adipose tissue RAAS activity is high (7, 12, 39). Thus, one explanation for these previously observed findings (25–27) is that higher vitamin D levels increase adiponectin levels by lowering adipose tissue RAAS activity.

We evaluated whether 25(OH)D concentrations were positively associated with circulating adiponectin, using a study design that meticulously controlled and adjusted for age, gender, race, hypertension status, and circulating RAAS activity in a Clinical Research Center (CRC). As increased adiposity is a known modifier of relationships involving vitamin D and adiponectin (7, 39), we also evaluated whether BMI was an effect modifier of the relationship between 25(OH)D and circulating adiponectin. We hypothesized that if BMI modified the relationship between 25(OH)D and adiponectin, this could indirectly implicate the adipose tissue RAAS as a potential mediator for this association, because its activity burden increases with higher adiposity states (13, 40).

Methods and procedures

Study population

This cross-sectional analysis was performed on the data gathered from subjects studied in the International Hypertensive Pathotype (HyperPATH) Consortium. The HyperPATH study is an ongoing, multi-site study aimed at investigating the pathophysiologic and genotypic mechanisms involved in hypertension and cardiovascular diseases. The participants were studied under one common protocol (see below) at four collaborating centers: Brigham and Women’s Hospital (Boston, MA, USA), University of Utah Medical Center (Salt Lake City, UT, USA), Vanderbilt University Hospital (Nashville, TN, USA), and Hôpital European Georges Pompidou (Paris, France). All samples obtained were sent to a central laboratory for analysis (Brigham and Women’s Hospital).

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 original HyperPATH study. The 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 dietary sodium (HS) and low dietary sodium balance (LS) in sequence.

Following the original study, 25(OH)D measurements were performed on all available frozen plasma of subjects with hypertension (n = 345). As gender, race, and hypertension status may all influence adiponectin concentrations (28–31) and RAAS physiology (41–43), we restricted the current cross-sectional analysis to Caucasian men with 25(OH)D measurements classified as having hypertension and successfully maintained in sodium balance per study protocols (below) and used their available frozen plasma to measure total adiponectin concentrations to comprise the final study population (n = 115).

The HyperPATH study protocol

The HyperPATH study design uses a rigorous study protocol, conducted in CRCs, designed to minimize modifiable confounders of the circulating RAAS (dietary sodium intake, body posture, diurnal variation, and medications). Measurement of the adipose tissue RAAS was not undertaken in the HyperPATH study; however, the adipose tissue RAAS has been shown to function autonomously from the circulating RAAS and is not regulated by the traditional feedback from volume and sodium balance (44). To avoid interference with circulating RAAS assessment, participants taking angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or mineralocorticoid receptor antagonists, were withdrawn from these medications 3 months before study initiation. β-Blockers were withdrawn 1 month before study initiation. If needed for blood pressure control, subjects were treated with amlodipine and/or hydrochlorothiazide; however, these medications were stopped 3 weeks prior to laboratory evaluation.

Subjects were sequentially maintained in LS (≤ 10 mmol/24 h) and then in HS (≥ 200 mmol/24 h) for 5–7 days each, using diets provided by the CRC metabolic kitchen. Both study diets also included fixed quantities of potassium (80 mmol/day) and calcium (1000 mg/day). Study diets were not controlled for macronutrient or calorie intake. After completion of each diet phase, participants were admitted to the institutional CRC and maintained in a supine position overnight. External sodium balance and diet compliance were confirmed on admission to the CRC with a 24 h urine sodium excretion of ≥ 150 mmol for HS and ≤ 30 mmol for LS. For each diet phase, on the morning following admission, baseline blood sampling was obtained after overnight supine rest, collected on ice and centrifuged immediately for 20 min, and plasma separated and frozen without preservatives until assayed. Blood samples were processed at a central...
Biochemical assessments

All 115 subjects had a single plasma 25(OH)D level measured at baseline on the first day of the study (Diasorin, Inc., Stillwater, MN, USA; intra-assay variation 4.4–8.3%, inter-assay variation 6.2–12.5%). Circulating RAAS activity was assessed via plasma renin activity (PRA) (Diasorin, Inc.; intra-assay variation 4.6–10%, inter-assay variation 5.6–7.6%) using previously described methods with a lower limit of detection of 0.10 ng/ml per h (45), and serum aldosterone (Siemens, Los Angeles, CA, USA; intra-assay variation 2.5–5.4%, inter-assay variation 3.8–15.7%) measured from the morning baseline blood sampling of both HS and LS phases. Plasma total adiponectin (ALPCO Diagnostics, Inc., Salem, NH, USA; intra-assay variation 5.0–5.4%, inter-assay variation 6%), plasma glucose, and insulin were also measured from these blood samples. The homeostasis model assessment index (HOMA-IR) was calculated from plasma glucose and insulin values ((glucose) × (insulin)/405) (46) and used in multivariable analyses as a general representation of insulin resistance.

Statistical methods

Sequential analyses were performed to evaluate i) the effect of dietary sodium/RAAS modulation on circulating adiponectin, ii) the association of BMI with adiponectin on each diet, iii) the association of 25(OH)D with adiponectin on each diet, and iv) whether BMI modified the relationship between 25(OH)D and adiponectin, two multivariable interaction models were used. BMI was used as a categorical variable in the first interaction model and as a continuous variable in the second for concordance. These interaction models included age, 25(OH)D, BMI, HOMA-IR, and an interaction term between BMI and 25(OH)D. To account for a multiple testing, a Bonferroni-adjusted P value of 0.025 for significance was applied to these two interaction models. The level for significance for all other tests conducted was set at α = 0.05, with all reported P values as two tailed. Data analyses were performed using SAS statistical software, v9.1 (Cary, NC, USA).

Results

Population characteristics

The mean age of the study population was 48.4 years old (S.D. = 7.7, range 25–66). They were overweight with a mean BMI of 27.9 kg/m² (S.D. = 3.3, range 20.3–35.3) and had a mean 25(OH)D concentration of 22.6 ng/ml (S.D. = 8.8, range 7.3–58.0), consistent with vitamin D insufficiency by current clinical consensus (48). As anticipated, HS balance resulted in increased blood pressure, suppression of circulating RAAS activity, and lower HOMA-IR, when compared with LS balance (49–51) (Table 1). Consistent with previous observations in lean normotensive men (22, 23), adiponectin concentrations in this population of overweight hypertensive men were significantly higher in HS balance where circulating RAAS activity was suppressed, when compared with LS balance where RAAS activity was high (Table 1). Mean 25(OH)D

Table 1 Study population characteristics in LS and HS balance. Results reported as mean (s.d.) for normally distributed variables and median (interquartile range) for non-normally distributed variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>LS</th>
<th>HS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h urine sodium (mmol)</td>
<td>13.5 (7.6)</td>
<td>238.2 (64.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>132.2 (18.1)</td>
<td>143.7 (18.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79.3 (11.1)</td>
<td>88.1 (11.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.4 (1.7, 3.6)</td>
<td>2.0 (1.4, 3.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adiponectin (μg/ml)</td>
<td>2.4 (1.8, 3.4)</td>
<td>2.9 (2.3, 4.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PRA (ng/ml per h)</td>
<td>3.7 (1.1, 4.5)</td>
<td>0.50 (0.26, 0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>16.7 (12.2, 24.8)</td>
<td>4.1 (2.7, 7.0)</td>
<td>&lt;0.0001</td>
</tr>
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</table>

LS, low dietary sodium; HS, high dietary sodium.
concentrations expectedly declined with increasing categories of BMI (7, 8) (27.4 ± 11.8, 22.4 ± 7.6, and 20.4 ± 7.7 ng/ml for lean, overweight, and obese individuals respectively; P = 0.01).

Adiponectin and BMI

The continuous association between BMI and adiponectin, which is known to be an inverse relationship (3), was analyzed on each study diet to evaluate the influence of the circulating RAAS on this relationship. In LS balance where circulating RAAS activity was high, higher BMI was associated with lower circulating adiponectin (univariate \( \beta = -0.034 \) (−0.05, −0.01), \( P < 0.01 \)), even after multivariable adjustments (adjusted \( \beta = -0.025 \) (−0.048, −0.001), \( P = 0.03 \)). Similarly, in HS balance where RAAS activity was suppressed, this relationship paralleled the inverse relationship seen in LS, but as expected, with higher adiponectin concentrations for all values of BMI both before (univariate \( \beta = -0.038 \) (−0.06, −0.02), \( P < 0.001 \)) and after multivariable adjustments (adjusted \( \beta = -0.027 \) (−0.050, −0.004), \( P = 0.02 \); Fig. 1).

As circulating RAAS activity was inversely associated with adiponectin (Table 1), but the relationship between BMI and adiponectin appeared to be independent of circulating RAAS activity or dietary sodium balance, we examined components of circulating RAAS activity as a function of BMI. In the context of our dietary conditions, BMI was not associated with either PRA or serum aldosterone (Table 2).

Adiponectin and 25(OH)D

The association between 25(OH)D and adiponectin was evaluated under each dietary condition. A positive relationship between 25(OH)D and adiponectin was observed in LS balance (univariate \( \beta = 0.011 \) (0.002, 0.019), \( P = 0.01 \)) that remained significant after multivariable adjustments (adjusted \( \beta = 0.009 \) (0.001, 0.018), \( P = 0.03 \)). Although the graphical relationship between 25(OH)D and adiponectin concentrations in HS appeared to parallel that seen in LS (Fig. 2), this trend was not statistically significant (univariate \( \beta = 0.007 \) (−0.001, 0.016), \( P = 0.08 \) (Fig. 2).

BMI influences the relationship between adiponectin and 25(OH)D

The relationship between 25(OH)D and adiponectin was evaluated as a function of BMI and was observed to strengthen with increasing BMI status, with maximal magnitude and significance in the obese subgroup (Table 3). We employed adjusted interaction models to assess whether BMI was a statistically significant effect modifier of the relationship between 25(OH)D and adiponectin and observed that the positive association between 25(OH)D and adiponectin strengthened with increasing BMI categories (LS: \( P \) interaction < 0.01; HS: \( P \) interaction < 0.01); higher 25(OH)D concentrations were associated with higher circulating adiponectin with progression to obesity. The association between 25(OH)D and adiponectin also strengthened with increasing BMI as a continuous measure in LS (\( P \) interaction < 0.01) but was marginally non-significant in HS (\( P \) interaction = 0.06).

Discussion

The relationship between vitamin D, adiponectin, the RAAS, and obesity is complex and intertwined. We evaluated whether the positive association between 25(OH)D and adiponectin was independent of circulating RAAS activity and also hypothesized that this association would strengthen with increasing BMI. The latter hypothesis could indirectly support a mechanism of vitamin D-mediated lowering of the adipose tissue RAAS resulting in higher circulating adiponectin concentrations.

We observed several notable findings in this analysis. First, we found that in Caucasian hypertensive men who were generally overweight, total adiponectin was inversely related to circulating RAAS activity when modulated by dietary sodium intake. We also observed that adiponectin was inversely associated with BMI and positively associated with 25(OH)D regardless of dietary sodium intake and circulating RAAS activity (known modulators of circulating adiponectin (22, 23)). Finally, the association between 25(OH)D and adiponectin strengthened with increasing BMI and was only significant among obese individuals, where the burden of adipose tissue RAAS activity is expected to be higher (12, 13, 40).
RAAS may play but rather may generate novel

make conclusions about the specific role adipose tissue
cross-sectional study did not include direct measure-
ment could raise circulating adiponectin in obesity
With this hypothesized mechanism, vitamin D supple-
importance of our cross-sectional observations is
negatively regulated by vitamin D (10, 11, 35, 36, 38).
(21); the adipose tissue RAAS may in turn may be
activity (19–24), and an inverse relationship between
vitamin D and RAAS activity (11, 35–38). We speculate
activity (19–24) . Similarly, we also observed a decrease in
adiponectin with increased circulating RAAS activity
but in a cohort of largely overweight and hypertensive
men with comparatively unfavorable metabolic profiles
and lower adiponectin concentrations; raising
adiponectin in this population may improve cardiovas-
cular risk (4), while hypoadiponectinemia may worsen
it (5, 6).
As expected, we observed that adiponectin concen-
trations declined with increasing BMI (3). The strength
of association between BMI and adiponectin concen-
trations was the same irrespective of sodium balance (LS
or HS) or circulating RAAS activity, suggesting that the
inverse relationship between adiponectin and adiposity
may be independent of circulating RAAS activity. We
observed no association between BMI and individual
circulating RAAS components; in contrast, an inverse
association between circulating and adipose tissue
RAAS activity with adiponectin is well established
(19–24). This raised the possibility that higher local
RAAS activity within the adipose tissue compartment
could exert important local or paracrine influences that
determine the lower adiponectin concentrations with
obesity. The adipose tissue RAAS is not influenced by
the traditional sodium homeostasis and blood pressure
feedback mechanisms (44) and has been shown to
modulate adiponectin concentrations in transgenic
mice (21). In these animal models, mice lacking the
angiotensinogen gene exhibited higher adiponectin
concentrations when compared with wild-type mice;
however, in knockout mice who expressed angiotensi-
nogen only in adipose tissue, adiponectin declined back
to wild-type levels.
We postulated that understanding the relationship
between vitamin D and adiponectin may provide further
insight into the hypothesized role the adipose tissue
RAAS plays in regulating adiponectin in obesity. Vitamin D metabolites have been shown to exhibit an
inverse relationship with renin as well as local tissue
RAAS activity, implicating vitamin D as an endogenous
antagonist of the RAAS by inhibiting renin expression
(10, 11, 33, 35–38, 53). Furthermore, vitamin D status
is intertwined with the obesity epidemic in that higher
adiposity is associated with vitamin D deficiency (8).
Assimilating these prior observations, we hypothesized that 25(OH)D deficiency could explain the
augmented adipose tissue RAAS activity and resultant changes in adiponectin concentrations in
obesity. Since activity of the adipose tissue RAAS
increases with progressive adiposity (12), we speculated that the association between 25(OH)D and adiponectin

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>LS</th>
<th>HS</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>0.02</td>
<td>-0.04, 0.59</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>0.03</td>
<td>0.00, 0.84</td>
</tr>
</tbody>
</table>

β, effect estimate; CI, confidence interval.

As obesity is a state of hypoadiponectinemia (7, 8)
and relative vitamin D deficiency (1, 2), the clinical
importance of our cross-sectional observations is
providing data to suggest that vitamin D supple-
mentation may raise adiponectin levels in obesity,
an outcome which is associated with lower cardiovas-
cular risk (3–6). The mechanistic implications of our
observations may be understood in the context of prior
studies that have shown increased local tissue
RAAS activity in obesity (13, 15, 17, 40, 52), reduction
of adiponectin concentrations with increased RAAS
activity (19–24), and an inverse relationship between
vitamin D and RAAS activity (11, 35–38). We speculate
that our findings may indirectly support the adipose
tissue RAAS as an important negative paracrine
regulator of adiponectin secretion in adipose tissue
(21); the adipose tissue RAAS may in turn may be
negatively regulated by vitamin D (10, 11, 35, 36, 38).

With this hypothesized mechanism, vitamin D supple-
mentation could raise circulating adiponectin in obesity
by downregulating adipose tissue RAAS activity. As our
cross-sectional study did not include direct measure-
ments of the adipose tissue RAAS, it was not designed to
make conclusions about the specific role adipose tissue
RAAS may play but rather may generate novel
hypotheses regarding the mechanism for our
associations.

Our findings are consistent with and extend the work
of others. Prior investigations have demonstrated
reciprocal changes in adiponectin when modulating
the circulating RAAS with dietary sodium in a
population of lean and healthy normotensive men (22, 23).
Similarly, we also observed a decrease in
adiponectin with increased circulating RAAS activity
but in a cohort of largely overweight and hypertensive
men with comparatively unfavorable metabolic profiles
and lower adiponectin concentrations; raising
adiponectin in this population may improve cardiovas-
cular risk (4), while hypoadiponectinemia may worsen
it (5, 6).

![Figure 2](https://viafreeaccess.com/bioScience/2018/11/21/2018/08/06/34AM/)

**Figure 2** The univariate relationships between 25(OH)D and adiponectin plotted in LS (gray) and HS (black) balance, with 95% confidence intervals for each regression line (For LS balance: univariate β = 0.011 (0.002, 0.019), P = 0.01, for HS balance: univariate β = 0.007 (−0.001, 0.016), P = 0.08).
whether its role is independent of vitamin D metabolites has been associated with the RAAS (54); however, implications of our associations. Parathyroid hormone tissue RAAS are needed to confirm the mechanistic in vitro peptide system, vasopressin, etc.). Future studies are required to evaluate the effect on circulating 25(OH)D concentrations on adiponectin at the time of study; therefore, we did not adjust for these factors. This analysis consisted of only 115 individuals and thus may not have been adequately powered to detect some trends that fell short of statistical significance; however, our observations are consistently linked to those that have previously described adipose tissue RAAS physiology and regulation (9, 13, 52) and the relationship between vitamin D and the RAAS (35–38). We studied a population of male Caucasians with hypertension; thus, the generalizability of our results to other races, female gender, and blood pressure status is still uncertain. On the other hand, a major strength of our study was that subjects underwent a paired intervention design with meticulous control for gender, race, sodium/RAAS status, and hypertension phenotype, all of which can confound measures of the RAAS and adiponectin and result in unreliable observations (22, 23, 28, 30, 31).

Adipose tissue is an endocrine organ that produces adiponectin and a local tissue RAAS; with progression to obesity, activity of the adipose tissue RAAS increases and adiponectin concentrations decrease. Though adiponectin concentrations are known to decline with higher RAAS activity and higher BMI, we observed that the inverse association between BMI and adiponectin was independent of circulating RAAS activity. Furthermore, 25(OH)D was positively associated with adiponectin, especially in obesity, and this relationship appeared to be independent of circulating RAAS activity. As 25(OH)D deficiency is especially prevalent in obesity, future studies to evaluate the relationship between vitamin D supplementation and adiponectin, as well as the role of the adipose tissue RAAS in this relation, are warranted.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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