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THE INDEPENDENT ASSOCIATION BETWEEN 25-HYDROXYVITAMIN D AND ADIPONECTIN AND ITS RELATION WITH BMI IN TWO LARGE COHORTS: the NHS and the HPFS

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Abstract

Low 25-hydroxyvitamin D (25[OH]D) and adiponectin levels are both associated with obesity and cardiovascular disease. Cross-sectional studies have suggested that 25(OH)D concentrations are positively associated with adiponectin, and that this relation may strengthen with increasing BMI. However, these studies had small samples sizes and did not account for many known confounders of adiponectin levels. We evaluated whether 25(OH)D was independently associated with circulating adiponectin in two large populations, and whether BMI modified this relationship. Cross-sectional analyses were performed on 1206 women from the Nurses' Health Study I and 439 men from the Health Professionals Follow-Up Study. Multivariable linear regression was used to analyze the independent association between 25(OH)D and adiponectin after controlling for potential confounders. Effect modification by BMI was examined by creating interaction terms between vitamin D and BMI. 25(OH)D concentrations were positively associated with circulating adiponectin in univariate analyses, and also independently associated with adiponectin after multivariable adjustments in both populations (women: β=0.06, P<0.001; men: β=0.07, P<0.05). BMI did not significantly modify the relation between 25(OH)D and adiponectin in either population. Higher 25(OH)D concentrations were independently associated with higher adiponectin concentrations in large populations of women and men. Since lower levels of 25(OH)D and adiponectin are associated with higher cardio-metabolic risk, assessing the effect of vitamin D supplementation on adiponectin levels is warranted.

Keywords

Vitamin D; adiopnectin; Body-mass index; obesity

INTRODUCTION

Adiponectin is a peptide hormone secreted by adipose tissue that is associated with favorable cardio-metabolic profiles (1, 2), while vitamin D is an essential steroid metabolite for skeletal development that has recently been implicated with numerous extra-skeletal effects (3). Lower levels of 25-hydroxyvitamin D (25[OH]D) and adiponectin are both independently associated with cardiovascular and metabolic morbidities (1-6). Since both of

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these biochemical derangements are also highly prevalent in obesity (1, 5, 7), they may represent a potential explanation for the increased cardiovascular risk seen with obesity.

Recent studies have suggested an association between 25(OH)D deficiency and hypoadiponectinemia (8-10), raising interest into whether vitamin D supplementation may represent a method to improve circulating adiponectin concentrations. Furthermore, it has been shown that the magnitude of the positive association between 25(OH)D and adiponectin may strengthen with higher body-mass index (BMI) (10). These prior findings were reported in relatively small cross-sectional studies that did not account for numerous potential confounders, as adiponectin concentrations are known to be influenced by age (11), gender (11), race (12), BMI (5, 11), diabetes and hypertension status (5, 11, 13), anti-hypertensive drug use (14), dietary electrolyte intake (14), dietary patterns (15), physical activity (16), alcohol intake (17), and menopausal status (18).

Since confirmation of an independent positive relationship between vitamin D and adiponectin could have significant impact in the management of cardiovascular and metabolic risk in obese individuals, we sought to evaluate the independent association between 25(OH)D and circulating adiponectin in large cohorts of women from the Nurses' Health Study I (NHS) and men from the Health Professional's Follow-Up Study (HPFS). Given the prior observation that the association between 25(OH)D and adiponectin may be influenced by BMI (10), we also evaluated whether BMI was an effect modifier of this relation.

METHODS AND PROCEDURES

Study Populations

The NHS I and HPFS have both been previously described (19). Briefly, the NHS cohort was assembled in 1976, when 121,700 female nurses aged 30-55 years returned a mailed questionnaire. Subsequent questionnaires have been mailed every 2 years to update information on health-related behaviors, diet, and medical events. In 1989, blood samples were submitted by 32,826 participants (the NHS "blood cohort") for biochemical analysis. The HPFS cohort was assembled in 1986, when over 50,529 male health professionals, aged 40-75 years, returned a mailed questionnaire. As with the NHS, biennial questionnaires have been returned by HPFS participants to update health and lifestyle related information. Blood samples were submitted by more than 18,025 participants (the HPFS "blood cohort") in 1989.

We selected the subset of participants with previously measured 25(OH)D and total adiponectin levels (n=1206 for NHS, n=439 for HPFS), and complete information available on pertinent co-variates for analysis (see below). These individuals had pre-existing measurements of 25(OH)D and total adiponectin for the purposes of previously reported nested case-control studies evaluating cancer endpoints (20-22).

Biochemical Analyses

Plasma total adiponectin was measured in several batches using an enzyme-linked immunosorbant assay (Linco Research, Inc., St. Charles, MO); coefficients of variation ranged from 7-13%. 25(OH)D concentrations were measured in several batches using the radioimmunoassay from Diasorin Inc. (Stillwater, MN); the coefficient of variation for this assay ranged from 5-9%.

Statistical Analyses

Demographic data for the NHS and HPFS cohorts are presented as means with standard deviations, and were also stratified by clinically relevant BMI categories (lean <24.9, overweight 25.0-29.9, obese ≥ 30.0 kg/m^2). One-way analyses of variance were used to determine statistical differences between BMI categories.

The primary analysis was to evaluate the independent association between 25(OH)D and adiponectin concentrations using multivariable linear regression in each cohort; all assumptions for linear regression analysis were met. The co-variates included in the multivariable models included all known and available predictors of adiponectin: age, race, gender, BMI, diabetes status, hypertension status, anti-hypertensive drug use, dietary sodium, calcium, and potassium intake, a prudent dietary pattern score, physical activity, and alcohol intake (5, 11-17, 23). Prudent dietary pattern scores were derived from semi-quantitative food frequency questionnaires as previously described (23). In women from NHS, we also adjusted for menopausal status (18). Dietary calcium and potassium intake included that from food sources as well as supplements. Information to assess insulin resistance was not assessed in these cohorts. Since adiponectin measurements in these two cohorts were performed over separate time intervals for different studies in the past (20-22), we adjusted for the batch number in which adiponectin assays were performed in all analyses, to adjust for any assay variation. Since most individuals included in this analysis had lab measurements as part of prior nested case-control studies to evaluate future cancer endpoints, we also adjusted for case-control status in all multivariable models as an extra effort to minimize bias (i.e., whether individuals who were selected to have their 25[OH]D and adiponectin measured because they were known to be either a case or a control in prior nested case-control studies) (20-22). As a sensitivity analysis, we re-examined the independent association between 25(OH)D and adiponectin after excluding all individuals who were selected as cases in prior case-control studies, although this markedly reduced the sample sizes for analysis. Linear regression results are reported with effect estimates for the association (β), the standardized β (ST β), and associated *P*-value.

To evaluate whether BMI was an effect modifier of the relation between 25(OH)D and adiponectin, we performed adjusted interaction analyses including all the aforementioned co-variates as well as an interaction term between BMI and 25(OH)D as continuous variables.

RESULTS

Population Characteristics

The mean 25(OH)D level was 24.4 ± 9.4 ng/mL in women from NHS and 28.7 ± 9.9 ng/mL in men from HPFS, consistent with vitamin D insufficiency in both cohorts by current clinical convention (3). As expected, women had higher adiponectin concentrations than men (17.9 ± 7.7 vs. 10.0 ± 8.1 μg/mL) (11), and post-menopausal women had higher adiponectin levels than pre-menopausal women (18.3 ± 7.7 vs. 15.7 ± 7.0 μg/mL) (18). Both study populations exhibited expected trends in demographic, physical, and dietary characteristics when stratified by BMI categories (Table 1 and Table 2).

The Relationship Between 25(OH)D and Adiponectin

In univariate analyses, 25(OH)D concentrations were positively associated with adiponectin in both cohorts (women: β=0.12, *P*<0.001; men: β=0.08, *P*<0.05) (Table 3). Following multivariable adjustments for biologically relevant and known univariate predictors of adiponectin, 25(OH)D remained independently associated with adiponectin in both cohorts (Table 4).

In our sensitivity analyses, we excluded participants who were selected as cases in prior nested case-control analyses (20-22), and found similar effect estimates for the association between 25(OH)D and adiponectin. With much smaller sample sizes, the association remained statistically significant in women (n=768; β=0.13, $P<0.001$), but a non-significant trend in men (n=245; β=0.06, $P=0.21$), possibly due to decreased statistical power.

Effect Modification by BMI

Prior studies observed a strengthening of the relation between 25(OH)D and adiponectin with higher BMI (10). There was a suggestion of higher effect estimates with higher BMI categories in the NHS cohort, but this trend was less apparent in the HPFS cohort, mainly due to the observations among the obese subgroup of HPFS (Table 5). We evaluated whether BMI was a statistically significant effect modifier of the association between 25(OH)D and adiponectin by performing adjusted interaction analyses including all aforementioned co-variates and an interaction term between BMI and 25(OH)D. We detected no statistically significant interaction in either NHS or HPFS cohorts; the positive relation between 25(OH)D and adiponectin was not modified by BMI.

DISCUSSION

In this large cross-sectional study, we analyzed the independent association between 25(OH)D and adiponectin in two large cohorts after accounting for many known predictors of adiponectin, and observed an independent positive association between 25(OH)D and adiponectin. This finding may have significant clinical relevance in the context of obesity, since progressive adiposity is associated with the deficiencies of adiponectin and vitamin D for reasons that remain unexplained (1, 5, 7). Since low levels of both adiponectin and 25(OH)D are associated with cardiovascular diseases and metabolic morbidities (1-6), interventions to improve these abnormalities may be clinically relevant. A positive association between 25(OH)D concentrations and circulating adiponectin has been suggested in prior studies with small sample sizes, but they did not account for many known confounders of adiponectin (8-10).

Our findings are consistent with and extend those of others. Gannage-Yared et al. first showed that higher 25(OH)D levels associated with higher adiponectin levels, but in a relatively small population of young and lean subjects with vitamin D sufficiency (8); the adverse metabolic sequelae of vitamin D insuffciency and low adiponectin levels may not be apparent in this demographic. Similarly, Nimitphong et al. showed a positive relation between 25(OH)D and adiponectin, but again in a small sample of lean individuals (9). We previously demonstrated an independent association between 25(OH)D and adiponectin in a small cohort of older hypertensive individuals who were mostly overweight and of higher cardiovascular risk (10); however, we were unable to adjust for many potential confounders of the association between 25(OH)D and adiponectin. Our current findings are relevant in that they confirm prior observations in a much larger population of older individuals, with vitamin D insufficiency, and with a representative distribution of lean, overweight, and obese subjects. Furthermore, we observed that the positive association between 25(OH)D and adiponectin was independent of many known major confounders of adiponectin and 25(OH)D levels, thereby providing greater confidence in this relation.

The clinical implications of our findings are best assessed in the context of the current global epidemics of obesity and vitamin D deficiency (3, 24); both conditions are increasing in prevalence worldwide, and are associated with cardiovascular disease and mortality (4-6, 24-26). Since obesity is a state of adiponectin deficiency (5), our observed associations suggest that prospective studies to further evaluate whether vitamin D supplementation

could represent a method to raise circulating adiponectin and improve the unfavorable cardio-metabolic profiles in obesity are warranted (12, 27).

We previously showed that the positive association between 25(OH)D and adiponectin strengthened with progression to obesity, where both deficiencies are most apparent (10). Several prior investigations provide potential explanations for this observation; vitamin D negatively regulates the expression of renin and subsequent activity of the renin-angiotensin system (6, 28-33), whereas adipocytes produce all the components of a local adipose-tissue renin-angiotensin system whose activity in turn inhibits adiponectin secretion (34-38). Since the activity of the adipose-tissue renin-angiotensin system increases with higher adiposity (36, 37, 39), we previously hypothesized that increased adipose-tissue renin-angiotensin system activity may represent a potential mechanism for the relative hypoadiponectinemia seen in obesity (10); the positive relation between 25(OH)D concentrations and circulating adiponecitn may be mediated by the negative regulation of the adipose-tissue renin-angiotensin system by vitamin D metabolites. In our current study, we observed a trend towards higher effect estimates for the association between 25(OH)D and adiponectin with higher BMI categories; however, BMI as a continuous variable was not a statistically significant effect modifier of this relationship. Despite this lack of significance, the strengthening of this association with higher adiposity in the NHS cohort may signify true effect modification by BMI that we were not powered to detect. Our previous observation that BMI could significantly modify the relationship between 25(OH)D and adiponectin (10) was made in a study where all participants were evaluated under meticulously controlled dietary sodium and renin-angiotensin-aldosterone system activity conditions, which are known to significantly alter adiponectin levels. The lack of regulation of these factors in the current observational study may have added variability to adiponectin measurements.

Our findings must be taken in the context of our study design. First, our findings were cross-sectional associations, and thus cannot prove causality or directionality. However, our findings in this large, well-controlled, analysis confirm several prior smaller and less controlled observational studies; thus, they provide convincing support for future prospective studies. Parathyroid hormone and vitamin D have an intertwined relationship; although we adjusted for dietary calcium intake, we did not have parathyroid hormone levels, and thus could not determine whether they confounded the association between 25(OH)D and adiponectin. We adjusted our multivariable models for many known and available predictors of adiponectin, but we acknowledge that there may be many other variables that influence adiponectin and thus our observed associations could result from residual confounding. Our analysis was focused on evaluating the physiologic effect of 25(OH)D concentrations on adiponectin at the time of study; though the time of the year and seasonality are known to influence 25(OH)D levels (3), we are not aware of any data or proposed mechanisms suggesting that these factors influence our outcome variable adiponectin. Furthermore, both adiponectin and 25(OH)D were measured from the same blood sample, with no difference in time of day or season; therefore we did not adjust the association between 25(OH)D and adiponectin for seasonality or time of year. We did not have information to assess for insulin resistance in these cohorts; however, prior studies have shown the association between 25(OH)D and adiponectin to be independent of insulin resistance (8-10). We speculate that one potential biologic mechanism accounting for the positive association between 25(OH)D levels and adiponectin is regulation of the local adipose-tissue renin-angiotensin system; however, since we did not directly measure this factor, we are limited in making any further conclusions.

Obesity is a global epidemic that is associated with low levels of 25(OH)D and adiponectin, cardiovascular disease, and death (5, 25, 26). Our cross-sectional findings suggest that 25-hydroxyvitamin D concentrations are positively associated with circulating adiponectin

concentrations. Since increasing adiponectin levels may reduce cardiovascular risk (12, 27), future studies to evaluate the effect of vitamin D therapy on circulating adiponectin, especially in obesity, are warranted.

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Table 1

Characteristics of the Nurse's Health Study population stratified by clinically relevant BMI categories

Data are reported as mean ± standard deviation or percents (%).

VARIABLE	BMI<24.9	BMI 25.0-29.9	BMI≥30.0	*P*
N	584	392	230	-
Age (years)	57.3 ± 6.9	57.7 ± 6.5	57.0 ± 7.0	0.87
Race (% white)	96.4	96.2	94.3	0.23
BMI (kg/m^2)	22.4 ± 1.7	27.1 ± 1.3	33.9 ± 3.8	<0.001
Menopausal status (% yes)	82.5	87.2	80.4	0.94
25(OH)D (ng/mL)	25.9 ± 9.8	23.3 ± 9.2	22.0 ± 8.4	<0.001
Adiponectin (μg/mL)	20.4 ± 7.5	16.5 ± 7.1	13.9 ± 6.8	<0.001
Systolic Blood Pressure (mmHg)	123 ± 14	129 ± 14	133 ± 14	<0.001
Diastolic Blood Pressure (mmHg)	76 ± 8	79 ± 8	82 ± 8	<0.001
Dietary Sodium Intake (mg/day)	1815 ± 335	1847 ± 337	1886 ± 352	0.007
Dietary Potassium Intake (mg/day)	2935 ± 490	2909 ± 502	2819 ± 603	0.008
Dietary Calcium Intake (mg/day)	1066 ± 508	1044 ± 531	918 ± 460	<0.001
Alcohol intake (grams/day)	6.5 ± 10.3	5.0 ± 8.9	3.8 ± 9.0	<0.001
Prudent dietary score	0.12 ± 0.97	0.13 ± 0.95	0.07 ± 0.94	0.56
Physical activity (METS/week)	19.2 ± 26.1	15.8 ± 34.7	10.9 ± 11.6	<0.001
Diabetes Status (%yes)	0.5	2.6	4.4	<0.001
Hypertension Status (% yes)	19.4	32.1	45.2	<0.001
Use of Any Anti-Hypertensive Drug (%yes)	17.8	26.5	38.7	<0.001

Table 2

Characteristics of the Health Professionals Follow-Up study population stratified by clinically relevant BMI categories

Data are reported as mean ± standard deviation or percents (%).

VARIABLE	BMI<24.9	BMI 25.0-29.9	BMI≥30.0	*P*
N	171	191	56	-
Age (years)	66.4 ± 7.5	65.9 ± 7.4	63.9 ± 7.5	0.05
Race (%white)	96.4	99.4	100	0.08
BMI (kg/m^2)	22.9 ± 1.4	26.9 ± 1.3	32.6 ± 2.1	<0.001
25(OH)D (ng/mL)	29.6 ± 11.1	28.1 ± 8.8	27.4 ± 8.2	0.08
Adiponectin (μg/mL)	11.4 ± 9.8	9.5 ± 7.3	7.9 ± 5.2	0.002
Systolic Blood Pressure (mmHg)	128 ± 13	132 ± 14	135± 13	<0.001
Diastolic Blood Pressure (mmHg)	82 ± 10	85 ± 9	88 ± 7	<0.001
Dietary Sodium Intake (mg/day)	2049 ± 486	2057 ± 449	2116 ± 604	0.07
Dietary Potassium Intake (mg/day)	3553 ± 637	3468 ± 545	3428 ± 632	0.12
Dietary Calcium Intake (mg/day)	937± 383	912 ± 346	938 ± 396	0.81
Alcohol intake (grams/day)	12.8 ± 15.3	14.9 ± 19.2	13.9 ± 16.1	0.45
Prudent dietary pattern score	0.08 ± 0.93	0.02 ± 0.94	−0.06 ± 1.32	0.38
Physical activity (METS/week)	46.2 ± 73.1	35.0 ± 32.4	28.7 ± 30.3	0.01
Diabetes Status (%yes)	3.5	4.7	5.4	0.49
Hypertension Status (% yes)	36.3	45.6	51.8	0.02
Use of Any Anti-Hypertensive Drug (%yes)	25.7	36.6	37.5	0.03

TABLE 3

Pearson correlation coefficients for all continuous variables in the A) NHS cohort, and B) HPFS cohort.

A)

	Age (y)	BMI (kg/m^2)	25(OHD) (ng/mL)	Adiponectin (μg/mL)	Dietary Sodium Intake (mg/day)	Dietary Potassium Intake (mg/day)	Dietary Calcium Intake (mg/day)	Alcohol Intake (grams/day)	Prudent Dietary Pattern Score	Physical Activity (METS/week)
Age (y)	1.00	−0.02	0.03	0.14*	0.07	0.22*	0.13*	0.07*	−0.01	−0.004
BMI (kg/m^2)		1.00	−0.18*	−0.33*	0.06	−0.10*	0.13*	−0.09*	−0.02	−0.13*
25(OHD) (ng/mL)			1.00	0.14*	0.008	0.13*	0.18*	0.04	−0.02	0.18*
Adiponectin (μg/mL)				1.00	−0.08*	0.11*	0.13*	0.07*	−0.004	0.09*
Dietary Sodium Intake (mg/day)					1.00	0.18*	0.07*	−0.05*	0.03	−0.04
Dietary Potassium Intake (mg/day)						1.00	0.34*	0.07*	0.09*	0.16*
Dietary Calcium Intake (mg/day)							1.00	−0.07*	0.11*	0.06*
Alcohol Intake (grams/day)								1.00	0.13*	0.005
Prudent Dietary Patter Score									1.00	0.14*
Physical Activity (METS/week)										1.00

B)

	Age (y)	BMI (kg/m^2)	25(OHD) (ng/mL)	Adiponectin (μg/mL)	Dietary Sodium Intake (mg/day)	Dietary Potassium Intake (mg/day)	Dietary Calcium Intake (mg/day)	Alcohol Intake (grams/day)	Prudent Dietary Pattern Score	Physical Activity (METS/week)
Age (y)	1.00	−0.07	0.003	0.14*	−0.01	0.16*	0.06	0.01	0.08	0.04
BMI (kg/m^2)		1.00	−0.14*	−0.15*	0.12*	−0.05	−0.06	0.06	−0.03	−0.14*
25(OHD) (ng/mL)			1.00	0.09*	0.04	0.06	0.12*	0.16*	0.02	0.18*
Adiponectin (μg/mL)				1.00	0.03	0.07	0.06	0.009	−0.04	0.04

B)

	Age (y)	BMI (kg/m^2)	25(OHD) (ng/mL)	Adiponectin (μg/mL)	Dietary Sodium Intake (mg/day)	Dietary Potassium Intake (mg/day)	Dietary Calcium Intake (mg/day)	Alcohol Intake (grams/day)	Prudent Dietary Pattern Score	Physical Activity (METS/week)
Dietary Sodium Intake (mg/day)					1.00	−0.06	0.14*	−0.19*	−0.04	−0.05
Dietary Potassium Intake (mg/day)						1.00	−0.34*	−0.28*	0.45*	0.07
Dietary Calcium Intake (mg/day)							1.00	−0.13*	0.16*	0.03
Alcohol Intake (grams/day)								1.00	−0.10*	0.001
Prudent Dietary Patter Score									1.00	0.10*
Physical Activity (METS/week)										1.00

* $P<0.05$.

Table 4

Multivariable linear regression results

Effect estimates (β), standardized β, and *P*-values for the association between each variable and adiponectin are depicted for both study populations.

	NHS			HPFS		
	β	**Standard β**	***P***	**β**	**Standard β**	***P***
Age (years)	0.09	0.08	0.02	0.10	0.09	0.02
Race (white)	−2.2	−0.05	0.04	−0.78	−0.01	0.72
BMI (kg/m^2)	−0.39	−0.24	<0.001	−0.39	−0.16	<0.001
Post-menopausal Status (yes)	1.4	0.07	0.05		N/A	
25(OH)D (ng/mL)	**0.06**	**0.08**	**0.003**	**0.07**	**0.08**	**0.04**
Dietary Sodium Intake (mg/day)	−0.001	−0.06	0.03	0.0006	0.03	0.39
Dietary Potassium Intake (mg/day)	0.001	0.07	0.05	−0.0002	−0.01	0.77
Dietary Calcium Intake (mg/day)	0.0008	0.05	0.07	0.0005	0.02	0.59
Alcohol intake (grams/day)	0.06	0.07	0.005	0.008	0.02	0.70
Prudent dietary pattern score	−0.44	−0.05	0.10	0.07	0.007	0.86
Physical activity (METS/week)	0.005	0.02	0.50	0.0006	0.004	0.91
Diabetes Status (yes)	−3.0	−0.05	0.05	−2.1	−0.05	0.20
Hypertension Status (yes)	−1.2	−0.07	0.04	0.71	0.04	0.42
Use of Any Anti-Hypertensive Drug (yes)	−0.55	−0.03	0.35	−0.36	−0.02	0.69

Table 5

Multivariable linear regression results stratified by adiposity status

The effect estimates (β) for the relationship between 25(OH)D and adiponectin stratified by clinically relevant BMI category.

	NHS			HPFS		
	N	**β**	***P***	**N**	**β**	***P***
BMI < 24.9 kg/m^2	584	0.05	0.10	171	0.05	0.36
BMI 25.0-29.9 kg/m^2	392	0.06	0.16	191	0.14	0.008
BMI ≥ 30.0 kg/m^2	230	0.11	0.09	56	−0.02	0.80