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BRIEF ARTICLE

High adiponectin levels fail to protect against the risk of hypertension and, in women, against coronary disease: involvement in autoimmunity?

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Abstract

AIM: To investigate whether serum adiponectin protects against cardiometabolic risk in a population sample with prevailing metabolic syndrome.

METHODS: Middle-aged adults representative of a general population with baseline circulating adiponectin measurements (n = 1224) were analyzed prospectively at a mean of 3.8 years' follow-up, using continuous values or sex-specific tertiles. Total adiponectin was assayed by an ELISA kit. Type-2 diabetes was identified by criteria of the American Diabetes Association. Hypertension was defined as a blood pressure ≥ 140 mmHg and/or ≥ 90 mmHg and/or use of antihypertensive medication. Outcomes were predicted using Cox proportional hazards regression analysis in models that were controlled for potential confounders.

RESULTS: In models of multiple linear regression, sex hormone-binding globulin, fasting insulin (inverse) and, in men, age were significant independent covariates of serum adiponectin which further tended in women to be positively associated with serum creatinine. Cox regression analyses for incident coronary heart disease (CHD), adjusted for sex, age, non-HDL cholesterol, waist circumference and C-reactive protein, revealed significant inverse association with adiponectin tertiles in men but not women (HR = 0.66; 95%CI: 0.32-1.38 for highest tertile). Cox regression for type-2 diabetes in a similar model (wherein glucose replaced non-HDL cholesterol), adiponectin tertiles appeared to protect in each gender. HR for incident hypertension roughly displayed unity in each of the adiponectin tertiles (P-trend = 0.67).

CONCLUSION: High adiponectin levels failed to protect against the development of hypertension and, in women, against CHD, presumably paralleling impairment in renal function as well. Involvement of adiponectin in autoimmune complex with loss of antioxidative-antiatherogenic properties may be underlying.

Key words: Adiponectin; Antioxidative function; Coronary heart disease; Creatinine; Type-2 diabetes; Hypertension

Core tip: The issue of whether serum adiponectin protects against cardiometabolic risk in people prone to metabolic syndrome was studied in 1224 Turkish adults at a mean of 3.8 years' follow-up. High adiponectin levels were surprisingly positively associated independently with serum creatinine in women and

further failed to protect against the development of hypertension in both sexes. In multivariable adjusted Cox proportional hazards regression analyses, protection against type-2 diabetes was apparent, but women were not protected against incident coronary heart disease by high serum adiponectin. Involvement of circulating adiponectin in autoimmune complex with loss of mainly antioxidative properties may be underlying.

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INTRODUCTION

Serum adiponectin has been recognized in the past decade to be in an inverse relationship with hypertension[1] and low circulating adiponectin is equally recognized as a risk factor for hypertension, independent of its effects on insulin resistance and diabetes mellitus[2]. Plasma adiponectin levels correlated inversely more strongly with insulin levels and insulin resistance than the degree of obesity[3]. Higher adiponectin concentrations in diabetic men had reduced odds for renal dysfunction compared with the lowest adiponectin quartile[4]. These observations and numerous experimental studies[5] have shown that serum adiponectin exerts protective functions against cardiometabolic disorders, including hypertension, *via* insulin-sensitizing, anti-inflammatory and antiatherogenic actions.

Yet, marked elevations of plasma adiponectin levels have been reported in chronic kidney disease (CKD). In view of such an inverse relationship with renal function, the opinion has been expressed that the cardioprotective role of adiponectin in patients with CKD remains controversial[5]. Adiponectin levels were shown to be inversely associated with the glomerular filtration rate[6,7] which still needs a satisfactory explanation.

We have previously reported in Turkish adults that adiponectin levels were not only inconsistently related to excess adiposity, but also provided epidemiological evidence that serum adiponectin was markedly attenuated in its anti-inflammatory activities in women[8]. Moreover, in a cross-sectional analysis, serum adiponectin was not associated with diabetes and hypertension in men[9].

In order to evaluate further the questionable protection by adiponectin against cardiometabolic disorders, we designed a prospective study after an intermediate follow-up of our original study sample wherein cross-sectional associations of adiponectin were also evaluated. Such a study might shed light on the determinants of attenuated activities of adiponectin and might also explain partly why a cardioprotective role of adiponectin is lacking in patients with CKD.

MATERIALS AND METHODS

Population sample

This study sample was recruited from the 2005/06 follow-up survey of the longitudinal Turkish Adult Risk Factor Study (TARF), a representative sample of adults in Turkey, the sampling details of which were described previously[9,10]. The study was approved by the Ethics Committee of the Istanbul University Medical Faculty. Written informed consent for participation was obtained. Partial logistical support was provided by the Turkish Ministry of Health. Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system, sampling of blood and recording of a resting 12 lead electrocardiogram. Serum concentrations of adiponectin were assayed among randomly selected fasting participants in a total of 561 men and 663 women, aged 37-79 years.

Measurement of risk factors

Blood pressure (BP) was measured with an aneroid sphygmomanometer (Erka, Bad Tölz, Germany) in the sitting position on the right arm, and the mean of two recordings 3 minutes apart was recorded. Waist circumference was measured at the level midway between the lower rib margin and the iliac crest. Body mass index was calculated as weight divided by height squared (kg/m^2). Cigarette smoking status was categorized into never, former and current smokers.

Blood samples were collected, spun at 1000 g, shipped to Istanbul and stored in deep-freeze at -75 ℃ until analyzed. Serum concentrations of hsC-reactive protein (CRP), apolipoprotein (apo) B, apo A-I, complement C3 and lipoprotein (Lp)(a) were measured by nephelometry (BN Prospec, Behring Diagnostics, Westwood, MA). Serum concentration of total adiponectin was assayed by a sandwich enzyme-linked immunosorbent assay system (Adiponectin ELISA BioVendor, BioVendor Lab. Medicine, Inc, Czech Republic) at a central laboratory. Serum concentrations of total cholesterol, fasting triglycerides, glucose, HDL cholesterol (HDL-C, directly) and low-density lipoprotein cholesterol (directly) were determined by using enzymatic kits from Roche Diagnostics (Mannheim, Germany) with a Hitachi 902 autoanalyzer. Serum concentrations of sex hormone-binding globulin (SHBG), insulin and thyroid stimulating hormone (TSH) were measured by the electrochemiluminescence immunoassay ECLIA on Roche Elecsys 2010 using Roche kits (Roche Diagnostics, Mannheim, Germany).

Definitions

Hypertension was defined as a blood pressure ⩾ 140 mmHg and/or ⩾ 90 mmHg and/or use of antihypertensive medication. Type-2 diabetes was diagnosed with the criteria of the American Diabetes Association[11], namely by self report or when plasma fasting glucose was ⩾ 7 mmol/L or when 2-h postprandial glucose was

Table 1 Characteristics of sample (n = 1224) by gender and serum adiponectin (in μg/mL) tertiles

	n	Men (n = 561)							Women (n = 663)						
		1	4.94[1]	2	8.50	3	15.36	Anova	1	6.12[1]	2	10.87	3	19.67	Anova
		Mean	SD	Mean	SD	Mean	SD	*P*-trend	Mean	SD	Mean	SD	Mean	SD	*P*-trend
Age (yr)	1224	52.2	10.1	53.8	11	58.1[4]	11.9	< 0.001	52.8	10.3	53.5	11.9	57.1[4]	12	< 0.001
BMI (kg/m^2)	1213	28.2	4	29.3	4.3	27.3	4.5	0.23	31.8[4]	6	30.3	4.8	30.1	5.7	0.003
Waist circumfer. (cm)	1217	97.3	11.1	96.8	10.6	95	11.9	0.11	94.3	12.7	92.1	11.4	91.2	12.7	0.024
Systolic BP (mmHg)	1217	120.6	18.8	121.3	19.6	121.8	20.3	0.83	130.5	23.9	126.4	21.7	127.3	23.7	0.15
Diastolic BP (mmHg)	1217	77.8	10.8	77.7	10.3	77.6	10.6	0.98	80.8	11.5	79.7	10.4	80	11.8	0.54
Complement C3 (g/L)	610	1.36	0.27	1.29	0.27	1.23	0.27	0.007	1.44	0.29	1.37	0.33	1.24	0.24	< 0.001
CRP[3] (mg/L)	1143	2.26	1.25-5.06	2.11	1.02-3.9	1.42[4]	0.76-3.2	< 0.001	2.72	1.15-6.33	2.61	1.21-6.18	2.29	1.08-4.0	0.025
Total cholest. (mg/dL)	1213	191.3	40	194.8	38	190	40.3	0.46	201	41.7	205.4	53	204.9	44.3	0.54
Fast. glucose, (mg/dL)	1124	99	39	99.6	37.8	94	25.8	0.27	101.9	43.9	99	38.2	93.7	32	0.093
ApoB (mg/dL)	1116	107.6	26.7	105.3	28.9	100.4	46.9	0.15	106	26.3	104.3	32.5	106.9	37.5	0.72
Creatinine (mg/dL)	1144	1.02	0.19	1.02	0.22	0.99	0.22	0.24	0.78	0.21	0.79	0.18	0.84	0.42	0.066
Fast. triglycer.[3] (mg/dL)	1123	160.8[4]	108-227	138.1	100-187	126.2	89-174	< 0.001	146.2	108-206	133.5	99.9-182	117[4]	83.5-164	< 0.001
HDL-cholest. (mg/dL)	1207	35.6	8.3	39.5	9.8	43[4]	11.3	< 0.001	43.9	11.5	45.6	10.6	49.4[4]	11.7	< 0.001
Apo A-I (mg/dL)	1103	129.7	25	134.7	25.1	138.9	25.8	0.004	144.3	26.4	145.7	29.9	152.6	28.1	0.008
Lp (a)[3] (mg/dL)	764	8.16	3.8-18.2	7.93	3.2-19.4	9.36	3.4-20.6	0.52	12.1	5.3-24.5	13.3	5.7-23.6	12.4	4-29.4	0.85
Thyroid SH[3] (mIU/L)	532	1.06	0.7-1.6	1.05	0.6-1.7	1.01	0.67-1.5	0.89	1.53	0.97-2.45	1.47	0.84-2.3	1.37	1.0-2.46	0.70
Current/former smok (%)	1218	58.4	20	47.9	21.1	45.9	29	0.035	16	3.7	18.6	3.6	14.7	3.7	0.87
Prevalent diabetes[2] (%)	1219	11.8		12.6		13.1		0.93	17.7		12.1		12.9		0.18
Incident CHD, *n* (%)	1061	13 (8.2)		11 (6.7)		4 (2.5)		0.086	21 (11.1)		8; 4		16 (8.4)		0.029

[1]Geometric mean adiponectin value of the tertile; [2]Excluded from the study; [3]Median and interquartile range; [4]Values differing from both of the other tertiles. CRP: C-reactive protein; BMI: Body mass index; BP: Blood pressure; CHD: Coronary heart disease; HDL: High-density lipoprotein; LP: Lipoprotein.

> 11 mmol/L. MetS was identified when 3 out of the 5 criteria of the National Cholesterol Education Program ATP-Ⅲ were met, modified for prediabetes (fasting glucose 5.56-6.95 mmol/L)[12] and further for male abdominal obesity using as cut-point ⩾ 95 cm, as assessed in the TARF study[13].

Information on the mode of death was obtained from first-degree relatives and/or health personnel of the local health office. Cause of death was assigned with the consideration also of pre-existing clinical and laboratory findings elicited during biennial surveys. CHD death comprised of death from heart failure of coronary origin and fatal coronary event. Nonfatal CHD was identified by the presence of angina pectoris, a history of myocardial infarction with or without accompanying Minnesota codes of the ECG[14] or a history of myocardial revascularization. Typical angina and, in women, age > 45 years were prerequisite for a diagnosis when angina was isolated. ECG changes of "ischemic type" of greater than minor degree (codes 1.1-2, 4.1-2, 5.1-2, 7.1) were considered as myocardial infarct sequelae or myocardial ischemia, respectively.

Statistical analysis

Descriptive parameters were shown as mean ± standard deviation or in percentages. Distribution in variables with skewed distribution [total adiponectin, CRP, SHBG, insulin, lipoprotein (a) and TSH] was shown in median and interquartile range and log-transformed analyses were used. ANOVA *P*-trend analyses and pairwise comparisons with post hoc Tukey HSD were made to detect significance between groups; two-sided *t*-tests and Pearson's chi-square tests were used to analyze the differences between means and proportions of other groups. Multiple linear regression analyses were performed with continuous parameters related to inflammation. To detect nonlinearity of associations with outcome, tertiles of adiponectin (6.9-11.7 in men and 8.8-14.9 women μg/mL formed the intermediate tertiles) were assessed. Cox proportional hazard regression models were used for incident cases of CHD, diabetes and hypertension after exclusion of prevalent cases, at a mean follow-up of 3.82 years. HR estimates and 95%CI were obtained in models that adjusted for sex, age and relevant confounders, expressed in terms of 1-SD increment. A value of $P < 0.05$ on the two-tail test was considered statistically significant. Statistical analyses were performed using SPSS-10 for Windows.

RESULTS

Geometric mean total adiponectin values in women (10.9 μg/mL) were higher by 27% than in men (8.6 μg/mL, $P < 0.001$). MetS was identified in 46% of individuals at baseline (9). Mean follow-up period constituted 3.82 ±1.47 years (range 2 to 6 years) which yielded a total follow-up 3820 person-years for incident diabetes; 3340 person-years for incident CHD, after exclusion of prevalent cases at baseline (160 and 150 cases, respectively) and participants lost to follow-up (64 and 199 cases, respectively). Fifty-two new cases of diabetes (12.6 per 1000 person-years) and 73 of CHD (17.6 per 1000 person-years) developed during the follow-up.

Characteristics of the sample population are presented in Table 1, separately for men and women and stratified by serum adiponectin tertiles.

When correlations between log-transformed Lp (a),

Table 2 Linear regression analysis for serum adiponectin

	Total		Men		Women			Total		Men		Women	
	β coeff.	*P* value	β coeff	*P* value	β coeff	*P* value		β coeff	*P* value	β coeff	*P* value	β coeff	*P* value
Model 1	*n* = 513		*n* = 252		*n* = 261		Model 2	*n* = 454		*n* = 223		*n* = 231	
Sex (female)	1.20	< 0.001					Sex (female)	1.285	< 0.001				
Age (11 yr)	1.05	0.055	1.10	0.005	0.997	0.93	Age (11 yr)	1.04	0.13	1.067	0.079	1.007	0.88
Fasting insulin[1]	0.79	0.009	0.80	0.016	0.79	0.033	C-reactive protein[1]	0.90	0.057	0.83	0.011	0.98	0.80
SHBG1 (nmol/L)	2.14	< 0.001	1.76	0.001	2.02	< 0.001	SHBG1	1.97	< 0.001	1.77	0.002	2.08	< 0.001
Creatinine (0.25 mg/dL)	1.04	0.67	0.992	0.82	1.085	0.052	Fasting insulin[1]	0.84	0.026	0.83	0.06	0.86	0.20
							Creatinine (0.25 mg/dL)	1.04	0.14	1.01	0.78	1.081	0.086
							Waist circumference (12 cm)	1.023	0.41	1.021	0.57	1.025	0.52
							Lipoprotein(a)[1]	1.003	0.94	1.07	0.38	0.96	0.60

All models were significant ($P < 0.001$), explained 16%/17% of adiponectin variance in genders combined, 14%/16% in men and 12% in women. [1]Log-transformed values. SHBG: Sex hormone-binding globulin.

creatinine and apoB were examined separately in sex-specific adiponectin tertiles, in men, Lp (a) was significantly correlated with apo B (0.20, $P = 0.035$) in the mid-tertile and tended to be so with creatinine (0.16, $P = 0.089$) in the lowest adiponectin tertile. In women, Lp (a) and creatinine were not correlated in the adiponectin top tertile and were inversely correlated (-0.24, $P = 0.004$) in the mid-tertile.

Table 2 shows findings of a multiple linear regression analysis for baseline covariates of circulating adiponectin in two significant models. In Model 1, apart from the female sex, levels of SHBG (positively) and insulin (inversely) were associated in each gender, while creatinine was positively associated in women with adiponectin at borderline significance. When waist circumference, CRP and Lp (a) were further added in Model 2, CRP emerged a further inverse covariate in men, beyond the persisting female sex, circulating SHBG and insulin as significant and, in women, creatinine as borderline significant covariates.

Table 3 demonstrates results of multivariable Cox proportional hazard regression analyses of adiponectin tertiles for the development of CHD, diabetes and hypertension, separately by gender. With respect to type-2 diabetes, fasting glucose and waist girth were significant predictors in each sex and the highest adiponectin tertile was a significantly inverse predictor in the total sample.

CHD risk was predicted in a multivariable Cox model adjusted also for CRP by non-HDL-cholesterol only at borderline significance in men and waist girth in the whole sample, while HRs in the higher two tertiles of adiponectin revealed significant inverse associations (Table 3). In women in contrast, an inverted J-shaped risk curve was apparent inasmuch as RR in the highest tertile did not reach significance, whereas in the mid-tertile HR seemed to be in protective direction more than anticipated.

Cox model for incident hypertension comprising sex, age, waist girth, CRP and adiponectin tertiles disclosed female sex (HR = 1.63), age (HR = 1.62) and waist circumference to be significant predictors. Adiponectin tertiles were not significantly associated in either sex, and slightly tended in men to be associated with elevated risk of hypertension.

DISCUSSION

In this prospective population-based study in middle-aged adults, we extended our previously reported evidence[8,9] for impaired anti-inflammatory/antioxidative and atheroprotective properties of high serum adiponectin levels, insofar as the mid and highest tertiles were not protective against risk of hypertension in both sexes and the highest tertile not against risk of CHD in women. Serum adiponectin in women, at variance from that in men, tended to be independently, positively and linearly associated with creatinine concentrations. Collectively, the provided evidence suggested that an autoimmune process involving adiponectin may operate, rendering the inability to protect against hypertension and, in women, against CHD, as well as in contributing to renal functional impairment. These findings diverge in part from those previously reported; details and possible reasons are discussed below.

Risk of hypertension and CHD

An independent inverse relationship between adiponectin and hypertension[1,2,15-17] or blood pressure has been repeatedly demonstrated. In the prospective case-control study on South Chinese adults, diabetic patients were excluded[17]. The action of adiponectin is believed to be due to protection against endothelial dysfunction mediated by AMP-activated protein kinase-eNOS signaling and COX-2-prostaglandin I_2 signaling pathways, changes in macrophage function and up-regulation by renin-angiotensin system inhibition[18]. Nonetheless, BP was not found to be related to plasma adiponectin levels in 180 overweight and obese Asian subjects[19]. In the current study, prospective analysis of the development of hypertension in 126 subjects among 661 non-hypertensive men and women at baseline showed a lack in protective function of the intermediate and high adiponectin tertiles in either sex, independent of waist girth and CRP concentrations. Relative risks were even above unity. This may be attributed to alterations of the adipocytokine secondary to involvement in autoimmune activation

Table 3 Cox regression analyses of serum adiponectin tertiles for incident diabetes, coronary heart disease and hypertension, adjusted for sex, age and relevant confounders

	Total HR	95%CI	Men HR	95%CI	Women HR	95%CI
Diabetes	40/761[2]		21/333[2]		19/428[2]	
Adiponectin mid-tertile	0.64	0.32-1.31	0.83	0.30-2.28	0.35	0.11-1.09
Adiponectin top-tertile	0.26	0.10-0.69	0.28	0.07-1.17	0.23	0.06-0.88
Fasting glucose (25 mg/dL)	1.60	1.22-2.04	1.49	1.08-2.09	2.25	1.35-3.72
Waist circumference (12 cm)	1.88	1.43-2.46	2.04	1.44-2.88	1.78	1.13-2.78
Creatinine (0.25 mg/dL)	1.08	0.74-1.58	0.77	0.37-1.60	1.18	0.87-1.60
C-reactive protein[1], 3-fold	1.21	0.97-1.52	1.10	0.80-1.51	1.36	0.96-1.73
Coronary disease	66/805[2]		25/358[2]		41/447[2]	
Adiponectin mid-tertile	0.54	0.30-0.97	0.8	0.34-1.92	0.39	0.17-0.90
Adiponectin top-tertile	0.49	0.26-0.91	0.31	0.09-1.05	0.66	0.32-1.38
Non-HDL cholester. (35 mg/dL)	1.07	0.87-1.28	1.37	0.97-1.93	0.93	0.70-1.19
Waist circumference (12 cm)	1.46	1.18-1.82	1.28	0.89-1.84	1.60	1.22-2.08
Creatinine (0.25 mg/dL)	1.20	0.91-1.58	1.36	0.85-2.17	1.05	0.69-1.60
C-reactive protein[1], (3-fold)	1.12	0.95-1.32	1.06	0.81-1.39	1.18	0.95-1.47
Hypertension	120/541[2]		53/274[2]		67/267[2]	
Adiponectin mid-tertile	1.08	0.71-1.91	1.23	0.62-2.43	1.03	0.56-1.89
Adiponectin top-tertile	0.77	0.55-1.59	1.08	0.51-2.30	0.64	0.33-1.24
Waist circumference (12 cm)	1.41	1.14-1.74	1.28	0.93-1.76	1.53	1.14-2.06
Creatinine (0.25 mg/dL)	1.06	0.82-1.37	1.15	0.80-1.66	1.08	0.74-1.59
C-reactive. protein[1], 3-fold	0.96	0.85-1.09	1.08	0.90-1.30	0.90	0.76-1.06

[1]Log-transformed. All models were additionally sex- and age-adjusted. Referent low adiponectin tertile (< 6.9 men and < 8.8 μg/mL women). [2]Number of incident cases/number at risk. Mean creatinine values at baseline were 0.994 in men and 0.776 mg/dL in women, and ages 53.5 and 53 years, respectively.

(as outlined below).

In regard to the atheroprotective property of adiponectin, cohort studies have yielded conflicting results. The large Rancho Bernardo study[20] reported divergent associations between serum adiponectin levels and combined prevalent and incident CHD and mortality, in contrast to the German cross-sectional case-control study overwhelmingly on males[21] which reported lower multi-adjusted odds ratios in increasing adiponectin quintiles. In essential agreement with the findings of Lawlor *et al*[22] who reported a lack of prediction of CHD by adiponectin in women, we found that the highest adiponectin tertile in women appeared not to protect against the CHD risk, despite an apparent significant protection in men. The interesting gender difference is consistent with the notion of loss of antioxidative properties mainly in postmenopausal women who exhibit a reduced concentration of SHBG, a major determinant of adiponectin[8], and a notable positive association with serum creatinine.

Sex-specific positive association with serum creatinine

Our linear regression models for baseline adiponectin concentrations demonstrated similar associations across sexes with respect to SHBG and insulin levels, but diverged regarding serum creatinine. Inverse associations (as noted in men) are anticipated between circulating adiponectin and creatinine which emerged to be positive in women, albeit at $P = 0.052$. This is consistent with a setting in which high adiponectin levels in a subset of the female sample were converted pro-oxidative to mediate endothelial dysfunction, acquiring attenuated atheroprotective effects, concomitantly with a reduced glomerular filtration rate. In view of our recent reports of higher CHD risk in women in the bottom creatinine quartile compared with the two intermediate quartiles[23,24], immune complex formation with adiponectin may be suggested.

Diabetes risk

In regard to the risk of type-2 diabetes, circulating adiponectin seemed to exert a protective effect. This is in line with previous reports on low adiponectin levels and diabetes risk[16,25-27]. A multi-SNP genotypic risk score tested in nearly 40000 individuals was positively associated with the risk of type-2 diabetes[28]. A protective effect found against diabetes parallels our finding of a significant linear and inverse association of adiponectin with fasting insulin. Current findings highlight that the insulin-sensitizing property of adiponectin may be retained while anti-oxidative and macrophage properties related to protection against hypertension and CHD may be attenuated.

Autoimmune activation in mechanistic explanation of findings

Adiponectin may well function in women with a pro-inflammatory state as an immune component, directed presumably against oxidized creatinine, may assume pro-inflammatory properties and induce impairment in endothelial and renal function, independent of low circulating SHBG and hyperinsulinemia. This view is supported by the highest compared with the intermediate adiponectin tertile not significantly protecting against CHD risk. The involvement of adiponectin in immune activation in women may result both in endothelial dysfunction-mediated renal dysfunction (CRP elevation) and failure to protect against CHD risk. This may explain the concomitantly raised risk of myocardial infarction and

all-cause mortality observed in patients with decreasing renal function[29] and is consistent with our hypothesized mechanism[30].

That the described lack of association in women between the high adiponectin tertile and CHD risk was not related to potential inadequate statistical power of the sample is negated by the mid-tertile displaying a significant inverse RR, coupled to the observation that the power of the top tertile in men did disclose a significant inverse RR. Thus, the lack of protection against CHD risk appears a valid gender-specific phenomenon.

Accounting for the lack of useful prognostic value of adiponectin in renal failure

Studies demonstrated that adiponectin concentrations were paradoxically inversely associated with glomerular filtration rates[6,7] and that in advanced kidney disease patients, cardiovascular and all-cause mortality was raised with increasing adiponectin levels[31]. Our relevant finding, together with these observations, indicates that circulating adiponectin and creatinine may parallel each other under conditions of a pro-inflammatory state. In studying the relationship of plasma adiponectin with inflammatory biomarkers and metabolic status in 180 patients with mild to moderate CKD, Norata and co-workers emphasized that, given that adiponectin synthesis is not increased and excretion not impaired, the reason for the increased adiponectin level was still unclear[32]. Our proposed hypothesis of adiponectin involvement in autoimmune activation can explain these phenomena hitherto unaccounted for.

Limitations and strengths

The comparatively brief follow-up limited the outcomes sought in a substantial proportion of the study sample, limiting the statistical power in fully assuring of not dealing with a chance finding in certain analyses, yet still did not preclude the emergence of significant findings in the opposite sex or the other adiponectin tertile. Residual confounding may not be completely excluded. We did not document the postulated hypothesis by immunoassays, if this is ever possible; however, both present findings and those previously reported support each other in this direction. The large, population-based study sample exhibiting a relatively high prevalence of enhanced low-grade inflammation forms strength, while possibly partly limiting applicability of findings to some other ethnic populations at large. Availability of measurements of diverse relevant variables that are not commonly studied in previous reports on adiponectin forms a further strength of the study.

In conclusion, added to our previous report of impaired protective properties of high circulating adiponectin in middle-aged Turkish adults, elevated levels were found to be not protective against the risk of hypertension in both genders and in women against CHD risk. At variance from men, serum adiponectin in women tended to be independently and positively associated with creatinine concentrations. We propose that involvement of adiponectin in autoimmune activation may underlie both the lack of stated protection and a concomitant presumable contribution to renal functional impairment.

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COMMENTS

Background

Serum adiponectin exerts protective functions against cardiometabolic disorders, including hypertension, *via* insulin-sensitizing, anti-inflammatory and antiatherogenic properties. Yet, adiponectin levels are often inversely associated with glomerular filtration rate which still needs a satisfactory explanation.

Research frontiers

Gender and the presence of metabolic syndrome/pro-inflammatory state modulate cardiometabolic risk and might modulate the protective function of serum adiponectin. The authors analyzed baseline covariates of adiponectin and found that serum creatinine was, surprisingly, a positive independent covariate. In prospective analyses, although incident type-2 diabetes appeared to be protected by the high adiponectin tertile, no evidence of protection was elicited against incident hypertension and, in women, against coronary heart disease. These findings suggested impairment of some properties of serum adiponectin due to enhanced low-grade inflammation and autoimmune activation.

Innovations and breakthroughs

This study offers a potential explanation to the controversies on the role of serum adiponectin in chronic kidney disease, but shows also that part of the properties (antioxidative) of this cytokine may become impaired, analogous to that recently documented regarding high-density lipoprotein, resulting in lack of protection against hypertension risk and, sex-specifically, against future coronary heart disease (CHD) risk. As responsible for the modulating phenomenon, the authors hypothesize that autoimmune activation in women is linked to serum creatinine and adiponectin to mediate renal dysfunction and the associated CHD risk.

Applications

This knowledge may be utilized in population screening and more precise undertaking of preventive measures against diabetes and coronary heart disease, as well as in assessment of individual cardiometabolic risk. The hypothesis put forward also opens new avenues of research in the area of pathogenesis of chronic kidney disease and coronary heart disease.

Peer review

The authors examined whether and to what extent circulating adiponectin protects against the risk of hypertension, diabetes or coronary heart disease, separately in each gender. The study revealed that serum adiponectin was positively and independently associated in women linearly with serum creatinine, a pro-inflammatory compound. Prospective multivariable analyses disclosed that the development of CHD risk was not reduced in women by the highest adiponectin tertile, nor was the incident hypertension risk in either gender. By showing on the other hand that adiponectin tertiles protected against incident type-2 diabetes, evidence was provided that insulin-sensitizing properties remained intact, as opposed to the loss of antioxidative and antiatherogenic action. The results suggest that the operation of autoimmune activation involving adiponectin and creatinine may contribute to the pathogenesis of elevated BP and CHD. This may carry implications in both risk assessment and prevention of cardiometabolic risk, warranting new avenues for research.

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