Increased apolipoprotein A-I levels mediate the development of prehypertension among Turks

Artmış apolipoprotein A-I düzeyleri prehipertansiyon gelişmesine Türk yetişkinlerinde aracılık etmektedir

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ABSTRACT

Objective: We aimed to assess whether apolipoprotein (apo) A-I levels that generated type-2 diabetes and coronary disease among Turks contribute to prehypertension and hypertension.
Methods: A population-based sample of 2207 adults (mean age 53±11 years) was studied prospectively over a 6.5 years' follow-up. Individuals with hypertension and/or prehypertension were excluded at baseline.
Results: At baseline, levels of apoA-I increased in each sex, from the normotensive to prehypertensive and hypertensive group (by mean 7.6 mg/dL, p<0.001) concomitantly with age, waist circumference, fasting triglycerides, apoB, C-reactive protein (CRP) and homeostasis model assessment. In logistic regression models, adjusted for confounders comprising waist circumference or triglycerides, prehypertension was predicted independently by apoA-I at RRs of 1.23 (95%CI 0.97; 1.52)] or 1.32 (95%CI 1.04; 1.74), respectively. Despite showing a positive association, apoA-I did not independently predict in similar models the development of hypertension; the determinants were rather waist circumference, or fasting triglycerides or CRP [RR 1.16 (95%CI 1.05; 1.28)] and, in women, diabetes. In a linear regression analysis for circulating apoA-I including 10 variables, apoB and in men systolic blood pressure were positively associated.
Conclusion: In contributing to prehypertension, the pro-inflammatory apoA-I, mediated by apoB, is independent of triglyceridemia. Other inflammatory processes conjointly are likely mechanistically involved in the development of hypertension in a population with prevalent metabolic syndrome. *(Anadolu Kardiyol Derg 2013; 13: 306-14)*
Key words: Apolipoproteins, C-reactive protein, diabetes type-2, obesity, prehypertension, systemic inflammation, regression analysis

ÖZET

Amaç: Türk yetişkinlerinde, tip 2 diyabete ve koroner kalp hastalığına sürüklediği gösterilen apolipoprotein (apo) A-I düzeylerinin prehipertansiyon ve hipertansiyonla ilişkili olup olmadığı araştırılmaya değerdir.
Yöntemler: Popülasyona dayalı bir örneklem (2207 kişi, ort. yaş 53±11) öne dönük biçimde 6.5 yıl boyunca izlendi. Başlangıçta hipertansiyon ve/veya prehipertansiyonu olan bireyler dışlandı.
Bulgular: Başlangıçtaki apoA-I düzeyleri her iki cinsiyette, yaş, bel çevresi, açlık trigliseridleri, apoB, C-reaktif protein (CRP) ve homeostaz model değerlendirmesi ile birlikte, normotansif gruptan, prehipertensif ve hipertansif gruplara doğru (ort. 7.6 mg/dL, p<0.001) yükseldi. Bel veya trigliseridin katıldığı kovaryatlar için ayarlanan lojistik regresyon modellerinde, prehipertansiyon apoA-I tarafından bağımsız olarak [1.23 (%95 GA 0.97; 1.52)] veya 1.32'lik (%95 GA 1.04; 1.74) nisbi risk oranlarıyla öngörüldü. Pozitif ilişkisine rağmen, apoA-I benzer modellerde hipertansiyon gelişmesini bağımsız olarak öngörmedi; belirleyiciler daha ziyade bel çevresi veya açlık trigliseridi veya CRP [RR 1.16 (%95 GA 1.05; 1.28)] ve kadında, diyabet idi. Serum apoA-I için 10 değişkenden oluşan bir lineer regresyon analizinde apoB ve erkekte sistolik kan basıncı ilişkili bulundu.

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Sonuç: Prehipertansiyona katkı yapmakta, apoB'nin aracılık ettiği pro-inflammatory apoA-I trigliseridden bağımsızdır. Metabolik sendrom prevalansı yüksek popülasyonlarda hipertansiyon gelişmesinden diğer yangı süreçlerinin hep birlikte sorumlu olması muhtemeldir.
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Anahtar kelimeler: Apolipoproteinler, C-reaktif protein, diyabetes tip 2, obezite, prehipertansiyon, sistemik yangı, regresyon analizi

Introduction

Beyond activation of the renin-angiotensin system, obesity, insulin resistance and a proinflammatory state have been recognized as determinants (1) in the multifactorial pathophysiology of hypertension. The proinflammatory state, known to be interrelated with obesity and smoking habit, was reported to antidate at least by several years the onset of overt hypertension (2). Less attention has been paid to the determining factors of prehypertension. Body mass index (BMI or waist girth as determinants of prehypertension was found to be modulated by gender (3), insulin resistance was reported to be associated with prehypertension in a Spanish cohort (4), and ethnic differences among Americans were shown to play a role in the population-attributable risk of prehypertension (5). Adiposity and triglycerides were consistently higher from childhood through adulthood in prehypertensive subjects (6). Findings of the ATTICA study (7) which revealed an association between prehypertension and increased C-reactive protein (CRP) levels, independently of other coexisting risk factors, suggested a proinflammatory nature of prehypertension. We also reported previously among Turks that BMI and circulating CRP were determinants of developing prehypertension (8). The role of apolipoprotein A(apoA)-I which generally has anti-inflammatory and atheroprotective properties has scarcely been examined in the development of prehypertension and hypertension.

The TARF study was first to document in a general population that elevated levels of apoA-I did not protect against risk of type-2 diabetes but, paradoxically, rather conferred such risk (9, 10). Cholesterol concentrations in high-density lipoprotein (HDL) (carriers of apoA-I particles) were shown not to protect Turkish women also against incident coronary heart disease (CHD) (11, 12). These observations may be explained by a hypothesis that, under conditions of a proinflammatory state/oxidative stress, apoA-I may be converted from an anti-inflammatory and anti-atherogenic particle to a pro-inflammatory one. Certain populations with a high prevalence of metabolic syndrome (MetS) and segments of populations prone to impaired glucose tolerance seem to provide such circumstances of proinflammatory state/oxidative stress.

It is of interest, therefore, to explore longitudinally the role of apoA-I levels in the development of prehypertension and hypertension in a cohort representative of middle-aged Turkish adults in whom MetS and diabetes are highly prevalent (13). Several other inflammatory variables or related states in the prediction of incident prehypertension and hypertension (such as CRP, triglycerides, waist girth, smoking status and diabetes) as well as determinants of apo A-I were also studied.

Methods

Population sample

The Turkish Adult Risk Factor Study is a prospective survey on the prevalence of cardiac disease and risk factors in adults in Turkey carried out periodically since 1990 in 59 communities throughout the geographical regions (14). It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions and for rural-urban distribution (14). Measurements of serum apoA-I and lipoprotein (a) (Lp(a)) were performed at the follow-up visits in 2001/'02 through 2005/'06 in participants 32 years of age or older; hence, this formed the baseline. 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 electrocardiogram.

The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the İstanbul University Ethics Committee. Individuals of the cohort signed consent for participation after having read an explanatory note.

Measurements of risk variables

Blood pressure (BP) was measured at all examinations by physicians in participants in the sitting position on the right arm, and the mean of two recordings at least 3 min apart was recorded. Waist circumference was measured with a tape (Roche LI95 63B 00), the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. Self-reported cigarette smoking was categorized into never smokers, former smokers (discontinuance of 3 months or more) and current smokers (regularly 1 or more cigarettes daily).

Blood samples collected into dry vacutainers were spun and sera shipped on cooled gel packs to Istanbul to be stored in deep-freeze at -75°C, until analyzed at a central laboratory. Serum concentrations of total cholesterol, fasting triglycerides, glucose, HDL-cholesterol (HDL-C plus 2nd generation, directly without precipitation) and creatinine were determined by using enzymatic kits from Roche Diagnostics with a Hitachi 902 autoanalyzer. Low-density lipoprotein (LDL)-cholesterol values were computed with the Friedewald formula. Concentrations of insulin were determined by the chemiluminescent immunometric method using Roche kits and Elecsys 1010 immunautoanalyzer (Roche Diagnostics, Mannheim, Germany). Concentrations of serum CRP, apolipoprotein A-I and B were measured by the Behring nephelometry (Behring Diagnostics, Marburg, Germany).

Definitions and outcomes

Hypertension (HT) was defined as a blood pressure ≥140 mmHg and/or ≥90 mmHg, and/or use of antihypertensive medica-

tion. Prehypertension*n* was defined as a blood pressure 120-139 mmHg or 80-89 mmHg. Individuals with *diabetes* were diagnosed with criteria of the American Diabetes Association (15), namely when plasma fasting glucose was ≥126 mg/dL (or 2-h postprandial glucose >200 mg/dL) and/or the current use of diabetes medication. Homeostasis model assessment (HOMA) was calculated with the following formula (16): insulin (mIU/L) x glucose (in mmol/L)/22.5. Values of the baseline examination were used to evaluate prospective developments.

Statistical analysis

Statistical analyses were performed using SPSS-10 for Windows (SPSS Inc., Chicago, Ill., Nr. 9026510). Descriptive parameters are shown as mean ±standard deviation (SD) or in percentages. Log-transformed values were used for CRP, Lp(a) and HOMA index, due to their skewed distribution. Two-sided t-tests and Pearson's chi-square tests served to analyze the differences in means and proportions between groups. ANOVA and pairwise comparisons with Tukey HSD were made to detect significance between groups of estimated means. After exclusion of the cohort with the dependent variable at baseline examination, estimates (and 95% confidence intervals) for relative risk (RR) of a dependent variable was obtained by use of logistic regression analyses in models that controlled for potential confounders. Such models comprised 7-8 variables linked closely in this population to the development of prehypertension and hypertension (8). 1 SD increment in apoA-I was represented by 35 mg/dL and in fasting log-triglycerides by 66% of variation; 1 SD of waist circumference corresponded among men and women to 11 and 13 cm, respectively. A value of $p<0.05$ on the two-sided test was considered statistically significant.

Results

Overall, 2207 participants (of whom 1044 men) formed the study sample. Mean age of participants was 53±11 years, and mean follow-up constituted 6.5±3.0 years (total 14,350 person-years). Of the total sample, 22% was under antihypertensive medication at baseline. Normotensives (n=1104, 50%), prehypertensives (301, 14%) and hypertensives (802, 36%) formed the BP categories. Age in prehypertensives were 4 years older than normotensives but 6 years younger than hypertensives ($p<0.001$).

Male prehypertensives had high triglycerides, HDL and fibrinogen, medium apoA-I and glucose and low LDL-C. Female prehypertensives had virtually identical HDL and fibrinogen, medium triglycerides, apoA-I and LDL-cholesterol. Female hypertensives had further elevations in triglycerides, glucose and fibrinogen.

Table 1 shows additionally that mean concentrations of apoA-I increased significantly in each sex from normotensives to hypertensives, prehypertensive individuals lying in between (in combined sexes 131.3 to 138.9 mg/dL, $p<0.001$ compared to normotensives, $p=0.073$ between preHT (134.3 mg/dL) and normotension). This paralleled significant increases in fasting triglycerides and CRP. Levels of Lp(a) were similarly distributed among the BP groups in women, whereas they decreased insignificantly by 15% in men.

Covariates of apolipoprotein A-I

Findings of a linear regression analysis of baseline apoA-I with concomitant sex, age, smoking status, waist circumference, fasting glucose and triglycerides, HDL-cholesterol, apoB, systolic and diastolic BP are shown in Table 2. In the highly significant model in each sex, 28% of the apoA-I variance was explained in men and 19% in women. Apart from HDL-cholesterol, apoB was positively associated (accounting for a 4mg-change in apoA-I) in each sex. In addition in men, waist circumference was modestly inversely associated and systolic BP was significantly and positively associated with circulating apoA-I.

Predictors of prehypertension

Prehypertension developed in 107 of 877 initially normotensive participants at follow-up (corresponding to an incidence of 1.8% per annum). In a multiple logistic regression, age and waist circumference were the foremost significant predictors of newly developing prehypertension (Table 3) but apoA-I level tended to predict positively and independently in women and in the whole sample. When serum fasting triglycerides replaced in the model waist circumference and smoking status (Model 2), apoA-I proved to significantly predict prehypertension in both genders (RR 1.32, 95%CI 1.04; 1.74) and in men.

Predictors of hypertension from normotension and/or prehypertension

Of 1213 normotensive and prehypertensive adults at baseline, 346 developed hypertension at follow-up. A multiple logistic regression analysis comprising the 6 independent variables as in Model 1 for prehypertension, disclosed again age and waist circumference as significant predictors added to female sex and diabetes in women (Table 4). Of 960 men and women who were normotensive at baseline and followed up, 222 developed hypertension (corresponding to an incidence of 1.4% per annum). In logistic regression analysis in a similar model, no essential alterations were observed except for smoking in men (Model 1). ApoA-I was not significant with an RR (1.04) over unity. Replacing triglycerides in Model 2 and CRP in Model 3 for waist circumference and smoking status, yielded the substituted variables as added predictors of the development of hypertension; apoA-I retained an insignificant RR of 1.04.

Discussion

In a prospective analysis of a middle-aged population sample in whom (using modified ATP III criteria) MetS prevailed in 44% of those aged 30 or over (17), we found that serum apoA-I levels were a significant positive risk factor among normotensive individuals of incident prehypertension, additive to age, fasting triglyc-

Table 1. Baseline characteristics of the study sample, stratified by gender and blood pressure groups

Variables		Men (n=1044)								Women (n=1163)					
		Normotensive		Prehypertensive		Hypertensive				Normotensive		Prehypertensive		Hypertensive	
	n	587		156		301		*p trend		517		145		501	
		Mean	SD	Mean	SD	Mean	SD	Men	Women	Mean	SD	Mean	SD	Mean	SD
Age, years	2207	49	10.5	53.2	11.7	59.2	10.7	<0.001	<0.001	48	10.5	52.2	11.7	58.2	10.7
Waist circumference, cm	2201	91.3***	10.2	94.5	10	99.5***	10.9	<0.01	<0.01	87**	12	91.6	11.8	98***	12.2
Systolic BP, mmHg	2202	112***	9.6	129.4	7.2	148***	20.5	<0.01	<0.01	112.3***	10.3	130.3	5.7	151.7***	23.6
Diastolic BP, mmHg	2202	73.5***	7.5	81.8	7	92***	12.5	<0.01	<0.01	73***	8	82	5	92***	13.4
Total cholesterol, mg/dL	2207	186.9	38.4	196.2	40	204	38	<0.01	<0.01	187	38.4	196	40	204.2**	38
HDL-cholesterol, mg/dL	2207	38.1	10.9	38.9	12	37.8	11.3	0.59	0.71	47	12	47	13.6	46.4**	13
Fast.triglycerides, mg/dL[a]	1433	138	1.74	155	1.74	155	1.74	0.056	<0.001	109.6	1.55	120.2	1.70	145**	1.62
Apolipoprotein A-I, mg/dL	2207	125	29	128.3	23	131.3	38	0.013	0.043	138.7	29	140.7	33	143.4	30
Apolipoprotein B, mg/dL	2194	108	33	112	32	117.7*	35	<0.01	<0.01	101.7	33	110	35.5	117.6	33
Fasting glucose, mg/dL	1488	94	26.5	100	31	105**	41.3	<0.01	<0.05	95.3	32	97.7	29.3	104**	35.5
Fibrinogen, g/L	1605	2.97	1.11	3.16	1.12	2.99	1.10	0.23	0.39	3.19	1.08	3.22	0.98	3.30	1.11
Lipoprotein(a), mg/dL[a]	1361	9.23	3.1	8.98	2.5	7.85	2.8	0.24	0.84	11.5	2.9	11.7	2.7	12.1	3.0
HOMA index[a]	910	1.47	2.19	1.72	2.12	2.09***	2.04	<0.001	<0.001	1.46	2.19	1.70	1.93	2.20***	1.96
Creatinine, mg/dL	1511	0.96	0.16	0.99	0.20	1.08	0.43	<0.001	<0.001	0.75	0.15	0.80	0.17	0.84*	0.35
C-reactive protein, mg/L[a]	1719	1.73	2.98	1.74	2.26	2.47b	3.00	<0.001	<0.001	1.69	3.02	2.34	2.65	3.20***	2.73
Current smoking, %	2131	60.3		56		35.4		<0.001	<0.001	24.2		20.1		10.8	
Diabetes, n, %	2207	21	3.6	13	8.3	35	11.6	<0.001	<0.001	19	3.7	3	2.1	61	12.2
Statin use, n, %	2207	5	0.9	1	0.6	11	3.6	<0.01	<0.001	6	1.2	4	2.8	28	5.6

[a]geometric mean values. An SD-value of 1.62 for triglycerides in hypertensive women indicates 90 and 235 as CIs

[b]p<0.01 from normotensive group. Difference from the prehypertensive group, **<0.01, *** <0.001. *p trend by ANOVA

BP - blood pressure, HDL - high-density lipoprotein, HOMA - homeostasis model assessment

Table 2. Linear regression analysis for independent covariates of apo A-I levels (mg/dL), by gender

Variables	Total (n=1452†)			Men (n=662)			Women (n=790)		
	β coeff.*	SE	p	β coeff. *	SE	p	β coeff. *	SE	p
Gender, female	3.0	1.7	0.074						
Age, 11 years	-0.23	0.07	0.76	-0.76	0.99	0.44	0.23	1.12	0.84
HDL-cholesterol, 12 mg/dL	13.4	0.73	<0.001	14.2	1.01	<0.001	12.6	1.07	<0.001
Apo B, 34 mg/dL	4.0	0.78	<0.001	4.32	1.05	<0.001	3.57	1.12	0.002
Systolic BP, 25 mmHg	2.38	1.35	0.081	5.0	2.0	0.013	0.72	1.90	0.70
Diastolic BP, 12 mmHg	1.45	1.09	0.19	0.5	1.46	0.73	2.2	1.6	0.17
Current vs never smoking	-2.14	1.84	0.24	-1.90	1.17	0.41	-2.12	2.83	0.46
Fast. triglycerides¶ 1.66-fold	1.36	1.34	0.28	1.55	1.41	0.13	1.02	1.47	0.85
Waist circumfer., 11/13 cm	-0.82	0.78	0.30	-2.05	1.05	0.049	0.09	1.18	0.94
Fast. glucose, 30 mg/dL	-0.24	0.69	0.73	-0.96	0.90	0.29	0.52	1.02	0.62
explained apoA-I variance, %	26			28			19		

Each model was significant (p<0.001). ¶Log-transformed values

*For each 1-SD increment in the independent variables, the corresponding change in apoA-I level (in mg/dL) is shown by the β coefficient (SE)

†All 10 variables (especially fasting glucose and triglycerides) were available only in 66% of the sample.

Apo - apolipoprotein, BP - blood pressure, circumfer - circumference, fast.- fasting, HDL - high-density lipoprotein

Table 3. Logistic regression analysis for prediction of incident prehypertension from normotensives, by gender

	Total		Men		Women	
	RR	95% CI	RR	95% CI	RR	95% CI
Model 1*	**102/840†**		**53/465†**		**49/375†**	
Sex, female	1.38	0.83; 2.30				
Age, 11 years	1.66	1.36; 2.06	1.84	1.38; 2.45	1.49	1.03; 2.15
Waist circumference, 11/13 cm	1.44	1.14; 1.82	1.38	1.01; 1.92	1.58	1.09; 2.27
Apolipoprotein A-I, 35 mg/dL	1.23	0.97; 1.52	1.11	0.78; 1.57	1.37	0.97; 1.93
Current vs never smoking	0.92	0.55; 1.56	0.60	0.31; 1.19	1.40	0.65; 3.02
Diabetes, yes/no	1.55	0.60; 4.01	0.52	0.11; 2.56	6.55	1.59; 27.1
Statin usage, yes/no	4.46	0.89; 22.3	0.01	NS	30.2	2.7; 333
Model 2 *‡	**69/555†**		**36/297†**		**33/258†**	
Sex, female	1.27	0.73; 2.22				
Age, 11 years	1.75	1.35; 2.36	1.90	1.35; 2.69	1.61	1.06; 2.43
Fasting triglycerides¶ 1.66-fold	1.10	0.89; 1.36	1.15	0.88; 1.51	0.97	0.67; 1.40
Apolipoprotein A-I, 35 mg/dL	1.32	1.04; 1.74	1.42	1.000; 2.00	1.23	0.81; 1.87
Diabetes, yes/no	1.93	0.68; 5.43	0.41	0.05; 3.40	11.2	2.29; 54.7
Statin usage, yes/no	2.43	0.19; 31.7	0.02	NS	2847	NS

*Hypertensive individuals at baseline were excluded ‡and fasting triglyceride values were unavailable in the cohort.
¶ log-transformed values. Statins were used in 5 men and 3 women in the lowest model.
Significant values are highlighted in boldface. NS: not significant
†number of cases/number at risk

erides and largely independent also of waist circumference. In contrast, apoA-I did not play a significant role in progression from normo- (and prehypertension) to hypertension independent of age and waist circumference. This observation was in line with and extended our previous reports on the pro-inflammatory nature of apoA-I among Turkish adults, inducing diabetes and CHD. Among a regression model comprising 10 variables, apoB and, in men, systolic BP were positively and linearly associated with circulating apoA-I, suggesting a pro-inflammatory role of an aggregated complex of apoB to apoA-I in leading to prehypertension.

This study is distinct from the previous report of 4 years ago (8) in that the current one is limited to participants in whom apoA-I measurement was available at baseline, the mean age of the cohort was 4 years older, diabetes at baseline was not excluded and, not the impact, but the predictors of prehypertension were under focus, with special reference to apoA-I.

Pro-inflammatory nature of prehypertension

Present data showed that circulating apoA-I increased from normotensive to prehypertensive and hypertensive individuals in each sex concomitantly with age, waist circumference, triglycerides, apoB, CRP and HOMA index. In the development of prehypertension, apoA-I levels were a predictor additively to triglycerides irrespective of the presence of diabetes which diverged in the sexes, being not a covariate in men but a strong determinant in women in whom notably normotensives are fewer than in men. The nature of apoA-I as both a covariate of inflammatory markers and a determinant of prehypertension is unexpected insofar as apoA-I is known to possess anti-inflammatory properties; this suggests its conversion to an inflammatory lipoprotein. Such pro-inflammatory HDL is well recognized to contribute to oxidative damage and lead to accelerated atherosclerosis even in chronic rheumatic diseases (18). It is noteworthy that apoA-I has been reported to be combined during oxidation to LDL (apoAI-LDL) which could mark in a cross-sectional study coronary artery disease more accurately than CRP (19), although the relation to hypertension was not specifically investigated.

In the Honolulu Heart Program on 1177 Japanese-American men, followed up over a mean 11 years, CHD incidence was highest in the group with high apoA-I/HDL-C≤40 mg/dL (20), a group that had by far the highest triglyceride and lowest Lp(a) values. Collectively, these findings suggest to us existence of dysfunctional high apoA-I levels in Japanese-American men and are consistent with aggregation of Lp(a) to apoA-I in the setting of hypertriglyceridemia, as the authors underlined.

We hypothesize and have unpublished evidence that apoA-I may become pro-inflammatory by aggregation to Lp(a) in an attempt to counteract the latter as an antigen under enhanced inflammation and/or oxidative stress. This conversion of properties may make apoA-I diabetogenic and atherogenic (9, 11). Alteration in lipoprotein structure and function commonly observed in enhanced inflammation or minor renal dysfunction

Table 4. Logistic regression analysis for prediction of incident hypertension by gender

	Total		Men		Women	
	RR	95% CI	RR	95% CI	RR	95% CI
Hypertension from NT & PreHT*	**346/1213†**		**163/647†**		**183/566†**	
Sex, female	2.03	1.46; 2.82				
Age, 11 years	1.98	1.71; 2.28	1.90	1.56; 2.31	2.24	1.78; 2.80
Waist circumference, 11/13 cm	1.66	1.43; 1.92	1.78	1.48; 2.22	1.53	1.23; 1.91
Apolipoprotein A-I, 35 mg/dL	1.01	0.87; 1.19	1.04	0.81; 1.32	0.93	0.75; 1.19
Current vs never smoking	1.06	0.76; 1.49	1.30	0.80; 2.12	0.81	0.49; 1.34
Diabetes, yes/no	0.95	0.48; 1.89	0.47	0.18; 1.21	4.01	1.16; 13.9
Statin usage, yes/no	1.41	0.39; 5.09	1.68	0.27; 10.4	1.36	0.21; 8.83
Hypertension from normotension						
Model 1	**222/960†**		**103/515†**		**119/445†**	
Sex, female	2.36	1.58; 3.53				
Age, 11 years	2.00	1.67; 2.38	1.78	1.40; 2.26	2.50	1.92; 3.28
Waist circumference, 11/13 cm	1.68	1.41; 2.01	1.90	1.46; 2.45	1.47	1.14; 1.91
Apolipoprotein A-I, 35 mg/dL	1.04	0.87; 1.28	1.07	0.81; 1.47	0.98	0.73; 1.32
Current vs never smoking	1.36	0.90; 2.04	2.27	1.18; 4.39	0.85	0.46; 1.58
Diabetes, yes/no	1.30	0.58; 2.93	0.49	0.15; 1.66	7.09	1.76; 28.6
Statin usage, yes/no	3.32	0.71; 15.6	3.01	0.41; 22.0	7.02	0.41; 120
Model 2‡	**159/645†**		**68/329†**		**91/316†**	
Sex, female	2.16	1.43; 3.27				
Age, 11 years	2.10	1.73; 2.58	1.75	1.31; 2.31	2.74	2.04; 3.69
Apolipoprotein A-I, 35 mg/dL	1.04	0.84; 1.37	0.99	0.70; 1.37	1.11	0.81; 1.57
Fast. triglycerides¶ 1.66-fold	1.32	1.13; 1.52	1.36	1.11; 1.65	1.18	0.93; 1.50
Diabetes, yes/no	1.95	0.85; 4.49	0.84	0.25; 2.88	8.00	1.85; 34.6
Statin usage, yes/no	1.39	0.10; 19.8	1.87	0.16; 22.5	too few	NS
Model 3	**208/885†**		**96/468†**		**112/417†**	
Sex, female	1.64	1.17; 2.32				
Age, 11 years	2.00	1.67; 2.36	1.62	1.28; 2.04	2.16	2.02; 3.48
Apolipoprotein A-I, 35 mg/dL	1.04	0.84; 1.28	1.04	0.78; 1.42	1.00	0.75; 1.37
C-reactive protein¶ 3-fold	1.16	1.05; 1.28	1.13	0.98; 1.31	1.13	0.97; 1.31
Diabetes, yes/no	1.71	0.76; 3.85	0.77	0.23; 2.57	6.91	1.80; 26.4
Statin usage, yes/no	2.05	0.35; 12.1	1.14	0.11; 11.7	511	NS

*Hypertensive individuals at baseline were excluded ‡and fasting triglyceride values were unavailable in the cohort.
¶ log-transformed values. Significant values are highlighted in boldface. NS: not significant
†number of cases/number at risk Diabetes was present in 17 men and 12 women in the lowest model.
NT&PreHT, normotensive and prehypertensive individuals

includes apoA-I that is replaced by serum amyloid A diminishing the ability of HDL to protect against cytokine action of endothelium (21-23). Turks appear to be alike Asian Indians who exhibit relatively high Lp(a) levels unrelated to allele frequencies or short apo(a) isoforms (24). Evidence was obtained in 360 diabetic patients with coronary artery disease in the PERISCOPE study that glimepiride-induced changes in percent atheroma volume were inversely correlated with apoA-I (more strongly than with LDL-cholesterol or apoB) (25), being consistent with a pro-inflammatory nature of apoA-I in this treatment arm.

Systemic inflammation, triglycerides and development of hypertension

In a total of 341 type-1 diabetic patients, compared with the remaining patients, proliferative diabetic retinopathy was found to be associated with increased levels of Lp(a) in whom apoA-I concentrations were insignificantly elevated as well (26). Hypertension was significantly more frequent in this group implying the involvement of these proinflammatory lipoproteins in both hypertension and the severe retinopathy. Furthermore, 146 young women with previous hypertensive disease of pregnancy (gestational hypertension and preeclampsia) disclosed signs of enhanced low-grade inflammation within the first decade after delivery, consisting of higher levels of triglycerides, apoB, CRP, lower concentrations of HDL-cholesterol, apoA-I and adiponectin (27). Authors conjectured if these metabolic defects preceded the manifestations of hypertensive disease of pregnancy.

In line with this is our finding that high atherogenic index of plasma, reflecting in women a pro-inflammatory state, predicts hypertension (at 7-years' follow-up) via close involvement in pro-inflammatory status (17). Finally, in 190 affected sibling pairs from a cohort of Asian Indian families with a strong history of premature coronary artery disease, the Sac-1 single nucleotide polymorphism in the APOC3 gene and hypertension were contributory factors to this atherogenic trait; circulating apoA-I in participants (distinct from HDL-cholesterol) was highly significantly and positively correlated with serum apoB and triglycerides (28). Triglyceride-rich lipoproteins are considered to be able to fan the flame of inflammation in several ways (29) one of which is that very low-density lipoprotein (VLDL) that bear apoC-III can increase monocytoid cell adhesion to endothelial cells (30).

In the meta-analysis by the ERFC (31) in 22 prospective studies involving over 90,000 individuals, the apoA-I quintile 2 proved to protect against CHD risk compared with the lowest quintile by nearly 20%. Yet, onwards from 1.44 g/L for combined sexes (in the 3 highest quintiles), no significant protection could be elicited from figure 3 in that meta-analysis. This suggests that, even in a nearly exclusively Western population sample of middle-aged and elderly adults, intermediate and high apoA-I levels may be highly heterogeneous comprising well-functioning and dysfunctional apoA-I particles.

It is not fully clear why apoA-I induced the development of prehypertension but -at higher concentrations- was not involved independently in hypertension. The roles of both waist circumference and of advanced age representing increasing global pro-oxidant processes and diminished sex hormones are likely more pertinent in hypertension per se. Compared to prehypertensive individuals, hypertensive ones were, indeed, 6 years older. Factors other than inflammation-related endothelial dysfunction might be required for the development of hypertension such as activation of the renin-angiotensin system and arterial stiffness, etc, during which process the mildly BP-elevating effect of the pro-inflammatory apoA-I is reduced to a minor role. The independent association of diabetes as a determinant of future prehypertension/hypertension was striking among women alone, again suggesting the probable influence of inflammatory mediators.

ApoB and systolic BP as covariates of apoA-I

In the development of hypertension (though not of prehypertension), female sex was a strong independent determinant, additive to the powerful ones such as age and waist girth. This suggests that inflammatory mediators of vascular origin, unrelated to abdominal obesity and not included in the model (such as CRP, vascular and intercellular adhesion molecules-1, serum amyloid A, etc.) may have been involved in hypertension mechanistically, more than in men.

Present findings and those of others discussed indicate that any relevant degree of pro-inflammatory state/oxidative stress offsetting the balance of anti-inflammatory processes may be prominently involved in the development of prehypertension or hypertension, be it low levels or dysfunctional high levels of apoA-I, HDL particles or adiponectin, or elevated concentrations of CRP, apoB or gamma-glutamyltransferase (32). High levels of pro-inflammatory apoA-I may thereby be accounted for a prospective association with diabetes, CHD and prehypertension.

Clinical implications of such recognition relate to prevention and management of (pre)hypertension. Lending more weight than hitherto in prevention to dietary aspects, exercise and to medication supplementing antihypertensive drugs with insulin sensitizing or anti-inflammatory drugs might prove beneficial in managing obese hypertensive individuals resistant to a conventional approach.

Study limitations

Our follow-up may not have been long enough to allow the emergence of the inflammatory effects of the heterogeneous apoA-I in the development of hypertension. The generalizability of our findings may be limited to populations with a high prevalence of MetS or to those population segments prone to impaired glucose tolerance. Inflammation biomarkers other than those herein studied may be contributing to the prediction of hypertension. Despite a prospective design of the study, caution is deemed in interpreting causality from results of an observational study.

Conclusion

High apoA-I levels predicted the development of prehypertension, additively to serum triglyceride levels, the presence of diabetes and other relevant covariates. Hypertension, significantly associated with high apoA-I levels was not independently predicted by these levels but rather by wide waist girth, triglycerides or CRP reflecting a role of global enhanced low-grade inflammation, especially in women.

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