

Original Paper

Plasma Lipoprotein(a) Levels and Atherosclerotic Renal Artery Stenosis in Hypertensive Patients

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Key Words

Lipoprotein(a) • Homocysteine • Prothrombotic state • Renovascular hypertension • Ischemic nephropathy

Abstract

Background/Aims: The contribution of emergent cardiovascular risk factors to atherosclerotic renal artery stenosis (ARAS) is debated. We investigated the relationship of lipoprotein(a) and prothrombotic factors with ARAS in hypertension. **Methods:** In 50 hypertensive patients with angiographic evidence of ARAS and 58 hypertensive patients who had comparable cardiovascular risk factor burden but no evidence of renovascular disease, we measured renal function, lipoprotein(a), homocysteine, and hemostatic-fibrinolytic markers. **Results:** Patients with ARAS were more frequently smokers and had longer duration of hypertension, heavier antihypertensive treatment, and worse renal function than controls. Lipoprotein(a) was higher in patients with ARAS than controls, whereas no differences were found in homocysteine and all hemostatic variables. Multivariate analysis showed that lipoprotein(a) was associated with ARAS independent of other confounders including renal function and history of coronary heart, cerebrovascular, and peripheral artery disease. **Conclusion:** Lipoprotein(a) might contribute to the development of ARAS and detection of elevated levels of this lipoprotein could raise the suspicion of renovascular disease in patients with high blood pressure.

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Introduction

Atherosclerotic renal artery stenosis (ARAS) has a prevalence comprised from 5 to 10% in the adult general population [1], prevalence that increases substantially in patients with or without hypertension undergoing angiographic examination of the coronary tree [2] or peripheral arteries [3]. Possible consequences of ARAS are secondary renovascular hypertension [4, 5] and renal insufficiency [4, 6] caused by ischemic nephropathy. For these reasons, ARAS is now considered a relevant cause of end-stage renal failure and need for dialysis [7]. Although recent studies indicate that revascularization of ARAS does not confer significant benefit over medical therapy in patients with hypertension or chronic kidney disease [8], early diagnosis and treatment of ARAS might modify the natural history of these patients and their cardiovascular and renal outcomes. Unless suspected because of hypertension resistant to treatment or incipient renal failure, early identification of ARAS is difficult to obtain and despite many surrogate tests have been put forward for non-invasive evaluation [9], direct renal angiography remains the gold standard for diagnosis [10].

In addition to hypertension itself [11, 12], other traditional cardiovascular risk factors, including aging [12-14], diabetes mellitus [11], smoking [12, 15], and dyslipidemia [12] have been associated to ARAS, although their role was not confirmed in all studies [16, 17]. Moreover, a variety of conditions that are commonly referred as “emergent” risk factors might be associated with ARAS and contribute to its development [18]. Among these conditions, elevated lipoprotein(a) levels and a prothrombotic state might be of particular interest because both have been shown to have specific relevance for the development of organ damage in hypertensive patients [19, 20]. Previous studies have suggested a possible contribution to ARAS of plasma fibrinogen [21, 22] and homocysteine [23] levels, whereas the role of lipoprotein(a) remains unclear [21, 24, 25], most likely because none of the studies conducted so far has been specifically designed to investigate its role. This study was designed to investigate whether plasma levels of lipoprotein(a) and hemostatic and fibrinolytic markers are associated with ARAS and can predict its presence in hypertensive patients.

Patients and Methods

Patients

Fifty consecutive hypertensive patients (age 67 ± 10 yr.; 36 men, 14 women) with ARAS detected at renal artery angiography were included in a cross-sectional study. Hypertensive patients were recruited at the Hypertension clinic of our University where they were referred for evaluation. Blood pressure was measured by a validated automated device (Omron M6, OMRON Healthcare Co., Kyoto, Japan) after each patient had been supine for 15 min and the average of three readings obtained in 5 min was recorded [26]. In all patients, hypertension was diagnosed according to established guidelines when systolic blood pressure was 140 mm Hg or more and/or diastolic blood pressure was 90 mm Hg or more at least twice on 3 different visits [27]. All the patients were white, lived in the north-east of Italy, and were representative of the hypertensive population in this area [26].

To determine the cause of hypertension, all patients seen at the clinic are routinely screened with clinical and laboratory testing [28] that include analysis of medical records, physical examination, urine analysis, blood biochemistries, duplicate measurements of 24-hour creatinine clearance and urinary sodium excretion, plasma active renin and aldosterone, urinary cortisol and catecholamines, electrocardiogram, echocardiography, and renal ultrasound with duplex Doppler examination of intrarenal vessels [29]. Renal angio-MRI scan or angio-CT scan, adrenal MRI/CT-scan and additional functional tests are performed when indicated [27, 28]. Renal angiography was performed in all patients in whom increased intrarenal duplex systolic velocity was detected and/or renal artery stenosis was demonstrated either at angio-MRI or angio-CT scan. Angio-MRI or angio-CT scan were done in all hypertensive patients in whom secondary hypertensive disease was suspected due to one or more of the following conditions: severe elevation of

blood pressure with sudden onset or worsening, poor blood pressure response to drug therapy (persistent blood pressure increase with 2 or more drugs), persistent hypokalemia, detection of an abdominal bruit, worsening of renal function (with a 24-hour creatinine clearance of less than 60 ml/min/1.73 m² of body surface area) either spontaneous or induced by use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II-receptor blockers (ARB), difference of more than 1.5 cm in length between the two kidneys at renal ultrasound [27]. Predefined exclusion criteria were age younger than 25 years or older than 80 years, renal failure with 24-hour creatinine clearance of less than 30 ml/min/1.73 m², urinary protein excretion greater than 1.0 g/day, congestive heart failure, recent (less than 6 months) myocardial infarction, unstable angina, or stroke, and presence of concomitant diseases that could affect renal function. Fifty patients with severe ARAS were therefore selected upon angiographic demonstration of renal artery stenosis of 70% or more in one or more major renal vessels. Patients with lesser degree of renal artery narrowing were excluded. No patient had angiographic characteristics of fibromuscular dysplasia or other types of renal artery disease. Renal and cardiovascular complications of hypertension were assessed by a complete history and physical examination, and laboratory tests that included duplicate measurements of 24-hour creatinine clearance and urinary protein excretion, ECG, echocardiography, and ultrasound examination of aorta, carotid, and iliac arteries. Additional tests included treadmill exercise test, myocardial perfusion scan, coronary angiography, and cerebral CT-scan and were performed when indicated.

Patients with ARAS were compared with 58 hypertensive patients who were consecutively selected during the same time period and using the same criteria as patients with renal artery stenosis, but who had no evidence of renal artery stenosis at angio-MRI or angio-CT scan and/or renal angiography. Patients were classified as smokers if they had smoked for at least 5 years, and up to 1 year before the study. Dyslipidemia was defined by a non-HDL cholesterol of 130 mg/dl or more and/or as current use of lipid-lowering medication [30]. At the time of the study, patients were allowed to keep their usual unrestricted diet. The study received approval by the local Institutional Review Board and informed consent was obtained from all patients.

Laboratory measurements

A sample of venous blood was obtained from each patient in the sitting position in the morning after an overnight fast and without venous stasis. Blood was collected into silicone-treated glass tubes, where it was mixed with 10% of its volume of 0.1 mmol/l tri-sodium citrate and immediately centrifuged at 1,700g for 20 min at 4°C. Plasma was separated and frozen at -80 °C until being assayed, usually within one month after sampling. Plasma lipids measurement was performed as reported previously [31] and LDL-cholesterol was calculated with the formula of Friedwald. Plasma concentrations of lipoprotein(a) were determined by the Macra® Lp(a) Enzyme Linked Immunosorbent Assay (ELISA) kit (Trinity Biotech PLC, Bray, Ireland) a method that is highly correlated with the reference method used by the WHO for the standardization of the lipoprotein(a) assay [32]. The intra- and inter-assay coefficients of variation for lipoprotein(a) measurements were from 2% to 7% and from 6% to 9%, respectively. Plasma fibrinogen, D-dimer, prothrombin fragment 1+2, plasminogen-activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA), and antithrombin III were determined as reported previously [33, 34]. Briefly, plasma fibrinogen was measured by a functional assay in an automatic coagulometer autoanalyzer (intra-assay and inter-assay coefficient of variation: 5.1 and 6.8%, respectively); D-dimer was measured immunoenzymatically (intra-assay and inter-assay coefficient of variation: 5.3 and 7.1%, respectively); prothrombin fragment 1+2 plasma levels were evaluated by ELISA (intra-assay and inter-assay coefficient of variation: 5.5 and 11.2%, respectively); PAI-1 was assayed by enzyme immunoassay (intra-assay and inter-assay coefficient of variation: 4.6 and 6.8%, respectively); antithrombin III was determined by a functional chromogenic assay (intra-assay and inter-assay coefficient of variation: 7.4 and 8.6%, respectively). All measurements were done in duplicate.

Statistical analysis

Data are presented as mean ± SD for variables with normal distribution and as median (inter-quartile range) for skewed variables. Normally distributed variables were compared with the Student's *t* test. Variables with skewed distribution were analysed after logarithmic transformation. The Pearson χ^2 test was used to compare frequency distributions. Relationships between continuously distributed variables were examined by linear regression analysis and the correlation was expressed by the Pearson's

Table 1. Clinical characteristics of the study patients

Characteristics	All patients (n=108)	ARAS (n=50)	No ARAS (n=58)	P
Age, years	65 ± 9	67 ± 10	64 ± 9	0.064
Males, n (%)	70 (65)	36 / 14	34 / 24	0.147
BMI, kg/m ²	27.5 ± 4.7	27.3 ± 4.6	27.7 ± 4.9	0.647
Systolic blood pressure, mm Hg	162 ± 21	162 ± 23	162 ± 19	0.981
Diastolic blood pressure, mm Hg	91 ± 14	89 ± 13	93 ± 15	0.185
Duration of hypertension, years	11 [4 - 20]	12 [8 - 19]	10 [5 - 17]	0.146
Smokers*, n (%)	31 (29)	17 (34)	12 (22)	0.120
Diabetes mellitus, n (%)	37 (34)	19 (38)	18 (31)	0.447
Dyslipidemia†, n (%)	53 (49)	25 (50)	28 (48)	0.858
Coronary heart disease, n (%)	28 (26)	19 (38)	9 (15)	0.008
Cerebrovascular disease, n (%)	13 (12)	7 (14)	6 (10)	0.561
Peripheral artery disease, n (%)	25 (23)	21 (42)	4 (7)	<0.001
Anti-hypertensive drugs, n	2.2 ± 1.6	2.7 ± 1.6	1.7 ± 1.6	0.004
Beta-blockers, n (%)	55 (51)	30 (60)	25 (43)	0.185
Diuretics, n (%)	49 (45)	26 (52)	23 (40)	0.375
Calcium-channel blockers, n (%)	53 (49)	27 (54)	26 (45)	0.608
RAS-blockers, n (%)	63 (58)	32 (64)	31 (53)	0.555
Alpha-blockers, n (%)	15 (14)	9 (18)	6 (10)	0.335
Lipid-lowering agents, n (%)	11 (10)	4 (8)	7 (12)	0.540

Data are expressed as mean ± SD or as median [interquartile range] for variables not normally distributed. Comparison among patients with or without atherosclerotic renal artery stenosis (ARAS) was done by the Student *t* test or Kruskal-Wallis rank test for variables not normally distributed. BMI, body mass index; RAS, renin-angiotensin system.

*Patients were classified as smokers if they had smoked for at least 5 years, and up to 1 year before the study; †Dyslipidemia was defined by a non-HDL cholesterol level of 130 mg/dl or more.

correlation coefficient. Multiple linear regression analysis was performed to identify which variables were independently associated with ARAS and logistic regression analysis to identify which variables predicted the presence of ARAS in hypertensive patients. Two-tailed probability value of less than 5% was considered to indicate statistical significance. All data analyses were performed using Stata 9.2 (StataCorp LP, TX, USA).

Results

Among 50 hypertensive patients with angiographic evidence of ARAS, 2 had bilateral stenosis, 2 had unilateral stenosis of the main renal artery and one or more of its branches, and the remaining 46 had unilateral stenosis of the main renal artery. The clinical characteristics of hypertensive patients with or without ARAS are summarized in Table 1. Patients with ARAS used a significantly greater number of anti-hypertensive drugs than patients without ARAS, although the relative frequency of use of different types of these drugs and on-treatment blood pressure levels were comparable in the two groups. Hypertensive patients with ARAS had greater prevalence of coronary heart and peripheral artery disease than patients without ARAS, whereas prevalence of smoking, diabetes, and dyslipidemia was not different.

Table 2 shows the biochemical variables of the study patients. Hypertensive patients with ARAS had higher plasma creatinine and lower 24-hour creatinine clearance than patients without ARAS. Patients with ARAS had also comparable total, HDL, and LDL-cholesterol, and triglyceride levels to patients without ARAS, whereas plasma lipoprotein(a) was significantly higher in patients with ARAS, with a 62% increase in the average plasma concentration. Prevalence of ARAS increased progressively from 31, to 42 and 67% across plasma lipoprotein(a) tertiles (Figure 1). No significant differences between hypertensive

Table 2. Biochemical variables of the study patients

Variable	All patients (n=108)	ARAS (n=50)	No ARAS (n=58)	P
Creatinine, mg/dl	1.15 ± 0.50	1.27 ± 0.49	1.05 ± 0.49	0.026
Creatinine clearance, ml/min/1.73 m ²	52 ± 16	48 ± 16	57 ± 15	0.001
Glucose, mg/dl	103 ± 31	106 ± 35	101 ± 26	0.461
Uric acid, mg/dl	5.9 ± 1.5	6.0 ± 1.4	5.7 ± 1.6	0.317
Total cholesterol, mg/dl	194 ± 47	191 ± 42	196 ± 49	0.574
HDL-cholesterol, mg/dl	55 ± 15	52 ± 13	57 ± 16	0.082
LDL-cholesterol, mg/dl	116 ± 43	114 ± 34	117 ± 46	0.705
Triglycerides, mg/dl	113 [81-140]	117 [85-155]	110 [80-134]	0.083
Lipoprotein(a), mg/dl	12.8 [5.6-24.5]	16.5 [9.5-33.8]	10.2 [4.4-16.7]	0.002
C-reactive protein, mg/L	3.0 [3.0-6.0]	4.0 [3.0-9.4]	3.0 [3.0-4.8]	0.200
Homocysteine, μmol/l	12.7 [9.6-16.7]	13.5 [10.2-18.5]	12.2 [9.5-14.5]	0.175
PT, INR	1.07 ± 0.29	1.05 ± 0.12	1.09 ± 0.38	0.373
PTT, sec	29 ± 5	29 ± 6	29 ± 4	0.543
Fibrinogen, mg/dl	362 [325-430]	357 [330-424]	368 [317-432]	0.629
D-dimer, ng/ml	206 [150-347]	263 [150-384]	150 [150-301]	0.079
F1+2, pmol/l	407 [180-750]	438 [173-750]	380 [180-770]	0.641
PAI-1, ng/ml	11.0 [6.3-28.8]	9.4 [6.0-25.2]	11.8 [8.6-32.9]	0.333
t-PA, ng/ml	4.17 ± 2.63	4.58 ± 2.57	3.75 ± 2.73	0.470
Antithrombin III, %	97 ± 12	95 ± 12	99 ± 13	0.182

Data are expressed as mean ± SD or as median [interquartile range] for variables not normally distributed. Comparison among patients with or without atherosclerotic renal artery stenosis (ARAS) was done by the Student *t* test or Kruskal-Wallis rank test for variables not normally distributed. PT, prothrombin time; PTT, partial thromboplastin time; F1+2, prothrombin fragment 1+2; PAI-1, plasminogen-activator inhibitor-1; t-PA, tissue plasminogen activator.

patients with and without ARAS were observed in C-reactive protein, homocysteine, and all hemostatic and fibrinolytic variables under study. Among hypertensive patients with ARAS, lipoprotein(a) levels were not significantly different between those with documented history of coronary heart, cerebrovascular, and peripheral artery disease (22.8 [10.5-39.6] mg/dl) and those without such history (14.7 [4.4-22.1] mg/dl; *P*=0.088).

Univariate correlation analysis showed that lipoprotein(a) levels were inversely related with creatinine clearance (*r*=-0.232, *P*=0.024). In a multiple linear regression analysis, presence of ARAS was included as the dependent variable and de-

mographic and anthropometric variables, blood pressure levels, smoking habit, diabetes, creatinine clearance, LDL-cholesterol, coronary heart and peripheral artery disease as independent variables. Analysis showed that peripheral artery disease (β =0.445, *P*<0.001),

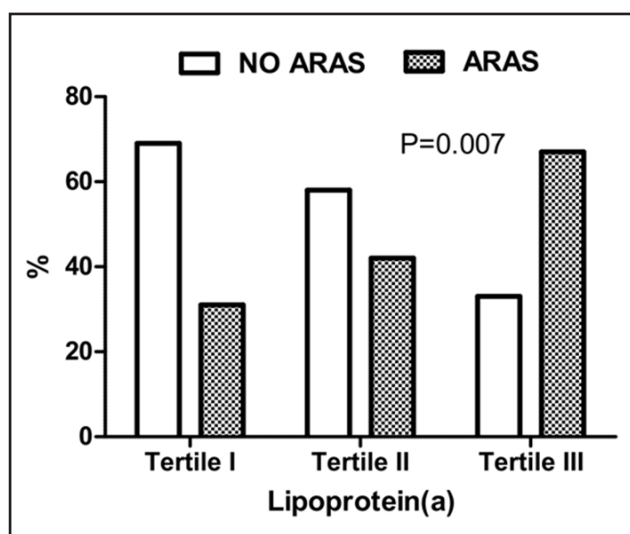


Fig. 1. Bar-graph showing the relative prevalence of hypertensive patients with or without atherosclerotic renal artery stenosis (ARAS) across tertiles of plasma lipoprotein(a) levels.

Table 3. Logistic regression analysis with atherosclerotic renal artery stenosis as the dependent variable

Variable	Odds Ratio	95% CI	P
Age	0.99	0.89 - 1.09	0.817
Male gender	0.92	0.25 - 1.27	0.165
Body mass index	0.94	0.83 - 1.13	0.669
Systolic blood pressure	1.03	0.99 - 1.08	0.129
Duration of hypertension	1.08	1.01 - 1.15	0.023
Diabetes	1.24	0.43 - 1.86	0.517
Smoke	0.58	0.55 - 3.16	0.768
Coronary heart disease	2.14	0.31 - 1.51	0.349
Peripheral artery disease	5.35	1.46 - 3.67	<0.001
Creatinine clearance	0.95	0.89 - 1.01	0.057
LDL-cholesterol	0.98	0.96 - 1.01	0.056
Lipoprotein(a) levels (III vs. I tertile)	3.70	1.28 - 10.73	0.016

lower creatinine clearance ($\beta=-0.259$, $P=0.032$) and higher lipoprotein(a) levels ($\beta=0.233$, $P=0.046$) were independently associated with ARAS. Logistic regression analysis that included the same variables as in multivariate regression (Table 3) showed that presence of ARAS was predicted by plasma lipoprotein(a) levels in the highest tertile with an odds ratio of 3.70 versus the lowest lipoprotein(a) tertile ($P=0.016$).

Discussion

A variety of factors could contribute to development and progression of atherosclerotic plaques in major renal arteries leading to renovascular hypertension and/or ischemic nephropathy. In addition to more traditional cardiovascular risk factors, a role might be played by the so called emergent risk factors and the findings of this study demonstrate that elevated levels of lipoprotein(a) are strongly associated with angiographic evidence of ARAS in hypertensive patients. This association is independent of demographic and anthropometric variables, blood pressure levels, smoking, diabetes, and dyslipidemia and, most important, of renal function. Different from lipoprotein(a), no association of hemostatic variables and a prothrombotic state with ARAS has been observed in this study.

Lipoprotein(a) is a heterogeneous lipoprotein whose plasma concentrations varies over a broad range with a distribution that is skewed to low levels [35]. The apolipoprotein(a) gene is the major gene controlling plasma lipoprotein(a) levels [36] and these levels are not modified by either dietary or pharmacologic interventions [37], although a significant decrease in lipoprotein(a) was reported with use of nicotinic acid [38] and studies conducted in hypertensive patients have reported an inverse relationship of lipoprotein(a) levels with alcohol [28] and omega-3 polyunsaturated acid [39] consumption. Longitudinal studies have demonstrated that high plasma lipoprotein(a) is an independent risk factor for atherosclerosis and major cardiovascular events [40, 41]. There is also evidence that elevated lipoprotein(a) is strongly and independently associated with presence and severity of hypertension-related cardiac, vascular, and renal damage [42]. Similarly, significant contribution to cardiovascular and renal damage in hypertensive patients has been reported for plasma fibrinogen and D-dimer [43] indicating a role for a prothrombotic state. It must be noticed that in addition to its proatherogenic properties, lipoprotein(a) has prothrombotic effects due to the structural homology with plasminogen. Therefore an interaction between this lipoprotein and the coagulation/fibrinolytic system might have an impact on ARAS and become critical for cardiovascular and renal outcomes of hypertensive patients [19, 20].

Identification of factors that are associated and predispose to ARAS could be important for early detection of disease and may help to prevent the consequences on systemic blood

pressure and renal function. The relationship of emergent risk factors for atherosclerosis and ARAS has been investigated in a limited number of previous studies [18], most of which were conducted in small groups of patients. Park et al. [21] detected ARAS (defined by narrowing of arterial lumen by 50% or more) in 28 of 270 patients who underwent coronary angiography and reported that higher plasma fibrinogen was independent predictor of ARAS with an odds ratio of 1.63 (analyzed by a 100 mg/dl increment in plasma fibrinogen). Later on, this association was confirmed in hypertensive patients with narrowing of a renal artery by 50% or more [44]. Furthermore, in 27 patients with ARAS fibrinogen levels were related to an increased rate of restenosis after 1 year of renal artery angioplasty [22]. Levels of homocysteine were reported to be higher in 58 patients with angiographic evidence of ARAS and impaired renal function than in normotensive subjects [23]. However, another study that reported higher homocysteine levels in patients with ARAS than healthy controls could not demonstrate any significant change in these levels 6 months after renal angioplasty [45], therefore questioning the relevance of homocysteine as an independent marker of ARAS. With regard to lipoprotein(a), findings are even more controversial because plasma levels in patients with ARAS have been reported to be higher [24], unchanged [21], or even lower [25] than in subjects without ARAS. A non-significant trend to increased lipoprotein(a) was reported in 26 hypertensive patients with secondary hypertension due to ARAS in comparison to patients with essential hypertension [46]. In addition to the limited statistical power of some of these studies, inconsistencies might be explained by important differences in methodology of selection of patients with ARAS and respective controls, methods used to detect ARAS, criteria used to define critical narrowing of the renal arteries, and inclusion of patients with advanced impairment of renal function. The present study was specifically designed to investigate the relationship of emergent risk factors with ARAS in hypertension and this is why: a) all patients with ARAS had hypertension and were compared with hypertensive subjects with comparable cardiovascular risk who were selected using the same criteria except for evidence of ARAS; b) in all patients ARAS was diagnosed by renal angiography; c) in all patients critical stenosis of renal vessels was defined by stringent criteria (narrowing of 70% or more); d) patients with advanced renal failure were excluded. With these specific strengths in the study design, results demonstrate that lipoprotein(a) is independently associated and predicts presence of ARAS in hypertensive patients. This observation might have implications for the identification of ARAS in these patients, an issue that will have to be examined in appropriately designed studies.

Some limitations of the study should be discussed. First, the cross-sectional design does not permit to establish evidence of a causal relationship of lipoprotein(a) with ARAS. Second, it is known that circulating levels of lipoprotein(a) are inversely related with glomerular filtration rate in patients with early stages of renal insufficiency [47] and are associated with worse cardiovascular and renal outcomes [31]. Therefore, increased lipoprotein(a) levels in patients with ARAS, as reported in the present study, might result from reduced renal function. As stated above, in this study we excluded patients with 24-hour creatinine clearance of less than 30 ml/min/1.73 m² and, most important, multivariate regression analysis indicated that the association of lipoprotein(a) with ARAS was independent of renal function. Third, the association of lipoprotein(a) levels with ARAS reported in the study could simply reflect a contribution of this lipoprotein to progression of systemic atherosclerosis. It must be noticed, however, that multivariate logistic analysis showed that this association was independent of other atherosclerosis-related diseases and no significant difference in lipoprotein(a) levels was observed between hypertensive patients with or without history of cardiovascular events. Last, use of a clinic sample might limit the possibility to extend the conclusions of this study to the general population because a bias in the referral of patients to the source of care.

Conclusion

This study demonstrates a strong association of lipoprotein(a) with ARAS in hypertensive patients. This association is independent of renal function and suggests a specific role for this lipoprotein in the pathogenesis of atherosclerosis in major renal vessels. The strength and independence of the association between lipoprotein(a) and ARAS together with the ability of lipoprotein(a) to predict presence of ARAS suggests that measurement of this lipoprotein might be useful in the diagnostic work-up of hypertensive patients to identify those who are at risk of secondary renovascular disease. Appropriately designed and powered studies will be needed to investigate the sensitivity and specificity of lipoprotein(a) levels in detection of ARAS and to test the possible benefits on cardiovascular and renal outcomes of drug treatments or dietary intervention that reduce its plasma levels.

Disclosure Statement

The authors have no conflict of interest related to the contents of this study to disclose.

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