The relationship between plasma renin activity and serum lipid profiles in patients with primary arterial hypertension

Tomasz Pizoń[1,2] (iD), Marek Rajzer[1], Wiktoria Wojciechowska[1],
Małgorzata Wach-Pizoń[3] (iD), Tomasz Drożdż[1] (iD),
Katarzyna Wróbel[2], Krystian Gruszka[1], Marta Rojek[1],
Tomasz Kameczura[4], Artur Jurczyszyn[5], Janusz Kąkol[2]
and Danuta Czarnecka[1]

Abstract

Introduction: The aim of the study was to evaluate clinical and biochemical differences between patients with low-renin and high-renin primary arterial hypertension (AH), mainly in reference to serum lipids, and to identify factors determining lipid concentrations.

Materials and methods: In untreated patients with AH stage 1 we measured plasma renin activity (PRA) and subdivided the group into low-renin (PRA < 0.65 ng/mL/h) and high-renin (PRA ⩾ 0.65 ng/mL/h) AH. We compared office and 24-h ambulatory blood pressure, serum aldosterone, lipids and selected biochemical parameters between subgroups. Factors determining lipid concentration in both subgroups were assessed in regression analysis.

Results: Patients with high-renin hypertension ($N = 58$) were characterized by higher heart rate ($p = 0.04$), lower serum sodium ($p < 0.01$) and aldosterone-to-renin ratio ($p < 0.01$), and significantly higher serum aldosterone ($p = 0.03$), albumin ($p < 0.01$), total protein ($p < 0.01$), total cholesterol ($p = 0.01$) and low-density lipoprotein cholesterol (LDL-C) ($p = 0.04$) than low-renin subjects ($N = 39$). In univariate linear regression, only PRA in the low-renin group was in a positive relationship with LDL-C ($R^2 = 0.15$, $\beta = 1.53$ and $p = 0.013$); this association remained significant after adjustment for age, sex, and serum albumin and aldosterone concentrations.

Conclusions: Higher serum levels of total and LDL-C characterized high-renin subjects, but the association between LDL-C level and PRA existed only in low-renin primary AH.

Introduction

The renin-angiotensin-aldosterone system (RAAS) maintains a key role in blood pressure (BP) regulation.[1,2] Its overactivity is responsible for a wide array of adverse effects in the cardiovascular system, which, due to the elevation of angiotensin II (Ang II) and aldosterone concentrations, lead to an increase in BP, extracellular fluid volume expansion, hypercoagulability, activation of the inflammatory cascade, and acceleration of the fibrosis processes in the heart and vessels.[3–5] Moreover, the negative cross-talk between Ang II and insulin signalization might be responsible for carbohydrate metabolism dysregulation

[1]1st Department of Cardiology, Interventional Electrocardiology and Arterial Hypertension, Jagiellonian University Medical College, Kraków, Poland
[2]Department of Observational and Internal Medicine, University Hospital, Kraków, Poland
[3]Department of Clinical and Environmental Allergology, University Hospital, Kraków, Poland
[4]Faculty of Medicine, University of Rzeszów, Poland
[5]Department of Hematology, Jagiellonian University Medical College, Kraków, Poland

Corresponding author:
Marek Rajzer, 1st Department of Cardiology, Interventional Electrocardiology and Arterial Hypertension, Jagiellonian University Medical College, 17 Kopernika Street, Kraków, 31-501, Poland.
Email: rajzer37@interia.pl

and its cardiovascular consequences.[6] Ang II via angiotensin II receptor type 1 (AT1) stimulates cholesterol synthesis, low-density lipoprotein cholesterol (LDL-C) oxidation and its incorporation into the vascular wall.[7]

The consequence of increased RAAS activity is a higher prevalence of cardiovascular complications, mostly resulting from atherosclerosis. Apart from commonly known RAAS effects indirectly contributing to an acceleration of atherosclerosis, the system may also act directly, for example through an increase in LDL-C oxidation.[8]

In adipocytes, RAAS is involved in lipid metabolism, i.e. Ang II modulates lipolysis, lipogenesis and adipocyte differentiation.[9] In macrophages, Ang II stimulates cholesterol synthesis and decreases high-density lipoprotein (HDL) cholesterol-induced cholesterol efflux.[10,11] The last effect is probably common for cholesterol membrane transport in other cells. Moreover, Ang II has a stimulatory effect on LDL-C oxidation and LDL-C degradation by macrophages, which is more pronounced in patients with arterial hypertension.[12] The last effect of Ang II might be mediated by oxidized low-density lipoprotein receptor 1 (OLR1) activity modulation through the AT1 receptor.[13] The decrease in total cholesterol and LDL-C as a result of angiotensin converting enzyme (ACE) inhibition by enalapril, as well as the amplification of anticholesterolaemic effect of simvastatin by enalapril described by Nazzaro et al., could be considered as indirect proof that RAAS overactivity can promote abnormalities in the lipid profile.[14]

Increased RAAS activity was confirmed in unstable atherosclerotic plaques.[15] The interaction between RAAS activity and LDL-C can also be bidirectional, i.e. increased LDL-C might stimulate the RAAS.

Hyperlipidaemia (including increased LDL-C) induced by overfeeding in mice has been positively associated with an upregulation of the RAAS components.[16] Incubation of vascular smooth muscle cells with LDL-C upregulates AT1 receptor gene expression.[17] A similar mechanism of action, i.e. by upregulation of AT1 gene expression, has been proven for oxidized LDL.[18,19] The upregulation of the AT1 receptor may lead to a downregulation of renin levels.

Taking into consideration the literature cited above, there is enough theoretical evidence to suspect a relationship between RAAS activity and serum cholesterol. Most authors state that no direct relationship between RAAS activity and serum lipid concentration exists.[20–22] However, positive correlations between LDL-C and RAAS components have been shown in several human studies.[23,24]

In the Framingham Heart Offspring Study, the prevalence of hyperlipidaemia among subjects with arterial hypertension (AH) was 40% in men and 33% in women, respectively.[25] Such high frequencies of hypercholesterolaemia in subjects with AH may be partially explained by an association between renin and lipid metabolism, as well as the predominance of primary hypertension with high renin levels (60–70%).[26] The presence of hypercholesterolaemia, as found by Borghi et al., can also promote AH development through its interaction with the circulating components of the RAAS.[27]

The aim of the study

The main aim of this study was the evaluation of clinical and biochemical differences between patients with low-renin and high-renin AH, with particular reference to serum lipids. The secondary aim was the identification of factors determining serum lipid concentrations in low- and high-renin hypertension.

Materials and methods

Study design

This was an observational, cross-sectional study performed in the hypertension outpatient department of the 1st Department of Cardiology, Jagiellonian University Medical College in Kraków, Poland. The participants were enrolled to the study from a group of consecutively admitted patients over 6 months, after considering inclusion and exclusion criteria. Enrolment was stopped after reaching the sufficient number of participants needed to obtain the statistically significant difference in LDL-C level between study subgroups. According to plasma renin activity (PRA) values, the study group was subdivided into low-renin and high-renin groups. We then evaluated the differences between subgroups in selected clinical and biochemical parameters, with special reference to serum lipid concentrations. In regression analysis, we also tested factors determining low-density lipoprotein cholesterol serum concentration in each subgroup.

Study group inclusion and exclusion criteria. Ninety-seven patients were enrolled (a similar number of men and women), aged 30–75 years, with uncomplicated primary stage 1 AH according to the 2013 European Society of Hypertension (ESH)/European Society of Cardiology Guidelines (i.e. arterial BP values $\geqslant$ 140/90 mmHg and $<$ 160/100 mmHg).[28] Patients with previously diagnosed and treated hypertension were included in the study after a minimum 6-week drug washout period. In order to exclude secondary hypertension in all patients, abdominal ultrasound examination with renal Doppler flow assessment was performed. Subjects with suspected renal artery stenosis were subsequently excluded from our study. Other exclusion criteria were the following: a history of coronary artery disease (i.e. myocardial infarction, angina pectoris or history of coronary revascularization), as well as: cardiac valvular disease, atrial fibrillation, prior stroke or transient ischaemic attack; antiplatelet, anticoagulant, or lipid-lowering therapy; and acute or chronic inflammation,

cancer, chronic kidney disease (defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2) or liver failure.

Insulin-treated diabetic patients and pregnant women were also excluded. Moreover, we decided not to include patients with aldosterone-to-renin ratio (ARR) > 100 ng/dL/ng/mL/h and aldosterone concentration > 30 ng/dL, although no typical indications to perform screening for primary aldosteronism were present according to the Endocrine Society Guidelines.[29]

Study procedures. All subjects signed an informed consent form before being included in this study. The study was performed in accordance with the Declaration of Helsinki of 1975 for Human Research and was approved by the Jagiellonian University Ethics Committee (decision number: KBET/7/B/2007).

In accordance with the recommendations of the ESH,[28] office BP and heart rate (HR) were measured twice with an interval of 1 min using an Omron M5-I oscillometric device (Omron Healthcare Co., Japan), and mean values were calculated and used in the final analysis. Twenty-four-hour ambulatory BP monitoring (ABPM) was performed using a SpaceLabs 90207 recorder (SpaceLabs Inc., Richmond, Washington, USA) according to the ESH working groups' practice guidelines,[30] with automatic measurements taken at 15-min intervals during daily activity and 20-min intervals during nighttime hours. After overnight fasting, blood was collected from the antecubital vein.

The measurements of serum concentrations of albumin, total protein, creatinine, urea, potassium, sodium, total cholesterol (TC), HDL cholesterol (HDL-C), LDL-C and triglycerides (TGs) were performed. Serum TC was determined using the enzymatic cholesterol oxidase-phenol+aminophenazone (CHOD-PAP) method. TG levels were determined by enzymatic colorimetric method using glycerol-3-phosphate oxidase-phenol+aminophenazone (GPO-PAP). HDL-C was obtained using the Abell–Kendall direct enzymatic colorimetric method by. Finally, LDL-C levels were calculated using the Friedewald formula.[31]

All of these routine biochemical assessments were performed using a Hitachi 917/Modular P analyzer (Roche Diagnostics Ltd).[32] eGFR was calculated using the modification of diet in renal disease formula.[33]

Blood samples for the measurement of serum concentration of aldosterone and plasma renin activity were centrifuged at 3000 × g, then plasma (ethylenediaminetetraacetic acid) were immediately separated and frozen at −75°C until laboratory analysis. Serum aldosterone concentration was determined by radioimmunoassay using an ALDO-RIACT kit (Cisbio Bioassays, Codolet, France), with a limit of detection of 7 pg/mL and a coefficient of variation < 7.5%. PRA was determined from the same sample by radioimmunoassay using an Ang I RIA KIT (Beckman Coulter,

Immunotech, Prague, Czech Republic), with a sensitivity of 0.07 ng/mL and coefficient of variation < 6.0%.

Statistical analysis. Statistical analyses were performed using STATISTICA 12 software (StatSoft, Inc., Tulsa, OK, USA). The results are expressed as numerical values and percentages for categorical variables, and mean values and SDs for continuous variables. Comparisons between study groups were made using the Student's *t*-test for independent samples in cases of continuous variables and χ^2 for qualitative variables. The Mann–Whitney *U* test was performed for abnormal distribution. Univariate and multivariate regression analyses were used to determine the influence of independent factors on LDL-C in study subgroups. Differences were considered statistically significant at $p < 0.05$.

Results

Within the group of 97 patients with primary AH, comprised of 48 men and 49 women with a mean age of 53.4 years, 58 patients had PRA value greater than or equal to 0.65 ng/mL/h (the 'high-renin hypertension group') and 39 had a PRA lower than 0.65 ng/mL/h (the 'low-renin hypertension group'). The high- and low-renin groups did not differ in age, sex, body mass index, BP levels (in office measurements and ABPM) or treatment used. In the study group, 82 (84%) patients were antihypertensive therapy naïve, while 15 patients (16%) had been previously treated with one or a combination of two low-dose antihypertensive drugs. The pharmacotherapy of the patients from the latter group was the following: two patients received slow-release indapamide (1.5 mg) as a monotherapy for 1–4 months, one patient was taking lisinopril (5–10 mg) twice daily as a monotherapy for a period of 2–3 months, another two were on perindopril (5 mg) once daily for a period of 1–3 months, two received valsartan (80 mg) once daily for a period of 1–3 months, one received verapamil (120 mg/day) for 1–3 months, two received carvedilol (6.125–12.5 mg) twice daily for a period of 1–4 months, two received metoprolol succinate 50 mg/day (one for a period of 2 months and one for 3 months) and finally three patients received combination therapy consisting of indapamide (0.625 mg) plus perindopril (2.5 mg) once daily for 2–3 months. The treatments mentioned above were withdrawn at least 6 weeks before the study enrollment. None of the patients included in the study was previously subject to lipid-lowering therapy or a special dietary regime.

The only clinical difference between the groups was higher mean daily HR in ABPM in the group with high PRA (Table 1). Serum sodium and ARR were lower in the high-renin group. Serum aldosterone, albumin and total protein were significantly higher in the high-renin group than in the low-renin group. Analysing the serum lipid profiles, we found significantly higher levels of TC and

Table 1. Anthropometric and clinical characteristics of low-renin and high-renin hypertensives.

Variable	Low-renin group	High-renin group	*p*-value
N	39	58	
Age (years)	56.1 (11.0)	51.6 (13.2)	0.08[a]
Male (%)	18.0 (46.2)	30.0 (51.7)	0.56[b]
Weight (kg)	81.3 (17.0)	80.3 (14.0)	0.75[a]
Height (cm)	169.5 (7.7)	169.6 (8.7)	0.96[a]
BMI (kg/m^2)	28.2 (4.9)	27.9 (4.5)	0.79[a]
Waist (cm)	93.6 (13.8)	93.2 (11.6)	0.89[a]
Waist/height ratio	0.552 (0.005)	0.622 (0.004)	0.43[a]
Smoking: no (%)	7.0 (17.9)	5.0 (8.6)	0.98[b]
Diabetes mellitus: no (%)	2 (5.1)	5 (8.6)	0.54[b]
SBP (mmHg)[c]	160.5 (15.0)	153.3 (17.0)	0.58[a]
DBP (mmHg)[c]	96.0 (8.2)	94.6 (10.4)	0.53[a]
SBP 24 h (mmHg)	130.8 (9.5)	132.2 (9.2)	0.53[a]
DBP 24 h (mmHg)	79.3 (7.4)	81.9 (7.7)	0.16[a]
HR 24 h (beats/min)	72.4 (8.5)	76.6 (9.9)	0.04[a]
SBP day (mmHg)	130.6 (12.1)	131.4 (12.3)	0.77[a]
DBP day (mmHg)	81.1 (8.4)	82.2 (10.5)	0.58[a]
HR day (beats/min)	76.6 (10.0)	80.8 (10.8)	0.06[a]
SBP night (mmHg)	117.1 (12.0)	117.2 (11.6)	0.95[a]
DBP night (mmHg)	69.3 (7.9)	69.9 (10.0)	0.77[a]
HR night (beats/min)	64.8 (8.4)	67.3 (8.5)	0.16[a]

Low-renin group: PRA $<$ 0.65 ng/mL/h; high-renin group: PRA $\geqslant$ 0.65 ng/mL/h. Data are expressed as means (SD) or number of persons (%).
[a]Derived from the Student's *t*-test.
[b]Derived from the χ^2 test.
[c]Mean of two measurements,
BMI: body mass index; SBP: office systolic blood pressure; DBP: office diastolic blood pressure; SBP 24 h: systolic blood pressure in 24-hour ambulatory blood pressure monitoring; DBP 24 h: diastolic blood pressure in 24-hour ambulatory blood pressure monitoring; HR 24 h: heart rate in 24-hour ambulatory blood pressure monitoring; SBP day: systolic blood pressure during awake period in 24-hour ambulatory blood pressure monitoring; DBP day: diastolic blood pressure during awake period in 24-hour ambulatory blood pressure monitoring; HR day: heart rate during awake period in 24-hour ambulatory blood pressure monitoring; SBP night: systolic blood pressure during sleep period in 24-hour ambulatory blood pressure monitoring; DBP night: diastolic blood pressure during sleep period in 24-hour ambulatory blood pressure monitoring; HR night: heart rate during sleep period in 24-hour ambulatory blood pressure monitoring.

Table 2. Biochemical parameters in low-renin and high-renin hypertensives.

Variable	Low-renin group	High-renin group	*p*
N	39	58	
TC (mmol/L)	5.1 (0.7)	5.6 (1.0)	0.01[a]
LDL-C (mmol/L)	3.0 (0.6)	3.4 (1.0)	0.04[a]
HDL-C (mmol/L)	1.4 (0.4)	1.5 (0.6)	0.37[a]
TGs (mmol/L)	1.5 (1.2)	1.7 (1.0)	0.57[a]
Serum creatinine (µmol/L)	66.8 (14.1)	66.5 (11.9)	0.89[a]
eGFR (mL/min/1.73m^2)	95.7 (20.7)	98.0 (17.5)	0.55[a]
Serum urea (mmol/L)	5.4 (1.2)	5.8 (1.4)	0.19[a]
Serum sodium (mmol/L)	139.2 (2.4)	137.8 (2.3)	$<$ 0.01[a]
Serum potassium (mmol/L)	4.2 (0.3)	4.2 (0.3)	0.21[a]
PRA (ng/mL/h)	0.32 (0.15)	2.34 (2.40)	$<$ 0.001[b]
ALDO (ng/dL)	13.4 (5.7)	17.2 (8.8)	0.03[b]
ARR (ng/dL/ng/mL/h)	52.1 (34.3)	11.1 (7.1)	$<$ 0.01[b]
TP (g/L)	72.5 (4.1)	75.9 (4.1)	$<$ 0.01[a]
Albumin (g/L)	44.3 (2.2)	45.8 (2.7)	$<$ 0.01[a]

Low-renin group: PRA $<$ 0.65 ng/mL/h; high-renin group: PRA $\geqslant$ 0.65 ng/mL/h. Data are expressed as means (SD) or number of persons (%).
[a]Derived from the Student's *t*-test.
[b]Derived from Mann–Whitney *U* test.
TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TGs: triglycerides; eGFR: estimated glomerular filtration rate; PRA: plasma renin activity; ALDO: aldosterone serum concentration; ARR: aldosterone-to-renin ratio; TP: total protein.

Table 3. Univariate and multivariate regression of factors associated with low-density lipoprotein cholesterol in low- and high-renin groups.

	Low-renin group			High-renin group		
	β coefficient	SE	*p*-value	β coefficient	SE	*p*-value
Univariate analysis						
	$R^2 = 0.15$			$R^2 = 0.006$		
PRA (ng/mL/h)	1.53	0.59	0.013	−0.05	0.08	0.55
Multivariate analysis						
	$R^2 = 0.29$			…		
PRA (ng/mL/h)	1.57	0.59	0.012			
Age (years)	−0.015	0.009	0.11			
Sex (two female and one male)	−0.10	0.17	0.55			
Aldosterone (ng/dL)	−0.002	0.001	0.24			
Albumin (g/L)	−0.020	0.05	0.24			

PRA: plasma renin activity; β-coefficient: standardized (regression) coefficient; SE: standard error; R^2: R^2 coefficient of determination.
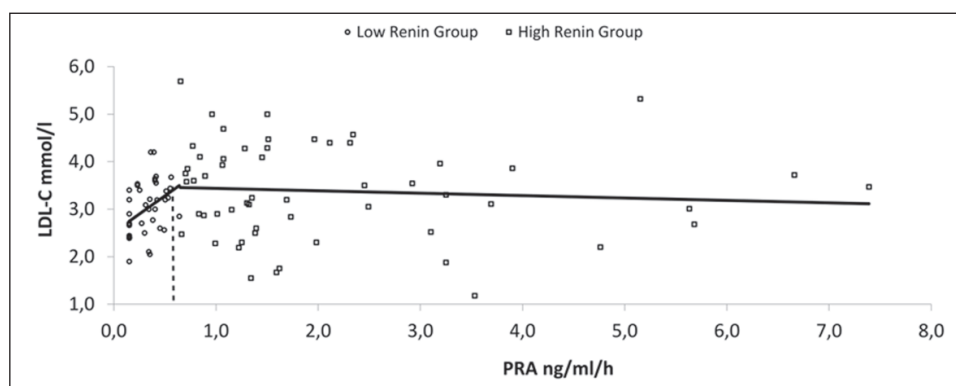
Figure 1. Association of low-density lipoprotein cholesterol with plasma renin activity in study subgroups: low-renin hypertension (low-density lipoprotein cholesterol = 2.51 +1.53 plasma renin activity; R^2= 0.15; *p* = 0.013); high-renin hypertension (low-density lipoprotein cholesterol = 3.49 − 0.05 plasma renin activity; R^2 =0.006; *p* = 0.55).
Circle: low-renin subject; square: high-renin subject. Dotted line shows plasma renin activity level of 0.65 ng/mL/h.
LDL-C: low-density lipoprotein cholesterol; PRA: plasma renin activity.

LDL-C in the high-renin group (Table 2). In the group of high-renin patients, univariate regression revealed a lack of association between LDL-C serum levels and PRA; however, both the levels of LDL-C and PRA in this group were significantly higher than in the low-renin group (Table 3). In contrast, in the low-renin group, a positive association between LDL-C and PRA was found (Table 3 and Figure 1). This association remained significant after adjustment for age, sex, and aldosterone and albumin levels. The proposed multivariate regression analysis model explains 29% of the LDL-C variability in low-renin subjects (Table 3). The LDL-C level in this subgroup was mainly determined by PRA.

Discussion

The main finding of this study were higher levels of LDL-C and total cholesterol in the high-renin than in the low-renin hypertensive group. Moreover, in the low-renin, but not in the high-renin group, PRA remained in significant independent association with the LDL-C level. We also observed higher daily HR and lower serum sodium in the high-renin group than in the low-renin group. The first result might be explained by the well-known physiological mechanism of sympathetic nervous system activation by the RAAS. We do not have data about sodium load in our participants, but we suppose that sodium intake might contribute to the obtained differences in serum sodium levels between the low- and high-renin groups. Additionally, in the low-renin group, there was a lower serum aldosterone level than in the high-renin group. The most common cause of low-renin and low-aldosterone hypertension is high sodium intake.[34]

Lipid metabolism disturbances are the most widely recognized cardiovascular risk factors, and multiple associations between RAAS and lipid metabolism disturbances have been extensively studied in basic sciences. Some clinical studies indicate that a reduction of hyperlipidaemia and RAAS blockade may have a synergistic,

favourable influence on patients with hypertension and/or with other atherosclerosis manifestations.[13,35] This might be of special importance among patients similar to one of our groups, where higher PRA was accompanied with higher TC and LDL-C levels.

Three large clinical trials have provided results on the relationship between the RAAS and serum cholesterol. Plasma renin concentration (PRC) was associated with an increased risk of cardiovascular events in a large community-based cohort (without antihypertensive medication) in the Prevention of REnal and Vascular ENd-stage Disease (PREVEND study).[36] In this cohort, in opposition to the low-renin hypertensive group in our study, there was no association between serum cholesterol and PRC. In the high cardiovascular risk group of the Heart Outcomes Prevention Evaluation (HOPE) study, high PRA was an independent predictor of major vascular events and mortality. Despite the fact that neither TC nor LDL-C in this group were significantly higher in patients with high PRA, there was a trend towards higher TC and LDL-C levels in the upper quintiles of PRA,[37] which is partially consistent with our results. In the cohort of the Framingham Heart Study, higher plasma renin was associated with greater short-term mortality, but not with cardiovascular disease (CVD) incidence, in the community. The hyperlipidaemic index total/HDL cholesterol ratio analysed by the authors was similar in all quartiles of renin concentration, but was higher in patients with arterial hypertension than in the general population.[38] It is very likely that the selection of the group of patients with hypertension in our study could have influenced the obtained result, i.e. higher LDL-C levels in high-renin subjects.

There were no differences in BP values between low- and high-renin groups in our study. However, in most studies, there is a rather negative correlation between PRA and the level of BP,[36,38] except for the study of Alderman and co-workers.[39] High-renin patients in our study were characterized by higher serum aldosterone and higher HR. The last finding might be considered as an indirect measure of increased RAAS activity. A positive association between plasma renin activity and HR was previously demonstrated.[36,40,41]

Surprisingly, in the whole group as well as in the high-renin subjects, we did not observe an association between PRA and cholesterol levels. On the contrary, the low-renin patients showed significant association between PRA and LDL-C, even after adjustment for age, sex, and aldosterone and albumin levels. The lack of association between PRA and LDL-C in high-renin hypertensive subjects in our study may be explained by another factor affecting LDL-C stronger than PRC that was not identified in our analyses. Looking at the large dispersion of LDL-C values in this group, it is very likely that it is not one but a few different factors. Speculatively, we may propose one of them to be the difference in (pro)renin level or (pro)renin receptor activity, which are both potent factors that influence different metabolic pathways including hepatic LDL-C turnover and, of course, its serum level.[42–45] Moreover, RAAS overactivity may lead to liver dysfunction promoting inflammation, lipodystrophy, liver steatosis and lipid metabolism disturbances.[46–48] Feltenberger et al. demonstrated the reversibility of the aforementioned effects by an oral formulation of Ang (1–7) in mice.[49] However, all the patients in our study were free of liver disease (according to the exclusion criteria); the differences in local (liver) activity of other types of angiotensins may be a potential factor explaining the differences between the low-renin and high-renin groups concerning PRA and LDL-C association. Other explanation is the fact, already confirmed in the literature, that high-renin hypertension is more common than low-renin hypertension;[26,34] probably due to large number of patients, this group is much more heterogeneous than low-renin hypertensives.

Zhu et al. showed a significant positive correlation between PRA and LDL-C among a group of young (below 40 years of age) male hypertensive subjects.[23] The comparison of our results with those obtained by Zhu et al. is somewhat difficult because of numerous methodological differences. Zhu et al. did not dichotomize patients according to their renin status. An association of LDL-C and PRA in our study was observed only in the low-renin subjects. Moreover, the study mentioned above included only men, the mean age of the participants was significantly lower than in our study, and patients were treated with antihypertensive drugs (including drugs influencing RAAS activity) and statins.

Long et al. showed in their study that in hypercholesterolaemic patients, RAAS activity (Ang II) correlated positively with TC and LDL-C levels before and after statin treatment. The lowering of serum cholesterol with statins was associated with decreased circulatory RAAS activity (Ang II and ACE). The observation concerning the relationship between RAAS activity and LDL-C levels is partially similar to our findings, but these authors did not divide their group into two subgroups (i.e. high and low renin). The findings of Long et al. confirm that a cross-talk between PRA and cholesterol levels exists.[24]

Some authors, including a recent publication by Hannich et al., have reported a positive association between serum aldosterone levels and LDL-C.[50] In our study we did not observe any association between serum aldosterone and LDL-C. Furthermore, in multivariate regression, the positive association between PRA and LDL-C in the low-renin AH group was not altered after adjustment to aldosterone levels. The most probable reason for the difference between the results obtained by Hannich et al. and those from our study are different groups (general population versus patients with arterial hypertension in our study).

Our patients with low-renin hypertension fulfilled the criteria for the diagnosis of low-renin primary hypertension (LREH), due to the elimination of secondary hypertension according to the strict exclusion criteria used.

LREH patients are characterized by increased local RAAS activity. The plasma Ang II level among these subjects is normal, while adrenal renin content, vascular Ang II formation and the plasma level of (pro)renin are elevated.[26,42] LREH patients are also considered to have lower risk of CVD occurrence.[51] In our study this characteristic was complemented by lower TC and LDL-C.

As PRA distribution is a continuum, if we considered only LREH patients, LDL-C remained in significant association with PRA. For higher values of PRA this association disappeared, as shown in Figure 1.

The strength of our study is that, to our knowledge, it is the first description in the literature of a positive association between PRA and LDL-C in well-phenotyped and untreated LREH patients. The main limitation of the study is the small sample size, as well as the lack of adjustment of renin profiles to sodium urinary excretion and the lack of data about physical activity in the study group. Another limitation of our study is the adoption of restrictive exclusion criteria, to select a group of patients with mild AH who were free of cardiovascular complications, and other diseases and conditions that could affect the results (including subjects treated with lipid-lowering drugs). This improves the internal consistency and validity of the study, but limits usefulness of the findings for the whole population.

Conclusions

Patients with high-renin arterial hypertension are characterized by higher serum levels of TC and LDL-C, but the association between LDL-C level and PRA exists only in low-renin, and not in high-renin, hypertensive subjects.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

ORCID iDs

Tomasz Pizoń (iD) https://orcid.org/0000-0001-5995-3314
Małgorzata Wach-Pizoń (iD) https://orcid.org/0000-0002-3345-3060
Tomasz Drożdż (iD) https://orcid.org/0000-0001-5602-1300

References

1. Laragh JH. *Laragh's lesson in renin system pathophysiology for treating hypertension and its fatal cardiovascular consequences*. New York: Elsevier, 2002.

2. Pizoń T, Rajzer M and Kameczura T. The role of renin–angiotensin–aldosterone system in etiology and pathogenesis of arterial hypertension and its systemic complications - what remains from Laragh and Alderman idea? *Arterial Hypertens* 2011; 15: 371–382.

3. Ferrario CM and Strawn WB. Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. *Am J Cardiol* 2006; 98: 121–128.

4. Funder JW and Reincke M. Aldosterone: A cardiovascular risk factor? *Biochim Biophys Acta* 2010; 1802: 1188–1192.

5. Marney AM and Brown NJ. Aldosterone and end-organ damage. *Clin Sci* 2007; 113: 267–278.

6. Ramalingam L, Menikdiwela K, LeMieux M, et al. The renin angiotensin system, oxidative stress and mitochondrial function in obesity and insulin resistance. *Biochim Biophys Acta Mol Basis Dis* 2017; 1863: 1106–1114.

7. Nickenig G, Baumer AT, Temur Y, et al. Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men. *Circulation* 1999; 100: 2131–2134.

8. Keidar S, Kaplan M, Hoffman A, et al. Angiotensin II stimulates macrophage-mediated oxidation of low density lipoproteins. *Atherosclerosis* 1995; 115: 201–215.

9. Yvan-Charvet L and Quignard-Boulangé A. Role of adipose tissue renin–angiotensin system in metabolic and inflammatory diseases associated with obesity. *Kidney Int* 2011: 79: 162–168.

10. Keidar S, Attias J, Heinrich R, et al. Angiotensin II atherogenicity in apolipoprotein E deficient mice is associated with increased cellular cholesterol biosynthesis. *Atherosclerosis* 1999; 146: 249–257.

11. Kaplan M, Avirama M, Knop C, et al. Angiotensin II reduces macrophage cholesterol efflux: a role for the AT-1 receptor but not for the ABC1 transporter. *Biochem Biophys Res Commun* 2002; 290: 1529–1534.

12. Keidar S, Kaplan M, Shapira C, et al. Low density lipoprotein isolated from patients with essential hypertension exhibits increased propensity for oxidation and enhanced uptake by macrophages: a possible role for angiotensin II. *Atherosclerosis* 1994; 107: 71–84.

13. Morawietz H, Rueckschloss U, Niemann B, et al. Angiotensin II induces LOX-1, the human endothelial receptor for oxidized low-density lipoprotein. *Circulation* 1999; 100: 899–902.

14. Nazzaro P, Manzari M, Merlo M, et al. Distinct and combined vascular effects of ACE blockade and HMG-CoA reductase inhibition in hypertensive subjects. *Hypertension* 1999; 33: 719–725.

15. Mazzolai L and Hayoz D. The renin-angiotensin system and atherosclerosis. *Curr Hypertens Rep* 2006; 8: 47–53.

16. Ni J, Ma K-L, Wang C-X, et al. Activation of renin-angiotensin system is involved in dyslipidemia-mediated renal injuries in apolipoprotein E knockout mice and HK-2 cells. *Lipids Health Dis* 2013; 12: 49.

17. Nickenig G, Sachinidis A, Michelsen F, et al. Upregulation of vascular angiotensin II receptor gene expression by low-density lipoprotein in vascular smooth muscle cells. *Circulation* 1997; 95: 473–478.

18. Li D, Saldeen T, Romeo F, et al. Oxidized LDL upregulates angiotensin II type 1 receptor expression in cultured human coronary artery endothelial cells: the potential role

of transcription factor NF-kappa B. *Circulation* 2000; 102: 1970–1976.

19. Nickenig G, Sachinidis A, Seewald S, et al. Influence of oxidized low-density lipoprotein on vascular angiotensin II receptor expression. *J Hypertens Suppl.* 1997; 15: 27–30.

20. Grote K, Drexler H and Schieffer B. Renin-angiotensin system and atherosclerosis. *Nephrol Dial Transplant* 2004; 19: 770–773.

21. Nickenig G and Harrison DG. The AT1-type angiotensin receptor in oxidative stress and atherogenesis: part I: oxidative stress and atherogenesis. *Circulation* 2002; 105: 393–396.

22. Umemoto S. Angiotensin II type 1 (AT1) receptor deficiency halts the progression of age-related atherosclerosis in hypercholesterolemia: molecular link between the AT1 receptor and hypercholesterolemia. *Hypertens Res* 2008; 31: 1495–1497.

23. Zhu H, Li D, Feng X, et al. Plasma renin activity and low-density lipoprotein cholesterol level: potential risk factors of premature cardiovascular disease in young male people with hypertension. *Int J Clin Exp Med* 2016; 9: 23605–23611.

24. Long H, Wang L, Su H, et al. Increased circulatory RAS activity can be inhibited by statins in patients with hypercholesterolemia. *J Renin Angiotensin Aldosterone Syst* 2015; 16: 126–130.

25. Lloyd-Jones DM, Evans JC, Larson MG, et al. Cross-classification of JNC VI blood pressure stages and risk groups in the Framingham Heart Study. *Arch Intern Med* 1999; 159: 2206–2212.

26. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. *Am J Hypertens* 2001; 14: 837–854.

27. Borghi C, Veronesi M, Cosentino E, et al. Interaction between serum cholesterol levels and the renin-angiotensin system on the new onset of arterial hypertension in subjects with high-normal blood pressure. *J Hypertens* 2007; 25: 2051–2057.

28. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.

29. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016; 101: 1889–1916.

30. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013; 31: 1731–1768.

31. Friedewald WT, Levy RI and Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; 18: 499–502.

32. Horowitz GL, Zaman Z, Blanckaert NJC, et al. Modular analytics: a new approach to automation in the clinical laboratory. *J Auto Meth Manag Chem* 2005; 1: 8–25.

33. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002; 39: S1–S266.

34. Mulatero P, Verhovez A, Morello F, et al. Diagnosis and treatment of low-renin hypertension. *Clin Endocrin* 2007; 67: 324–334.

35. Chen J and Mehta JL. Interaction of oxidized low-density lipoprotein and the renin-angiotensin system in coronary artery disease. *Curr Hypertens Rep* 2006; 8: 139–143.

36. De Boer RA, Schroten NF, Bakker SJ, et al. Plasma renin and outcome in the community: data from PREVEND. *Eur Heart J* 2012; 33: 2351–2359.

37. Verma S, Gupta M, Holmes DT, et al. Plasma renin activity predicts cardiovascular mortality in the Heart Outcomes Prevention Evaluation (HOPE) study. *Eur Heart J* 2011; 32, 2135–2142.

38. Parikh NI, Gona P, Larson MG, et al. Plasma renin and risk of cardiovascular disease and mortality: the Framingham Heart Study. *Eur Heart J* 2007; 28: 2644–2652.

39. Alderman MH, Madhavan S, Ooi WL, et al. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. *N Eng J Med* 1991; 324: 1098–1104.

40. Adachi H, Enomoto M, Fukami A, et al. Plasma renin activity and resting heart rate in a population of community-dwelling Japanese: the Tanushimaru study. *Am J Hypertens* 2015; 28: 894–899.

41. Rifkin DE, Khaki AR, Jenny NS, et al. Association of renin and aldosterone with ethnicity and blood pressure: the multi-ethnic study of atherosclerosis. *Am J Hypertens* 2014; 27: 801–810.

42. Schroten NF, Gaillard CA, van Veldhuisen DJ, et al. New roles for renin and prorenin in heart failure and cardiorenal crosstalk. *Heart Fail Rev* 2012; 17: 191–201.

43. Ren L, Sun Y, Lu H, et al. (Pro)renin receptor inhibition reprograms hepatic lipid metabolism and protects mice from diet-induced obesity and hepatosteatosis. *Circ Res* 2018; 122: 730–741.

44. Lu X, Meima ME, Nelson JK, et al. Identification of the (pro)renin receptor as a novel regulator of low-density lipoprotein metabolism. *Circ Res* 2016; 118: 222–229.

45. Strong A and Musunuru K. (Pro)renin receptor and LDL clearance. An old player joins a new game. *Circ Res* 2016; 118: 187–189.

46. Mohib MM, Hasan I, Chowdhury WK, et al. Role of angiotensin II in hepatic inflammation through MAPK pathway: a review. *J Hep* 2016; 2: 1–8.

47. Lubel JS, Herath CB, Burrell LM, et al. Liver disease and the renin-angiotensin system: recent discoveries and clinical implications. *J Gastroenterol Hepatol* 2008; 23: 1327–1338.

48. Simões e Silva AC, Miranda AS, Rocha NP, et al. Renin angiotensin system in liver diseases: Friend or foe? *World J Gastroenterol* 2017; 23: 3396–3406.

49. Feltenberger JD, Andrade JM, Paraíso A, et al. Oral formulation of angiotensin-(1–7) improves lipid metabolism and prevents high-fat diet-induced hepatic steatosis and inflammation in mice. *Hypertension* 2013; 62: 324–330.

50. Hannich M, Wallaschofski H, Nauck M, et al. Physiological aldosterone concentrations are associated with alterations of lipid metabolism: observations from the general population. *Int J Endocrinol* 2018; 2018: 4128174.

51. Sahay M and Sahay RK. Low renin hypertension. *Indian J Endocrinol Metab* 2012; 16: 728–739.