

Higher risk of chronic kidney disease and progressive kidney function impairment in primary aldosteronism than in essential hypertension. Case-control study

María Fernández Argüeso

Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal

Eider Pascual-Corrales

Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal

Nuria Bengoa Rojano

Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal

Ana García Cano

Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal

Lucía Jiménez Mendiguchía

Ramon y Cajal University Hospital: Hospital Universitario Ramon y Cajal

Marta Araujo-Castro (✉ martaazul.2a@hotmail.com)

Hospital Universitario Ramon y Cajal <https://orcid.org/0000-0002-0519-0072>

Research Article

Keywords: Primary aldosteronism, chronic kidney disease, essential hypertension, cardiometabolic profile

Posted Date: February 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-238982/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Endocrine on April 2nd, 2021. See the published version at <https://doi.org/10.1007/s12020-021-02704-2>.

Abstract

Purpose: To study the differences in the prevalence, risk, and grade of control of different cardiometabolic comorbidities in patients with primary aldosteronism (PA) and essential hypertension (EH) matched by age, sex, and blood pressure levels at diagnosis.

Methods: Case-control study of a secondary base (PA patients in follow-up in a tertiary hospital between 2018-20). Controls were patients with EH, matched by age, sex, and baseline diastolic (DBP) and systolic blood pressure (SBP).

Results: Fifty patients with PA and 50 controls were enrolled in the study. At diagnosis, PA patients had a higher prevalence of chronic kidney disease (CKD) than controls (18.4% vs. 2.1%, $P=0.008$). No differences were detected in the prevalence of other cardiometabolic comorbidities nor in their degree of control ($P>0.05$). All patients received antihypertensive medical treatment and 10 PA patients underwent unilateral laparoscopic adrenalectomy.

After a median follow-up of 31.9 [IQR=1.0-254.8] months, PA patients presented a greater degree of declination of kidney function than controls (Average decrease in glomerular filtration rate (MDRD-4) -17.6 ± 3.1 vs -2.8 ± 1.8 ml/min/1.73m², $P<0.001$). There were no differences in the grade of SBP ($P=0.840$) and DBP control ($P=0.191$), nor in the risk of developing other comorbidities or in their degree of control.

Conclusions: PA patients have a prevalence of CKD ten times higher than those with EH matched by age, sex, and blood pressure levels. Furthermore, the risk of kidney function impairment throughout the follow-up is significantly greater in PA patients and is independent of the degree of blood pressure control.

Introduction

Primary aldosteronism (PA) is a condition that is a result of the autonomous excessive production of aldosterone that escapes regulation from angiotensin or plasma potassium concentrations (1). PA is considered the main cause of secondary hypertension, estimating that 5–10% of cases of arterial hypertension are caused by this condition (2).

There is compelling evidence to suggest that prolonged exposure to high aldosterone concentrations has a deleterious effect on the cardiovascular system and is associated with target organ damage, independently of blood pressure control (3)(4). Nonetheless, current evidence regarding the link between PA and cardiometabolic risk independently of blood pressure levels is conflicting; some studies point towards an increased risk of metabolic syndrome (5) and cardiovascular and cerebrovascular events compared to patients with essential hypertension (EH) (3, 6) and others reporting no differences (7–10).

So, although generally a higher cardiometabolic risk has been reported in PA patients than in similar patients with EH, the evidence is limited by small sample size and potential confounding factors that had not been evaluated. Therefore, the aim of our study was to analyze the differences in the prevalence, risk

during follow-up, and grade of control of the different cardiometabolic comorbidities in PA patients and controls with EH matched by sex, age, and blood pressure levels, and try to find out the question about the differences in the cardiometabolic risk in PA and EH patients after adjusting by possible confounding factors.

Methods

Patients.

All patients with a confirmed diagnosis of PA who had their last follow-up visit between 2018 and 2020 were included as cases in this study. During this period, the diagnosis of PA was made in 52 patients. Patients with PA and concomitant autonomous cortisol secretion (ACS)-defined as dexamethasone suppression test $> 1.8\mu\text{g/dl}$ - were excluded ($n = 2$) (11). A control group was selected from the ADRENAL INCIDENTALOMA register at Ramón y Cajal University Hospital (RCUH), which contains information from 730 patients with adrenal incidentalomas (AIs). 50 patients with AIs without any hormonal secretion (no diagnosis of PA, pheochromocytoma, Cushing's syndrome, or/and ACS) and with essential hypertension (EH) were selected using cumulative sampling. PA and EH were matched 1:1 for age, sex, systolic (SBP), and diastolic blood pressure (DBP) at the diagnosis (Fig. 1). This study was approved by the local ethics committee of the RCUH.

Clinical evaluation

Data on demographic factors (age and sex), comorbidities (hypertension, type II diabetes mellitus, obesity, dyslipidemia, chronic kidney disease (CKD) and cardiovascular and cerebrovascular diseases), has been collected, as well as further data about medical treatment with antihypertensive, oral antidiabetic and lipid-lowering medications, insulin and antiplatelet agents. Figures about physical evaluation as SBP, DBP, and body mass index (BMI (kg/m^2)) was also included. SBP and DBP measurements were made with an electronic device. All these variables were collected at the diagnosis and at the last visit to our unit.

We defined CKD as a glomerular filtration rate (GFR) $< 60 \text{ mL/min/1.73m}^2$ (GFR was estimated with the modification of diet in renal disease formula (MDRD-4)) for a period of more than 3 months (12). The following factors have been considered cardiovascular disease: history of ischemic and/or hypertensive heart disease, heart failure, arrhythmias, and/or valvular heart disease. Cerebrovascular disease included ischemic and/or hemorrhagic stroke and transient ischemic attack. Microalbuminuria was defined as a urinary albumin-creatinine ratio between 30–300 mg/g and proteinuria more than 300 mg/g.

PA was diagnosed based on positive case detection of plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio $> 20 \text{ ng/dL/h}$ or PAC/plasma renin concentration (PRC) ratio $> 1.8 \mu\text{UI/mL}$, with a PAC $> 15 \text{ ng/dl}$ and at least one positive result from a confirmatory test, (all patients underwent a saline infusion test except one patient who underwent a captopril test), except in those patients with

spontaneous hypokalemia, plasma renin below detection levels plus PAC > 20 ng/dL. (10) (2). Renin and aldosterone determinations were performed after the withdrawal of antihypertensive drugs that might interfere with the results and with oral potassium supplementation if plasma potassium was < 3.5 mEq/L.

Adrenal vein sampling (with cosyntropin stimulation) was performed in 19 patients with a successful sampling in 5 of them (selectivity index > 2 in both adrenal veins).

Laboratory test

Data has been collected on fasting plasma glucose, glycated hemoglobin (HbA1c), total cholesterol, HDL-c, LDL-c, triglycerides, serum creatinine, uric acid, GFR (MDR-4), microalbuminuria, proteinuria, parathyroid hormone (PTH), sodium, and serum potassium at the initial, at the diagnosis and at the last visit into our unit. Measurement of aldosterone and PRA or PRC was performed in all patients (PA and controls) and all controls underwent a 1 mg dexamethasone suppression test (13).

Laboratory assays

PRA (by the generation of angiotensin I in vitro) and PAC was measured using a radioimmunoassay (Beckman Coulter). The mean intraassay and inter-assay coefficients of variation (CV) for PRA, were < 11.3% and < 20,9% respectively with a least detectable activity of 0.20ng/dL/h, and the mean intraassay and inter-assay coefficients of variation (CV) for PAC, were < 12.6% and < 17.2% respectively with a least detectable concentration 1.44 pg/mL.

Since October 2018, PAC and PRC were measured using a chemiluminescence immunoassay (LIASON assay from Diasorin) with an analytical sensitivity (least detectable concentration) of 1,45 ng/dL for aldosterone and < 0,53 µUI/mL for renin. The functional sensitivity (analyte concentration at which the inter-assay CV < 20 %) is 1,6 to 1,96 µUI/mL for PRC and 1,91 ng/dL for PAC.

Statistical analysis

Case-control study of secondary base (follow-up PA patients at the HURC between 2018-20). Controls were patients with EH, matched 1:1 by age, sex, and baseline DBP and SBP. The analysis was performed with STATA 15. Data for continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range and as percentages (and absolute values) for categorical variables. Normality was tested using the Shapiro-Wilk normality test and homogeneity of variances using the Levene's test. The Student *t* or U-Mann Whitney tests were used for quantitative variables depending on normality assumption and the *X2 test* for qualitative variables. The odds ratio (OR) for qualitative variables was calculated using logistic regression. Multivariant logistic regression analysis was performed to analyze the influential of possible confounding factors. Hazard ratios through follow-up were calculated from Cox regression analyses. Comparisons between paired-samples (baseline vs follow up evaluation values) were assessed by paired t-test. The level of *P* < 0.05 was considered statistically significant for all the analyses.

Results

Baseline clinical characteristics

Fifty patients with PA and 50 with EH were included. As a result of the matching process, age, sex, and SBP and DBP were similar between cases and controls. 54.9% of PA patients presented unilateral forms according to imaging tests (CT and/or MRI) and in the remaining were bilateral. Hypertension was present in 100% of PA and hypokalemia (serum potassium <3.5 mEq/L) in 36.2%. No differences were detected in the proportion of patients with SBP ≥ 160 and/or DBP ≥ 100 mmHg at diagnosis among patients with PA and EH (25% vs 20.5%, $P=0.619$), but the mean number of antihypertensive drugs necessary to BP control was significantly higher in patients with PA than in controls (2.7 ± 0.2 vs 1.8 ± 0.2 , $P=0.001$). The baseline characteristics of the patients at their first hospital evaluation are shown in **Table 1**.

Baseline cardiometabolic profile

At diagnosis, a ten-fold higher prevalence of CKD was observed in patients with PA than in controls (OR=10.6, 95% CI=1.28-87.1). These differences persisted after adjusting by age, type 2 diabetes, and obesity (adjusted-OR=9.4, 95%CI=1.10-80.2). Besides, patients with PA presented significantly higher levels of PTH than controls (**Table 1**). Any clinical or analytical factor was specifically associated with an increased risk of CKD ($P > 0.05$).

No differences were observed in the prevalence of other comorbidities, including cardiovascular disease (**Table 1**). However, when the causes of cardiovascular disease were analyzed separately, a higher prevalence of ischemic heart disease was detected in patients with PA (12.0 vs 2.0%, $P=0.050$), but not in hypertensive heart disease ($P=0.307$), valvular disease ($P=0.079$), arrhythmias ($P=1.00$) and heart failure ($P=1.000$). There were also no differences in the proportion of patients under lipid-lowering drugs ($P=0.142$), oral antidiabetic ($P=0.741$), insulin ($P=0.913$), or antihypertensive ($P=1.00$) treatment between groups.

Cardiometabolic profile throughout the follow-up

All patients were treated with antihypertensive drugs and 10 patients with PA underwent unilateral laparoscopic adrenalectomy. The antihypertensive of choice was antagonist of mineralocorticoid receptors in 32 patients with PA (12 eplerenone (median doses 75mg/day [range 25-100] and 20 spironolactone (median doses 50 mg/day [range 25-100])), but in any control.

After a median follow-up of 31.9 [IQR=1.0-254.8] months, patients with PA presented a greater deterioration of kidney function than controls (GFR $-17.63.1$ vs -2.8 ± 1.8 ml/min / $1.73m^2$, $P < 0.001$). The only other factor associated with a greater risk of impaired kidney function was the presence of CKD at diagnosis ($P=0.008$). PA was an independent risk factor of impaired kidney function since statistical

significance persists after adjusting by age, CKD, type 2 diabetes and obesity (non-adjusted β = -14.8, 95%CI = -22.04 to -7.57; adjusted β = -19.66, 95%CI = -19.66 to -2.74)

No differences were found in the degree of control of SBP (P = 0.840), DBP (P = 0.191), or in the risk of developing other comorbidities or in their degree of control throughout the follow-up. However, PA patients were under a mean of 2.5 ± 0.2 antihypertensive drugs compared to 1.9 ± 0.2 in the case of patients with EH (P = 0.034) (**Table 2**).

Discussion

In this study, we have found that patients with PA have a ten-fold higher prevalence of CKD at diagnosis and a higher risk of progressive kidney function impairment during follow-up than EH controls matched by age, sex, and blood pressure levels. Moreover, the prevalence of ischemic heart disease was six times higher in PA patients.

We found a prevalence of CKD more than ten times greater in patients with PA than controls. Similar results have been reported previously (14–17), and it is consistent with the harmful effects documented not only on the cardiovascular system but also on kidney function in long-standing PA (18)(19). Several clinical studies have reported possible kidney abnormalities such as proteinuria and decreased GFR in relation to plasma aldosterone concentration regardless of other known risk factors (14)(15). Often this damage is masked until the treatment of PA is performed (20). Elevated aldosterone levels have been suggested to cause glomerular hyperfiltration, which explains the decrease in GFR after treatment, and the severity of excess aldosterone in the pretreatment period seems to be the most important risk factor for deterioration of the renal function (18)(17)(21). This decrease is greater in patients with PA than in those with EH after the initiation of antihypertensive treatment, therefore the decrease in renal function cannot be attributed only to the decrease in blood pressure, and the alternative and more probable explanation is the resolution of aldosterone-induced glomerular hyperfiltration after treatment (20)(21). Some studies have shown that the treatment of PA with mineralocorticoid receptor antagonists and surgery lowers GFR as volume expansion and glomerular hyperfiltration are mitigated (17)(22)(18). Thus, it seems clear that PA, regardless of the influences of blood pressure, is associated with a much higher risk of adverse renal outcomes compared to EH. Our hypothesis is that the higher risk of CKD in PA could be attributed to the effect of mineralocorticoid receptor activation by aldosterone in the context of volume expansion (23).

In our cohort of patients with PA, any clinical or hormonal characteristic was useful to predict CKD. However, the PAPY study found that plasma aldosterone, BMI, and age significantly predicted GFR (15). Wu *et al.* identified older age, diabetes mellitus, lower BMI, lower serum potassium, and higher PRA as factors related to kidney impairment in PA patients (24). Moreover, other authors demonstrated that pretreatment plasma aldosterone, plasma renin, plasma potassium, and pretreatment eGFR are independent predicting factors for the decline in GFR (18)(19); and others (21) that urinary albumin excretion and potassium were the only two independent predictors. The fact that any risk factor of GFR

declination has been identified in our study could be justified by the matched process that eliminates differences in some known factors that affect kidney function and the similar cardiometabolic profile of both patient groups.

Another important finding was the significantly increased levels of PTH in patients with PA than in EH controls. The most plausible explanation in our study for this hyperparathyroidism is a secondary cause due to the higher prevalence of CKD in our cohort of PA. This theory is supported by other authors (25) (26). However, other authors (27)(28) have reported an increase in PTH levels in PA patients regardless of kidney function and vitamin D status. The exact mechanism by which aldosterone stimulates PTH remains unknown. However, evidence exists that aldosterone may impact on mineral homeostasis by increasing renal and fecal loss of calcium and magnesium and in turn, this may stimulate the secretion of PTH (29). Nevertheless, we cannot rule out a bidirectional interaction between the two hormonal systems as other studies have previously suggested (30)(31). The authors found the presence of mineralocorticoid and angiotensin II type 1 receptors in adenomatous tissue of the parathyroid gland, which could lead that both aldosterone and angiotensin II increased PTH secretion.

Although, globally, we could not demonstrate differences in the risk of cardiovascular disease between PA patients and controls, ischemic heart disease was six times significantly more common in PA patients than in EH controls. This is in agreement with the reported previously by several authors (3)(6)(32). Milliez *et al.* (3), were the first to demonstrate a significantly higher rate of myocardial infarction (4.0% vs 0.6%, $P < 0.005$) in a large cohort of patients with PA in comparison with EH patients matched by age, gender, BP, smoking history, creatinine and serum glucose levels. The French cohort of Savard *et al.* (6) also showed that patients with PA had a two-fold and 2.6-fold higher prevalence of coronary artery disease and nonfatal myocardial infarction, respectively. Moreover, a recent meta-analysis (33) including 3838 patients with PA and 9284 patients with EH with comparable baseline characteristics found that those patients with PA were at increased risk for coronary artery disease (OR 1.77, 95% CI = 1.10–2.83) compared with controls. Nevertheless, other authors (8–10) found no differences in the risk of ischemic heart disease. This discrepancy may be due to the lower incidence of coronary arterial disease in the Japanese population compared with Western countries. Racial differences and/or small number of events might explain the lack of significant difference in the analysis of ischemic heart disease risk (10). Likewise, in the work by Takeda *et al.* (8) EH controls were matched for age and gender but not for BP level.

During follow-up, our cohort of PA patients experienced a higher risk of deterioration of kidney function than controls, despite similar levels of SBP and DBP. Similar results were previously reported (24). There is limited information about the effect of prolonged aldosterone excess on kidney function (34); however, significant histological damage of the kidney has been noted in PA patients (35). There is evidence which supports that increased aldosterone is an independent contributor to small- and note-sized arterial injury and nephropathy (35), and that aldosterone-induced structural damage may affect primarily intrarenal vessels as a result of chronic hypertensive injury and aldosterone-related endothelial dysfunction (35)(19) (36). Furthermore, the glomerular hyperfiltration in PA plays a role in the progression of CKD (24), and the

excessive urinary albumin excretion could be an indicator of target-organ damage associated with PA (37). Moreover, PA without suppression of plasma renin was associated with the histological evidence of renal arteriosclerosis (38), and higher pretreatment renin concentrations were associated with a lower probability of curing hypertension and less improvement of albuminuria after treatment of PA (19). Therefore, an evolutionary pattern of kidney impairment in PA from initial functional adaptation to irreversible structural damage has been proposed (24).

As limitations of our study, it should be mentioned that it is a retrospective study, so no conclusions can be drawn in terms of causality. However, the presence of the matching process by age, sex, and degree of BP control limits the possibility of confusing factors and provides greater robustness to the results. Nevertheless, the fact that patients with PA needed more antihypertensive drugs than controls at diagnosis could introduce a bias as it could be related with a more severe hypertension and/or of longer duration. One strength of the study is a relatively large number of patients were included in the study. Another possible limitation of this study, it could be that patients with non-functioning incidentalomas were selected as controls, classified as such with classical hormonal studies, but that it cannot be ruled out that there is a secretion of other steroid hormones that could increase the cardiometabolic risk of these patients and reduce differences in the cardiometabolic profile between PA and EH patients (39)(40)(41).

Conclusion

Patients with PA have a prevalence of CKD ten times higher than those with EH matched by age, sex, and blood pressure levels. Furthermore, the risk of kidney function impairment throughout the follow-up is significantly greater in PA patients and independent of the degree of blood pressure control.

Declarations

Compliance with Ethical Standards:

Financial Support:

SENDIMAD: BECA SENDIMAD de Ayuda a la Investigación en Endocrinología, Nutrición y Diabetes 2019

IRYCIS: Convocatoria intramural de ayudas a proyectos de investigación de investigadores noveles, investigadores clínicos asociados y/o grupos emergentes del Hospital Universitario Ramón y Cajal

Conflict of Interest: The authors have no conflict of interest

Ethical approval: All procedures performed in the participants of the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Not applicable (Ethical Commit have approved the exemption of informed consent due to the observational and retrospective nature of the study, with any risk for the patients included)

References

1. Araujo-castro M. Tratamiento del hiperaldosteronismo primario. *Med Clin (Barc)*. 2020;22;S0025-7753(20)30323-7. doi: 10.1016/j.medcli.2020.04.029.
2. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(5):1889-916. doi: 10.1210/jc.2015-4061.
3. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol*. 2005;45(8):1243-8. doi: 10.1016/j.jacc.2005.01.015.
4. Rossi GP, Boscaro M, Ronconi V, Funder JW. Aldosterone as a cardiovascular risk factor. *Trends Endocrinol Metab*. 2005;16(3):104-7. doi: 10.1016/j.tem.2005.02.010.
5. Šomlóová Z, Widimský J, Rosa J, Wichterle D, Štrauch B, Petrák O, et al. The prevalence of metabolic syndrome and its components in two main types of primary aldosteronism. *J Hum Hypertens*. 2010;24(10):625-30. doi: 10.1038/jhh.2010.65.
6. Savard S, Amar L, Plouin PF, Steichen O. Cardiovascular complications associated with primary aldosteronism: A controlled cross-sectional study. *Hypertension*. 2013;62(2):331-6. doi: 10.1161/HYPERTENSIONAHA.113.01060.
7. Matrozkova J, Steichen O, Amar L, Zacharieva S, Jeunemaitre X, Plouin PF. Fasting plasma glucose and serum lipids in patients with primary aldosteronism a controlled cross-sectional study. *Hypertension*. 2009;53(4):605-10. doi: 10.1161/HYPERTENSIONAHA.108.122002.
8. Takeda R, Matsubara T, Miyamori I, Hatakeyama H, Morise T. Vascular complications in patients with aldosterone producing adenoma in Japan: comparative study with essential hypertension. The Research Committee of Disorders of Adrenal Hormones in Japan. *J Endocrinol Invest*. 1995 ;18(5):370-3. doi: 10.1007/BF03347840.
9. Nishimura M, Uzu T, Fujii T, Kuroda S, Nakamura S, Inenaga T, et al. Cardiovascular complications in patients with primary aldosteronism. *Am J Kidney Dis*. 1999;33(2):261-6. doi: 10.1016/s0272-6386(99)70298-2.
10. Ohno Y, Sone M, Inagaki N, Yamasaki T, Ogawa O, Takeda Y, et al. Prevalence of Cardiovascular Disease and Its Risk Factors in Primary Aldosteronism A Multicenter Study in Japan. *Hypertension*. 2018;71(3):530-537. doi: 10.1161/HYPERTENSIONAHA.117.10263
11. Rossi R, Tauchmanova L, Luciano A, Di Martino M, Battista C, Del Viscovo L, et al. Subclinical Cushing's syndrome in patients with adrenal incidentaloma: Clinical and biochemical features. *J Clin Endocrinol Metab*. 2000;85(4):1440-8. doi: 10.1210/jcem.85.4.6515.

12. Levey AS, Coresh J, Bolton K, Culleton B, Harvey KS, Ikizler TA, et al. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(2 Suppl 1):S1-266.
13. Araujo-Castro M, Iturregui Guevara M, Calatayud Gutiérrez M, Parra Ramírez P, Gracia Gimeno P, Hanzu FA, et al. Practical guide on the initial evaluation, follow-up, and treatment of adrenal incidentalomas Adrenal Diseases Group of the Spanish Society of Endocrinology and Nutrition. *Endocrinol Diabetes Nutr.* 2020;67(6):408-419. doi: 10.1016/j.endinu.2020.03.002
14. Kawashima A, Sone M, Inagaki N, Takeda Y, Itoh H, Kurihara I, et al. Renal impairment is closely associated with plasma aldosterone concentration in patients with primary aldosteronism. *Eur J Endocrinol.* 2019 ;181(3):339-350. doi: 10.1530/EJE-19-0047.
15. Rossi GP, Bernini G, Desideri G, Fabris B, Ferri C, Giacchetti G, et al. Renal damage in primary aldosteronism: Results of the PAPY study. *Hypertension.* 2006;48(2):232-8. doi: 10.1161/01.HYP.0000230444.01215.6a
16. Hundemer GL, Baudrand R, Brown JM, Curhan G, Williams GH, Vaidya A. Renin phenotypes characterize vascular disease, autonomous aldosteronism, and mineralocorticoid receptor activity. *J Clin Endocrinol Metab.* 2017;102(6):1835-1843. doi: 10.1210/jc.2016-3867.
17. Sechi LA, Novello M, Lapenna R, Baroselli S, Nadalini E, Colussi GL, et al. Long-term renal outcomes in patients with primary aldosteronism. *J Hypertens.* 2007 ;25(7):1443-50. doi: 10.1097/HJH.0b013e328126855b.
18. Kramers BJ, Kramers C, Lenders JWM, Deinum J. Effects of Treating Primary Aldosteronism on Renal Function. *J Clin Hypertens.* 2017;19(3):290-295. doi: 10.1111/jch.12914
19. Catena C, Colussi GL, Nadalini E, Chiuch A, Baroselli S, Lapenna R, et al. Relationships of plasma renin levels with renal function in patients with primary aldosteronism. *Clin J Am Soc Nephrol.* 2007 ;2(4):722-31. doi: 10.2215/CJN.00050107
20. Ribstein J, Du Cailar G, Fesler P, Mimran A. Relative glomerular hyperfiltration in primary aldosteronism. *J Am Soc Nephrol.* 2005;16(5):1320-5. doi: 10.1681/ASN.2004100878
21. Iwakura Y, Morimoto R, Kudo M, Ono Y, Takase K, Seiji K, et al. Predictors of decreasing glomerular filtration rate and prevalence of chronic kidney disease after treatment of primary aldosteronism: Renal outcome of 213 cases. *J Clin Endocrinol Metab.* 2014;99(5):1593-8. doi: 10.1210/jc.2013-2180
22. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Renal outcomes in medically and surgically treated primary aldosteronism. *Hypertension.* 2018;72(3):658-666. doi: 10.1161/HYPERTENSIONAHA.118.11568.
23. Vaidya A, Mulatero P, Baudrand R, Adler GK. The Expanding Spectrum of Primary Aldosteronism: Implications for Diagnosis, Pathogenesis, and Treatment. *Endocr Rev.* 2018;39(6):1057-1088. doi: 10.1210/er.2018-00139.
24. Wu VC, Yang SY, Lin JW, Cheng BW, Kuo CC, Tsai CT, et al. Kidney impairment in primary aldosteronism. *Clin Chim Acta.* 2011;412(15-16):1319-25. doi: 10.1016/j.cca.2011.02.018

25. Hene RJ, Boer P, Koomans HA, Dorhout Mees EJ. Plasma aldosterone concentrations in chronic renal disease. *Kidney Int.* 1982;21(1):98-101. doi: 10.1038/ki.1982.14
26. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. *Kidney Int.* 2008;74(3):389-90. doi: 10.1038/ki.2008.169.
27. Pilz S, Kienreich K, Drechsler C, Ritz E, Fahrleitner-Pammer A, Gaksch M, et al. Hyperparathyroidism in patients with primary aldosteronism: Cross-sectional and interventional data from the GEOH study. *Clin Endocrinol Metab.* 2012;97(1):E75-9. doi: 10.1210/jc.2011-2183
28. Maniero C, Fassina A, Seccia TM, Toniato A, Iacobone M, Plebani M, et al. Mild hyperparathyroidism: A novel surgically correctable feature of primary aldosteronism. *J Hypertens.* 2012;30(2):390-5. doi: 10.1097/HJH.0b013e32834f0451.
29. Vidal A, Sun Y, Bhattacharya SK, Ahokas RA, Gerling IC, Weber KT. Calcium paradox of aldosteronism and the role of the parathyroid glands. *Am J Physiol Heart Circ Physiol.* 2006;290(1):H286-94. doi: 10.1152/ajpheart.00535.2005.
30. Brown JM, Williams JS, Luther JM, Garg R, Garza AE, Pojoga LH, et al. Human interventions to characterize novel relationships between the renin-angiotensin-aldosterone system and parathyroid hormone. *Hypertension.* 2014;63(2):273-80. doi: 10.1161/HYPERTENSIONAHA.113.01910
31. Lenzini L, Prisco S, Vanderriele PE, Lerco S, Torresan F, Maiolino G, et al. PTH Modulation by Aldosterone and Angiotensin II is Blunted in Hyperaldosteronism and Rescued by Adrenalectomy. *J Clin Endocrinol Metab.* 2019;104(9):3726-3734. doi: 10.1210/jc.2019-00143.
32. Born-Frontsberg E, Reincke M, Rump LC, Hahner S, Diederich S, Lorenz R, et al. Cardiovascular and cerebrovascular comorbidities of hypokalemic and normokalemic primary aldosteronism: Results of the German conn's registry. *J Clin Endocrinol Metab.* 2009;94(4):1125-30. doi: 10.1210/jc.2008-2116.
33. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* 2018;6(1):41-50. doi: 10.1016/S2213-8587(17)30319-4.
34. Reincke M, Rump LC, Quinkler M, Hahner S, Diederich S, Lorenz R, et al. Risk factors associated with a low glomerular filtration rate in primary aldosteronism. *J Clin Endocrinol Metab.* 2009 ;94(3):869-75. doi: 10.1210/jc.2008-1851.
35. Hollenberg NK. Aldosterone in the development and progression of renal injury. *Kidney Int.* 2004;66(1):1-9. doi: 10.1111/j.1523-1755.2004.00701.x.
36. Rocha R, Stier CT. Pathophysiological effects of aldosterone in cardiovascular tissues. *Trends Endocrinol Metab.* 2001;12(7):308-14. doi: 10.1016/s1043-2760(01)00432-5.
37. Jean-Michel H, Mimran A. Albuminuria in untreated patients with primary aldosteronism or essential hypertension. *J Hypertens.* 1995;13(12 Pt 2):1801-2.
38. Oelkers W, Diederich S, Bähr V. Primary hyperaldosteronism without suppressed renin due to secondary hypertensive kidney damage. *J Clin Endocrinol Metab.* 2000 ;85(9):3266-70. doi:

10.1210/jcem.85.9.6819.

39. Kotłowska A, Puzyn T, Sworczak K, Stepnowski P, Szefer P. Metabolomic biomarkers in urine of cushing's syndrome patients. *Int J Mol Sci.* 2017;18(2):294. doi: 10.3390/ijms18020294.
40. Peppas M, Boutati E, Koliaki C, Papaefstathiou N, Garoflos E, Economopoulos T, et al. Insulin resistance and metabolic syndrome in patients with nonfunctioning adrenal incidentalomas: A cause-effect relationship? *Metabolism.* 2010;59(10):1435-41. doi: 10.1016/j.metabol.2010.01.007
41. Araujo-Castro M, Robles Lázaro C, Parra Ramírez P, Cuesta Hernández M, Sampedro Núñez MA, Marazuela M. Cardiometabolic profile of non-functioning and autonomous cortisol-secreting adrenal incidentalomas. Is the cardiometabolic risk similar or are there differences? *Endocrine.* 2019;66(3):650-659. doi: 10.1007/s12020-019-02066-w.

Tables

Table 1. Baseline characteristics of cases and controls

	Primary aldosteronism (n=50)	Essential hypertension (n=50)	Measure of association	P value
Age (years)	57.7 [IQR 34.9-77.2]	60.9 [IQR 47.9-68.3]	d=-2.5, 95%CI=-6.9-1.9	0.303
Females	42.9% (n=21)	45.8% (n=22)	OR=1.1, 95%CI=0.5-2.5	0.768
Type 2 diabetes	22.0% (n=11)	22.9% (n=11)	OR=0.9, 95%CI=0.4-2.5	0.913
Dislipemia	42.0% (n=21)	54.2% (n=26)	OR=0.6, 95%CI=0.3-1.4	0.228
Cardiovascular	26.0% (n=13)	18.0% (n=9)	OR=1.6, 95%CI=0.6-4.2	0.334
Cerebrovascular	6.0% (n=3)	2.0% (n=1)	OR=3.1, 95%CI=0.3-31.1	0.307
CKD	18.4% (n=9)	2.1% (n=1)	OR=10.6, 95%CI=1.3-87.1	0.008
Microalbuminuria	26.5% (n=9)	0%	NC	0.152
Proteinuria	14.7% (n=5)	0%	NC	
Obesity	43.2% (n=19)	51.2% (n=22)	OR=0.7, 95%CI=0.3-1.7	0.456
% of patients on antihypertensive drugs	100% (n=50)	100% (n=50)	NC	
Number of antihypertensives	2.7±1.20	1.8±1.25	d=-1.0, 95%CI=0.4-1.5	0.001
% of patients on lipid-lowering drugs*	51.2% (n=22)	54.2% (n=26)	OR=0.9, 95%CI=0.4-2.0	0.775
BMI (kg/m2)	30.7 [IQR 22.4-37.6]	30.4 [IQR 23.2-39.7]	d=-0.8, 95%CI=-3.5-2.0	0.691
SBP (mmHg)	143.8±2.9	139.8±2.5	d=4.0, 95%CI=-3.6-11.7	0.297
DBP (mmHg)	85.5±1.5	85.8±1.2	d=-0.3, 95%CI=-4.1-3.6	0.888
Glucose (mg/dl)	101 [IQR 75-160]	97.5 [IQR 78-158]	d=4.1, 95%CI=-7.2-15.4	0.289
HbA1c (%)	5.8 [IQR 5.3-7.9]	5.8 [IQR 5.3-9.1]	d=-0.3, 95%CI=-1.0-0.4	0.365
Uric acid (mg/dl)	5.5 [IQR 3.2-8]	5.4 [IQR 3.8-7.6]	d=0.2, 95%CI=-0.4-0.9	0.537

Calcium (mg/dl)	9.4±0.1	9.4±0.1	d=-0.1, 95%CI=-0.3-0.1	0.601
Phosphorus	3.1±0.1	3.3±0.1	d=-0.2, 95%CI=-0.6-0.1	0.198
PTH (ng/dL)	88.3±5.6	47.4±4.4	d=40.9, 95%CI=12.9- 68.9	0.006
GFR (MDRD4)	85.2±3.8	84.5±2.1	d=0.8, 95%CI=-7.8-9.4	0.862
LDL-c (mg/dl)	117.0±5.5	120.8±5.7	d=-4.1, 95%CI=-19.8- 11.6	0.601
HDL-c (mg/dl)	46.4±1.7	51.6±3.4	d=-5.1, 95%CI=-12.8-2.5	0.183
Triglycerides	125.3±9.9	116.8±7.2	d=8.6, 95%CI=-15.9- 33.0	0.488
PAC	48.9±5.6	13.4±1.5	d=35.5, 95%CI=23.8- 47.1	<0.001
PRA	0.6±0.1	2.2±0.7	d=-1.6, 95% CI=-3.0 -0.1	0.035

BMI = body mass index; CKD = chronic kidney disease; DBP = diastolic blood pressure; GFR = glomerular filtration rate (ml / min / 1.73m²); NC = not calculable; PAC= plasma aldosterone concentration; PRA= plasma renin activity; SBP = systolic blood pressure. d makes reference to the differences between mean or median value in patients with primary aldosteronism and control group; OR = odds ratio; IQR= interquartile range

*Information about treatment with lipid-lowering drugs was not available in 2 patients with primary aldosteronism and in 7 patients with essential hypertension

Measure of association of qualitative variables were calculated with logistic regression model (OR and confident interval) and with t and U-Mann Whitney tests for quantitative variables (d and confident intervals).

Table 2. Clinical and analytical differences throughout follow-up in patients with primary hyperaldosteronism vs controls.

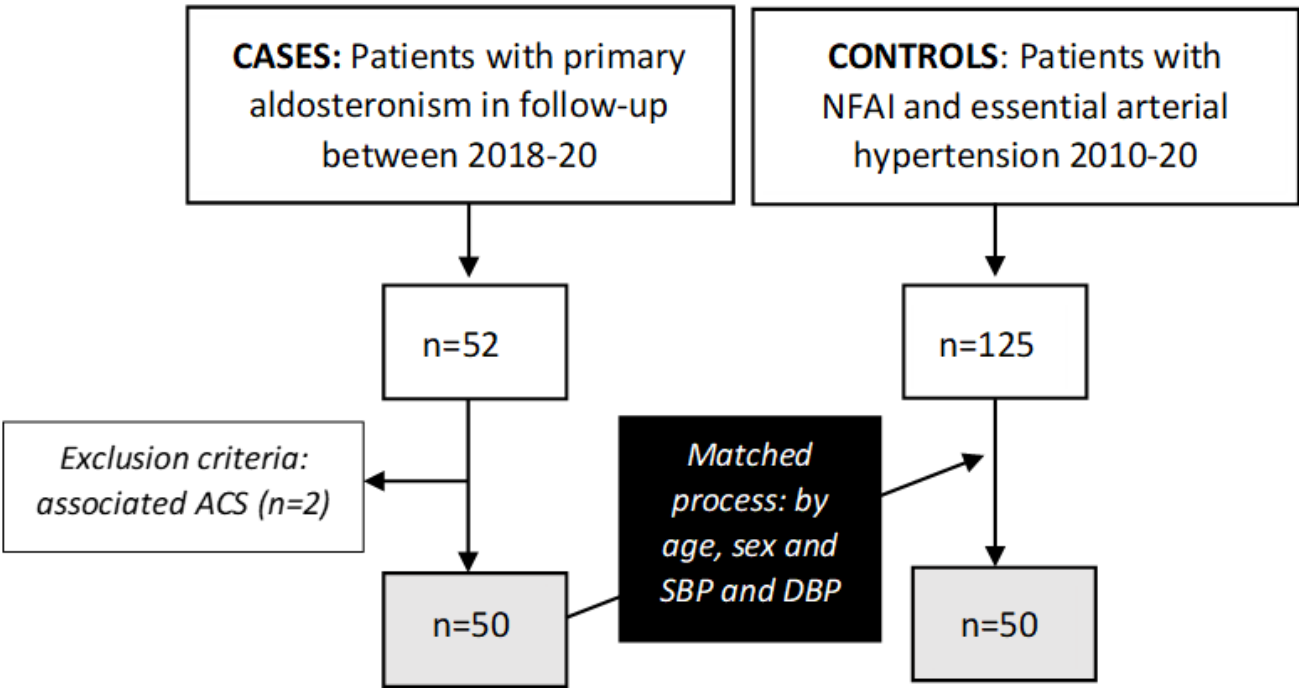
	Primary aldosteronism (n=50)	Essential hypertension (n=50)	Measure of association	P value
New diabetes	5.4% (2/37)	9.1% (1/11)	HR= 0.5, 95% CI=0.0-5.8	0.658
New dislipemia	19.2% (5/26)	12.5% (1/8)	HR=1.6, 95%CI= 0.2-13.8	0.662
New cardiovascular	2.4% (1/41)	0%	NC	0.339
New cerebrovascular	0%	0%	NC	NA
New obesity	0%	0%	NC	NA
New CKD	8.3% (3/36)	0%	NC	0.283
Δ antihypertensive drugs	-0.2±1.6	0.2±0.7	d=-0.4, 95%CI -0.98-0.11	0.115
ΔSBP (mmHg)	-8.2±3.4	-6.6±6.8	d=-1.6, 95%CI=-16.9-13.8	0.838
ΔDBP (mmHg)	-3.2±1.7	0.5±2.1	d=-3.7, 95%CI=-10.9-3.6	0.316
Δglucose (mg/dl)	0.6±3.4	-0.1±2.9	d=0.7, 95% CI=-11.4-12.9	0.904
ΔHbA1c (%)	0.0±0.2	0.1±0.1	d=0.0, 95%CI= -1.0-1.0	0.963
ΔGFR (MDRD-4)	-17.6±3.1	-2.8±1.8	d=-14.8, 95% CI=-22.0-7.6	<0.001
Δ uric acid (mg/dl)	2.7±2.4	0.4±0.2	d=2.3, 95%CI=-2.5-7.0	0.342
ΔLDL-c (mg/dl)	-8.6±6.7	-8.9±8.8	d=0.3, 95%CI=-24.6-25.2	0.980
ΔHDL-c (mg/dl)	-0.2±1.7	-0.3±2.7	d=0.1, 95% CI=-6.6-6.7	0.984
ΔTriglycerides (mg/dl)	34.2±17.8	-9.1±15.5	d=43.3, 95% CI=-21.3-107.9	0.184

Δ = mean increase (value at the last visit - value at the initial visit); BMI = body mass index; CKD = chronic kidney disease; DBP = diastolic blood pressure; GFR = glomerular filtration rate (ml / min / 1.73m²); NC = not calculable; SBP = systolic blood pressure.

HR = hazard ratio; d = differences in the mean value at the last follow-up and the initial visit

Measure of association of qualitative variables were calculated with cox regression model (HR and confident interval) and with paired t test for quantitative variables (d and confident intervals).

Figures



ACS= autonomous cortisol secretion; NFAI= non-functioning adrenal incidentalomas; SBP= systolic blood pressure; DBP= diastolic blood pressure.

Figure 1

Cases and controls selection process