# DIABETES MELLITUS IN PRIMARY ALDOSTERONISM IS ASSOCIATED WITH CORTISOL CO-SECRETION

J. Gerards1, D. Heinrich2, C. Adolf2, C. Meisinger3, W. Rathmann4, L. Sturm2, N. Nirschl2, M. Bidlingmaier2, F. Beuschlein2,5, B. Thorand3, A. Peters3, M. Reincke2, M. Roden3,4, M. Quinkler1

1 *Endokrinologie in Charlottenburg, Endokrinologie Praxis am Stuttgarter Platz, Berlin, Germany*

2 *Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Ziemssenstr.1, 80336 München, Germany*

3 *Helmholtz Zentrum München, German Research Center of Environmental Health, Institute of Epidemiology, Neuherberg, Germany*

5 Helmholtz

Zentrum Mu¨ nchen, German Research Center of Environmental Health, Institute of Epidemiology, Neuherberg

Helmholtz

Zentrum Mu¨ nchen, German Research Center of Environmental Health, Institute of Epidemiology, Neuherberg

Helmholtz

Zentrum Mu¨ nchen, German Research Center of Environmental Health, Institute of Epidemiology, Neuherberg

4 *Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany*

5 *Klinik für Endokrinologie, Diabetologie und Klinische Ernährung, Universitätsspital Zürich, Zürich, Switzerland*

5 Helmholtz

Zentrum Mu¨ nchen, German Research Center of Environmental Health, Institute of Epidemiology, Neuherberg

Helmholtz

Zentrum Mu¨ nchen, German Research Center of Environmental Health, Institute of Epidemiology, Neuherberg

Helmholtz

Zentrum Mu¨ nchen, German Research Center of Environmental Health, Institute of Epidemiology, Neuherberg

**Corresponding author:**

Marcus Quinkler, MD

Endocrinology in Charlottenburg

Stuttgarter Platz 1

D 10627 Berlin, Germany

Tel. (+49)-30-2132004; Fax. (+49)-30-2132005

email: marcusquinkler@t-online.de

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**Abstract:**

*Context:* Primary aldosteronism (PA) is associated with higher cardiovascular morbidity and metabolic risks. Recent studies report glucocorticoid co-secretion as a relevant phenotype of PA, which could contribute to associated risks, including diabetes mellitus (T2DM). The relationship between autonomous cortisol secretion (ACS) and glucose metabolism in PA has not been investigated.

*Objective:* To evaluate the prevalence of impaired glucose homeostasis in PA patients according to cortisol co-secretion.

*Methods:* We performed oral-glucose-tolerance-test (OGTT) and complete testing for hypercortisolism (1mg-dexamethasone-suppression-test (DST), late-night-salivary-cortisol (LNC), 24hour-urinary-free-cortisol (UFC)) in 161 newly diagnosed PA patients of the German Conn Registry. 76 of 161 patients were reevaluated at follow-up. We used the population-based KORA-F4 study to perform a 1:3 matching regarding sex, age, and BMI.

*Results:* At the time of diagnosis, 125 patients (77.6%) had a pathological response in at least one of the Cushing screening tests; T2DM was diagnosed in 6.4% of these cases. Patients with pathological DST exhibited significant higher 120min plasma glucose in OGTT and were significantly more often diagnosed with T2DM than patients with normal DST (20% vs. 0.8%, p<0.0001) and matched controls from the KORA cohort (20.6% vs. 4%.; p=0.013). PA patients without ACS tended to have higher HOMA-IR than KORA control subjects (p=0.05). In 76 patients with one-year follow up, no significant changes in the prevalence of prediabetes and T2DM were seen.

*Conclusion:* ACS appears frequently in PA patients and seems to be associated with impaired glucose metabolism resulting in a higher prevalence of T2DM. PA itself seems to enhance insulin resistance.

**Key Words:** hyperaldosteronism, cortisol, diabetes mellitus, HbA1c, oral glucose tolerance test, insulin resistance

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Zentrum Mu¨ nchen, German Research Center of Environmental Health, Institute of Epidemiology, Neuherber

## **Introduction**

Primary aldosteronism (PA) is the most common form of secondary hypertension that affects 4.3 to 9.0% of hypertensive patients (1). Patients with aldosterone excess are at a higher risk of cardiovascular events and metabolic comorbidities in comparison to patients with essential hypertension (2-4). Recent studies have proven a broader metabolic influence of PA than previously suggested including impaired insulin-secretion (5), insulin-sensitivity (6) and other effects of aldosterone on glucose metabolism (7). These mechanisms lead to a higher prevalence of the metabolic syndrome and type 2 diabetes mellitus (T2DM) in PA patients (8). However, some aspects of impairment of glucose homeostasis in PA are still unresolved.

In the past, cortisol co-secretion in primary aldosteronism has been discussed on the basis of several case studies or case series (9-14). Recently, we have investigated a large multi-center cohort of PA patients and revealed that glucocorticoid co-secretion is a phenotype frequently found in PA which might contribute to associated metabolic risks (15). Specifically, our findings suggest that cortisol excess in PA also plays a part in impaired glucose metabolism. However, further investigations of an underlying correlation have not been undertaken yet.

Therefore, we analyzed autonomous cortisol secretion (ACS) and glucose metabolism in detail in newly diagnosed PA patients of the German’s Conn Registry. In addition, we used the population-based KORA-F4 and -S4 study (Cooperative-Health-Research-in-the-region-of-Augsburg) with a 1:3 matching regarding sex, age, and BMI for comparison.

## **Methods**

### Study Population

#### The German Conn Registry

The study population consists of 161 patients that were recruited in two centers (Munich; Berlin) of the German Conn Registry. The German Conn Registry is a multicenter-registry that investigates therapy, comorbidities and the longtime-outcome in PA-patients throughout Germany since 2008 (16). The investigated cohort was obtained between February 2013 and April 2017.

For inclusion in the registry, patients had to meet the diagnostic criteria for PA, as stated in the guidelines of the Endocrine Society (17). Patients were usually screened with high blood pressure and abnormal aldosterone to renin ratio (ARR) and then underwent one or more confirmatory tests (saline infusion, fludrocortisone suppression, captopril test, oral salt loading test with elevated excretion of aldosterone and metabolites in urine). Before implementation of those tests, anti-hypertensive medication has been changed whenever possible or indicated (deduction of beta-blockers, central-alpha-agonists, angiotensin-converting-enzyme-blocker, angiotensin-receptor-blocker for at least one week and mineralocorticoid receptor antagonists (MRA) for at least four weeks prior testing), in order to prevent influences on renin-angiotensin-aldosterone-system and thus test results. The diagnosis was then made decentralized in the synopsis of all clinical and laboratory findings.

Subtype identification (aldosterone producing adenoma (APA) vs. bilateral adrenal hyperplasia (BAH)) was performed via adrenal imaging (MRI or CT) and adrenal vein sampling (AVS), which was realized in 95.7% (n=154) of patients and successful in 92.5% (n=149) of those. During AVS, blood is obtained from both adrenal veins and from a peripheral vein. We assessed blood samples for hormone levels of both aldosterone and cortisol, in order to correct a dilution effect and confirm correct catheterization (17). Catheterization was performed without cosyntropin stimulation and was considered successful when cortisol levels in both adrenal veins were at least twice as high as in vena cava inferior. Unilateral aldosterone excess was considered to be present in patients with a lateralization index ((aldosterone left/cortisol left)/(aldosterone right/cortisol right) or vice versa) of at least 4:1.

For the present study, PA patients were only included if they underwent oral glucose tolerance test (OGTT) and complete testing for hypercortisolism, including 1mg dexamethasone suppression test (DST), 24hour urinary free cortisol (UFC) and late-night salivary cortisol (LSC) at baseline visit. Patients with missing data for aldosterone, renin, potassium, OGTT or blood pressure were excluded. We assessed glucose metabolism by laboratory measurement and OGTT, according to the American Diabetes Association (18).

76 of 161 patients had a follow-up visit one year after therapy initiation with MRA or adrenalectomy (ADX).

#### KORA-Study

The KORA-F4 study (Cooperative Health Research in the region of Augsburg) is the 7-year-follow-up examination of the population-based cohort study KORA-S4 (19,20). Baseline-examinations of KORA-S4 were conducted in 1999-2001, 1353 of patients aging 55-74 had an OGTT (21). 1202 patients were re-investigated in 2006-2008 as part of KORA-F4, and 887 patients without known or newly diagnosed T2DM at baseline participated in an OGTT (20).

Investigations included a standard medical interview, physical examination, blood withdrawal, and OGTT in all individuals without known T2DM after an overnight fasting period of ≥8h (22,23).

The ethics committees of the University of Munich and all participating centers approved the protocol of the Conn's registry. The study of the KORA survey was approved by the Ethics Committee of the Bavarian Medical Association. We obtained written informed consent from all participants, and strictly adhered to data protection policies.

### Definitions and laboratory measurements

In PA patients as well as in controls standard laboratory measurements were performed immediately and decentralized. In order to test for hypercortisolism, we performed 1mg DST and acquired LSC, as well as 24hour UFC in all patients at baseline visit. Autonomous cortisol co-secretion (ACS) as an indicator for hypercortisolism was assumed when DST, LSC or UFC were above normal reference values (≥51 nmol/l; >1.45 ng/ml; >150 µg/24hours, respectively). Reference values were determined following the Guidelines of the Endocrine Society (24).

Blood pressure (BP) was measured up to three times on each arm after 5 minutes of resting with standard sphygmomanometers. Body mass index (BMI) was calculated as body weight (kg) per heights2 (m2).

The homeostasis model assessment of insulin resistance (HOMA-IR) score was calculated (fasting serum insulin (mU/l) \* fasting plasma glucose (mg/dl) /405) for patients of the German’s Conn Registry and (fasting plasma glucose (mmol/l) \* fasting serum insulin (mU⁄ l) ⁄ 22.5) for KORA-F4-patients. In order to investigate glucose metabolism, we performed an OGTT at baseline visit in all patients and measured HbA1c (%) in patient’s blood samples. Only non-diabetic patients received an OGTT (no intake of antidiabetic drugs, no diagnosis by a physician, no reported T2DM by the patient). OGTT was performed in fasting patients (at least 8 hours) with 75g glucose dissolved in 300ml of water. Blood samples were obtained before glucose load (fasting plasma glucose; FPG), at 60 minutes and 120minutes (2h glucose) after glucose load. Patients were diagnosed with either T2DM, prediabetes or normal glucose metabolism, according to the American Diabetes Society (18): newly detected T2DM was defined if HbA1c ≥6.5%, FPG ≥126 mg/dl or glucose at 120 minutes of OGTT ≥200mg/dl. Prediabetes was defined by HbA1c (5.7-6.4%) or OGTT result in either impaired FPG (100-125 mg/dl in OGTT) or impaired glucose tolerance (IGT 140-199 mg/dl in OGTT). The term prediabetes includes isolated impaired FPG, isolated IGT and both combined.

### Matching and Statistical analysis

Matching was performed sex-stratified and further matching variables were age and BMI-category (<25; 25-29; ≥30kg/m2). In order to be able to achieve a 1:3 matching, four young patients (<32 years) from the German-Conn-Registry had to be excluded. Blood-pressure was not chosen as a matching variable, as KORA-patients are population-representative whereas PA patients form a hypertensive cohort. KORA patients with type 1 diabetes or drug induced diabetes were excluded, as well as patients with ARR >20. This 1:3 matching resulted in 471 matched controls for 157 PA patients. Differences between PA patients and controls were obtained using conditional regression analysis.

Statistical analysis was carried out using IBM SPSS Statistics 25.0 (IBM, Ehningen, Germany). Data are displayed as mean and standard deviation (mean ± SD) for normally distributed continuous data, and as median; 25th and 75th percentile for continuous variables without normal distribution. Categorical variables are displayed as percentage or numbers. Variables were assessed for normal distribution using Shapiro-Wilk test.

To compare normal and pathological subgroups we used either Mann-Whitney U test or unpaired t-test for continuous data and Chi2 test for categorical variables. For paired data comparing baseline and follow-up visit, we used McNemar for categorical data and Wilcoxon’s test or paired t-test for continuous data. T-Tests (paired or unpaired) was only applied if normal distribution in both subgroups was given. Differences were considered statistically significant when *P* ≤0.05*.*

## **Results**

In 161 investigated PA patients, ACS was identified in 77.6% (n=125; 61 with one, 58 with two, and 6 with three pathological tests), whereas 22.4% (n=36) showed a normal response in all three tests for hypercortisolism (noACS). We found no differences in age, BMI, BP, potassium or lipid parameters between the groups (**Table 1**). However, women with ACS had a significantly higher WHR than women without ACS (**Table 1**). PA patients with ACS had significantly higher ARR in comparison to the noACS subgroup (79.2; 43.6-141 vs. 60.0; 30.6-94.9; *p=0.029*), and showed a higher lateralization rate (50.4% vs. 30.6%; *p=0.035*). T2DM was diagnosed in 6.4% of the PA patients with ACS, while no T2DM was apparent in any patients of the noACS subgroup (*p=0.119*) (**Figure 1**). The prevalence of prediabetes (27.8% vs 27.2%; p=0.945) and of the metabolic syndrome (19.4% vs. 16.0%; *p=0.626*) was not different between the noACS and the ACS subgroup (**Figure 1**). Also, no differences were detected regarding FPG, 2h plasma glucose levels or HOMA-IR.

We further analyzed ACS depending on the DST results only: 35 of 161 patients (21.7%) were found to have a pathological response in DST (pathDST). PA patients with pathDST displayed a tendency towards a higher 2h plasma glucose levels (*p=0.053*) in OGTT than PA patients with normalDST (**Figure 2**). This resulted in a significantly higher prevalence for T2DM in the pathDST-subgroup (20% vs. 0.8%, *p<0.0001*). However, FPG, HbA1c, HOMA-IR and the prediabetes prevalence were not different between pathDST and normalDST subgroups. Also, no differences were seen in other clinical and lab parameters.

To further explore these findings, we matched 158 patients of our cohort 1:3 by sex, age, and BMI-category with controls from the KORA-F4 cohort. We further aimed to differentiate between effects of aldosterone excess and ACS on glucose homeostasis by using the KORA control cohort. In a first step, we compared the characteristics of PA patients without ACS (n=35) to matched KORA controls (n=105) (**Table 2)**. PA patients without ACS showed no difference in fasting plasma glucose or 2h plasma glucose levels in OGTT compared to matched controls. However, HOMA-IR was higher with a borderline significance (*p=0.051*) than in matched controls (**Table 2**) indicating insulin resistance due to hyperaldosteronism. However, PA patients without ACS showed slightly lower HbA1c, but a significantly higher WHR than matched controls (**Table 2**). Furthermore, LDL (115±29.9 vs. 135±39.4; *p=0.010*) and cholesterol levels (194±33.5 vs. 217.5±40.5; *p=0.004*) were significantly lower in PA patients without ACS than controls.

The next step was to compare PA patients with ACS, proven by pathological DST (pathDST), (n=34) with matched controls from KORA cohort (n=102) (**Table 3**). PA patients with ACS showed no difference in fasting plasma glucose or HOMA-IR compared to matched controls. However, the 2h plasma glucose levels in OGTT were significantly higher (*p=0.001*) than in matched controls (**Table 3**) indicating impaired glucose tolerance. This subgroup of PA patients with ACS also presented with significantly lower HbA1c and higher WHR (**Table 3**), as well as lower triglycerides (78.5; 57.5-127 vs. 98.5; 64.0-253; *p=0.041*) and cholesterol levels (201±34.6 vs. 218±41.6; *p=0.041*) than matched controls.

We also compared 63 PA patients with a pathLSC to matched KORA individuals (n=189). Thereby, we detected lower fasting plasma glucose levels in PA patients with pathLSC compared to matched controls, while no difference in HOMA-IR was evident. However, similar to patients with pathDST, the 2h plasma glucose levels in OGTT were also significantly higher (*p=0.002*) in PA patients with pathLSC than in matched controls, whereas they presented with significantly lower HbA1c and higher WHR. The same pattern was found for the 93 PA patients with pathUFC and their matched KORA cohort (n=279): no difference in HOMA-IR was found, but significantly (p<0.0001) higher 2h plasma glucose levels in OGTT was seen in PA patients with pathUFC.

We further evaluated additive effects when considering multiple pathological tests. Two pathological test results for hypercortisolism showed greater significance regarding differences in 2h plasma glucose in OGTT (p=0.001) compared to matched KORA subjects. Due to a small number of patients with three pathological test results for hypercortisolism (n=6), statistical analysis was not performed.

76 of 161 patients received follow-up visit one year after initiation of therapy (32.9% ADX; 63.2% MRA; 3.9% other therapies) and characteristics are showed in **Table 4**. At follow-up, patients showed a significant (*p<0.001*) decrease in BP, an increase in potassium and decrease in ARR. BMI and WHR did not change; however, HbA1c levels were significantly higher at follow-up. 23.7% of the follow-up patients were in the noACS-subgroup (n=18), and 76.3% in the ACS-subgroup (n=58).

In PA patients without ACS no significant changes in prevalence of prediabetes or T2DM were seen between baseline and follow-up (**Figure 3a**). Also, in PA patients with ACS, no significant changes in prevalence of prediabetes or T2DM were observed (**Figure 3b**), even when some patients improved from the T2DM to the prediabetes and from the prediabetes group to the normal-glucose-homeostasis group, other patients worsened on follow-up to the prediabetes or T2DM group.

## **Discussion**

Patients with PA are characterized by a significantly increased risk to develop further comorbidities, including cardiovascular, renal and cerebrovascular disease. These risks are usually significantly higher than in hypertensive patients and thus are attributed to aldosterone excess (2-4).

Among others, APA induced hypokalemia is stated as a secondary cause for T2DM by the American Diabetes Association (18). Diabetes prevalence in PA ranges from 8.2% to 23%, depending on the study population and the applied diagnostic criteria (8,25-28). Even though some studies could not show an increased risk for PA patients to develop T2DM (26,28) other studies are in favor of this assumption. For example, a retrospective cohort of the German Conn’s registry established a significantly increased risk for T2DM (23% vs. 13%, *P*=0.03) in comparison to hypertensive control subjects (27). These results were confirmed by a prospective study of Hanslik et al. who could demonstrate a prevalence of 17.2% for T2DM in PA patients, which was significantly higher than in their population-based control cohort (8).

Different mechanisms that lead to glucose impairment in PA have been discussed. One major contributing factor for PA patients to develop T2DM seems to be hypokalemia, which impairs insulin release by pancreatic beta-cells (29). Other mechanism that lead to impaired glucose tolerance in PA include reduced insulin sensitivity and impaired insulin signaling and thus reduced glucose uptake in peripheral tissue, including liver, skeletal muscle and adipose tissue (30-32).Furthermore, aldosterone induces reactive oxygen species (ROS) and increases insulin-like growth-factor-1 expression, ultimately causing endothelial dysfunction which leads to an impaired glucose diffusion (33,34).

One further aspect of PA that might result in disturbances of glucose metabolism is glucocorticoid co-secretion. First, a possible cortisol co-secretion in PA patients could only be shown in a few patients of small sized retrospective cohorts (10,35). However, recently larger studies suggest that glucocorticoid excess (autonomous cortisol secretion, ACS) is a frequent finding in PA (15,36). We demonstrated a correlation of 24-hour glucocorticoid output with markers of insulin resistance - including fasting insulin, insulin after OGTT and HOMA-IR. Thus, indicating that glucocorticoid co-secretion might affect glucose homeostasis.

However, we now present the first study to evaluate the impact of ACS on the prevalence of T2DM in PA in comparison to a 1:3 matched control cohort. We prospectively investigated ACS with the help of three different tests for hypercortisolism and set them into context with results of OGTT. We could identify 125 patients (77.6%) with ACS in at least one of the tests and 34 patients (21.1%) with pathological response in DST alone. Until now smaller studies estimated the prevalence of cortisol excess in PA patients at 3.9%-33.3%, depending on the diagnostic criteria used (9-11,35). Most of the studies used DST as their main diagnostic criteria in combination with another feature of ACS, formerly named subclinical hypercortisolism. On this basis, we prove that ACS is a frequent finding in PA and should be considered as another factor of comorbidities in PA patients.

In our cohort, we could show that PA patients with ACS have a higher prevalence of T2DM than sex, age, and BMI-matched controls. In contrast to this, PA patients without ASC – and thus with aldosterone excess alone - could not be diagnosed with T2DM, but showed higher HOMA-IR values than their matched KORA-controls. HOMA-IR is known as a marker of hepatic glucose and insulin in the fasting state (37). This leads to the assumption that aldosterone might directly affect hepatic insulin-resistance. Previous studies have shown that aldosterone administration increases FPG and leads to an increased expression of gluconeogenetic enzymes (38), which might lead to the observed deterioration of HOMA-IR values.

Investigating the effect of ACS in PA on glucose homeostasis, we detected that PA patients with proven ACS showed higher 2h OGTT values and a higher prevalence of T2DM compared to matched KORA-controls. Thus, it seems that an additional ACS impairs glucose tolerance in the peripheral tissue*.* Possible mechanisms might include impairment of insulin-dependent glucose uptake in peripheral tissue (39) or enhanced gluconeogenesis via different mechanisms, including further induction of gluconeogenetic enzymes (40).

Interestingly, glucose parameters of our patients did not improve at follow-up. In patients treated with ADX the source of aldosterone and glucocorticoid excess seems to be removed and thus usually these patients perform better in follow-up studies than patients treated with MRA. Still, some patients treated with ADX do not show complete biochemical cure. The reasons for this were summarized recently and comprise surgery based on CT subtyping, different accuracy of simultaneous and sequential AVS or usage of different selectivity and lateralization indexes (41). In our study we suspect other possible influences such as increased age, unhealthy diet, physical inactivity or stress, or the small number of patients with follow-up data.

It is important to point out that in PA patients with ACS the cortisol hypersecretion might interfere with the interpretation of the AVS data, because up to now cortisol is used as normalization factor in AVS aldosterone measurements. Thus ACS in PA might lead to false interpretations of AVS, ultimately leading to inappropriate treatment. Thus, current diagnostic standards need to be reviewed in regard of other methods to assess AVS selectivity, such as plasma metanephrine measurements in AVS (42).

One limitation of the present study is that only 12 patients without T2DM at baseline agreed to redo an OGTT and ACS was not reevaluated at follow-up so that effects of glucocorticoids on glucose metabolism over time might be distorted. Furthermore, we did not investigate other factors that might influence the development of glucose intolerance, such as family history of diabetes or drug-induced diabetes. The strengths of our study are that the German Conn Registry, as well as the KORA-F4 study, collects data in a prospective and standardized manner. We can present a large-sized and well-characterized cohort with follow-up investigations*.* We could match our PA patients in a 1:3 sex, age, and BMI-based matching to patients from a population-based study, in order to achieve a case-control-design.

In conclusion, we show that our PA cohort possesses a high proportion of patients with ACS. We describe that T2DM and impaired 2h plasma glucose in OGTT is more prevalent in PA patients with ACS than in controls matched for sex, age, and BMI. These results give further evidence for the “Connshing” syndrome and point out the relevance for further investigation of the underlying mechanisms and especially associated risks such as T2DM.

###### **Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Table legends:**

**Table 1:** Characteristics of primary aldosteronism (PA) patients with autonomous cortisol secretion (ACS) in at least one test and of PA patients without ACS( patients with normal test results regarding hypercortisolism). WHR = waist-to-hip ratio; BMI = body mass index; BP= blood pressure; DST = dexamethasone suppression test; a two missings. b three missings. c six missings. d ten missings.

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| --- | --- | --- | --- |
| Characteristics | No ACS | ACS | *P* |
| n (%) | 36 (22.4) | 125 (77.6) | **0.000** |
| Male n (%) | 12 (33.3) | 71 (56.8) | **0.013** |
| Age (years) | 49.3±11.3 | 51.9±11.1 | 0.218 |
| BMI (kg/m2) | 27.0±4.7 | 27.3±5.1(26.5; 23.5-29.0) | 0.914 |
| Systolic BP (mmHg) | 143±18.0 | 149±17.6(147; 136-158) | 0.092 |
| Diastolic BP (mmHg) | 93.0±11.6 | 92.4±10.3 | 0.794 |
| Potassium (mmol/l) | 3.6±0.4(3.7; 3.4-3.9) | 3.6±0.4 | 0.979 |
| WHR | female (n=24) | male (n=12) | female (n=54) | male (n=71) | female | male |
| 0.8±0.1a | 0.9±0.1b | 0.9±0.3c(0.9; 0.8-1.0) | 1.0±0.1d | **0.036** | 0.670 |
| HbA1c (%) | 5.2±0.4(5.2; 4.9-5.5) | 5.2±0.4(5.2; 4.9-5.4) | 0.919 |
| HDL-cholesterol (mg/dl) | 63.4±17.1 | 60.0±15.8(59.0; 46.0-71.0) | 0.329 |
| LDL-cholesterol (mg/dl) | 115±29.8 | 119±34.1 | 0.533 |
| Triglycerides (mg/dl) | 98.8±44.8(91.0; 61.3-137) | 95.0±45.3(88.0; 62.5-115) | 0.633 |
| Cholesterol (mg/dl) | 194±33.0 | 194±34.9 | 0.983 |
| Statin therapy n(%) | 4 (11.1) | 11 (8.8) | 0.674 |
| Cortisol after 1mg DST(nmol/l) | 33.1±9.0 | 55.0±49.2(41.4; 30.3-57.9) | **0.001** |
| late night salivary cortisol (nmol/l) | 0.8±0.3 | 1.8±1.3(1.5; 0.9-2.3) | **0.000** |
| Urinary free cortisol (µg/24h) | 85.9±37.3 | 208±342(171; 103-258) | **0.000** |
| Hypo-/Normokalaemic PA (%) | 61.1/38.9 | 64.0/36.0 | 0.751 |
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| --- | --- | --- | --- |
| Characteristics | PA without ACS (n=35) | KORA(n=105) | *P* |
| male n (%) | 12 (43.3) | 36 (34.3) | *m* |
| Age (years) | 50.0±10.7 | 50.2±10.8(49.0; 43.0-57.0) | *m* |
| BMI (kg/m2) | 27.0±4.8 | 26.7±5.5(26.2; 21.8-29.6) | *m* |
| Systolic BP (mmHg) | 143±18.2 | 118±18.3 | **0.000** |
| Diastolic BP (mmHg) | 92.9±11.7 | 75.5±10.2 | **0.000** |
| WHR | 0.9±0.1a | 0.8±0.1(0.8; 0.8-0.9) | **0.011** |
| Potassium (mmol/l) | 3.6±0.4(3.7; 3.4-3.9) | 4.2±0.3 | **0.000** |
| HbA1c (%) | 5.2±0.4(5.2; 4.9-5.5) | 5.4±0.8(5.3; 5.1-5.5) | 0.054 |
| Fasting plasma glucose in OGTT(mg/dl) | 89.1±10.5(87.0; 80.0-95.0) | 94.9±27.5(90.0; 85.5-97.0) | 0.122 |
| 2h OGTT glucose (mg/dl) | 109±31.0 | 110±41.0(100; 84.0-126) b | 0.885 |
| HOMA-IR | 2.0±2.1(1.2;0.9-2.3) | 1.2±1.6(0.8; 0.5-1.3) | 0.051 |
| Diabetes mellitus (%)  | 0 | 3.8 | 0.483 |
| Prediabetes (%) | 28.6 | 24.8 | 0.647 |
|  |

**Table 2:** Characteristics of primary aldosteronism (PA) patients without autonomous cortisol secretion (ACS) and matched controls from the KORA cohort. WHR = waist-to-hip ratio; BMI = body mass index; BP= blood pressure; OGTT = oral glucose tolerance test; m = matched data. a 4 missings. b 2 missings.

**Table 3**: Characteristics of primary aldosteronism (PA) patients with pathological response in dexamethasone suppression test (pathDST) and matched controls from the KORA cohort. WHR = waist-to-hip ratio; BMI = body mass index; BP= blood pressure; OGTT = oral glucose tolerance test; m = matched data. a 2 missings. b 4 missings.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | PA with pathDST (n=34) | KORA(n=102) | *P* |
| male n (%) | **17 (50.0)** | **51 (50.0)** | *m* |
| Age (years) | 54.9±10.6 | 55.0±10.8(57.0; 46.0-64.3) | *m* |
| BMI (kg/m2) | 26.0±4.6(25.2; 23.0-27.7) | 26.0±4.5(35.0; 22.7-28.5) | *m* |
| Systolic BP (mmHg) | 151±21.1(151; 140.5-161) | 123±15-5 | **0.000** |
| Diastolic BP (mmHg) | 94.1±12.4 | 75.6±9.2 | **0.000** |
| WHR  | 1.0±0.4(0.9; 0.8-1.0)a | 0.9±0.1 | **0.000** |
| Potassium (mmol/l) | 3.5±0.4 | 4.2±0.3 | **0.000** |
| HbA1c (%) | 5.3±0.5 | 5.5±0.4(5.5; 5.2- 5.6) | **0.013** |
| Fasting plasma glucose in OGTT(mg/dl) | 95.0±16.5(92.0; 86.8-99.0) | 96.7±16.6(93.0; 87.0-103) | 0.579 |
| 2h OGTT glucose (mg/dl) | 139±51.0(127; 101-177) | 107±33.3(99-5; 86.0-120) b | **0.001** |
| HOMA-IR | 1.7±1.2(1.5; 0.8-2.2) | 1.6±2.3(0.9; 0.5-1.4) | 0.725 |
| Diabetes mellitus (%) \*1 | 20.6 | 4.9 | **0.013** |
| Prediabetes (%)\*2 | 23.5 | 43.1 | **0.034** |
|  |

**Table 4:** Characteristics of 76 patients with primary aldosteronism (PA) patients at baseline and at one-year follow-up. Number of hypertensives at follow-up does not include mineralocorticoid receptor antagonists (MRA). ADX = adrenalectomy; (no)ACS = no autonomous cortisol co-secretion in at least one test for hypercortisolism; BP = blood pressure; PAC = plasma aldosterone concentration; PRC = plasma renin concentration; ARR = aldosterone renin ratio; WHR = waist-to-hip ratio; BMI = body mass index; BP= blood pressure; a one missing. b 5 missing. c2 missings. d4 missings.

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | ADX (n=25) | MRA (n=48) | Others (n=3) |
| **Baseline** | **Follow-up** | ***P*** | **Baseline** | **Follow-up** | ***P*** | **Baseline** | **Follow-up** |
| noACS/ACS n (%) | 3/22 (12/88) | - | 15/33 (31.2/68.8) | - | 2/1 (66.7/33.3) |
| male n (%) | 11 (44.0) | - | 25 (52.1) | - | 2 (66.7) |
| Systolic BP (mmHg) | 145±13.4 | 137±17.0(136; 123-149) | 0.071 | 148±21.0(145; 133-159) | 131±16.7(128; 120-138) | **0.000** | 148±21.0 | 131±12.1 |
| Diastolic BP (mmHg) | 89.8±8.0 | 89.2±9.4 | 0.799 | 92.1±11.1 | 87.4±9.5 | **0.001** | 100±12.0 | 90.3±6.6 |
| Potassium (mmol/l) | 3.4±0.3 | 4.2±0.4 | **0.000** | 3.6±0.3 | 4.0±0.4 | **0.000** | 3.9±0.4 | 4.2±0.1 |
| PAC (ng/l) | 441±505(234; 137- 466) | 69.7±32.3 | **0.000** | 180±112(145; 110-195) | 255±161(225; 155-301) | **0.003** | 210±124 | 258±43.7 |
| PRC (ng/l) | 3.1±2.3(2.2; 1.2-4.6) | 15.6±25.7(7.6; 3.8-16.3) | **0.000** | 3.9±4.3(2.5; 1.4-4.2) | 10.5±14.1(5.8; 2.3-14.5) | **0.000** | 2.9±2.2 | 14.1±22.3 |
| ARR | 221±296(112; 43.4-289) | 14.2±15.8(7.8; 3.9-19.8) | **0.000** | 82.4±90.1(58.8; 31.6-97.7) | 55.8±53.8(30.7; 20.8-65.7) | 0.076 | 103±79.8 | 136±115 |
| Number of hypertensives | 1.7±0.8(2.0; 1.5-2.0) | 1.4±1.2(1.0; 0.0-2.0) | 0.160 | 1.6±0.8(2.0; 1.0-2.0) | 1.5±1.1(1.0; 1.0-2.0) | 0.471 | 1.3±0.6 | 1.7±1.2 |
| BMI | 28.9±6.3(28.6; 23.9-30.8) | 29.0±6.3 (28.6; 24.2-30.9) | 0.455 | 26.8±5.0 (25.3; 23.4-28.7) | 26.9±5.3(257; 23.2-29.2) | 0.919 | 26.7±5.8 | 26.4±5.2 |
| WHR | 1.0±0.2(1.0; 0.9-1.0) a | 1.0±0.1b | 0.126 | 0.9±0.1c | 0.9±0.1d | 0.875 | 1.5±1.0 | 0.8±0.1a |
| HbA1c (%) | 5.4±0.4 | 5.6±0.4 | 0.002 | 5.2±0.4 | 5.4±0.4a | **0.006** | 5.0±0.4 | 5.2±0.3 |
| HDL-cholesterol (mg/dl) | 59.8±13.5 | 54.0±13.1a | **0.008** | 62.3±19.1 | 58.7±18.2(58.5; 46.3-69.8) | 0.031 | 60.7±11.9 | 58.0±20.5 |
| LDL-cholesterol (mg/dl) | 121±41.0 | 127±35.5a | 0.490 | 117±32.7 | 115±37.8 | 0.576 | 104±4.2 | 114±12.5 |
| Triglycerides (mg/dl) | 90.2±44.3 (80.0; 56.5-110) | 114±45.0 | **0.001** | 101±43.8 | 132±87.2(120; 73.3-172) | **0.000** | 88.0±9.1 | 130±102 |
| Cholesterol (mg/dl) | 195±40.2 | 200±35.2 | 0.585 | 195±32.8 | 194±39.6(183; 163-219) | 0.400 | 179±9.1 | 194±26.5 |

**Figure legends:**

**Figure 1:** Frequencies in glucose metabolism alterations of patients with primary aldosteronism at baseline visit and complete testing for hypercortisolism (n=161). No autonomous cortisol secretion (ACS) – patients with normal test results regarding hypercortisolism; ACS – patients with pathological response in at least one test for hypercortisolism (dexamethasone suppression test, late-night salivary cortisol and/or urinary free cortisol).

**Figure 2:** Plasma glucose levels in oral glucose tolerance test (OGTT) of patients with primary aldosteronism (PA) depending on cortisol levels after dexamethasone suppression test (DST), (autonomous cortisol secretion: cortisol levels >50nmol/l). Lines at 126mg/dl and 200mg/dl indicating cut-offs for diagnosing diabetes mellitus by fasting plasma glucose and glucose after 120 minutes. Mild outliers (1.5-3xIQR) are displayed as circles and extreme outliers (> 3xIQR) displayed as stars.

**Figure 3:** Frequencies of glucose metabolism alterations in patients with primary aldosteronism (PA) **a)** without (n=18) and **b)** with (n=58) autonomous cortisol secretion (ACS) in at least one test at baseline and at follow up-visit after one year. Dashed lines indicate changes within different subgroups, based on diagnosis at baseline visit.