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Impaired Glucose Metabolism in Primary Aldosteronism Is Associated With Cortisol Cosecretion

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Context: Primary aldosteronism (PA) is associated with higher cardiovascular morbidity and metabolic risks. Recent studies report glucocorticoid cosecretion as a relevant phenotype of PA, which could contribute to associated risks, including type 2 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 patients with PA according to cortisol cosecretion.

Design: We performed oral glucose tolerance tests (OGTTs) and complete testing for hypercortisolism [1-mg dexamethasone suppression test (DST), late-night salivary cortisol, 24-hour urinary free cortisol] in 161 newly diagnosed patients with PA of the German Conn Registry. Seventy-six of 161 patients were reevaluated at follow-up. We compared our results to a population-based sample from the Cooperative Health Research in the Region of Augsburg (KORA)-F4 study matched to the participants with PA (3:1) by sex, age, and body mass index.

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 125 cases. Patients with a pathological DST exhibited significantly higher 2-hour plasma glucose in OGTTs and were significantly more often diagnosed with T2DM than were patients with a normal DST (20% vs 0.8%, $P < 0.0001$) and matched controls from the KORA study (20.6% vs 5.9%, $P = 0.022$). Patients with PA without ACS tended to have higher homeostatic model assessment of insulin resistance levels than did KORA control subjects ($P = 0.05$).

Abbreviations: ACS, autonomous cortisol secretion; ADX, adrenalectomy; ARR, aldosterone-to-renin ratio; AVS, adrenal vein sampling; BMI, body mass index; BP, blood pressure; DST, dexamethasone suppression test; FPG, fasting plasma glucose; HOMA-IR, homeostatic model assessment of insulin resistance; KORA, Cooperative Health Research in the Region of Augsburg; LSC, late-night salivary cortisol; MRA, mineralocorticoid receptor antagonist; OGTT, oral glucose tolerance test; PA, primary aldosteronism; pathDST, pathological response in a DST; pathLSC, pathological late-night salivary cortisol; T2DM, type 2 diabetes mellitus; UFC, urinary free cortisol; WHR, waist-to-hip ratio.

Conclusion: ACS appears frequently in patients with PA and is associated with impaired glucose metabolism, which could increase the risk of T2DM. PA itself seems to enhance insulin resistance. (*J Clin Endocrinol Metab* 104: 3192–3202, 2019)

Primary aldosteronism (PA) is the most common endocrine form of secondary hypertension that affects 4.3% to 9.0% of patients with hypertension (1). Patients with aldosterone excess are at a higher risk of cardiovascular events and metabolic comorbidities in comparison with 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 patients with PA (8). However, some aspects of impairment of glucose homeostasis in PA are still unresolved.

In the past, cortisol cosecretion in PA has been discussed on the basis of several case studies or case series (9–15). Recently, we have investigated a large multicenter cohort of patients with PA and revealed that glucocorticoid cosecretion is a phenotype frequently found in PA that might contribute to associated metabolic risks (16), including a higher risk of cardiovascular events as shown by Nakajima *et al.* (17). Specifically, our findings suggest that cortisol excess in PA also plays a role in impaired glucose metabolism. However, further investigations of the underlying mechanisms have not been undertaken yet.

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

Methods

Study population

German Conn Registry

The study population consists of 161 patients who were recruited in two centers (Munich and Berlin) of the German Conn Registry. The German Conn Registry is a multicenter registry that has investigated therapy, comorbidities, and the long-term outcome in patients with PA throughout Germany since 2008 (18). 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 (19). Patients were usually screened with high blood pressure (BP) and an 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 [including a standard oral glucose tolerance test (OGTT) and complete testing for hypercortisolism], antihypertensive medication was changed whenever possible or indicated [deduction of beta-blockers, central alpha agonists, angiotensin-converting enzyme blocker, angiotensin receptor blocker for at least 1 week, and mineralocorticoid receptor antagonists (MRAs) for at least 4 weeks prior to testing] to prevent influences on the renin–angiotensin–aldosterone system and thus test results. The diagnosis was then made decentralized in the synopsis of all clinical and laboratory findings according to the guidelines of the Endocrine Society.

Subtype identification (aldosterone-producing adenoma vs bilateral adrenal hyperplasia) 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 89.6% (n = 138) of those. During AVS, blood is obtained from both adrenal veins and a peripheral vein. We assessed blood samples for hormone levels of both aldosterone and cortisol to correct a dilution effect and confirm correct catheterization (19). 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 the 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 current study, all patients with PA underwent a standard OGTT and complete testing for hypercortisolism, including a 1-mg dexamethasone suppression test (DST), 24-hour urinary free cortisol (UFC), and late-night salivary cortisol (LSC) at baseline visit. Patients with missing data for aldosterone, renin, potassium, OGTT, or BP were excluded. Also, patients with PA with previously known diabetes mellitus were excluded. We assessed glucose metabolism by laboratory measurement and OGTT, according to the American Diabetes Association (20). Seventy-six of 161 patients had a follow-up visit 1 year after therapy initiation with MRAs or adrenalectomy (ADX). The Ethics Committees of the Klinikum of the University of Munich and of the Conn's registry participating centers approved the protocol. Personal data protection laws were strictly adhered to. All included patients gave their written informed consent.

KORA study

The KORA-F4 study is the 7-year follow-up examination of the population-based KORA-S4 study (21, 22). Baseline examinations of KORA-S4 participants were conducted in 1999 to 2001 (n = 4261) in men and women 25 to 74 years of age. In 1353 participants 55 to 74 years of age, an OGTT was performed at baseline (23). Of the participants, 3080 were reinvestigated in 2006 to 2008 as part of KORA-F4. These participants comprise the basis for the present analyses. Investigations included a standard medical interview, physical

examination, blood withdrawal, and an OGTT in all individuals without known T2DM after an overnight fasting period of ≥8 hours (24, 25).

The KORA studies were approved by the Ethics Committee of the Bavarian Medical Association. Written informed consent was obtained from all participants, and data protection policies were strictly adhered to.

Definitions and laboratory measurements

In patients with PA as well as in controls standard laboratory measurements were performed immediately and decentralized. Measurements of cortisol and ACTH were performed as previously described (26). The measurement of serum cortisol and plasma ACTH was performed with a solid-phase antigen-linked technique (cortisol; Liaison/DiaSorin, Saluggia, Italy) and chemiluminescence immunoassay (ACTH; Liaison/DiaSorin). Within- and between-assay coefficients of variation were <5% and 7% (cortisol) and <13% (ACTH), respectively. Urinary cortisol measurement was performed with a chemiluminescence immunoassay (Siemens ADVIA Centaur) with within- and between-assay coefficients of variation <7%. Salivary cortisol was measured by a luminescence immunoassay (IBL, Hamburg, Germany) with within- and between-assay coefficients of variation <9% and 6%.

To test for hypercortisolism, we performed a 1-mg DST and acquired LSC, as well as 24-hour UFC, in all patients at the baseline visit. 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, and >150 μg/24 h, respectively). Reference values were determined following the guidelines of the Endocrine Society (27).

BP was measured up to three times on each arm after at least 5 minutes of resting with standard sphygmomanometers. BMI was calculated as body weight (kilograms)/height (square meters).

The homeostatic model assessment of insulin resistance (HOMA-IR) score was calculated as ([fasting serum insulin (mU/L) × fasting plasma glucose (FPG) (mg/dL)]/405) for patients of the German Conn Registry and as ([fasting serum insulin (mU/L) × FPG (mmol/L)]/22.5) for KORA-F4 participants. HOMA-β, as estimate for β-cell function, was calculated using the following formula: 20 × [fasting insulin (μIU/mL)/FPG (mmol/L)] − 3.5). To investigate glucose metabolism, we performed an OGTT at baseline in all patients and measured HbA1c (%) in patients' blood samples. Only nondiabetic Conn patients and nondiabetic KORA participants (no intake of antidiabetic drugs, no diagnosis by another physician, no reported T2DM by the patient) received an OGTT.

An OGTT was performed after an overnight fast of at least 8 hours with 75 g of glucose dissolved in 300 mL of water. Blood samples were obtained before glucose load (FPG) and 120 minutes (2-hour glucose) after glucose load. Patients were diagnosed with either T2DM, prediabetes, or normal glucose metabolism, according to the American Diabetes Society (20): newly detected T2DM was defined by HbA1c ≥6.5%, FPG ≥126 mg/dL, or glucose at 120 minutes of OGTT ≥200 mg/dL. Prediabetes was defined by HbA1c (5.7% to 6.4%) or OGTT result in either impaired FPG (100 to 125 mg/dL in OGTT) or impaired glucose tolerance (140 to 199 mg/dL in OGTT). The term prediabetes includes isolated impaired FPG, isolated impaired glucose tolerance, and both combined. All KORA participants with clinically diagnosed diabetes who did not receive an OGTT were included in the diabetes group in analyses regarding diabetes prevalence.

Matching and statistical analysis

Sex-stratified matching was performed, and further matching variables were age (±5 years) and BMI category (<25, 25 to 29, and ≥30 kg/m^2). To be able to achieve a 3:1 matching, four young patients (<32 years of age) from the German Conn Registry had to be excluded. BP was not chosen as a matching variable, as KORA participants are population-based whereas patients with PA form a hypertensive cohort. KORA participants with type 1 or type 2 diabetes or drug-induced diabetes were excluded, as were participants with an ARR >20 and those with missing values of systolic or diastolic BP or fasting glucose or renin concentrations. This 3:1 matching resulted in 471 matched KORA participants (controls) for 157 patients with PA. Differences between patients with PA 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 ± SD for normally distributed continuous data, and as median (25th and 75th percentile) for continuous variables without normal distribution. Categorical variables are displayed as percentages or numbers. Variables were assessed for normal distribution using a Shapiro–Wilk test.

To compare normal and pathological subgroups, we used either a Mann–Whitney U test or an unpaired t test for continuous data and a χ^2 test for categorical variables. For paired data comparing baseline and follow-up visit, we used a McNemar test for categorical data and a Wilcoxon signed rank test or paired t test for continuous data. A t test (paired or unpaired) was only applied when normal distribution in both subgroups was given. Differences were considered statistically significant when $P \leq 0.05$.

Results

In 161 investigated patients with PA, 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 waist-to-hip ratio (WHR) than did women without ACS (Table 1). Patients with PA with ACS had a significantly higher ARR in comparison with the noACS subgroup [79.2 (43.6 to 141) vs 60.0 (30.6 to 94.9) $P = 0.029$] and showed a higher lateralization rate (49.6% vs 30.6%; $P = 0.043$). T2DM was diagnosed in 6.4% of the patients with PA with ACS, whereas no T2DM was apparent in any patients of the noACS subgroup ($P = 0.119$) (Fig. 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 (Fig. 1). Also, no differences were detected regarding FPG, 2-hour plasma glucose levels, or HOMA-IR.

In patients with PA with ACS, we found significant differences in ARRs (156 ± 156 vs 112 ± 185; $P = 0.006$) and potassium levels (3.5 ± 0.4 vs 3.7 ± 0.3 mmol/L; $P = 0.033$) between patients with

Table 1. Characteristics of Patients With PA With ACS in at Least One Test and of Patients With PA Without ACS (Patients With Normal Test Results Regarding Hypercortisolism)

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, y	49.3 ± 11.3	51.9 ± 11.1	0.218
BMI, kg/m^2	27.0 ± 4.7	27.3 ± 5.1 (26.5; 23.5–29.0)	0.914
Systolic BP, mm Hg	143 ± 18.0	149 ± 17.6 (147; 136–158)	0.092
Diastolic BP, mm Hg	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), 0.8 ± 0.1[a]	(n = 54), 0.9 ± 0.3[c] (0.9; 0.8-1.0)	**0.036**
Male	(n = 12), 0.9 ± 0.1[b]	(n = 71), 1.0 ± 0.1[d]	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
Total cholesterol, mg/dL	194 ± 33.0	194 ± 34.9	0.983
Statin therapy, n (%)	4 (11.1)	11 (8.8)	0.674
Basal cortisol, μg/dL	11.1 ± 4.9 (10.2; 7.7–12.9)	13.5 ± 5.3[a] (13.0; 10.0–16.5)	**0.004**
Basal ACTH, pg/mL	19.0 ± 20.0[e] (13.0; 7.0–23.5)	19.0 ± 17.5[f] (15.0; 8.5–23.0)	0.776
Cortisol after 1 mg DST, nmol/L	33.1 ± 9.0	55.0 ± 49.2 (41.4; 30.3–57.9)	**0.001**
LSC, ng/mL	0.8 ± 0.3	1.8 ± 1.3 (1.5; 0.9–2.3)	**0.000**
UFC, μg/24 h	85.9 ± 37.3	208 ± 342 (171; 103–258)	**0.000**
Hypokalemic/normokalemic PA, %	61.1/38.9	64.0/36.0	0.751

Data are displayed as mean ± SD for normally distributed continuous data, and as median (25th and 75th percentile) for continuous variables without normal distribution. The WHR was analyzed separately for men and women owing to different optimal values in males and females. Boldface indicates $P < 0.05$.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a]Two missing values.

[b]Three missing values.

[c]Six missing values.

[d]Ten missing values.

[e]Twelve missing values.

[f]Thirty missing values.

unilateral and bilateral disease; however, no differences were seen in parameters of glucose homeostasis. In patients with PA with noACS, potassium levels (3.3 ± 0.4 vs 3.7 ± 0.3 mmol/L; $P = 0.005$) significantly differed between patients with unilateral and bilateral disease; however, no differences were seen in parameters of glucose homeostasis.

We further analyzed ACS depending on the DST results only: 35 of 161 patients (21.7%) were found to have a pathological response in a DST (pathDST). Patients with PA with pathDST displayed a tendency toward higher 2-hour plasma glucose levels ($P = 0.053$) in OGTTs than did patients with PA with normalDST (Fig. 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 prediabetes prevalence were not different between the pathDST and normalDST subgroups. Also, no differences were seen in other clinical and laboratory parameters.

To further explore these findings, we matched 158 patients of our cohort 1:3 with participants of the KORA-F4 study. We further aimed to differentiate between effects of aldosterone excess and ACS on glucose homeostasis by using the KORA study. In a first step, we compared the characteristics of patients with PA without ACS (n = 35) to matched KORA controls (n = 105) (Table 2). Patients with PA without ACS showed no difference in FPG or 2-hour plasma glucose levels in OGTTs compared with matched controls. However, the HOMA-IR level was higher with a borderline significance ($P = 0.051$) than in matched controls (Table 2), suggesting insulin resistance due to hyperaldosteronism. Patients with PA without ACS showed no difference in HbA1c, but a significantly higher WHR than in matched controls (Table 2). Furthermore, low-density lipoprotein cholesterol (115 ± 29.9 vs 135 ± 39.4; $P = 0.010$) and total cholesterol levels (194 ± 33.5 vs 217.5 ± 40.5; $P = 0.004$) were significantly lower in patients with PA without ACS than in controls.

The next step was to compare patients with PA with ACS (n = 34), proven by pathDST, with matched controls from the KORA study (n = 102) (Table 3). Patients with PA

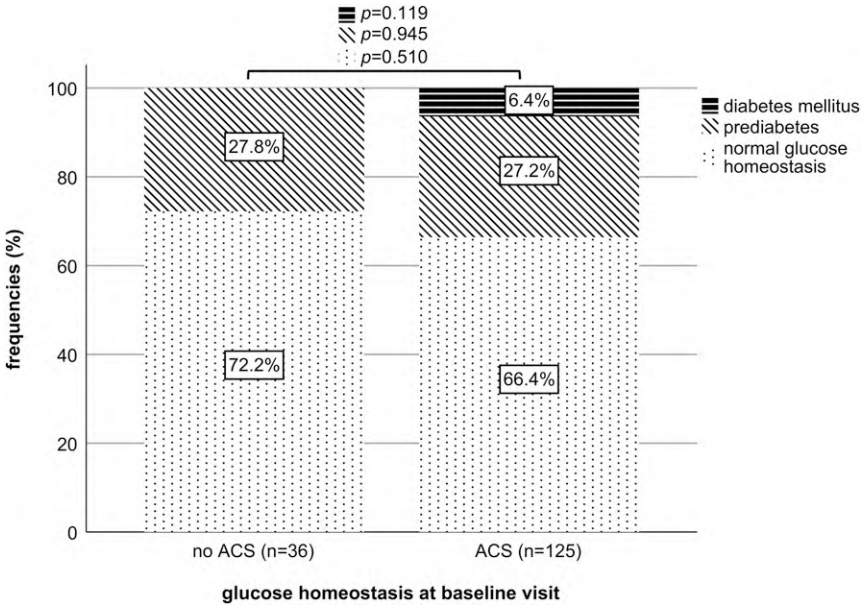

Figure 1. Frequencies in glucose metabolism alterations of patients with PA at baseline visit and complete testing for hypercortisolism (n = 161). No ACS indicates patients with normal test results regarding hypercortisolism; ACS indicates patients with a pathological response in at least one test for hypercortisolism (DST, LSC, and/or UFC).

with ACS showed no difference in FPG or HOMA-IR levels compared with matched controls. However, the 2-hour plasma glucose levels in OGTTs were significantly higher ($P = 0.001$) than in matched controls (Table 3), indicating impaired glucose tolerance. This subgroup of patients with PA with ACS also presented with significantly lower HbA1c and higher WHR (Table 3), as well as lower triglycerides [78.5 (57.5 to 127) vs 98.5 (64.0 to 253); $P = 0.041$] and cholesterol levels (201 ± 34.6 vs 218 ± 41.6; $P = 0.041$) than in matched controls.

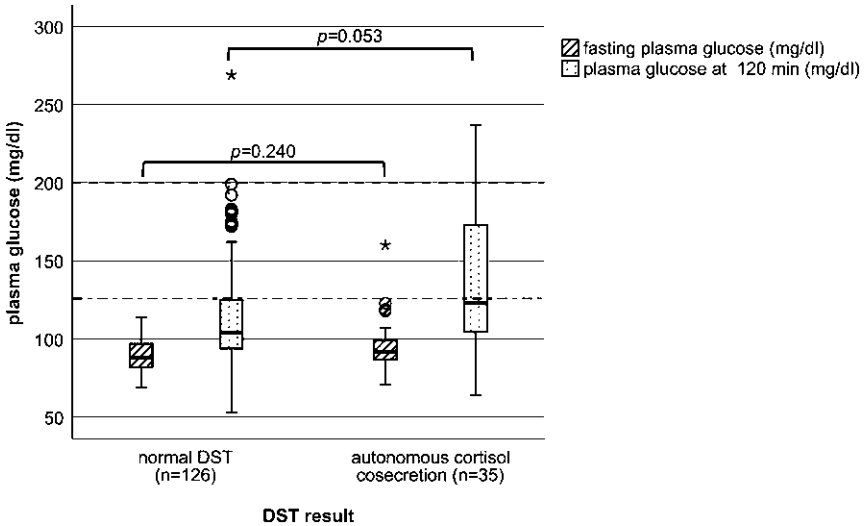

Figure 2. Plasma glucose levels in OGTTs of patients with PA depending on cortisol levels after DST (ACS: cortisol levels >50 nmol/L). Lines at 126 mg/dL and 200 mg/dL indicate cutoffs for diagnosing diabetes mellitus by FPG and glucose after 120 min. Mild outliers (1.5 to 3 × interquartile range) are displayed as circles, and extreme outliers (>3 × interquartile range) are displayed as stars.

We also compared 63 patients with PA with a pathological late-night salivary cortisol (pathLSC) to matched KORA individuals (n = 189). Thereby, we detected lower FPG levels in patients with PA with pathLSC compared with matched controls, whereas no difference in HOMA-IR levels was evident. However, similar to patients with pathDST, the 2-hour plasma glucose levels in OGTTs were also significantly higher ($P = 0.002$) in patients with PA with pathLSC than in matched controls, whereas they presented with significantly lower HbA1c and higher WHR. The same pattern [significantly ($P = 0.0004$) higher 2-hour plasma glucose levels in OGTTs] was found in 93 patients with PA with pathological UFC compared with their matched KORA controls (n = 279).

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

Seventy-six of 161 patients received a follow-up visit 1 year after initiation of therapy (32.9% ADX, 63.2% MRAs, 3.9% other therapies), and characteristics are shown in Table 4. At follow-up we documented postoperative adrenal insufficiency in 5 of the 25 ADX patients, with no difference in prevalence between ACS and noACS patients. Those five patients temporarily received hydrocortisone treatment, and no adrenal crisis occurred. At follow-up, patients showed a significant ($P < 0.001$) decrease in BP, an increase in potassium, and a decrease in the ARR. BMI and WHR did not change; however, HbA1c levels were significantly higher at follow-up. Of the follow-up patients, 23.7% were in the noACS subgroup (n = 18) and 76.3% were in the ACS subgroup (n = 58).

In patients with PA without ACS, no significant changes in the prevalence of prediabetes or T2DM were seen between baseline and follow-up (Fig. 3a).

Table 2. Characteristics of Patients With PA Without ACS and Matched Controls From the KORA Cohort

Characteristics	PA Without ACS (n = 35)	KORA (n = 105)	*P*
Male, n (%)	12 (34.3)	36 (34.3)	*m*
Age, y	50.0 ± 10.7	50.2 ± 10.8 (49.0; 43.0–57.0)	*m*
BMI, kg/m^2	27.0 ± 4.8	26.7 ± 5.5 (26.2; 21.8–29.6)	*m*
Systolic BP, mm Hg	143 ± 18.2	118 ± 18.3	**0.000**
Diastolic BP, mm Hg	92.9 ± 11.7	75.5 ± 10.2	**0.000**
WHR	0.9 ± 0.1[a]	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
FPG, mg/dL	89.1 ± 10.5 (87.0; 80.0–95.0)	94.9 ± 27.5 (90.0; 85.5–97.0)	0.122
2-h 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
HOMA-β , %	137 ± 185 (92.5; 57.3–133)	118 ± 55.6 (106; 73.7–150)	0.378
Diabetes mellitus, n (%)	0 (0)	5 (4.8)	0.432
Prediabetes, n (%)	10 (28.6)	24 (22.9)	0.532

Data are displayed as mean ± SD for normally distributed continuous data, and as median (25th and 75th percentile) for continuous variables without normal distribution. Boldface indicates $P < 0.05$.

Abbreviation: *m*, matching variables.

[a]Four missing values.

[b]Two missing values.

Also, in patients with PA with ACS, no significant changes in the prevalence of prediabetes or T2DM were observed (Fig. 3b), even when some patients improved from the T2DM group to the prediabetes group and from the prediabetes group to the normal glucose homeostasis group, and 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 patients with hypertension and thus are attributed to aldosterone excess (2–4).

Among others, aldosterone-producing adenoma–induced hypokalemia is stated as a secondary cause for T2DM by the American Diabetes Association (20). Diabetes prevalence in PA ranges from 8.2% to 23%, depending on the study population and the applied diagnostic criteria (8, 28–31). Even though some studies could not show an increased risk of T2DM in patients with PA (29, 31), other studies are in favor of this assumption. For example, a retrospective cohort of the German Conn Registry established a significantly

Table 3. Characteristics of Patients With PA With a pathDST and Matched Controls From the KORA Cohort

Characteristics	PA With pathDST (n = 34)	KORA (n = 102)	*P*
Male, n (%)	17 (50.0)	51 (50.0)	*m*
Age, y	54.9 ± 10.6	55.0 ± 10.8 (57.0; 46.0–64.3)	*m*
BMI, kg/m^2	26.0 ± 4.6 (25.2; 23.0–27.7)	26.0 ± 4.5 (35.0; 22.7–28.5)	*m*
Systolic BP, mm Hg	151 ± 21.1 (151; 140.5–161)	123 ± 15.5	**0.000**
Diastolic BP, mm Hg	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**
FPG, mg/dL	95.0 ± 16.5 (92.0; 86.8–99.0)	96.7 ± 16.6 (93.0; 87.0–103)	0.579
2-h 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
HOMA-β , %	88.5 ± 56.2 (71.4; 44.8–122)	108 ± 53.8 (102.3; 72.2–130)[b]	0.056
Diabetes mellitus, n (%)	7 (20.6)	6 (5.9)	**0.022**
Prediabetes n (%)	8 (23.5)	42 (41.2)	0.060

Data are displayed as mean ± SD for normally distributed continuous data, and as median (25th and 75th percentile) for continuous variables without normal distribution. Boldface indicates $P < 0.05$.

Abbreviation: *m*, matching variables.

[a]Two missing values.

[b]Four missing values.

Table 4. Characteristics of 76 Patients With PA at Baseline and at 1-Year Follow-Up

	ADX (n = 25)			MRAs (n = 48)			Others (n = 3)	
Variables	**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)	
Unilateral/bilateral/unknown	(25/0/0)			(9/35/4)			(2/0/1)	
Male, n (%)	11 (44.0)		—	25 (52.1)		—	2 (66.7)	
Systolic BP, mm Hg	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, mm Hg	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
No. 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 ± 0.1[b]	0.126	0.9 ± 0.1[c]	0.9 ± 0.1[d]	0.875	1.5 ± 1.0	0.8 ± 0.1[a]
HbA1c, %	5.4 ± 0.4	5.6 ± 0.4	**0.002**	5.2 ± 0.4	5.4 ± 0.4[a]	**0.006**	5.0 ± 0.4	5.2 ± 0.3
HDL cholesterol, mg/dL	59.8 ± 13.5	54.0 ± 13.1[a]	**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 ± 35.5[a]	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
Total 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

The number of patients with hypertension at follow-up does not include MRAs. noACS indicates no ACS in at least one test for hypercortisolism. Data are displayed as mean ± SD for normally distributed continuous data, and as median (25th and 75th percentile) for continuous variables without normal distribution. Boldface indicates $P < 0.05$.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAC, plasma aldosterone concentration; PRC, plasma renin concentration.

[a]One missing value.

[b]Five missing values.

[c]Two missing values.

[d]Four missing values.

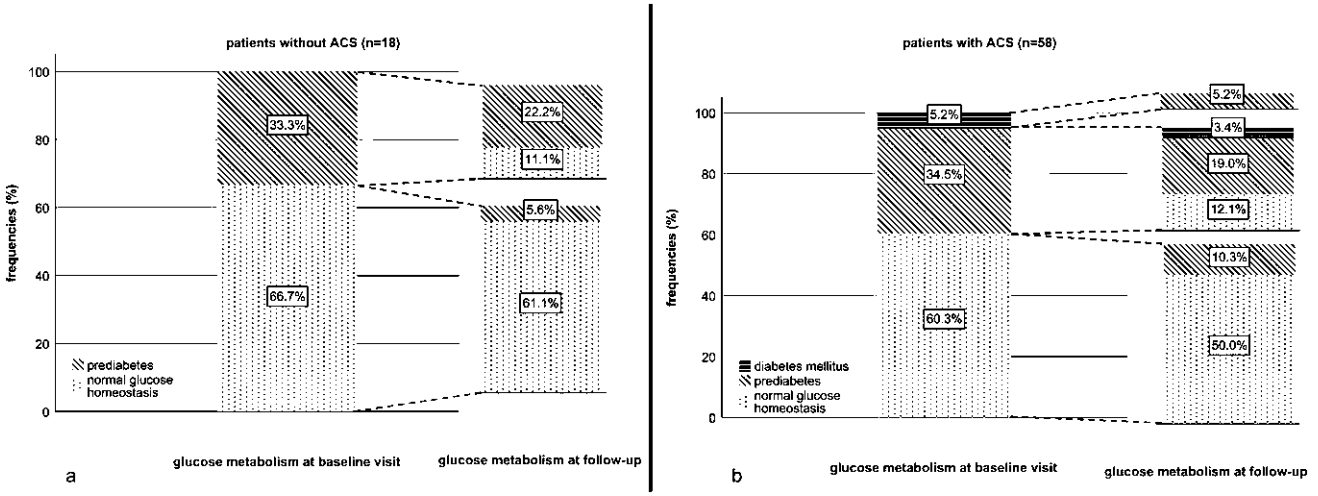

Figure 3. Frequencies of glucose metabolism alterations in patients with PA (a) without (n = 18) and (b) with (n = 58) ACS in at least one test at baseline and at follow up-visit after 1 year. Dashed lines indicate changes within different subgroups, based on diagnosis at baseline visit.

increased risk for T2DM (23% vs 13%, $P = 0.03$) in comparison with control subjects who are hypertensive (30). These results were confirmed by a prospective study of Hanslik *et al.* (8), who demonstrated a prevalence of 17.2% for T2DM in patients with PA, which was significantly higher than in their population-based control cohort.

Different mechanisms that lead to glucose impairment in PA have been discussed (32). One major contributing factor for patients with PA to develop T2DM seems to be hypokalemia, which impairs insulin release by pancreatic β-cells (33). 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 (34–36). Furthermore, aldosterone induces reactive oxygen species and increases IGF-1 expression, ultimately causing endothelial dysfunction, which leads to impaired glucose diffusion (37, 38). Finally, adipose tissue expresses both mineralocorticoid receptors and glucocorticoid receptors. Owing to absence of 11β-hydroxysteroid dehydrogenase type 2 in adipocytes, the mineralocorticoid receptor is thought to be at least partly occupied by cortisol originating from blood or from intracellular activation of cortisone by 11β-hydroxysteroid dehydrogenase type 1 (39). Therefore, we hypothesize that cortisol cosecretion in PA might alter adipocyte differentiation and subsequently influence insulin sensitivity and glucose homeostasis.

One further aspect of PA that might result in disturbances of glucose metabolism is glucocorticoid cosecretion. First, a possible cortisol cosecretion in patients with PA could only be shown in a few patients of small-sized retrospective cohorts (10, 17). However, recently larger studies suggest that glucocorticoid excess (ACS) is a frequent finding in PA (16, 40). We demonstrated a correlation of 24-hour glucocorticoid output with markers of insulin resistance, including fasting insulin, insulin after an OGTT, and HOMA-IR score, thus indicating that glucocorticoid cosecretion might affect glucose homeostasis.

However, to our knowledge, we now present the first study to evaluate the impact of ACS on the prevalence of T2DM in PA in comparison with a 1:3 matched control group. We prospectively investigated ACS with the help of three different tests for hypercortisolism and set them into context with results of OGTTs. We could identify 125 patients (77.6%) with ACS in at least one of the tests and 34 patients (21.1%) with a pathological response in DST alone. Until now, smaller studies estimated the prevalence of cortisol excess in patients with PA at 3.9% to 33.3%, depending on the diagnostic criteria used (9–11, 17). 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 patients with PA. Importantly, note that mild ACS contributes to lower bone mineral density, and it might have the same effect in our patients with PA with ACS (41).

In our cohort, we showed that patients with PA with ACS have a higher prevalence of T2DM than do sex-, age-, and BMI-matched controls. In contrast to this, patients with PA without ASC, and thus with aldosterone excess alone, could not be diagnosed with T2DM, but they showed higher HOMA-IR values than did their matched KORA controls. HOMA-IR is known as a marker of hepatic glucose and insulin in the fasting state (42). 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 (43), which might lead to the observed deterioration of HOMA-IR values.

By investigating the effect of ACS in PA on glucose homeostasis, we detected that patients with PA with proven ACS showed higher 2-hour glucose levels during the OGTTs and a higher prevalence of T2DM compared with matched KORA controls. Thus, it seems that an additional ACS impairs glucose tolerance in the peripheral tissues. Possible mechanisms might include impairment of insulin-dependent glucose uptake in peripheral tissue (44) or enhanced gluconeogenesis via different mechanisms, including further induction of gluconeogenetic enzymes (45). Furthermore, the presence of more than one abnormal test depicting cortisol excess seems to be associated with a greater risk of impaired glucose tolerance.

Interestingly, parameters of glycemia of our patients did not improve at follow-up after 12 months. This is in contrast to the study by Catena *et al.* (46), which showed improved glucose homeostasis after 6 months of treatment. However, this study included only 47 patients with PA, and glucose homeostasis worsened again during a longer follow-up (46). In our patients treated with ADX, the source of aldosterone and glucocorticoid excess seems to be removed, and thus these patients usually perform better in follow-up studies than do patients treated with MRAs. 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 (47). 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.

One limitation of the current 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. In addition, LSC, DST and UFC were not repeated after treatment, and, thus, we cannot rule out that mild cortisol excess persisted in some patients. 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 patients with PA in a 1:3 sex-, age-, and BMI-based matching to participants from a population-based study to achieve a case-control design. A further limitation of our study might be that in patients with PA with ACS the cortisol hypersecretion might interfere with the interpretation of the AVS data because until now cortisol, and not plasma metanephrine (48), has been used as the normalization factor in AVS aldosterone measurements.

In conclusion, we show that our PA cohort possesses a high proportion of patients with ACS. We describe that T2DM and impaired 2-hour plasma glucose in OGTT is more prevalent in patients with PA 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, especially associated risks such as T2DM.

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