Increased prevalence of diabetes mellitus and the metabolic syndrome in patients with primary aldosteronism of the German Conn's Registry

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Abstract

Design: Abnormalities in glucose homeostasis have been described in patients with primary aldosteronism (PA) but most studies show inconsistent results. Therefore, we aimed to compare the prevalence of type 2 diabetes mellitus and metabolic syndrome (MetS) in newly diagnosed PA patients to a matched control cohort of the background population.

Methods: In total, 305 PA patients of the prospective German Conn's Registry were compared to the population-based Study of Health In Pomerania (SHIP1; $n=2454$). A 1:1 match regarding sex, age, and BMI resulted in 269 matched pairs regarding type 2 diabetes and 183 matched pairs regarding MetS. Of the total, 153 PA patients underwent oral glucose tolerance testing (OGTT) at diagnosis and 38 PA patients were reevaluated at follow-up.

Results: Type 2 diabetes and MetS were significantly more frequent in PA patients than in the control population (17.2% vs 10.4%, $P=0.03$; 56.8% vs 44.8%, $P=0.02$ respectively). Also, HbA1c levels were higher in PA patients than in controls ($P<0.01$). Of the total, 35.3% of non-diabetic PA patients showed an abnormal OGTT ($\frac{1}{4}$ newly diagnosed type 2 diabetes and $\frac{3}{4}$ impaired glucose tolerance). PA patients with an abnormal OGTT at baseline presented with significantly improved 2 h OGTT glucose ($P=0.01$) at follow-up. We detected a negative correlation between 2 h OGTT glucose levels and serum potassium ($P<0.01$).

Conclusions: Type 2 diabetes and MetS are more prevalent in patients with PA than in controls matched for sex, age, BMI, and blood pressure. This may explain in part the increased cardiovascular disease morbidity and mortality in PA patients.

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Introduction

Primary aldosteronism (PA) has been reported with increasing frequency and accounts for ~4.3 and 9.5% of the respective hypertensive population in primary care and referred patients, leaving PA as the most common

form of secondary hypertension (1). In recent years, several studies have shown that comorbidities and mortalities are increased in PA patients compared to primary hypertensive patients (2, 3). This was related to

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the detrimental effect of aldosterone itself in combination with the high-salt content of the current Western diet (4, 5).

It is well known that the prevalence of obesity, diabetes, hypertension, and cardiovascular and chronic kidney disease are increasing worldwide. Obesity, insulin resistance and hypertension commonly cluster with other risk factors for cardiovascular or chronic kidney disease to form the metabolic syndrome (MetS), which is associated with increased cardiovascular disease morbidity and mortality (6). It is well established that inhibitors of the renin-angiotensin-aldosterone system (RAAS) reduce cardiovascular ischemic events and mortality (7, 8). Treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers also results in a significant reduction in cardiovascular (CV) events (10%) and mortality (17%) in hypertensive patients with diabetes mellitus (9). Furthermore, blocking the RAAS shows a significant 20% risk reduction in the incidence of new onset diabetes (10).

PA is now named as a risk factor and an endocrine cause of diabetes mellitus by the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (11). Previous studies have described abnormalities in glucose homeostasis and metabolism in patients with PA (12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22); however, they often showed inconsistent results due to limitations in sample size, lacking of a matched control group, or non-standardized diagnosis of PA. Nevertheless, there is growing evidence that aldosterone is involved in the pathogenesis of insulin resistance and MetS (23, 24). This may even be the case in subjects without PA. In a recent study, with 356 patients with essential hypertension and 102 normotensive control subjects of comparable age and BMI, a positive association with increasing plasma aldosterone levels was demonstrated for plasma glucose, insulin, C-peptides, and homeostasis model assessment (HOMA) (20). This relationship might contribute to the increased cardiovascular risk of high aldosterone levels, besides its detrimental effects on blood vessels and tissues.

In a previous study, Reincke *et al.* (25) reported that patients from the German Conn's Registry with confirmed PA had a higher diabetes prevalence than comparable hypertensive controls from a population-based study in south Germany. Yet, in that study only retrospective data of PA patients was analyzed and the diabetes prevalence was compared to a study located in a region within Germany with a low diabetes prevalence (26).

We therefore aimed to compare the prevalence of type 2 diabetes mellitus and MetS in the prospective patients of the German Conn's Registry with participants from the population-based Study of Health In Pomerania (SHIP1),

located in northeast Germany, a region with a high diabetes prevalence (26). Moreover, in a subsample, we analyzed whether therapy initiation (adrenalectomy or mineralocorticoid receptor antagonist therapy) improves the metabolic situation in patients with PA.

Methods

Study populations

The investigations in the patient-based (Multicenter Evaluation of Primary Hyperaldosteronism Diagnostic Testing, Subdifferentiation, Therapy, Outcome and Genetics (MEPHISTO)) and the population-based (SHIP1) studies were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants.

The MEPHISTO study ► MEPHISTO is the prospective phase of the German Conn's Registry, which was established in 2008. The cohort of this study was recruited between August 2008 and August 2013. The Conn's Registry documents prospectively diagnosis, treatment, and disease progress of patients with PA in Germany (27). The diagnostic criteria for PA required for inclusion in the registry are based on the guidelines of the Endocrine Society (28). All PA patients had an elevated aldosterone-to-renin ratio (ARR) and an abnormal confirmatory test (saline infusion test, fludrocortisone suppression test, captopril test, or oral salt loading test with demonstration of elevated excretion of aldosterone and its metabolites in urine). Adjustment of medication prior to screening and confirmation was performed whenever possible, with β -blockers, central α -2 agonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics withdrawn for at least 1 week, and mineralocorticoid antagonists at least for 4 weeks. The diagnosis of PA was centrally verified by review of all available data. Imaging and venous adrenal sampling were applied to differentiate into uni- or bilateral aldosterone excess (29, 30). Further details on the registry are given elsewhere (27). For the present study, all 305 prospective patients of the MEPHISTO study between 2008 and 2012 were included.

To determine whether type 2 diabetes mellitus or MetS are more frequent among the 305 prospective PA patients than among subjects without PA, the respective proportions were compared between 1:1 matched pairs of MEPHISTO patients and SHIP1 controls. For the comparison of the type 2 diabetes proportions, MEPHISTO patients

with type 1 diabetes mellitus or missing information on diabetes mellitus ($n=3$) and all patients with missing information in one of the matching factors sex, age, BMI, or blood pressure ($n=33$) were excluded. This resulted in a study population of 269 subjects. For the comparison of the MetS proportion, we additionally excluded all subjects with missing information on the MetS, its components, or LDL-cholesterol ($n=86$), which resulted in a study population of 183 subjects.

Among the 305 prospective MEPHISTO patients, glucose metabolism was further assessed in 153 patients from three centers (Munich, Berlin, and Wuerzburg) by laboratory measurements and oral glucose tolerance testing (OGTT) according to the American Diabetes Association (31). To establish factors associated with abnormal glucose metabolism, these 153 patients were divided into three groups according to their OGTT results: normal glucose tolerance (2 h serum glucose levels <7.8 mmol/l), impaired glucose tolerance (IGT, 2 h serum glucose levels 7.8–11.1 mmol/l), or type 2 diabetes (2 h serum glucose levels >11.1 mmol/l). Moreover, to assess the impact of hypokalemia on glucose metabolism, the OGTT results were compared between patients with hypo- and normokalemia in 152 patients with serum potassium levels. One year after initiation of PA therapy, patients without type 2 diabetes at baseline were invited to perform a second OGTT and 38 subjects agreed to this examination. Markers of glucose metabolisms were compared between baseline and follow-up visit in these 38 subjects as well as in eight subjects who presented with type 2 diabetes at baseline.

The SHIP study ► SHIP is a longitudinal, population-based study in northeast Germany. Study design and methods have been described previously (32, 33). Briefly, from a representative population sample of 7008 adult men and women, 4308 subjects participated in the baseline examinations between 1997 and 2001. In the first 5-year follow-up examination (SHIP1) between 2002 and 2006, 3300 subjects participated.

For the present study, we used data from SHIP1, as the plasma aldosterone concentration (PAC) and the plasma renin concentration (PRC) were not measured in the baseline study. The SHIP1 examination program comprised standardized medical examinations, including measurements of height, weight, waist circumference, blood sampling, and an extensive computer-aided personal interview. Medication intake was recorded and classified using the Anatomical Therapeutic Chemical Classification System (ATC) code. Systolic and diastolic

blood pressures were measured three times on the right arm of seated participants using a digital blood pressure monitor (HEM-705CP, OMRON Corporation, Tokyo, Japan). For statistical analyses, the mean of the second and third measurements was used. OGTTs were not performed.

To obtain a sample of healthy controls, we selected 2479 subjects with PAC, PRC, and ARR within the study-specific reference range (34). From the 2479 subjects, we excluded those with type 1 diabetes mellitus, missing information on diabetes mellitus or MetS ($n=15$), missing information in one of the matching factors sex, age, BMI, or blood pressure, missing information in the estimated glomerular filtration rate (eGFR) or the serum potassium concentration ($n=6$), and all pregnant women ($n=4$), which resulted in a study population of 2454 subjects.

Definitions and laboratory measurements

In both studies, type 2 diabetes was defined when subjects reported either a respective physician's diagnosis or had an HbA1c $\geq 6.5\%$. Type 2 diabetes was further defined in MEPHISTO patients who had fasting serum glucose concentrations ≥ 7.0 mmol/l or a respective OGTT result (2 h serum glucose concentration >11.1 mmol/l), and in SHIP1 participants with non-fasting serum glucose concentrations ≥ 11.1 mmol/l or intake of antidiabetic medication.

The MetS was defined based on the criteria by Alberti *et al.* (35). For SHIP1, this definition had to be adapted to compensate for the non-fasting blood sampling conditions. When subjects fulfilled at least three out of five diagnostic criteria, the MetS was present. These criteria include a waist circumference ≥ 94 cm in men or ≥ 80 cm in women; antidiabetic treatment or fasting glucose ≥ 5.6 mmol/l (MEPHISTO) or non-fasting glucose ≥ 8 mmol/l (SHIP1); HDL-cholesterol <1.0 mmol/l in men or <1.3 mmol/l in women; lipid-lowering treatment or fasting triglycerides ≥ 1.7 mmol/l (MEPHISTO), or non-fasting triglycerides ≥ 2.3 mmol/l (SHIP1); antihypertensive treatment, or systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 85 mmHg.

In both studies, BMI was calculated as weight (kg)/height² (m²). Hypokalemia was defined as serum potassium concentrations <3.5 mmol/l. The eGFR was calculated according to the four-variable modification of diet in renal disease formula.

Laboratory measurements in MEPHISTO were performed decentralized in each study center. The patients were instructed to fast for at least 8 h before the

examinations. All blood samples were taken in the mornings between 0800 and 1000 h from the cubital vein. Patients who performed baseline and/or follow-up OGTT drank 75 g glucose dissolved in 300 ml water after the fasting blood sample was taken. One and 2 h after glucose loading, second and third blood samples were taken respectively in which glucose and insulin concentrations were measured (36). Circulating aldosterone concentrations were measured as previously described (37).

Laboratory measurements in SHIP1 were performed centralized in a single laboratory. Blood samples were taken from the cubital vein of non-fasting participants in the supine position between 0800 and 2000 h. PAC and PRC were measured in EDTA plasma (PAC: Coat-A-Count Aldosterone, Siemens Healthcare Diagnostics, Eschborn, Germany and PRC: Renin III Generation, Cisbio Bioassay, Bagnols-sur-Cèze Cedex, France). Serum glucose was determined enzymatically (system: Hitachi 717 and reagents: Roche Diagnostics). The serum HbA1c concentration was determined by HPLC (Bio-Rad Diamat, Munich, Germany). The serum potassium concentration was measured by indirect potentiometry with ion-selective electrodes (QuikLYTE, Dade Behring, Eschborn, Germany).

Statistical analyses

For the comparison of the proportions of type 2 diabetes and MetS in MEPHISTO and SHIP1, we applied an individual 1:1 matching. The greedy matching algorithm, as implemented in a SAS macro (38), was used to select controls among the 2454 SHIP1 participants. First, we determined controls for the 269 MEPHISTO patients with known type 2 diabetes status. The controls were matched to the patients based on four matching factors; sex, age (± 5 years), BMI (< 25 , $25\text{--}30$, and > 30 kg/m²), and blood pressure ($< 140/90$, $140/90\text{--}160/100$, and $> 160/100$ mmHg). The 1:1 individual matching identified 250 pairs of patients and controls, which were further analysed. Second, we determined controls for the 183 MEPHISTO patients with known MetS status. The controls were matched to the patients based on three matching factors; sex, age (± 5 years), and blood pressure ($< 140/90$, $140/90\text{--}160/100$, and $> 160/100$ mmHg). As waist circumference is part of the MetS definition, BMI was not considered a matching factor in this analysis. The matching procedure identified one control to each of the patients, yielding a total of 183 pairs of MEPHISTO and SHIP1 participants.

We report mean and s.d. for continuous variables and numbers and proportion for categorical variables. For group comparisons between patients and controls, we used Kruskal–Wallis and χ^2 tests. For group comparisons regarding OGTT outcome among patients, Mann–Whitney *U* tests and paired *t*-tests (continuous data), or χ^2 tests (categorical data) were used. To illustrate the relationship between the serum potassium concentration and the 2 h OGTT glucose concentration in the MEPHISTO patients, we used a scatterplot with a linear regression line. *P* values < 0.05 were considered statistically significant. Statistical analyses were performed with SAS 9.1.3 (SAS Institute, Inc., Cary, NC, USA) and IBM SPSS Statistics 22.0.

Results

Type 2 diabetes was significantly more frequent in PA patients than in the sex-, age-, BMI-, and blood pressure-matched control population (17.2% vs 10.4%, $P=0.03$; Table 1). In both cohorts glucose levels significantly correlated with BMI (MEPHISTO: $r=0.24$, $P<0.01$ and SHIP: $r=0.27$, $P<0.01$). Also HbA1c levels were higher in PA patients than in controls. In contrast, serum potassium levels were significantly lower in PA patients compared to controls. The increased prevalence of type 2 diabetes was also the major aspect contributing to the significantly higher prevalence of the MetS in PA patients (56.8% vs 44.8%, $P=0.02$). Further, systolic blood pressure was higher in PA patients than in controls, despite blood pressure categories ($< 140/90$, $140/90\text{--}160/100$, and $> 160/100$ mmHg) were used as matching criteria. However, the PA patients displayed a better lipid profile with higher HDL- and lower LDL-cholesterol levels than the matched control population. In addition, we compared the subgroup of normokalemic PA patients ($n=107$) with matched controls from the SHIP1 cohort (Table 2). The normokalemic PA patients had still significantly lower potassium levels and a higher HbA1c, which was still in the normal range. However, the prevalence of type 2 diabetes in normokalemic PA compared to matched control patients was not significant any more ($P=0.56$).

In 153 PA patients we assessed glucose metabolism by an OGTT at PA diagnosis. A high percentage (35.3%) of patients showed an abnormal OGTT: 41 patients (26.8% of the total cohort) had an IGT, whereas 13 patients (8.5% of the total cohort) were diagnosed type 2 diabetes (Table 3). PA patients with an abnormal OGTT were significantly older, had a higher WHR and lower serum potassium levels than PA patients with a normal OGTT.

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Table 1 Type 2 diabetes mellitus and metabolic syndrome (MetS) in 1:1 matched pairs of patients with primary aldosteronism (MEPHISTO) and controls (SHIP1). Data are means $\pm$ s.d. or proportions. Group differences were tested with Kruskal–Wallis tests (continuous data) or χ^2 tests (categorical data). Matching according to sex, age (± 5 years), BMI (< 25 , 25 – 30 , and > 30 kg/m²), and blood pressure ($< 140/90$, $140/90$ – $160/100$, and $> 160/100$ mmHg). As waist circumference is part of the MetS definition, BMI was not considered a matching factor in the analysis for MetS.

Characteristics	Type 2 diabetes (250 pairs)			MetS (183 pairs)		
	MEPHISTO	SHIP1	P	MEPHISTO	SHIP1	P
Men (%)	64.4	64.4	1.00	66.1	66.1	1.00
Age (years)	52.5 $\pm$ 11.2	52.7 $\pm$ 11.0	0.89	51.9 $\pm$ 10.9	52.0 $\pm$ 10.8	0.92
BMI (kg/m ²)	28.6 $\pm$ 5.1	28.3 $\pm$ 4.7	0.80	28.5 $\pm$ 4.8	28.1 $\pm$ 4.5	0.52
Systolic BP (mmHg)	152.3 $\pm$ 20.2	147.1 $\pm$ 19.6	0.02	153.3 $\pm$ 20.0	148.5 $\pm$ 20.0	0.03
Diastolic BP (mmHg)	91.7 $\pm$ 12.3	91.9 $\pm$ 11.7	0.64	93.6 $\pm$ 12.1	93.6 $\pm$ 11.1	0.95
Potassium (mmol/l)	3.5 $\pm$ 0.5 ^a	4.3 $\pm$ 0.3	< 0.01	3.4 $\pm$ 0.5	4.3 $\pm$ 0.4	< 0.01
Potassium substitution (%)	45.6 ^b	0.0	< 0.01	53.0 ^c	0.0	< 0.01
Type 2 diabetes (%)	17.2	10.4	0.03	16.9	12.0	0.18
HbA1c (%)	5.6 $\pm$ 0.7 ^d	5.3 $\pm$ 0.8	< 0.01	5.6 $\pm$ 0.7 ^e	5.4 $\pm$ 0.9	< 0.01
HbA1c (mmol/mol)	38 $\pm$ 7.7	34 $\pm$ 8.7		38 $\pm$ 7.7	36 $\pm$ 9.8	< 0.01
MetS (%)	–	–	–	56.8	44.8	0.02
Total cholesterol (mmol/l)	–	–	–	5.2 $\pm$ 1.0	5.7 $\pm$ 1.2	< 0.01
HDL-cholesterol (mmol/l)	–	–	–	1.4 $\pm$ 0.4	1.2 $\pm$ 0.4	< 0.01
LDL-cholesterol (mmol/l)	–	–	–	3.2 $\pm$ 0.9	3.6 $\pm$ 1.0	< 0.01
LDL-cholesterol/HDL-cholesterol	–	–	–	2.4 $\pm$ 0.9	3.6 $\pm$ 1.8	< 0.01
Triglycerides (mmol/l)	–	–	–	1.3 $\pm$ 0.8	2.1 $\pm$ 1.9	< 0.01

BP, blood pressure; SHIP1, Study of Health In Pomerania; potassium substitution, PA patients who required potassium supplementation.

^aFour missings.

^bSix missings.

^cOne missing.

^d104 missings.

^e62 missings.

In a further analysis, we split the PA patients into hypo- and normokalemic cohorts. In total, 46.7% of our PA patients had the normokalemic variant of PA (Table 4). Patients with the hypokalemic PA variant showed a significantly higher eGFR and higher glucose and insulin concentrations after 2 h of glucose intake (Table 4). Potassium levels significantly negatively correlated with 2 h glucose levels in OGTT at baseline (Fig. 1).

One year after initiation of PA therapy, we re-assessed a subsample of 38 PA patients without type 2 diabetes (27 patients with normal OGTT and 11 with IGT) and eight PA patients with type 2 diabetes at baseline. All PA patients showed normalized potassium levels, decrease of eGFR and a tendency in improvement of systolic and diastolic blood pressure (Table 5). In the cohort with IGT, treatment of PA significantly improved 2 h OGTT glucose levels (9.6 ± 1.7 – 8.3 ± 1.6 mmol/l, $P < 0.01$).

Discussion

The main finding of our study is that type 2 diabetes is more prevalent in untreated patients with PA than in controls matched for sex, age, BMI, and blood pressure.

Moreover, also the MetS is more prevalent in patients with PA than in control subjects.

Several studies have investigated the prevalence of hyperglycemia in PA and whether markers of glucose metabolism differ between patients with PA, essential hypertension and normotensive subjects. However, the findings are inconsistent (12, 13, 14, 15, 16, 18, 19, 21). Two smaller studies ($n = 24$ (14) and 63 subjects (15)) and one large study ($n = 1823$ subjects (21)) reported no association between PA and glucose metabolism (including insulin sensitivity index, HOMA, or quantitative insulin sensitivity check index (QUICKI)). The largest study in the field (21), including 460 patients with PA and 1363 controls with essential hypertension reported no differences regarding proportions of hyperglycemia or fasting glucose levels. On the other hand, there is evidence that patients with PA have a disturbed glucose metabolism (13, 16, 18, 19). Thirty PA patients had higher glucose, lower C-peptide levels and lower HOMA- β F index than 60 patients with essential hypertension (19). Furthermore, proportions of hyperglycemia, increased HOMA and MetS were higher in patients with PA compared to patients with essential hypertension (16) as well as compared to

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Table 2 Type 2 diabetes mellitus and metabolic syndrome (MetS) in 1:1 matched pairs of patients with normokalemic primary aldosteronism (MEPHISTO) and controls (SHIP1). Data are means $\pm$ s.d. or proportions. Group differences were tested with Kruskal–Wallis tests (continuous data) or χ^2 tests (categorical data). Matching according to sex, age (± 5 years), BMI (< 25 , 25 – 30 , and > 30 kg/m²), and blood pressure ($< 140/90$, $140/90$ – $160/100$, and $> 160/100$ mmHg). As waist circumference is part of the MetS definition, BMI was not considered a matching factor in the analysis for MetS.

Characteristics	Type 2 diabetes (107 pairs)			MetS (74 pairs)		
	MEPHISTO	SHIP1	P	MEPHISTO	SHIP1	P
Men (%)	37.4	37.4	1.00	39.2	39.2	1.00
Age (years)	54.1 $\pm$ 12.8	54.3 $\pm$ 12.4	0.94	53.0 $\pm$ 12.7	53.2 $\pm$ 12.4	0.90
BMI (kg/m ²)	28.7 $\pm$ 5.2	28.4 $\pm$ 4.5	0.98	28.5 $\pm$ 5.1	28.4 $\pm$ 4.8	0.73
Systolic BP (mmHg)	150.6 $\pm$ 20.5	146.8 $\pm$ 20.0	0.46	150.3 $\pm$ 20.3	147.7 $\pm$ 19.4	0.57
Diastolic BP (mmHg)	91.1 $\pm$ 12.3	90.7 $\pm$ 12.3	0.92	92.3 $\pm$ 12.0	91.8 $\pm$ 10.6	0.79
Potassium (mmol/l)	4.0 $\pm$ 0.3	4.4 $\pm$ 0.4	< 0.01	3.9 $\pm$ 0.3	4.3 $\pm$ 0.4	< 0.01
Potassium substitution (%)	31.8 ^a	0.0	< 0.01	37.8 ^b	0.0	< 0.01
Type 2 diabetes (%)	15.9	13.1	0.56	14.9	13.5	0.81
HbA1c (%)	5.7 $\pm$ 0.8 ^c	5.4 $\pm$ 0.9	< 0.01	5.7 $\pm$ 0.8 ^d	5.4 $\pm$ 0.8	< 0.01
MetS (%)	–	–	–	47.3	41.9	0.51
Total cholesterol (mmol/l)	–	–	–	5.3 $\pm$ 1.0	5.7 $\pm$ 1.2	0.01
HDL-cholesterol (mmol/l)	–	–	–	1.5 $\pm$ 0.4	1.2 $\pm$ 0.4	< 0.01
LDL-cholesterol (mmol/l)	–	–	–	3.2 $\pm$ 0.9	3.6 $\pm$ 1.1	0.02
LDL-cholesterol/HDL-cholesterol	–	–	–	2.4 $\pm$ 1.0	3.5 $\pm$ 1.7	< 0.01
Triglycerides (mmol/l)	–	–	–	1.4 $\pm$ 0.9	2.1 $\pm$ 2.3	< 0.01

BP, blood pressure; SHIP1, Study of Health In Pomerania.

^aThree missing.

^bOne missing.

^c48 missing.

^d28 missing.

normotensive subjects (18). However, the strongest argument in favor of a link between disturbed glucose homeostasis and PA are observed beneficial treatment effects showing restored insulin sensitivity after 6 months of PA treatment (18). Comparable to the study by Catena *et al.* (18), we investigated glucose metabolism before and after PA therapy initiation and confirmed their results. PA patients with IGT at baseline improved significantly in

their glucose profile 1 year after therapy initiation. This indicates that with normalization of potassium and aldosterone levels, glucose levels in OGTT also normalized despite unchanged BMI.

In our recent retrospective analysis of the German Conn's Registry (25), we calculated a type 2 diabetes prevalence of nearly 23% in 338 patients with PA. In 338 matched controls from the KORA cohort from southern

Table 3 Characteristics of 153 MEPHISTO patients with OGTT at baseline. Patients with abnormal OGTT were further diversified into type 2 diabetes and IGT. Data are means $\pm$ s.d. or *n* (proportion). Group differences were tested with Mann–Whitney *U* tests.

Characteristics	OGTT			Abnormal OGTT	
	Normal	Abnormal	P	IGT	Type 2 diabetes
<i>n</i> (%)	99 (64.7)	54 (35.3)	–	41 (75.9)	13 (24.1)
Age (years)	48.5 $\pm$ 9.8	54.0 $\pm$ 10.3	< 0.01	54.7 $\pm$ 10.0	51.8 $\pm$ 11.2
BMI (kg/m ²)	27.5 $\pm$ 4.5	29.0 $\pm$ 4.3	0.14	29.0 $\pm$ 4.4	29.0 $\pm$ 4.1
WHR	0.92 $\pm$ 0.09	0.99 $\pm$ 0.16	< 0.01	0.97 $\pm$ 0.09	1.06 $\pm$ 0.30
Systolic BP (mmHg)	151.1 $\pm$ 18.6	156.7 $\pm$ 21.2	0.01	155.0 $\pm$ 20.5	163.0 $\pm$ 23.5
Diastolic BP (mmHg)	94.6 $\pm$ 11.6	92.8 $\pm$ 13.1	0.57	92.7 $\pm$ 12.9	93.0 $\pm$ 14.4
Potassium (mmol/l)	3.50 $\pm$ 0.50	3.22 $\pm$ 0.45	< 0.01	3.20 $\pm$ 0.49	3.30 $\pm$ 0.28
eGFR (ml/min per 1.73 m ²)	89.5 $\pm$ 22.3	88.2 $\pm$ 21.3	0.69	84.8 $\pm$ 19.0	99.0 $\pm$ 25.2
Triglycerides (mg/dl)	106.0 $\pm$ 53.0	131.9 $\pm$ 81.0	0.06	136.6 $\pm$ 87.5	117.2 $\pm$ 56.2
PAC (ng/l)	232.6 $\pm$ 161.8	243.4 $\pm$ 201.0	0.93	247.6 $\pm$ 209.1	230.7 $\pm$ 182.3

BP, blood pressure; eGFR, estimated glomerular filtration rate; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PAC, plasma aldosterone concentration; WHR, waist-to-hip ratio.

Table 4 Characteristics of 152 MEPHISTO patients with OGTT and serum potassium concentration at baseline according to hypo- or normokalemia. The serum potassium concentration was not measured in one out of 153 prospective MEPHISTO patients. Hypokalemia was defined as serum potassium concentrations <3.5 mmol/l. Data are means $\pm$ s.d. or n (proportion). Group differences were tested with Mann–Whitney U tests.

Characteristics	Hypokalemia	Normokalemia	P
n (%)	81 (53.3)	71 (46.7)	–
Age (years)	49.4 ± 9.5	51.6 ± 11.1	0.33
WHR	0.96 ± 0.14	0.93 ± 0.10	0.07
BMI (kg/m^2)	28.2 ± 4.3	27.9 ± 4.7	0.78
Systolic BP (mmHg)	154.0 ± 19.0	152.2 ± 20.6	0.31
Diastolic BP (mmHg)	94.7 ± 12.4	93.4 ± 11.9	0.36
Potassium (mmol/l)	3.03 ± 0.29	3.83 ± 0.31	<0.01
eGFR (ml/min per 1.73 m^2)	93.4 ± 22.5	84.2 ± 20.3	<0.01
Triglycerides (mg/dl)	120.9 ± 68.3	108.7 ± 61.5	0.70
PAC (ng/l)	260.9 ± 202.3	203.1 ± 130.5	0.12
2 h OGTT glucose (mmol/l)	7.9 ± 2.7	6.7 ± 2.3	<0.01
2 h OGTT insulin (mU/l)	111.6 ± 93.9	80.4 ± 75.2	0.03

BP, blood pressure; eGFR, estimated glomerular filtration rate; OGTT, oral glucose tolerance test; PAC, plasma aldosterone concentration.

Germany the type 2 diabetes prevalence was 13% and significantly lower than in the PA patients. Also in the present study, using prospectively collected data, the type 2 diabetes prevalence was higher in the German Conn's Registry (17.2%) than in the control population from the SHIP cohort from northern Germany (10.4%). The patients selected for the retrospective study (25) were on average 61 years old, while the prospective patients selected for the present study were younger, with an average age of 52 years. This strongly contributes to the lower type 2 diabetes prevalence observed in the present compared to the previous study. In the retrospective study (25), patients and controls were matched for sex, age (± 10 years), systolic (± 10 mmHg), and diastolic blood pressures (± 5 mmHg). As BMI was not considered as a matching factor, patients and controls differed regarding their anthropometry, with control subjects having higher BMIs ($29.7 \pm 4.8 \text{ kg}/\text{m}^2$) than patients with PA (28.3 ± 4.7). In contrast, in the present study BMI was considered a matching variable and patients and controls did not significantly differ in their anthropometry. In general, the prevalence of type 2 diabetes is high in northeast Germany (26). In the SHIP baseline study the type 2 diabetes prevalence was 11.2% for subjects aged 45–75 years (26), corresponding to the proportion estimated in the controls for the present study. Thus, patients with PA have a significantly increased type 2 diabetes prevalence, even above that of a high-risk population. Moreover, the type 2 diabetes prevalence determined in patients with PA is in good agreement to data from France presenting a type 2 diabetes prevalence of 17% (21). In that study, however,

the type 2 diabetes prevalence was not significantly different from a large number of controls with essential hypertension (14%), however, the controls were only matched for age and sex and not for BMI.

Several mechanisms for glucose metabolism impairment in PA have been discussed. These include increased

Figure 1

Scatterplot with regression line (solid line) and 95% CIs (dashed lines) for the serum potassium concentration and the 2 h OGTT glucose concentration in 152 PA patients at baseline (β -coefficient: -1.10 , s.e.m.: 0.41 , P value: <0.01).

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Table 5 Characteristics of 38 MEPHISTO patients with OGTT at baseline and follow-up and of eight MEPHISTO patients with newly diagnosed type 2 diabetes at baseline. Data are means $\pm$ s.d. or *n*. Group differences were tested with paired *t*-tests.

Characteristics	Normal OGTT at baseline			IGT at baseline			Type 2 diabetes at baseline		
	Baseline	Follow-up	<i>P</i>	Baseline	Follow-up	<i>P</i>	Baseline	Follow-up	<i>P</i>
<i>n</i> (ADX/MRA)	27	27 (13/14)	–	11	11 (7/4)	–	8	8 (3/5)	–
WHR	0.90 $\pm$ 0.08	0.91 $\pm$ 0.08	0.16	1.01 $\pm$ 0.07	1.00 $\pm$ 0.08	0.99	0.95 $\pm$ 0.07	0.94 $\pm$ 0.07	0.15
BMI (kg/m ²)	26.6 $\pm$ 4.5	27.1 $\pm$ 4.4	0.03	30.9 $\pm$ 3.0	29.8 $\pm$ 2.4	0.24	30.1 $\pm$ 3.4	28.6 $\pm$ 3.8	0.09
Systolic BP (mmHg)	142.0 $\pm$ 16.4	133.3 $\pm$ 19.7	0.03	156.6 $\pm$ 21.6	145.9 $\pm$ 17.8	0.27	155.1 $\pm$ 25.3	149.8 $\pm$ 23.4	0.75
Diastolic BP (mmHg)	89.0 $\pm$ 11.6	83.7 $\pm$ 9.7	0.06	91.6 $\pm$ 16.7	88.2 $\pm$ 7.4	0.58	87.3 $\pm$ 18.6	89.7 $\pm$ 7.0	0.78
Potassium (mmol/l)	3.5 $\pm$ 0.4	4.0 $\pm$ 0.5	<0.01	3.1 $\pm$ 0.5	4.0 $\pm$ 0.3	<0.01	3.3 $\pm$ 0.3	4.0 $\pm$ 0.4	<0.01
eGFR (ml/min per 1.73 m ²)	88.2 $\pm$ 19.0	80.9 $\pm$ 19.7	<0.01	82.7 $\pm$ 15.3	73.9 $\pm$ 18.9	0.07	105.6 $\pm$ 19.9	83.9 $\pm$ 11.9	<0.01
PAC (ng/l)	178.4 $\pm$ 109.0	145.8 $\pm$ 101.5	0.32	208.6 $\pm$ 99.3	122.0 $\pm$ 159.3	0.26	224.5 $\pm$ 79.0	211.6 $\pm$ 125.5	0.84
2 h OGTT glucose (mmol/l)	5.3 $\pm$ 1.3	5.8 $\pm$ 2.0	0.11	9.6 $\pm$ 1.7	8.3 $\pm$ 1.6	<0.01	–	–	–
2 h OGTT insulin (mU/l)	63.7 $\pm$ 78.9	84.8 $\pm$ 82.8	0.07	182.0 $\pm$ 70.0	158.8 $\pm$ 83.5	0.31	–	–	–

BP, blood pressure; eGFR, estimated glomerular filtration rate; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PAC, plasma aldosterone concentration; WHR, waist-to-hip ratio; ADX, adrenalectomy; MRA, mineralocorticoid receptor antagonist therapy.

inflammation, oxidative stress, and a lower β -cell function, including a decrease of β -cell mass caused by elevated aldosterone levels (19, 23, 39). Insulin resistance in PA might also include direct aldosterone effects on insulin sensitivity in peripheral tissues. It has been described that aldosterone induces vascular insulin resistance, possibly via modification of proteins such as insulin receptor substrate 1, phosphatidylinositol 3-kinase, nitric oxide synthase, insulin-like growth factor 1 receptor, and the insulin receptor itself (40, 41). We showed recently by i.v. glucose tolerance testing, involving 22 patients with PA, 11 matched essential hypertensive subjects, and 11 normotensive controls, that aldosterone excess impairs first-phase insulin secretion. Moreover, adrenalectomy was able to restore insulin secretion in those patients (42).

Furthermore, a diabetogenic effect of hypokalemia itself has been proposed (43, 44). In our study, potassium levels significantly negatively correlated with 2 h glucose levels in OGTT, demonstrating that PA patients with hypokalemia had a worse glucose metabolic situation than PA patients with normokalemia. The important role of potassium influence on insulin secretion is endorsed by studies showing that thiazide-induced hypokalemia leads to diminished insulin secretion (45, 46). More recently, the Atherosclerosis Risk in Communities Study demonstrated in 12 209 participants that there is an inversed association between serum potassium and risk of incident diabetes (47). Also, *in vitro* data clearly showed that a

decrease in potassium concentrations result in an inhibition of insulin secretion (48). This explains the results of our cohort, demonstrating that the incidence of diabetes mellitus was lower in the subgroup of normokalemic compared to hypokalemic PA patients. Nevertheless, besides hypokalemia, direct effects of aldosterone excess might be involved in insulin regulation (49).

The increased type 2 diabetes prevalence in our study cohort appears also to be the determining factor concerning the higher prevalence of MetS in our cohort. Eighty-five Italian patients with PA and 381 patients with essential hypertension were studied in a non-matched approach by Fallo *et al.* (16) showing also that fasting plasma glucose seems to be the major component of MetS in PA. The prevalence of MetS was surprisingly low in Italy (25–45% in PA patients and 20–30% in essential hypertensives (16, 50, 51)) compared to our rates (56.8% in PA and 44.8% in controls). This might be due to national differences between Italy and Germany and/or due to the fact that we matched also for BMI. This is endorsed by data from the Czech Republic demonstrating a prevalence of MetS of 62% in bilateral and 34% in unilateral PA, and of 56% in essential hypertensives (52). The serum lipid profile is an important parameter in MetS. In recent studies, no differences in the serum lipid profile were detected between PA patients and patients with essential hypertension (16, 18, 19). However, those studies consisted of a low number of PA patients, which might have resulted in a loss

of significance. In our cohort, we demonstrated a significantly better lipid profile in PA patients than in age-, sex-, and BMI-matched controls. It is important to point out that French PA patients also had lower total cholesterol levels (5.4 ± 0.9 mmol/l vs 5.9 ± 1.1 mmol/l; $P < 0.0004$) than age-, gender-, and blood pressure-matched essential hypertensive controls despite an excess of cardiovascular events of the PA patients (3). However, in an Italian cohort there was no statistically significant difference in total cholesterol, LDL-cholesterol, or triglycerides between PA patients and essential hypertensive patients with MetS, but HDL-cholesterol levels were higher in the latter (48). Owing to the fact that up to now no studies have been published investigating a possible direct effect of aldosterone on lipid metabolism either *in vitro* or *in vivo*, it is pure speculation whether there is a causative correlation or if it is just the fact that PA patients are the healthier patients besides having PA.

The main shortcoming is a lack of investigation into potential mechanisms underlying the association between aldosterone excess and hyperglycemia. However, the present study is strengthened by the comprehensive and standardized data collection in the German Conn's Registry and in the SHIP study. This allowed us to perform a case-control study comparing patients and participants matched by sex, age, BMI, and blood pressure. Moreover, OGTT data was available in the PA patients, which additionally allowed us to assess prediabetic states. Unfortunately, only three centers of the MEPHISTO study performed baseline and follow-up OGTTs. Thus, our data may under- or overestimate the true diabetes prevalence in the PA patients. In SHIP1, prediabetic states were not assessed as there were no OGTTs. This restricted the comparison between PA patients and controls to manifest type 2 diabetes. Another limitation of our study arises from differences in laboratory methods used in MEPHISTO and in SHIP1, especially regarding the lipid profiles of patients and controls. In addition, time for blood drawing in the SHIP cohort was at any time from 0800 to 2000 h (rather than being restricted to morning hours), and hence the procedure for screening for PA was different from that for the PA patients and did not conform to established guidelines. A possible confounding factor might be the not strictly matched systolic blood pressure.

In conclusion, we describe that type 2 diabetes and MetS are more prevalent in patients with PA than in controls matched for sex, age, BMI, and blood pressure. This may explain in part the increased cardiovascular disease morbidity and mortality in PA patients.

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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Author contribution statement

G Hanslik, H Wallaschofski, M Quinkler, and A Hannemann contributed equally to this work. H Wallaschofski, A Hannemann, G Hanslik, and M Quinkler designed the study and wrote the manuscript. I Quack and L C Rump recruited patients. G Hanslik, A Dietz, A Riemer, K Lang, H S Willenberg, F Beuschlein, M Quinkler, and K Lang recruited patients, performed tests, and researched data. G Hanslik and A Hannemann performed statistical analysis. M Reincke, F Beuschlein, B Allolio, H S Willenberg, I Quack, L C Rump, H Wallaschofski, and M Quinkler reviewed/edited the manuscript.

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References

- Hannemann A & Wallaschofski H. Prevalence of primary aldosteronism in patient's cohorts and in population-based studies – a review of the current literature. *Hormone and Metabolic Research* 2012 **44** 157–162. (doi:10.1055/s-0031-1295438)
- Born-Frontsberg E, Reincke M, Rump LC, Hahner S, Diederich S, Lorenz R, Allolio B, Seufert J, Schirpenbach C, Beuschlein F *et al.* Cardiovascular and cerebrovascular comorbidities of hypokalemic and normokalemic primary aldosteronism: results of the German Conn's Registry. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1125–1130. (doi:10.1210/jc.2008-2116)
- 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. *Journal of the American College of Cardiology* 2005 **45** 1243–1248. (doi:10.1016/j.jacc.2005.01.015)
- Brown NJ. Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. *Nature Reviews. Nephrology* 2013 **9** 459–469. (doi:10.1038/nrneph.2013.110)

Clinical Study	G Hanslik and others	Aldosteronism and diabetes mellitus	173:5	674

- 5 Korte S, Strater AS, Druppel V, Oberleithner H, Jeggle P, Grossmann C, Fobker M, Nofer JR, Brand E & Kusche-Vihrog K. Feedforward activation of endothelial ENaC by high sodium. *FASEB Journal* 2014 **28** 4015–4025. (doi:10.1096/fj.14-250282)
- 6 Van Gaal LF, Mertens IL & De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006 **444** 875–880. (doi:10.1038/nature05487)
- 7 Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J & Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *New England Journal of Medicine* 2003 **348** 1309–1321. (doi:10.1056/NEJMoa030207)
- 8 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J & Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *New England Journal of Medicine* 1999 **341** 709–717. (doi:10.1056/NEJM199909023411001)
- 9 Hao G, Wang Z, Guo R, Chen Z, Wang X, Zhang L & Li W. Effects of ACEI/ARB in hypertensive patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled studies. *BMC Cardiovascular Disorders* 2014 **14** 148. (doi:10.1186/1471-2261-14-148)
- 10 Al-Mallah M, Khawaja O, Sinno M, Alzohaili O & Samra AB. Do angiotensin converting enzyme inhibitors or angiotensin receptor blockers prevent diabetes mellitus? A meta-analysis *Cardiology Journal* 2010 **17** 448–456.
- 11 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003 **26** (Suppl 1) S5–S20.
- 12 Ishimori M, Takeda N, Okumura S, Murai T, Inouye H & Yasuda K. Increased insulin sensitivity in patients with aldosterone producing adenoma. *Clinical Endocrinology* 1994 **41** 433–438. (doi:10.1111/j.1365-2265.1994.tb02573.x)
- 13 Sindelka G, Widimsky J, Haas T, Prazny M, Hilgertova J & Skrha J. Insulin action in primary hyperaldosteronism before and after surgical or pharmacological treatment. *Experimental and Clinical Endocrinology & Diabetes* 2000 **108** 21–25.
- 14 Strauch B, Widimsky J, Sindelka G & Skrha J. Does the treatment of primary hyperaldosteronism influence glucose tolerance? *Physiological Research* 2003 **52** 503–506.
- 15 Skrha J, Haas T, Sindelka G, Prazny M, Widimsky J, Cibula D & Svacina S. Comparison of the insulin action parameters from hyperinsulinemic clamps with homeostasis model assessment and QUICKI indexes in subjects with different endocrine disorders. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 135–141. (doi:10.1210/jc.2002-030024)
- 16 Fallo F, Veglio F, Bertello C, Sonino N, Della Mea P, Ermani M, Rabbia F, Federspil G & Mulatero P. Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 454–459. (doi:10.1210/jc.2005-1733)
- 17 Sasaki N, Iwase M, Arima H, Nohara S, Bandai S, Yao T, Fujii K & Iida M. Overt diabetes mellitus in a patient with combined primary aldosteronism and Cushing's syndrome. *Internal Medicine* 2006 **45** 1237–1242. (doi:10.2169/internalmedicine.45.1855)
- 18 Catena C, Lapenna R, Baroselli S, Nadalini E, Colussi G, Novello M, Favret G, Melis A, Cavarape A & Sechi LA. Insulin sensitivity in patients with primary aldosteronism: a follow-up study. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3457–3463. (doi:10.1210/jc.2006-0736)
- 19 Mosso LM, Carvajal CA, Maiz A, Ortiz EH, Castillo CR, Artigas RA & Fardella CE. A possible association between primary aldosteronism and a lower β -cell function. *Journal of Hypertension* 2007 **25** 2125–2130. (doi:10.1097/HJH.0b013e3282861fa4)
- 20 Colussi G, Catena C, Lapenna R, Nadalini E, Chiuch A & Sechi LA. Insulin resistance and hyperinsulinemia are related to plasma aldosterone levels in hypertensive patients. *Diabetes Care* 2007 **30** 2349–2354. (doi:10.2337/dc07-0525)
- 21 Matrozoza 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** 605–610. (doi:10.1161/HYPERTENSIONAHA.108.122002)
- 22 Giacchetti G, Sechi LA, Rilli S & Carey RM. The renin–angiotensin–aldosterone system, glucose metabolism and diabetes. *Trends in Endocrinology and Metabolism* 2005 **16** 120–126. (doi:10.1016/j.tem.2005.02.003)
- 23 Sowers JR, Whaley-Connell A & Epstein M. Narrative review: The emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. *Annals of Internal Medicine* 2009 **150** 776–783. (doi:10.7326/0003-4819-150-11-200906020-00005)
- 24 Cooper SA, Whaley-Connell A, Habibi J, Wei Y, Lastra G, Manrique C, Stas S & Sowers JR. Renin–angiotensin–aldosterone system and oxidative stress in cardiovascular insulin resistance. *American Journal of Physiology. Heart and Circulatory Physiology* 2007 **293** H2009–H2023. (doi:10.1152/ajpheart.00522.2007)
- 25 Reincke M, Meisinger C, Holle R, Quinkler M, Hahner S, Beuschlein F, Bidlingmaier M, Seissler J & Endres S. Is primary aldosteronism associated with diabetes mellitus? Results of the German Conn's Registry *Hormone and Metabolic Research* 2010 **42** 435–439. (doi:10.1055/s-0029-1246189)
- 26 Schipf S, Werner A, Tamayo T, Holle R, Schunk M, Maier W, Meisinger C, Thorand B, Berger K, Mueller G *et al.* Regional differences in the prevalence of known type 2 diabetes mellitus in 45–74 years old individuals: results from six population-based studies in Germany (DIAB-CORE Consortium). *Diabetic Medicine* 2012 **29** e88–e95. (doi:10.1111/j.1464-5491.2012.03578.x)
- 27 Schirpenbach C, Segmiller F, Diederich S, Hahner S, Lorenz R, Rump LC, Seufert J, Quinkler M, Bidlingmaier M, Beuschlein F *et al.* The diagnosis and treatment of primary hyperaldosteronism in Germany: results on 555 patients from the German Conn Registry. *Deutsches Ärzteblatt International* 2009 **106** 305–311. (doi:10.3238/arztebl.2009.0305)
- 28 Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr & Montori VM. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 3266–3281. (doi:10.1210/jc.2008-0104)
- 29 Mulatero P, Dluhy RG, Giacchetti G, Boscaro M, Veglio F & Stewart PM. Diagnosis of primary aldosteronism: from screening to subtype differentiation. *Trends in Endocrinology and Metabolism* 2005 **16** 114–119. (doi:10.1016/j.tem.2005.02.007)
- 30 Rieder A, Fischer E, Degenhart C, Reiser MF, Bidlingmaier M, Beuschlein F, Reincke M & Quinkler M. Age below 40 or a recently proposed clinical prediction score cannot bypass adrenal venous sampling in primary aldosteronism. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** E1035–E1039. (doi:10.1210/jc.2013-3789)
- 31 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012 **35** (Suppl 1) S64–S71.
- 32 Volzke H, Alte D, Schmidt CO, Radke D, Lohrer R, Friedrich N, Aumann N, Lau K, Piontek M, Born G *et al.* Cohort profile: The Study of Health In Pomerania. *International Journal of Epidemiology* 2011 **40** 294–307. (doi:10.1093/ije/dyp394)
- 33 John U, Greiner B, Hensel E, Ludemann J, Piek M, Sauer S, Adam C, Born G, Alte D, Greiser E *et al.* Study of Health In Pomerania (SHIP): a health examination survey in an east German region: objectives and design. *Sozial- und Präventivmedizin* 2001 **46** 186–194.
- 34 Hannemann A, Friedrich N, Ludemann J, Volzke H, Rettig R, Peters J, Reincke M, Doring A, Nauck M & Wallaschofski H. Reference intervals for aldosterone, renin, and the aldosterone-to-renin ratio in the population-based Study of Health In Pomerania (SHIP-1). *Hormone and Metabolic Research* 2010 **42** 392–399. (doi:10.1055/s-0030-1247545)

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- 35 Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM & Smith SC Jr. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009 **120** 1640–1645. (doi:10.1161/CIRCULATIONAHA.109.192644)
- 36 Luders S, Hammersen F, Kulschewski A, Venneklaas U, Zuchner C, Gansz A, Schnieders M, Pfarr E, Sturm CD, Paar WD *et al.* Diagnosis of impaired glucose tolerance in hypertensive patients in daily clinical practice. *International Journal of Clinical Practice* 2005 **59** 632–638. (doi:10.1111/j.1742-1241.2005.00518.x)
- 37 Fischer E, Reuschl S, Quinkler M, Rump LC, Hahner S, Bidlingmaier M & Reincke M. Assay characteristics influence the aldosterone to renin ratio as a screening tool for primary aldosteronism: results of the German Conn's Registry. *Hormone and Metabolic Research* 2013 **45** 526–531. (doi:10.1055/s-0033-1343448)
- 38 Bergstralh EJ & Kosanke JL. Computerized matching of cases to controls. Technical Report Number 56. The Mayo Foundation 1995. Available from <http://www.mayo.edu/research/departments-divisions/division-biomedical-statistics-informatics/technical-reports>. Accessed 14th April 2015.
- 39 Jin HM, Zhou DC, Gu HF, Qiao QY, Fu SK, Liu XL & Pan Y. Antioxidant N-acetylcysteine protects pancreatic β -cells against aldosterone-induced oxidative stress and apoptosis in female *db/db* mice and insulin-producing MIN6 cells. *Endocrinology* 2013 **154** 4068–4077. (doi:10.1210/en.2013-1115)
- 40 Sherajee SJ, Fujita Y, Rafiq K, Nakano D, Mori H, Masaki T, Hara T, Kohno M, Nishiyama A & Hitomi H. Aldosterone induces vascular insulin resistance by increasing insulin-like growth factor-1 receptor and hybrid receptor. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2012 **32** 257–263. (doi:10.1161/ATVBAHA.111.240697)
- 41 Urbanet R, Pilon C, Calcagno A, Peschechera A, Hubert EL, Giacchetti G, Gomez-Sanchez C, Mulatero P, Toffanin M, Sonino N *et al.* Analysis of insulin sensitivity in adipose tissue of patients with primary aldosteronism. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 4037–4042. (doi:10.1210/jc.2010-0097)
- 42 Fischer E, Adolf C, Pallauf A, Then C, Bidlingmaier M, Beuschlein F, Seissler J & Reincke M. Aldosterone excess impairs first phase insulin secretion in primary aldosteronism. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 2513–2520. (doi:10.1210/jc.2012-3934)
- 43 Corry DB & Tuck ML. The effect of aldosterone on glucose metabolism. *Current Hypertension Reports* 2003 **5** 106–109. (doi:10.1007/s11906-003-0065-2)
- 44 Fallo F, Federspil G, Veglio F & Mulatero P. The metabolic syndrome in primary aldosteronism. *Current Diabetes Reports* 2008 **8** 42–47. (doi:10.1007/s11892-008-0009-y)
- 45 Helderma JH, Elahi D, Andersen DK, Raizes GS, Tobin JD, Shockey D & Andres R. Prevention of the glucose intolerance of thiazide diuretics by maintenance of body potassium. *Diabetes* 1983 **32** 106–111. (doi:10.2337/diab.32.2.106)
- 46 Rowe JW, Tobin JD, Rosa RM & Andres R. Effect of experimental potassium deficiency on glucose and insulin metabolism. *Metabolism* 1980 **29** 498–502. (doi:10.1016/0026-0495(80)90074-8)
- 47 Chatterjee R, Yeh HC, Shafi T, Selvin E, Anderson C, Pankow JS, Miller E & Brancati F. Serum and dietary potassium and risk of incident type 2 diabetes mellitus: the Atherosclerosis Risk in Communities (ARIC) study. *Archives of Internal Medicine* 2010 **170** 1745–1751. (doi:10.1001/archinternmed.2010.362)
- 48 Howell SL & Taylor KW. Potassium ions and the secretion of insulin by islets of Langerhans incubated *in vitro*. *Biochemical Journal* 1968 **108** 17–24. (doi:10.1042/bj1080017)
- 49 Luther JM, Luo P, Kreger MT, Brissova M, Dai C, Whitfield TT, Kim HS, Wasserman DH, Powers AC & Brown NJ. Aldosterone decreases glucose-stimulated insulin secretion *in vivo* in mice and in murine islets. *Diabetologia* 2011 **54** 2152–2163. (doi:10.1007/s00125-011-2158-9)
- 50 Ronconi V, Turchi F, Rilli S, Di Mattia D, Agostinelli L, Boscaro M & Giacchetti G. Metabolic syndrome in primary aldosteronism and essential hypertension: relationship to adiponectin gene variants. *Nutrition, Metabolism, and Cardiovascular Diseases* 2010 **20** 93–100. (doi:10.1016/j.numecd.2009.03.007)
- 51 Iacobellis G, Petramala L, Cotesta D, Pergolini M, Zinmascosca L, Cianci R, De Toma G, Sciomer S & Letizia C. Adipokines and cardiometabolic profile in primary hyperaldosteronism. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 2391–2398. (doi:10.1210/jc.2009-2204)
- 52 Somloova Z, Widimsky J Jr, Rosa J, Wichterle D, Strauch B, Petrak O, Zelinka T, Vlkova J, Masek M, Dvorakova J *et al.* The prevalence of metabolic syndrome and its components in two main types of primary aldosteronism. *Journal of Human Hypertension* 2010 **24** 625–630. (doi:10.1038/jhh.2010.65)

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