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Title: Primary aldosteronism and obstructive sleep apnea: a cross-sectional multi-ethnic study

Manuscript number: HYPE201913833DR1

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PRIMARY ALDOSTERONISM AND OBSTRUCTIVE SLEEP APNEA: A CROSS-SECTIONAL MULTI-ETHNIC STUDY

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Short title: Primary aldosteronism and obstructive sleep apnea

Word count: abstract: 247; manuscript: 3527 (excluding references, figure legends and tables)

Abstract

The association between primary aldosteronism (PA) and obstructive sleep apnea (OSA) has been a matter of debate. 2016 Endocrine Society guideline recommends screening for PA all hypertensive patients with OSA.

We designed a multicentre, multi-ethnic, cross-sectional study to evaluate the prevalence of PA in patients with OSA and the prevalence of OSA in unselected patients with PA.

203 patients with OSA (102 Caucasians and 101 Chinese) were screened for PA and 207 patients with PA (104 Caucasians, 100 Chinese and 3 of African descent) were screened for OSA by cardio-respiratory polygraphy. Eighteen patients with OSA (8.9%) had PA (11.8% of Caucasian and 5.9% of Chinese ethnicity). In patients without other indications for PA screening, the prevalence of PA dropped to 1.5%. The prevalence of OSA in patients with PA was 67.6%, consistent in both Caucasian and Chinese patients. A correlation between aldosterone levels and apnea/hypopnea index was observed in Caucasian patients with PA (R^2 = 0.360, p = 0.013), but not in Chinese patients. Multinomial logistic regression confirmed a significant and independent association between plasma aldosterone levels and moderate to severe OSA diagnosis in Caucasian patients (OR 1.002, p=0.002).

In conclusion, aldosterone levels may contribute to the severity of OSA in Caucasian patients with hyperaldosteronism, but patients with OSA are not at high risk of PA. Results of the present study challenge the current recommendation of the Endocrine Society guideline that all patients with OSA should be screened for PA, irrespective of the grade of hypertension.

Key words: aldosterone, primary aldosteronism, obstructive sleep apnea, sleep disorders, apnea-hypopnea index

Introduction

Obstructive sleep apnea (OSA) is the most frequent secondary condition associated with resistant hypertension (RH). [1] Taking into account moderate and severe forms of OSA, the prevalence among patients with RH ranges from 45% to 80% and up to 95% among patients with refractory hypertension.[1-5] Primary aldosteronism (PA) is the most common secondary endocrine cause of hypertension, and its prevalence can be as high as 20% among patients with RH.[6] In agreement with these data, 2017 ACC/AHA hypertension guideline and the 2018 AHA Scientific Statement on Resistant Hypertension recommend screening all patients with RH for PA.[7,8] In patients with RH, rostral fluid displacement is related to the severity of OSA and treatment with mineralocorticoid receptor (MR) antagonists reduces legs-to-neck fluid redistribution and the apnea hypopnea index (AHI).[9-11] It has been speculated that the high prevalence of OSA in RH patients could be related to the high prevalence of autonomous aldosterone secretion in this specific subpopulation.[12]

In the last 20 years, several efforts have been devoted to investigate the bidirectional relationship between aldosterone levels and sleep apnea disorders: some studies identified an association between aldosterone levels and AHI, or OSA diagnosis, but only in specific subgroups of patients or exclusively in patients with RH, yielding conflicting results.[13]

Albeit supporting evidence is limited, the 2016 Endocrine Society (ES) guideline recommend screening for PA all the patients affected by arterial hypertension and OSA.[14] We report here the results of the HYpertensives with Primary aldosteronism aNd OSas (HYPNOS) study, undertaken to investigate the prevalence of PA in a large cohort of Caucasian and Chinese hypertensive patients with OSA, and the prevalence of OSA in a cohort of Caucasian and Chinese patients affected by PA.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study design and patients

The protocol was approved by the local ethical committees of all the participant centers and written informed consent was obtained from all patients recruited.

The cohort of the HYPNOS study was enrolled in seven different centers: four Italian centers (Turin, Ancona, Padova, Verona), one German center (Munich), one Chinese center (Chongqing), one Taiwanese center (Taipei) (Tables S1).

Between 10/2016 and 09/2018 410 patients were enrolled: 207 affected by PA (Group 1) (including 104 of Caucasian ethnicity, 100 of Chinese ethnicity and 3 of other origin) and 203 with OSA (Group 2) (102 Caucasians and 101 Chinese). The only criterion for inclusion in Group 1 was confirmed diagnosis of PA according with the Endocrine Society guideline, while criteria for inclusion in Group 2 were I) diagnosis of OSA with AHI ≥15 or AHI≥5 together with symptoms requiring Continuous Positive Airway Pressure (CPAP) treatment (such as daytime somnolence, fatigue, insomnia, mood disorders, or cognitive impairment), and II) a diagnosis of arterial hypertension according with European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline.[14-17] Criteria for exclusion were: for Group 1 patients with PA under MRA therapy or previously adrenalectomized for unilateral primary aldosteronism; for Group 2: any absolute contraindication to perform a confirmatory test for PA.

All 203 patients diagnosed with OSA were screened for PA and all 207 patients with PA diagnosis were evaluated for sleeping disorders.

Diagnosis of primary aldosteronism

PA was diagnosed according to 2016 ES guideline.[14] All interfering antihypertensive drugs were stopped at least 2 weeks before screening (at least 4 weeks for diuretics). At least one of saline infusion test, fludrocortisone suppression test or captopril challenge test was used to confirm PA diagnosis according to the centre protocol (Table S1). Subtype diagnosis was performed by computed tomography scanning of the adrenal glands and subsequent adrenal venous sampling (AVS). AVS data were interpreted according to the centers protocol (Table S1).

Obstructive sleep apnea measures

Sleep apnea was assessed with a validated cardio-respiratory polygraphy with at least 8 standard channels, recording oronasal flow, snoring, thoracic and abdominal respiratory movements, finger pulse oximetry, body position, and electrocardiogram. Apnea was defined as a reduction of oronasal flow ≥90% for ≥10 seconds. Hypopnea was defined as a ≥ 30 % reduction in oronasal flow for ≥10 seconds, associated with oxygen desaturation of ≥3% or arousal.[15] The Apnea Hypopnea Index (AHI) was defined as the total number of apneas plus hypopneas per hour of recording time. OSA was defined as AHI ≥5 and classified as mild (AHI ≥5 to <15), moderate (AHI ≥15 to <30), or severe (AHI ≥30). Epworth Sleepiness Scale (ESS) was administered to assess daytime sleepiness before CPAP treatment.

Hypertension, cardiovascular events, diabetes and metabolic syndrome definition

Blood pressure levels were assessed by three consecutive BP measurements in the sitting position, according to 2018 ESC/ESH guideline.[16,17] The list of validated devices used for BP measurement in the different centers is provided in the Online supplement. We defined arterial hypertension as systolic blood pressure (SBP) ≥ 140 mmHg and DBP ≥ 90 mmHg and we classified hypertension in three different grades according to 2018 ESC/ESH guideline.[16,17] The intensity of antihypertensive medication was calculated as daily defined

dose (DDD). We calculate defined daily dose with the online tool available at https://github.com/ABurrello/PASOPredictor/raw/master/00 - PASO Predictor.xlsm.[18]

Diabetes was defined according to 2015 American Diabetes Association criteria.[19]

Metabolic syndrome was defined according to International Diabetes Federation criteria.[20]

Statistical Analysis.

IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, New York) was used for statistical analyses. PAC, PRA, ARR, AHI, ESS, triglycerides and GFR data were analyzed with non-parametric test or log transformed due to non-normality, according to Kolmogorov-Smirnov test. Results are expressed for continuous variables with a normal distribution as mean ± standard deviation (SD). Non-normal distributions are expressed as median (interquartile range, IQR). Statistical significance between groups was calculated in normally distributed data by Student *t* test for independent samples. Mann-Whitney U test was used for non-normally distributed data and chi-square test or the Fisher exact test for qualitative variables. Pearson's correlation was performed to correlate aldosterone and AHI. Logistic regression models were performed to evaluate the odds ratio (OR) of the available variables for moderate-severe OSA. All the variables that had $p < 0.05$ at the univariate analysis or considered relevant on the basis of the descriptive analysis were included in the multinomial model. Multinomial logistic regression was performed to predict moderate to severe OSA diagnosis, correcting for age, sex, ethnicity, waist circumference, neck circumference, systolic blood pressure (SBP), high-density lipoprotein cholesterol (HDL), triglycerides, fasting glucose, PA subtype diagnosis, and plasma aldosterone or the categorical variable.

Results

OSA and PA cohorts

A total of 203 patients with OSA and indication for continuous positive airway pressure (CPAP) treatment were enrolled. According to AHI, 19 were affected by mild OSA (9.4%), 55 by moderate OSA (27.1%) and 129 by severe OSA (63.5%).

Two hundred and seven patients with PA were recruited: 97 patients were affected by unilateral aldosterone producing adenoma (APA), 63 by idiopathic hyperaldosteronism (IHA) and in 47 patients a definitive subtype diagnosis was not achieved, since the AVS was unsuccessful, not considered indicated by the treating physicians (for example because of advanced age) or refused by the patients. Clinical and biochemical parameters of the included patients are reported in Table 1.

Prevalence of PA in patients with OSA

The prevalence of PA in patients affected by OSA was 8.9 % (18/203, 95% CI 5.7–13.6), a figure not significantly different either from the 5.9% (p=0.10) observed in the general hypertensive population or from the 11.2% of the referral centers (p=0.32).[21,22]

Of note, in our cohort of patients affected by OSA, 136 out of 203 patients (67%) had at least another indication for being screened for PA (among SBP above 150 mmHg, DBP above 100 mmHg or hypokalemia), while in 67/203 patients (33%) the presence of OSA was the only indication. In this latter subgroup, only 1 patient (of Chinese ethnicity) was diagnosed as affected by PA, resulting in a prevalence of 1.5% (0.3–8.0).

After subtype diagnosis, ten patients were classified as affected by IHA, seven by APA and one patient, who refused AVS, was classified as undetermined (Figure 1A).

As expected, the prevalence of PA increased with the severity of hypertension: from 2.9% (1.0–8.1), in grade 1 to 22.0% (12.0–36.7) in grade 3 (p=0.001) (Figure S1A), while it was not different in OSA stages (Figure S1B); similarly, in the overall cohort, aldosterone and PRA levels were not different in the three OSA stages.

OSA patients with PA showed higher SBP, higher DBP and lower potassium levels compared with OSA patients without PA, as detailed in Table 2, while no difference was observed in terms of AHI or sleepiness symptoms.

We analysed factors associated with the diagnosis of PA in OSA cohort in adjusted and unadjusted analyses (Table S2 and S3): after correction for confounding variables, patients with higher SBP and lower potassium levels had an increased likelihood of having PA.

Compared with Caucasian OSA cohort, Chinese patients showed increased OSA severity and sleepiness symptoms and lower SBP and K^+ levels (Table 3).

The prevalence of PA was 11.8% (6.9–59.4) in Caucasian patients with OSA (12/102) and 5.9% (2.7–12.4;) in the Chinese cohort (6/101) (p=0.144) (Figure 1B-C). PRA levels were significantly lower in Caucasians (Table 3), even after exclusion of patients with PA (Table S4).

Prevalence of OSA in patients with PA

Of the 207 patients with a confirmed diagnosis of PA, 140 (67.6%; 61.0–73.6) had a diagnosis of OSA: 27.1% mild (21.5–33.5), moderate 21.7% (16.7–27.8) and severe 18.8% (14.1–24.7) (Figure 2A).

Considering that CPAP treatment is recommended in patients with AHI ≥ 15 even without symptoms or CV risk factors, we compared PA patients with moderate-severe OSA (AHI ≥ 15) to PA patients with mild or no OSA (AHI < 15), as detailed in Table 2.

While in the overall cohort of patients affected by PA, aldosterone levels did not differ significantly between patients with moderate-severe OSA and patients with mild or no OSA, subgroup analysis revealed that Caucasian patients affected by PA and AHI ≥15 had significantly higher aldosterone levels compared with patients with AHI <15 (802 pmol/L [IQR 555–1176] *vs* 646 pmol/L [436–914]; p=0.017), while no difference was present in Chinese patients with PA (Table S5).

Prevalence of OSA in patients with PA was similar in Chinese and Caucasian patients (Figure 2B-C), however, according to AHI, Chinese patients showed a more severe phenotype (p=0.016) (Table 4).

Taking into account only patients with a definitive subtype diagnosis of PA, OSA was more prevalent in PA patients with IHA than APA (75.8% [63.8–84.7] *vs* 59.2% [49.3–68.4]; p=0.031) (Figure S1C and Table S6). Consistently, patients with IHA had a higher BMI (p=0.002) and waist circumference, among females (p<0.001), compared with unilateral PA (Table S7). Pearson's analysis demonstrated a significant correlation between aldosterone levels and AHI in both unilateral (R^2=0.360; p=0.013) and bilateral (R^2=0.362; p=0.013) forms, and in the overall group of Caucasian patients with PA (R^2=0.225; p=0.016), but not in the Chinese cohort (Figure S2-S3). There was no significant association between aldosterone and AHI in non-PA patients (p=0.443), however, the absence of non-PA patients without OSA and the presence of few non-PA patients with mild OSA might have affected the results. Multinomial logistic regression demonstrated a significant association of aldosterone levels and moderate-severe OSA in all patients with PA (OR 1.001 [95% CI 1.000–1.002]; p=0.005), after correction for age, sex, waist and neck circumference, SBP, fasting glucose, HDL, triglycerides levels, ethnicity and subtype diagnosis (Tables S8-S9). Interestingly, the same analysis divided for ethnicity demonstrated a significant association only in Caucasian (OR 1.002 [1.001–1.003]; p=0.002), but not in Chinese patients with PA (OR 0.998 [0.998–1.002]; p=0.384). Other predictive factors of moderate-severe OSA were male sex and glucose levels in the Caucasian group with PA, and male sex, waist circumference and age in Chinese patients (Table S10).

We repeated the same analysis, dichotomizing serum aldosterone levels according with the median level of the global PA cohort, with a threshold of 750 pmol/l (27.04 ng/dl), demonstrating an OR of 8.264 (2.410–28.571; p=0.001) for Caucasian patients with

aldosterone ≥750 pmol/l. In agreement with previous results, no significant difference was present in Chinese patients with PA (Tables S11-S12).

Discussion

To the best of our knowledge, the HYPNOS study is the largest study aimed at assessing the prevalence of PA in a multi-ethnic cohort of patients affected by OSA and the first study aimed at assessing the prevalence of OSA in unselected patients affected by PA.

The main findings of our study are that, in the overall cohort of hypertensive patients affected by OSA, the prevalence of primary aldosteronism did not differ significantly from the prevalence observed in the general hypertensive population, while, in Caucasian patients affected by PA, aldosterone levels contribute to the severity of OSA.

Prevalence of PA in patients with OSA

The observed association between aldosterone excess and increased prevalence of cardio- and cerebrovascular comorbidities, which result into an increased risk for incident mortality, represents a strong rationale for pursuing the diagnosis of PA.[23,24] However, since there is not a typical phenotype to guide the clinicians, the Endocrine Society guideline identifies high-risk groups of hypertensive patients that should be screened for PA, including those with OSA.[14,25] While convincing evidence, including a cost-effectiveness study, supports the recommendation of screening patients with SBP above 150 mmHg, DBP above 100 mmHg, patients with RH, hypokalaemia or with an adrenal incidentaloma, the evidence for patients with OSA is limited.[26] According to a single study, the prevalence of PA in a referred group of hypertensive patients with OSA resulted to be 34%, but the sample size was small (53 patients) and all the recruited patients with OSA were symptomatic for sleepiness symptoms, which account only for a subgroup of patients with sleep apnea.[27,28]

In the HYPNOS study, the prevalence of PA in patients with OSA and requiring CPAP treatment, resulted to be 8.9%, a figure not significantly different either from the 5.9% observed in the general hypertensive population of the PATO study or from the 11.2% of the referred patients from the PAPY study.[21,22] Interestingly, when considering only the subgroup of patients without hypokalaemia or SBP ≥ 150 mmHg or DBP ≥ 100 or RH (the main indications for PA screening), a very low prevalence of 1.5% was detected.

The results of our subgroup analysis, showing that PA prevalence did not increase with the severity of OSA, that PRA and aldosterone levels were not significantly different in OSA stages and that severity of OSA was not associated with PA diagnosis, further support the epidemiological observation that patients affected by OSA do not represent a category of subjects with high prevalence of PA. The reported results are consistent in both ethnicities of Caucasian and Chinese patients.

Prevalence of OSA in patients with PA

OSA is a highly prevalent disorder in the general population, with a reported prevalence comprised between 9 and 38%, considering a cut-off of AHI ≥ 5.[29] Studies evaluating the prevalence of OSA in hypertensive cohorts reported a prevalence from 37 to 48% in Caucasian patients with hypertension and 70.5% in Chinese hypertensives.[30-33] In patients with RH the prevalence is remarkably high, up to 80%, and even higher in patients with refractory hypertension.[4]

We reported herein for the first time the prevalence of OSA in a large cohort of 207 unselected patients with PA, which resulted to be 67.6% in the overall cohort, 64.4% in Caucasian and 70.0% in Chinese patients respectively.

To date, the available data on the prevalence of OSA in patients with PA was limited to two small cohort of less than 50 patients affected by RH, showing a prevalence of 78.1% and 84%, respectively.[2,5] Moreover, it must be acknowledged that in the study by Gonzaga et al.

not in all patients the diagnosis of PA was in agreement with the Endocrine Society recommendations.

In our study, the prevalence of OSA in Caucasian patients with PA appears to be higher than previously reported, while the prevalence of OSA in Chinese patients with PA was similar to that reported in Chinese patients with essential hypertension.[30-33]

In agreement with a previous study, a correlation between aldosterone levels and AHI was present in Caucasian patients with PA, but not in the overall cohort or in the Chinese subgroup of patients with PA.[5]

The role of ethnic difference in OSA risk factors was previously evaluated by several studies, particularly focusing on the role of anthropometric differences in cranio-mandibular anatomy and different body fat distribution.[34,35] Furthermore, Asians salt intake is higher than in Caucasians, together with an augmented salt-sensitivity of blood pressure, potentially contributing to increased fluid retention.[36] Therefore, it is possible to speculate that the role of aldosterone might be less relevant in Chinese ethnicity, because of anatomical predisposing factors and a high salt intake.

In agreement with our observation, treatment with MR antagonists significantly reduced AHI and specific treatment of PA, either surgical or medical, reduced the number of apnea and hypopnea.[10,11,37]

In our study, patients with PA and moderate-severe OSA were older and more likely to be male than patients with PA and no or mild OSA. They also displayed larger neck circumference and a worse metabolic profile, confirming the role of sex, obesity and anatomical characteristics. In Caucasian patients with PA, aldosterone correlates with moderate-severe OSA even after correction for these confounding variables. This leads to the hypothesis that in the presence of the known risk factors for OSA, aldosterone can

independently act as a contributing factor to the development or worsening of OSA in Caucasian patients with PA.

A potential bidirectional relationship between OSA and diabetes has been postulated since patients with OSA more often display type 2 diabetes, and diabetic neuropathy can be associated with alterations of central control of respiration and upper airways neural reflexes.[38] Aldosterone excess can play a significant role in this complex interplay since it is associated with metabolic alterations including type 2 diabetes and play a significant role in patients with severe OSA by increasing blood pressure and worsening upper airways congestion.[11,23,39]

The strengths of our study are the large number of recruited patients with PA and with OSA, the multicenter and multi-ethnic composition of the cohorts, the use of screening, confirmatory and subtyping test for PA according to the most recent international guideline, and the systematic use of cardio-respiratory poligraphy to screen for OSA. Furthermore, the prevalence of PA in patients with OSA was evaluated in a single centre for Caucasians (Torino) and in a single centre for Chinese (Taipei).

The limits of the current study are: the slightly different cut-offs for screening, confirmatory and subtype diagnosis in the different centres, the use of different kits for aldosterone, PRA and renin measurements, the relatively low number of patients with PA with subtype differentiation in the Chinese group, the lack of a single scoring centre, the lack of sodium intake and ambulatory blood pressure measurement data. Additionally, the prevalence of OSA was not assessed in a cohort of patients affected by essential hypertension referred to our centres and multinomial logistic regression in the Chinese group was partially affected by the relatively low number of female patients with moderate-severe OSA.

Perspectives

Collectively, the results of the HYPNOS study challenge the current recommendation of the Endocrine Society guideline that all patients with arterial hypertension and OSA should be tested for PA, since a systematic screening would doubtlessly increase medical costs and consequences of false-positive case detection testing.

Further studies are recommended to better elucidate the potential role of a different ethnicity on the complex and bidirectional interplay between aldosterone and OSA and whether a different response in OSA severity is present after PA specific treatment.

Contributors

P.M. and W.V.-C. are co-principal investigators; F.B., D.A.H., A.M., J.P., F.P., M.M., S.Y., Y.H.,M.-C. H., C.S., F.P. and G.G. recruited the patients; A.M. analysed and interpreted the sleep studies of patients from Torino; F.B. and S.M. did the statistical analysis; F.B., S.M. and P.M. wrote the manuscript; Q.L., F.F., F.V., M.R., and V.-C.W. interpreted the data. All the authors critically reviewed the manuscript.

Sources of Funding

Data collection in Munich was supported by the Else Kröner-Fresenius Stiftung in support of the German Conns Registry-Else-Kröner Hyperaldosteronism Registry (2013_A182 and 2015_A171 to M.R.), the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No [694913] to M.R.) and by the Deutsche Forschungsgemeinschaft (DFG) (within the CRC/Transregio 205/1 "The Adrenal: Central Relay in Health and Disease" to M.R.).

Disclosures

The authors declare no competing interests.

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1

Novelty and Significance:

What Is New?

- The prevalence of PA among patients with hypertension and OSA is not different from the prevalence reported in primary care or referral centres.
- The prevalence of PA among patients without any other indications, other than OSA diagnosis, for PA screening is low.
- The prevalence of OSA in patients affected by PA is high and aldosterone correlates with AHI in moderate-severe OSA in Caucasian patients with hyperaldosteronism.

What Is Relevant?

- For PA screening, patients affected by OSA should follow the same recommendations of the general hypertensive population.
- Results of the present study challenge the current recommendations of the Endocrine Society guideline for PA screening.

Summary

- Patients affected by OSA do not represent a category at high risk for PA, however aldosterone can independently act as a contributing factor to the development or worsening of OSA in Caucasian patients with PA.
- Ethnic differences might play a role in the interplay between OSA and aldosterone overproduction.

Figure legends

Figure 1. Prevalence of primary aldosteronism in patients with obstructive sleep apnea

(**A**) Prevalence of primary aldosteronism (PA) in the overall group of patients affected by obstructive sleep apnea (OSA). PA diagnosis is divided according to subtype diagnosis:

aldosterone producing adenoma (APA), idiopathic hyperaldosteronism (IHA), undetermined subtype diagnosis. (**B**) Prevalence of PA in Caucasian patients with OSA. **(C)** Prevalence of PA in Chinese patients with OSA.

Figure 2. Prevalence of obstructive sleep apnea in patients with primary aldosteronism. (**A**) Prevalence of obstructive sleep apnea (OSA) in the overall group of patients affected by primary aldosteronism (PA). OSA diagnosis is dived according to OSA severity: OSA mild (AHI ≥ 5 and < 15), moderate (AHI ≥ 15 and < 30), severe (AHI ≥ 30). (**B)** Prevalence of OSA in Caucasian patients with PA. **(C)** Prevalence of OSA in Chinese patients with PA.

Tables

Table 1. Clinical and biochemical parameters of patients with diagnosis of OSA or PA

Parameters	**PA (n = 207)**	**OSA (n = 203)**
Age (years)	50 ± 10	50 ± 9
Ethnicity Caucasian Chinese African descent	 104 (50.2) 100 (48.3) 3 (1.5)	 102 (50.2) 101 (49.8) -
Sex Male Female	 116 (56.0) 91 (44.0)	 159 (78.3) 44 (21.7)
BMI (kg/m^2)	26.3 ± 4.1	32.2 ± 6.5
Neck circumference (cm)	38 ± 4	42 ± 4
Waist circumference (cm) Male Female	 97.6 ±10.5 88.4 ± 11.9	 107.3 ± 15.7 104.3 ± 18.4
Central Obesity No Yes	 54 (26.1) 153 (73.9)	 18 (8.9) 185 (91.1)

SBP* (mmHg)	157 ± 16	152 ± 19
DBP* (mmHg)	97 ± 11	94 ± 12
Antihypertension medication (defined daily dose)	1.10 (0.00-3.00)	1.83 (1.00-3.00)
Fasting glucose (mmol/l)	5.41 ± 1.39	6.44 ± 2.14
Total cholesterol (mmol/l)	4.52 ± 1.02	5.07 ± 1.11
LDL (mmol/l)	2.53 ± 0.85	3.10 ± 1.06
HDL (mmol/l)	1.28 ± 0.42	1.15 ± 0.36
Triglycerides (mmol/l)	1.22 (0.83-1.90)	1.48 (1.08-2.14)
GFR (ml/min/1.73m^2)	103 (84-122)	112 (94-137)
Sodium (mmol/l)	143 ± 3	140 ± 3
Potassium (mmol/l)	3.5 ± 0.6	4.0 ± 0.5
Diabetes No IFG Yes	 161 (77.8) 20 (9.7) 26 (12.6)	 88 (43.3) 49 (24.1) 66 (32.5)
Metabolic Syndrome No Yes	 124 (59.9) 83 (40.1)	 46 (22.7) 157 (77.3)

PA = primary aldosteronism; OSA = obstructive sleep apnea; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL = low density lipoproteins; HDL = high density lipoproteins; GFR= glomerular filtration rate; IFG = impaired fasting glucose. *at first visit. Values are mean ± SD, median (IQR) or absolute number (%).

Table 2. Clinical and biochemical parameters of patients affected by OSA with and without PA and patients affected by PA with AHI < or ≥ 15

	Patients with OSA (n = 203)			Patients with PA (n = 207)		
Parameters	**Non PA (n=185)**	**PA (n=18)**	**P value**	**AHI < 15 (n = 123)**	**AHI ≥ 15 (n = 84)**	**P value**
PRA (ng/mL/h)	1.90 (1.09-4.31)	0.42 (0.18-0.53)	< 0.001	0.3 (0.2-0.5)	0.1 (0.1-0.4)	0.072
Direct renin (mU/L)	-	-	-	2.1 (1.0-5.6)	2.0 (0.7-4.5)	0.402
Aldosterone (pmol/L)	419 (294-619)	865 (568-1429)	< 0.001	655 (455-965)	759 (495-1101)	0.098
AHI	37 (23-66)	38 (17-52)	0.607	4.4 (1.4-8.5)	28.1 (19.8-44.1)	< 0.001
ESS	8 (5-12)	8 (5-12)	0.626	6 (3-8)	6 (4-10)	0.472
Age (years)	50 ± 10	50 ± 9	0.984	48 ± 10	53 ± 9	0.001
Sex Male Female	 143 (77.3) 42 (22.7)	 16 (88.9) 2 (11.1)	0.255	 51 (41.5) 72 (58.5)	 65 (77.4) 19 (22.6)	< 0.001
BMI (kg/m^2)	32.1 ± 6.7	32.8 ± 4.5	0.682	25.7 ± 4.2	27.3 ± 3.8	0.004
Neck circumference (cm)	42 ± 4	44 ± 2	0.072	38 ± 4	40 ± 4	< 0.001
Waist circumference (cm) Male Female	 107.2 ± 16.3 103.8 ± 18.7	 107.9 ± 9.3 114.0 ± 1.4	 0.868 0.450	 95.4 ± 9.6 88.2 ± 12.9	 99.2 ± 10.9 89.0 ± 7.4	 0.049 0.800

Central Obesity No Yes	 18 (9.7) 167 (90.3)	 0 (0.0) 18 (100.0)	0.166	 38 (30.9) 85 (69.1)	 16 (19.0) 68 (81.0)	0.057
SBP* (mmHg)	151 ± 19	168 ± 16	< 0.001	155 ± 16	160 ± 16	0.040
DBP* (mmHg)	94 ± 12	100 ± 11	0.030	96 ± 11	98 ± 11	0.098
Antihypertensive medications (defined daily dose)	1.50 (0.71-2.53)	2.75 (1.37-4.0)	0.022	1.00 (0.00-3.00)	1.15 (0.00-2.50)	0.653
Fasting glucose (mmol/l)	6.43 ± 2.15	6.56 ± 2.00	0.807	5.12 ± 0.93	5.87 ± 1.82	0.001
Total cholesterol (mmol/l)	5.10 ± 1.12	4.75 ± 0.90	0.210	4.56 ± 0.98	4.47 ± 1.09	0.556
LDL (mmol/l)	3.14 ± 1.06	2.75 ± 1.00	0.137	2.58 ± 0.83	2.46 ± 0.88	0.337
HDL (mmol/l)	1.15 ± 0.36	1.15 ± 0.27	0.999	1.34 ± 0.40	1.19 ± 0.44	0.015
Triglycerides (mmol/l)	1.48 (1.09-2.11)	1.61 (1.02-2.82)	0.645	1.16 (0.81-1.70)	1.48 (0.99-2.28)	0.004
GFR (ml/min/1.73m^2)	110 (94-137)	125 (102-140)	0.420	105 (87-122)	99 (81-117)	0.190
Sodium (mmol/l)	140 ± 3	141 ± 4	0.111	142 ± 3	144 ± 3	0.011
Potassium (mmol/l)	4.0 ± 0.5	3.6 ± 0.5	0.002	3.6 ± 0.6	3.5 ± 0.6	0.213
Diabetes No IFG Yes	 81 (43.8) 43 (23.2) 61 (33.0)	 7 (38.9) 6 (33.3) 5 (27.8)	0.632	 105 (85.4) 11 (8.9) 7 (5.7)	 56 (66.7) 9 (10.7) 19 (22.6)	0.001

Metabolic Syndrome			0.963			0.125
No	42 (22.7)	4 (22.2)		79 (64.2)	45 (53.6)	
Yes	143 (77.3)	14 (77.8)		44 (35.8)	39 (46.4)	
CV events			0.660			0.262
No	161 (87.0)	15 (83.3)		114 (92.7)	74 (88.1)	
Yes	24 (13.0)	3 (16.7)		9 (7.3)	10 (11.9)	

PA = primary aldosteronism, OSA = obstructive sleep apnea, AHI = apnea hypopnea index, PRA = plasma renin activity, ESS = Epworth Sleepiness Scale, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL = low density lipoproteins, HDL = high density lipoproteins, GFR= glomerular filtration rate, IFG = impaired fasting glucose, CV = cardiovascular. *at first visit. Values are mean ± SD, median (IQR) or absolute number (%). *P* values are calculated with Student's *t* test, Mann-Whitney U test or chi square test.

Table 3. Clinical and biochemical parameters of patients with OSA stratified by ethnicity

Parameters	Caucasian (n=102)	Chinese (n=101)	P-value
AHI	27.7 (16.8-42.0)	55.7 (32.6-80.4)	< 0.001
ESS	6 (3-8)	11 (8-16)	< 0.001
PRA (ng/mL/h)	1.3 (0.5-2.5)	2.5 (1.1-5.1)	< 0.001
Aldosterone (pmol/L)	449 (298-681)	428 (310-624)	0.970
Age (years)	53 ± 8	47 ± 10	<0.001
Sex Male Female	 75 (73.5) 27 (26.5)	 84 (83.2) 17 (16.8)	0.096
BMI (kg/m^2)	30.8 ± 5.8	33.5 ± 6.9	0.003
Neck circumference (cm)	43 ± 3	42 ± 4	0.054
Waist circumference (cm) Male Female	 105.5 ± 10.6 106.0 ± 20.8	 108.7 ± 19.0 101.6 ± 13.9	 0.184 0.446
Central Obesity No Yes	 13 (12.7) 89 (87.3)	 5 (5.0) 96 (95.0)	0.051
SBP* (mmHg)	158 ± 16	146 ± 20	<0.001
DBP* (mmHg)	95 ± 9	93 ± 15	0.501
Antihypertensive medications (defined daily dose)	1.91 (1.00-3.07)	1.50 (0.50-2.50)	0.452
Fasting glucose (mmol/l)	5.81 ± 1.45	7.08 ± 2.50	<0.001
Total cholesterol (mmol/l)	5.50 ± 1.03	4.64 ± 1.02	<0.001
LDL (mmol/l)	3.40 ± 1.00	2.80 ± 1.03	<0.001
HDL (mmol/l)	1.29 ± 0.36	1.01 ± 0.29	<0.001
Triglycerides (mmol/l)	1.46 (1.04-2.08)	1.51 (1.16-2.32)	0.266
GFR (ml/min/1.73m^2)	115 (100-136)	107 (91-148)	0.388

Sodium (mmol/l)	141 ± 3	138 ± 3	<0.001
Potassium (mmol/l)	4.1 ± 0.4	3.8 ± 0.5	<0.001
Diabetes			< 0.001
No	68 (66.7)	20 (19.8)	
IFG	22 (21.6)	27 (26.7)	
Yes	12 (11.8)	54 (53.5)	
Metabolic Syndrome			< 0.001
No	36 (35.3)	10 (9.9)	
Yes	66 (64.7)	91 (90.1)	

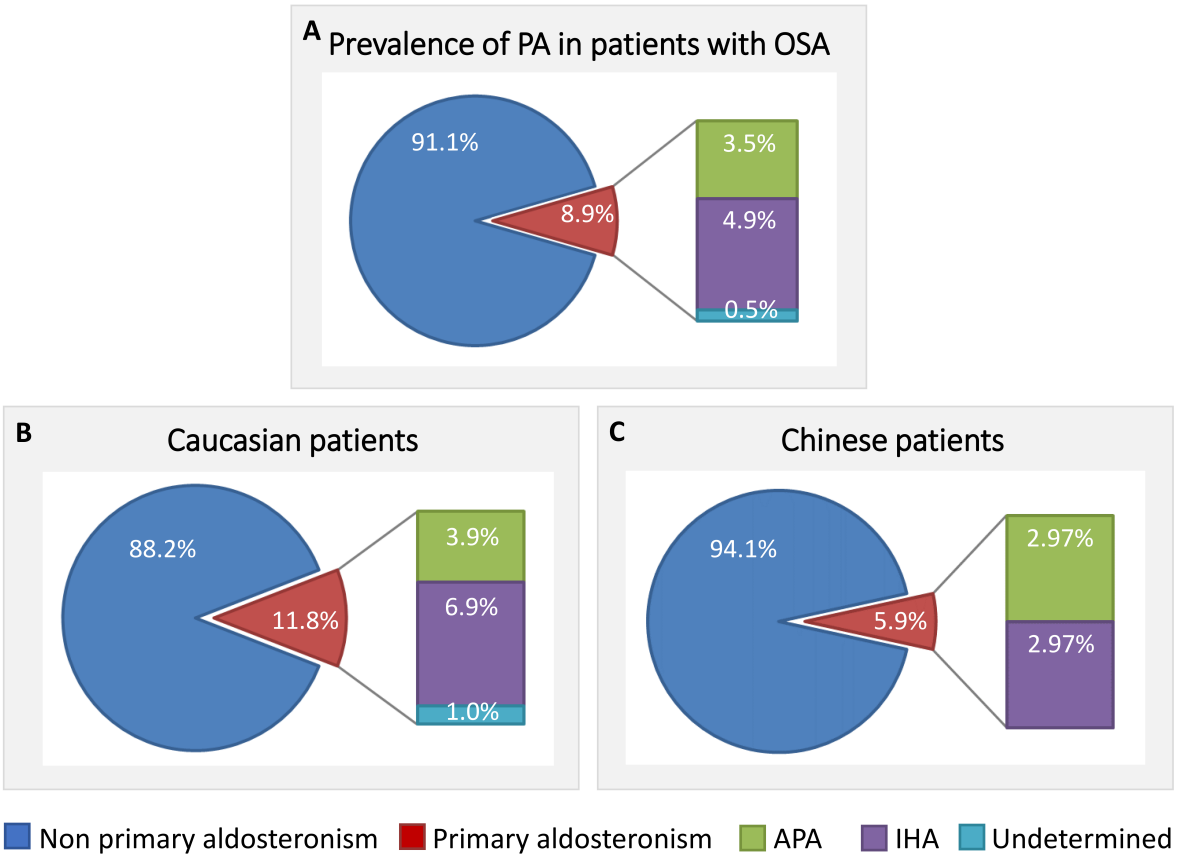
OSA = obstructive sleep apnea, AHI = apnea hypopnea index, PRA = plasma renin activity, ESS = Epworth Sleepiness Scale, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL = low density lipoproteins, HDL = high density lipoproteins, GFR= glomerular filtration rate, IFG = impaired fasting glucose. *at first visit Values are mean ± SD, median (IQR) or absolute number (%). *P* values are calculated with Student's *t* test, Mann-Whitney U test or chi square test.

Table 4. Clinical and biochemical parameters of patients with PA stratified by ethnicity

Parameters	**Caucasian (n=104)**	**Chinese (n=100)**	**P value**
AHI	8.5 (2.2-18.1)	14.5 (3.4-34.6)	0.022
ESS	6 (3-8)	6 (4-10)	0.179
OSA			0.016
No	37 (35.6)	30 (30.0)	
Mild	32 (30.8)	22 (22.0)	
Moderate	24 (23.1)	20 (20.0)	
Severe	11 (10.6)	28 (28.0)	
PRA (ng/mL/h)	0.25 (0.1-0.5)	-	-
Direct renin (mU/L)	2.6 (2.0-4.3)	1.7 (0.5-5.0)	0.005
Aldosterone (pmol/L)	671 (465-968)	699 (473-1078)	0.480
Age (years)	52 ± 10	47 ± 10	0.001
Sex			0.097
Male	64 (61.5)	50 (50.0)	
Female	40 (38.5)	50 (50.0)	
BMI (kg/m^2)	27.3 ± 4.4	25.4 ± 3.5	0.001

Neck circumference (cm)	40 ± 4	36 ± 5	< 0.001
Waist circumference (cm) Male Female	 99.7 ± 9.8 93.3 ± 14.7	 94.7 ± 10.8 84.4 ± 7.4	 0.012 0.001
Central Obesity No Yes	 26 (25.0) 78 (75.0)	 28 (28.0) 72 (72.0)	0.627
SBP* (mmHg)	158 ± 15	155 ± 18	0.180
DBP* (mmHg)	97 ± 9	96 ± 12	0.401
Antihypertension medication (defined daily dose)	2.00 (1.00-3.62)	0.00 (0.00-1.07)	< 0.001
Fasting glucose (mmol/l)	5.33 ± 1.06	5.51 ± 1.72	0.384
Total cholesterol (mmol/l)	4.81 ± 1.06	4.19 ± 0.85	< 0.001
LDL (mmol/l)	2.80 ± 0.86	2.23 ± 0.73	< 0.001
HDL (mmol/l)	1.38 ± 0.42	1.15 ± 0.38	< 0.001
Triglycerides (mmol/l)	1.15 (0.80-1.84)	1.39 (0.96-2.14)	0.047
GFR (ml/min/1.73m^2)	103 (86-127)	101 (81-119)	0.159
Sodium (mmol/l)	141 ± 2	145 ± 3	< 0.001
Potassium (mmol/l)	3.6 ± 0.5	3.4 ± 0.6	0.006
Diabetes No IFG Yes	 81 (77.9) 17 (16.3) 6 (5.8)	 78 (78.0) 2 (2.0) 20 (20.0)	< 0.001
Metabolic Syndrome No Yes	 55 (52.9) 49 (47.1)	 67 (67.0) 33 (33.0)	0.040

OSA = obstructive sleep apnea, AHI = apnea hypopnea index, PRA = plasma renin activity, ESS = Epworth Sleepiness Scale, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL = low density lipoproteins, HDL = high density lipoproteins, GFR= glomerular filtration rate, IFG = impaired fasting glucose. *at first visit Values are mean ± SD, median (IQR) or absolute number (%). *P* values are calculated with Student's *t* test, Mann-Whitney U test or chi square test.


A
Prevalence of PA in patients with OSA
91.1%
8.9%
3.5%
4.9%
0.5%
B
Caucasian patients
88.2%
11.8%
3.9%
6.9%
1.0%
C
Chinese patients
94.1%
5.9%
2.97%
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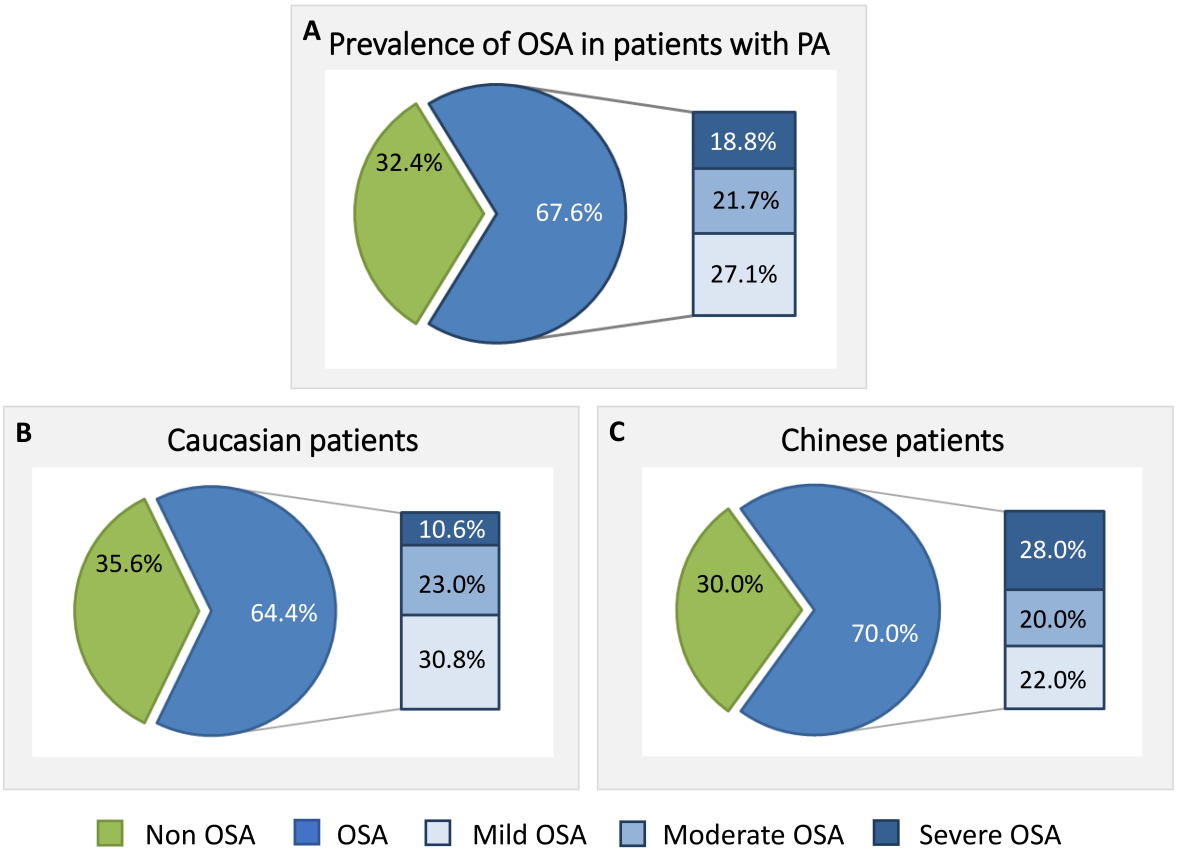
Non primary aldosteronism
Primary aldosteronism
APA
IHA
Undetermined


A
Prevalence of OSA in patients with PA
32.4%
67.6%
18.8%
21.7%
27.1%
B
Caucasian patients
35.6%
64.4%
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23.0%
30.8%
C
Chinese patients
30.0%
70.0%
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Non OSA
OSA
Mild OSA
Moderate OSA
Severe OSA