Journal of Psychiatric Research 172 (2024) 66–70

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Sleep disturbances in primary aldosteronism are associated to depressive symptoms - Could specific mineralocorticoidreceptors be a common pathway?

Christian Adolf [a], Harald Murck [b], Anna-Lina Sarkis [a], Holger Schneider [a], Ina Fischer [a], Axel Steiger [a], Leah T. Braun [a], Martin Reincke [a], Heike Künzel [a,*]

[a] Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU München, Ziemssenstraße 1, 80336, Munich, Germany
[b] Department of Psychiatry and Psychotherapy, Philipps University Marburg, Germany

ARTICLE INFO

Keywords:
Primary aldosteronism
Sleep
Depression
Anxiety

ABSTRACT

Symptoms of depression and anxiety are frequent in patients with primary aldosteronism (PA) and are supposed to be independent risk factors for cardiovascular diseases (CVD). As patients with PA have an increased cardiovascular risk compared to patients with essential hypertension, sleep disturbances, which often accompany depressive and anxiety symptoms, may be an additional contributor to the cardiometabolic consequences of PA. To clarify this possible link we investigated 132 patients with PA at baseline and after one year after initiation of treatment either by adrenalectomy (ADX) or mineralocorticoid-receptor-antagonist (MRA). Sleep disturbances and daytime sleepiness were assessed with Pittsburg sleep Inventory (PSQI) and Epworth sleepiness scale (ESS). Patients with PA showed pathological scores for sleep disturbances at baseline according to PSQI, with females being more affected (8.1 vs. 5.7 $p < 0.001$), which was significantly improved after initiation of specific treatment ($p = 0.002$). For ESS we found scores within the normal range, but higher than the general population, which significantly improved at follow-up ($p < 0.001$). The intensity of sleep disturbances was highly correlated with scores of anxiety and depression at baseline and follow-up. However, clinical and biochemical markers of PA (e.g. aldosterone, blood pressure) and metabolic markers did not show a consistent association with sleep changes. The degree of improvement in PSQI was significantly associated with the improvement of brief patients health questionnaire (PHQD) ($p = 0.0151$). Sleep disturbances seem not to be an independent risk factor for cardiovascular and metabolic problems in PA. They are strongly associated to depressive symptoms and maybe mediated by the same mineralocorticoid receptor circuits.

1. Introduction

Chronic hyperaldosteronism such as primary aldosteronism (PA) was found to be associated with symptoms of depression and anxiety. Studies suggest a mediation of these symptoms via the mineralocorticoid receptor (MR) within the CNS and a moderating effect of blood pressure (Murck, 2017). Sleep disturbances are strongly associated to metabolic and cardiovascular diseases (Cappuccio and Miller, 2017; Reutrakul and Van Cauter, 2018) and are linked with depression and anxiety. Additionally, they are a risk factor in psychiatric disorders e.g. for suicidal behavior (Bernert et al., 2015) (see Fig. 1).

In this context, Engler et al. investigated patients with PA, prior to specific treatment, in comparison to patients with major depression and healthy controls using polysomnography. They could not find a depression specific pattern in male patients with PA. However, female patients with PA showed a similar pattern of sleep-EEG parameters as

* Corresponding author.
E-mail address: Heike.Kuenzel@med.uni-muenchen.de (H. Künzel).

https://doi.org/10.1016/j.jpsychires.2024.01.042
Received 31 October 2023; Received in revised form 28 December 2023; Accepted 22 January 2024
Available online 8 February 2024

female patients with major depression.

The impact of the renin-angiotensin-aldosterone-system (RAAS) and the MR on sleep is still not fully understood. Renin plasma concentration is associated with non-REM-sleep (NREM), the NREM/REM-cycle and sleep efficiency index (Brandenberger et al., 1985). Like renin, aldosterone secretion is increased during sleep and to a lesser extent by circadian influence, as demonstrated in a sleep shift experiment (Charloux et al., 2001). Mechanistically, aldosterone works at only a few areas in the brain, which co-express the MR and the enzyme 11 beta hydroxysteroid dehydrogenase type 2 (11betaHSD2), which rapidly metabolizes cortisol and therefore allows aldosterone to bind to MR. This is best documented for the nucleus of the solitary tract, which is the entry point of the vagus nerve and is closely linked to autonomic, sleep and affect regulation (Gasparini et al., 2019). Due to the central action of aldosterone and the high prevalence of anxiety in depression in patients with PA we hypothesize that sleep quality is also negatively affected. Therefore, an evaluation of sleep quality and disturbances in patients with PA was performed to see whether these patients are at high risk for metabolic and cardiovascular events.

2. Methods

2.1. Patients and methods

For this study we included all patients with PA from the Munich center of the German Conn's Registry, who attended at least one baseline and follow-up visit after 6–12 months after initiation of specific treatment for PA. Patients with missing or incompletely answered questionnaires for Epworth sleepiness scale (ESS) (Johns, 1992) or Pittsburg sleep quality index (PSQI) (Buysse, Reynolds III, Monk, Berman and Kupfer, 1989) were excluded from further analysis. In total 132 patients fulfilled our inclusion criteria and the data could be analyzed. All patients gave written informed consent, and the protocol of the German Conn's Registry was approved by the Ethics Committee of the University of Munich.

Diagnosis and subtyping of PA was performed in accordance with Endocrine Society Practice Guidelines (Funder et al., 2016). Prior to that, antihypertensive medication with impact on aldosterone-to-renin-ratio (ARR) was stopped or whenever possible changed to medication with limited impact on ARR (e.g., verapamil, doxazosin). The ARR was used as screening test and if abnormal followed by confirmatory testing using saline infusion and/or captopril challenge test. PA subtyping was performed using adrenal vein sampling (Betz et al., 2011). All patients with unilateral disease were offered unilateral adrenalectomy. In case of contraindications for adrenalectomy or if patients refused surgery patients were medically treated with MRA as it was the case for patients with bilateral disease.

2.2. Questionnaires

To assess (symptoms of) sleep disorders we used the 8-item Epworth Sleepiness Scale (ESS) and the Pittsburgh Sleep Quality Index (PSQI), respectively. The ESS is a very well validated instrument for the assessment of sleepiness (Gonçalves et al., 2023) that can be used in the assessment of obstructive sleep apnea syndrome (Nogueira et al., 2013). The PSQI contains scores for subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The score is very well evaluated since 1989 (Buysse et al., 1989). Both questionnaires are well-established and validated. Depressive symptoms were assessed with the brief patient health questionnaire (PHQD), a well validated instrument for use in primary care to discriminate between mild, moderate and severe depressive symptoms (Gilbody et al., 2007a, b). For measuring anxiety the 7-item generalized anxiety disorder scale (GAD-7), a well established assessment scale for generalized anxiety disorder was used. This scale also correlates with the disability states (Ruiz et al., 2010).

2.3. Statistical analysis

All values are expressed as mean ± standard deviation, if not mentioned otherwise. Data between groups were compared using Mann-Whitney *U* test, Kruskal-Wallis test or chi-square test for numerical or categorical variable, respectively. Within-group changes from baseline to follow-up were calculated by Wilcoxon signed-rank test and McNemar's test for numerical or categorical variable, respectively. Spearman's Rank correlation coefficient was used to perform bivariate correlation analysis. Stepwise multiple regression analysis was used for multivariate analysis.

Two-tailed probability values of $p < 5\%$ were considered to be statistically significant. Statistical analysis was performed using standard statistical software (IBM SPSS Statistics for Windows, Version 26. Armonk, NY: IBM Corp.).

3. Results

3.1. Characteristics of the total cohort at baseline

Clinical and biochemical characteristics of study cohort are shown in Supplementary Table 1. Overall patients were 52 years old and fairly balanced for sex. All patients were suffering from PA as indicated by increased blood pressure and plasma aldosterone levels as well as suppressed plasma renin concentration. GAD-7 and PHQD score were increased. Quality of sleep, assessed by PSQI global score, was at a pathological level, whereas daytime sleepiness, measured by ESS, was in a normal range, although numerically higher than German population.

Men had significantly higher systolic blood pressure (153 vs. 145 mmHg, $p = 0.007$) and plasma aldosterone levels (232 vs. 177 ng/l, $p = 0.014$) as well as BMI ($p < 0.001$) and worse metabolic profile concerning triglycerides (118 vs 97 mg/dl $p = 0.003$) and HDL-cholesterol (52 vs. 65 mg/dl, $p < 0.001$; Table 1). Contrary, PSQI was significantly higher in women ($p = 0.001$), whereas ESS was comparable between both sexes. Moreover, symptoms of depression were more pronounced in women as assessed by PHQD ($p = 0.028$).

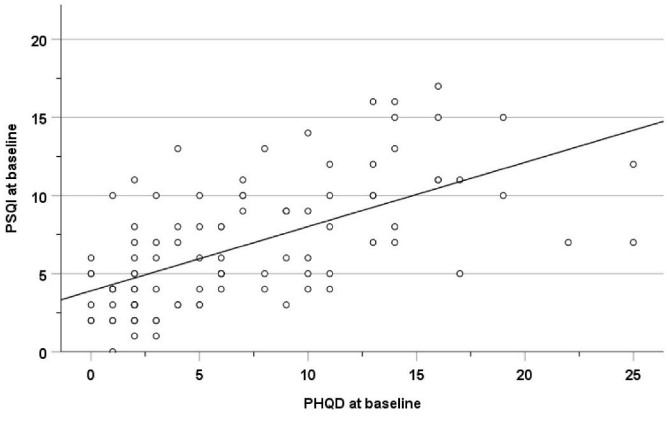

Fig. 1. Correlations between PSQI and PHQD at baseline.

Table 1
Baseline and follow-up characteristics of patients with primary aldosteronism according to gender.

Patient characteristics	Female cohort (n = 60)			Male cohort (n = 72)		
	Before treatment initiation	Follow-up after one year	p	Before treatment initiation	Follow-up after one year	p
Age [years]	49 ± 10#	–	–	55 ± 10	–	–
Duration of hypertension [months]	52 ± 109	–	–	25 ± 44	–	–
BMI [kg/m^2]	25.5 ± 4.7##	25.4 ± 4.5	0.711	29.4 ± 5.1	29.0 ± 4.5	0.567
Plasma aldosterone [ng/l]	177 ± 154#	251 ± 254	**0.008**	232 ± 209	187 ± 124	0.359
Plasma renin concentration [mU/l]	3.7 ± 2.7#	32.7 ± 113.0	**<0.001**	7.3 ± 14.4	33.4 ± 48.2	**<0.001**
Antihypertensive agents [DDD]	1.4 ± 1.3##	0.9 ± 0.8	**0.019**	2.7 ± 2.3	3.1 ± 2.5	0.104
SBP [mmHg]	145 ± 14#	129 ± 19	**<0.001**	153 ± 18	135 ± 13	**<0.001**
DBP [mmHg]	93 ± 11	88 ± 9	**0.006**	93 ± 12	88 ± 10	**0.001**
Serum potassium [mmol/l]	3.8 ± 0.4	4.3 ± 0.4	**<0.001**	3.7 ± 0.4	4.3 ± 0.4	**<0.001**
Total Cholesterol [mg/dl]	193 ± 32	194 ± 36	0.745	192 ± 34	191 ± 33	0.785
HDL-C [mg/dl]	65 ± 15#	62 ± 14	**0.027**	52 ± 14	49 ± 13	**0.036**
LDL-C [mg/dl]	113 ± 29	118 ± 35	0.055	121 ± 32	119 ± 31	0.306
Triglycerides [mg/dl]	97 ± 66#	108 ± 71	**0.009**	118 ± 62	142 ± 72	**<0.001**
Pro-BNP [pg/ml][a]	122 ± 96	65 ± 49	**<0.001**	147 ± 216	127 ± 260	**0.012**
PSQI global score[a]	8.1 ± 4.1##	6.9 ± 4.2	**0.008**	5.7 ± 3.3	5.2 ± 3.0	0.102
Sleep quality	1.5 ± 0.7##	1.2 ± 0.8	**0.006**	1.2 ± 0.7	0.9 ± 0.6	**0.005**
Sleep latency	1.6 ± 1.0##	1.3 ± 0.9	**0.008**	0.9 ± 0.8	0.9 ± 0.7	0.239
Sleep duration	0.9 ± 0.9	0.8 ± 0.9	0.291	0.7 ± 0.9	0.6 ± 0.8	0.253
Habitual sleep efficiency	1.1 ± 1.1#	0.9 ± 1.1	**0.046**	0.6 ± 1.0	0.7 ± 0.9	0.873
Sleep disturbances	1.5 ± 0.7#	1.5 ± 0.6	0.371	1.3 ± 0.5	1.1 ± 0.5	0.059
Use of sleep medication	0.2 ± 0.5	0.3 ± 0.8	0.163	0.1 ± 0.3	0.1 ± 0.4	0.157
Daytime dysfunction	1.4 ± 0.8#	1.0 ± 0.7	**0.001**	1.0 ± 0.8	0.9 ± 0.7	0.369
ESS[a]	8.3 ± 4.5	7.4 ± 4.1	**0.035**	7.7 ± 3.3	6.7 ± 3.4	**0.003**
GAD-7[a]	6.4 ± 4.4	4.9 ± 4.6	**0.004**	5.0 ± 4.1	4.0 ± 4.5	**0.006**
PHQD[a]	8.3 ± 5.8#	6.5 ± 5.7	**0.005**	6.2 ± 5.9	4.8 ± 5.1	**0.005**

Data are given as mean ± standard deviation. Significance is marked bold. Differences between baseline values of both groups were marked with ## for $p < 0.05$ and # for $p < 0.001$.

Abbreviations: DBP: diastolic blood pressure; DDD: defined daily doses; DST: dexamethasone suppression test; GAD-7: generalized anxiety disorder 7-item; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PSQI: pittsburg sleep quality index; PHQD: patient health questionnaire; SBP: systolic blood pressure.

[a] Due to incomplete data ESS (n = 125), Cortisol after DST (n = 103), Pro-BNP (n = 105), GAD-7 (n = 101) and PHQD (n = 100) were performed with a reduced number of patients as listed in brackets.

3.2. Follow-up characteristics of the total cohort

Initiation of specific treatment for PA resulted in several changes without a significant interaction with the treatment methods (ADX vs. MRA) with the exception of aldosterone, which increased with MRA, but decreased with ADX. Treatment resulted in a significant fall in systolic (150 vs 132 mmHg, $p < 0.001$) and diastolic blood pressure levels (93 vs 88 mmHg, $p < 0.001$). Moreover, pro-BNP (135 vs. 97, $p < 0.001$) was significantly improved and renin levels normalized (5.7 vs. 33.0, $p < 0.001$, Supplementary Table 1). From the metabolic profile we could detect a significant increase of triglycerides and a decrease in HDL-Cholesterol, whereas LDL-Cholesterol and fasting plasma glucose were unaltered as reported before (Adolf et al., 2016). Symptoms of depression and anxiety were significantly reduced at follow-up (Supplementary Table 1). Sleep quality and daytime sleepiness assessed by PSQI (6.8 vs. 6.0, p 0.002) and ESS (8.0 vs 7.0, $p < 0.001$) also significantly improved at follow-up but PSQI was still in a pathological range. When taking into account the PSQI subscores we could observe a significant improvement in the domains of sleep quality ($p < 0.001$), sleep latency ($p = 0.006$) and daytime dysfunction ($p = 0.003$).

Former studies provided evidence for gender differences for symptoms of depression and anxiety in patients with hyperaldosteronism (Apostolopoulou et al.,2014) (Murck et al., 2021). When splitting the cohort into two groups according to gender we could detect comparable changes in the metabolic profile concerning HDL-cholesterol and triglycerides (Table 1). Concerning PSQI we could find a significant improvement only in women (8.1 vs 6.9, $p = 0.008$). Nonetheless, the score remained still on a pathological level in women and was significantly higher compared to men at follow-up (6.9 vs 5.2, $p = 0.016$). ESS was significantly improved in both sexes as it was also the case for GAD-7 and PHQD.

3.3. Baseline characteristics of patients treated with either MRA or ADX

In total 88 patients received MRA therapy and 44 patients underwent ADX. Both cohorts were comparable for age, BMI, and blood pressure levels. However, patients planned to undergo ADX showed higher plasma aldosterone (286 vs 169, $p < 0.001$), pro-BNP levels (188 vs 115, $p = 0.037$), whereas potassium levels were significantly lower (3.6 vs 3.8, $p < 0.001$; Table 2). ESS and PSQI score were comparable between the two groups.

3.4. Follow-up characteristics of patients treated with MRA

After initiation of specific treatment for PA by MRA aldosterone and serum potassium levels significantly increased and SBP and DBP ($p < 0.001$) decreased, (both: $p < 0.001$; Table 1), which was also the case for PSQI. Overall ESS significantly decreased in men and showed a tendency to lower values in females at follow-up (Supplementary Table 2).

3.5. Follow-up characteristics of patients treated with ADX

In patients treated by ADX blood pressure and aldosterone were significantly decreased whereas plasma renin levels increased to a normal range (Table 1). However, PSQI and ESS only showed a tendency for improvement at follow-up, which was also the case for GAD-7 and PHQD, which may be due to the lower sample size of the ADX subjects in comparison to the MRA subjects. However, at least GAD-7 was in the normal range. These findings were comparable for men and women (Supplementary Table 3).

Table 2
Baseline and follow-up characteristics of patients with primary aldosteronism According to treatment modality.

Patient characteristics	ADX cohort (n = 44)			MRA cohort (n = 88)		
	Before treatment initiation	Follow-up after one year	p	Before treatment initiation	Follow-up after one year	p
Age [years]	52 ± 9	–	–	52 ± 11	–	–
Sex [f/m]	20/24			40/48		
Duration of hypertension [months]	34 ± 62	–	–	38 ± 89	–	–
BMI [kg/m^2]	27.7 ± 5.8	27.3 ± 4.6	0.876	27.5 ± 5.0	27.4 ± 5.0	0.744
Plasma aldosterone [ng/l]	286 ± 282	100 ± 59	**<0.001**	169 ± 99	274 ± 214	**<0.001**
Plasma renin concentration [mU/l]	7.4 ± 18.1	47 ± 134	**<0.001**	4.8 ± 4.3	26.3 ± 39.0	**<0.001**
Cortisol after DST [mg/dl][a]	1.9 ± 2.2	–	–	1.8 ± 1.7	–	–
Antihypertensive agents [DDD]	2.9 ± 2.1	1.4 ± 1.5	**<0.001**	1.8 ± 1.9	2.4 ± 2.4	**0.001**
SBP [mmHg]	150 ± 17	133 ± 22	**<0.001**	149 ± 17	132 ± 13	**<0.001**
DBP [mmHg]	93 ± 13	89 ± 10	0.070	93 ± 11	88 ± 9	**<0.001**
Serum potassium [mmol/l]	3.6 ± 0.4	4.3 ± 0.4	**<0.001**	3.8 ± 0.4	4.3 ± 0.4	**<0.001**
Total Cholesterol [mg/dl]	189 ± 34	194 ± 38	0.186	195 ± 33	192 ± 32	0.329
HDL-C [mg/dl]	59 ± 17	55 ± 16	0.051	57 ± 16	55 ± 14	**0.017**
LDL-C [mg/dl]	114 ± 34	122 ± 35	0.087	119 ± 29	117 ± 31	0.546
Triglycerides [mg/dl]	95 ± 47	130 ± 86	**<0.001**	115 ± 71	125 ± 72	**0.003**
Pro-BNP [pg/ml][a]	188 ± 256	137 ± 304	**0.006**	115 ± 115	81 ± 121	**<0.001**
PSQI global score	7.1 ± 4.0	6.5 ± 3.7	0.291	6.7 ± 3.8	5.8 ± 3.7	**0.001**
Sleep quality	1.3 ± 0.7	1.2 ± 0.6	0.405	1.3 ± 0.7	1.0 ± 0.8	**<0.001**
Sleep latency	1.1 ± 0.9	1.1 ± 0.8	0.686	1.3 ± 1.0	1.1 ± 0.8	**0.002**
Sleep duration	0.9 ± 1.0	0.7 ± 0.9	0.158	0.8 ± 0.9	1.0 ± 0.8	0.386
Habitual sleep efficiency	1.0 ± 1.1	0.8 ± 1.0	0.451	0.8 ± 1.0	0.7 ± 1.0	0.368
Sleep disturbances	1.3 ± 0.6	1.3 ± 0.5	>0.999	1.4 ± 0.6	1.3 ± 0.5	0.011
Use of sleep medication	0.1 ± 0.4	0.2 ± 0.6	0.161	0.1 ± 0.5	0.2 ± 0.6	0.347
Daytime dysfunction	1.3 ± 0.9	1.0 ± 0.7	**0.011**	1.1 ± 0.8	0.9 ± 0.7	0.096
ESS[a]	8.2 ± 3.9	7.7 ± 4.0	0.196	7.9 ± 3.9	6.7 ± 3.6	**<0.001**
GAD-7[a]	5.6 ± 4.3	4.4 ± 4.5	0.083	5.6 ± 4.3	4.1 ± 4.0	**<0.001**
PHQD[a]	7.1 ± 5.9	5.5 ± 5.4	0.124	6.6 ± 5.5	4.7 ± 5.0	**<0.001**

Data are given as mean ± standard deviation. Significance is marked bold. Differences between baseline values of both groups were marked with ## for $p < 0.05$ and # for $p < 0.001$.

Abbreviations: DBP: diastolic blood pressure; DDD: defined daily doses; DST: dexamethasone suppression test; GAD-7: generalized anxiety disorder 7-item; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PSQI: pittsburg sleep quality index; PHQD: patient health questionnaire; SBP: systolic blood pressure.

[a] Due to incomplete data ESS (n = 125), Cortisol after DST (n = 103), Pro-BNP (n = 105), GAD-7 (n = 101) and PHQD (n = 100) were performed with a reduced number of patients as listed in brackets.

3.6. Correlation analysis for the prediction of the improvement in PSQI and ESS

At baseline PSQI, ESS, GAD-7 and PHQD were strongly correlated with each other. Moreover, PSQI was found to be correlated with female sex ($r = -0.303$, $p < 0.001$) and ESS with lower systolic blood pressure ($r = -0.228$, $p = 0.011$) and ESS negatively with renin levels ($r = -0.227$, $p = 0.011$).

In multivariate analysis after adjusting for confounders we could show again an independent association between PSQI and female sex ($p = 0.015$) as well as PSQI and PHQD at baseline ($p = 0.007$). Moreover, the degree of improvement in PSQI was significantly associated with the improvement of PHQD ($p = 0.0151$).

ESS at baseline was significantly associated with PHQD ($p = 0.009$). Similarly, improvement of ESS was significantly correlated with change in PHQD ($p = 0.028$).

4. Discussion

A link between sleep and secretion of aldosterone has been shown before and several studies suggest a connection between PA and OSAS (Wang et al., 2021), which would further increase the metabolic burden in the course of the disease. The bidirectional relationship is not clear yet. So our intention was to screen patients with PA for sleep disturbances with PSQI and daytime sleepiness with ESS.

Overall, initiation of specific treatment for PA resulted in a significant improvement in sleep disturbances ($p = 0.002$) and daytime sleepiness ($p < 0.001$). Although our patients show scores for ESS above the norm values for the German population (Sauter et al., 2007) and improved after initiation of specific treatment, the cut off for pathological symptoms was not reached. The results of the ESS do not strongly support a probable relationship between OSAS and PA. The correlation between ESS and lower systolic blood pressure has been established, as clinically lower blood pressure is known to be associated with symptoms as fatigue. In patients being adapted to higher blood pressure, even a slight adjustment could cause a higher daytime sleepiness (Newton et al., 2009).

The scores for PSQI were on a pathological level at baseline and were normalized at follow-up. Although all rating scales showed a strong correlation in the first analysis at baseline, which could be seen as an overlap in symptoms of sleep disturbances, depression and anxiety, an independent correlation was found for PSQI, ESS and depression assessed by PHQD after adjusting for possible confounders. Another independent correlation was found for female sex and depression at baseline. The association of ESS and PSQI with depressive symptoms is also underlined by correlation of changes in these scales. Therefore, we consider sleep disturbances to be more part of the depressive symptoms than of anxiety. Engler et al., 2019 pointed out that changes in sleep EEG of female patients with PA do not differ significantly from female patients with depression in contrast to males. So, our data support previous results for an accentuation of depressive symptoms in female patients with PA. Additionally, results from our previous studies suggest different regulatory pathways for depression and anxiety via the MR, which was reflected by different response to treatment with either ADX or MRA. The biological mechanism might be a differential activation of MR at aldosterone sensitive brain areas. Especially the nucleus of the solitary tract (NTS) appears to play an important role central role in aldosterone induced depression. However, we could not find significant associations between PSQI and ESS with blood pressure levels nor with the metabolic profile, which suggests that other mediators, which are regulated via MR, for example angiotensin II or inflammatory markers may play a role, which need to be studied.

In conclusion sleep disturbance in patients with PA might not be an independent risk factor for developing a metabolic syndrome or metabolic disturbances. Nevertheless, we also cannot rule out a role of sleep disturbances in the psychiatric and metabolic symptoms of patients with PA. So physicians should actively ask after these symptoms and offer treatment.

CRediT authorship contribution statement

Christian Adolf: Formal analysis, Writing – original draft, Writing – review & editing. **Harald Murck:** Formal analysis, Writing – original draft, Writing – review & editing. **Anna-Lina Sarkis:** Data curation. **Holger Schneider:** Writing – original draft. **Ina Fischer:** Data curation. **Axel Steiger:** Writing – original draft, Writing – review & editing. **Leah T. Braun:** Writing – original draft. **Martin Reincke:** Funding acquisition, Project administration. **Heike Künzel:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Disclosure statement: The authors have nothing to disclose.

Acknowledgements

Funding is mentioned in the manuscript.

This work was supported by the Else Kröner-Fresenius Stiftung in support of the German Conn's Registry-Else-Kröner Hyperaldosteronism Registry (2013_A182, 2015_A171 and 2019_A104 to MR), the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 694913 to MR), by the Deutsche Forschungsgemeinschaft (DFG) (within the CRC/Transregio 205/1 "The Adrenal: Central Relay in Health and Disease" to CA and MR).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.01.042.

References

Adolf, C., Asbach, E., Dietz, A.S., Lang, K., Hahner, S., Quinkler, M., Rump, L.C., Bidlingmaier, M., Treitl, M., Ladurner, R., Beuschlein, F., Reincke, M., 2016. Worsening of lipid metabolism after successful treatment of primary aldosteronism. Endocrine 54, 198–205.

Apostolopoulou, K., Künzel, H.E., Gerum, S., Merkle, K., Schulz, S., Fischer, E., Pallauf, A., Brand, V., Bidlingmaier, M., Endres, S., Beuschlein, F., Reincke, M., 2014. Gender differences in anxiety and depressive symptoms in patients with primary hyperaldosteronism: a cross-sectional study. World J. Biol. Psychiatr. 15, 26–35.

Bernert, R.A., Kim, J.S., Iwata, N.G., Perlis, M.L., 2015. Sleep disturbances as an evidence-based suicide risk factor. Curr. Psychiatr. Rep. 17, 554.

Betz, M.J., Degenhart, C., Fischer, E., Pallauf, A., Brand, V., Linsenmaier, U., Beuschlein, F., Bidlingmaier, M., Reincke, M., 2011. Adrenal vein sampling using rapid cortisol assays in primary aldosteronism is useful in centers with low success rates. Eur. J. Endocrinol. 165, 301–306.

Brandenberger, G., Follenius, M., Muzet, A., Ehrhart, J., Schieber, J.P., 1985. Ultradian oscillations in plasma renin activity: their relationships to meals and sleep stages. J. Clin. Endocrinol. Metab. 61, 280–284.

Buysse, D.J., Reynolds III, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr. Res. 28, 193–213.

Cappuccio, F.P., Miller, M.A., 2017. Sleep and cardio-metabolic disease. Curr. Cardiol. Rep. 19, 110.

Charloux, A., Gronfier, C., Chapotot, F., Ehrhart, J., Piquard, F., Brandenberger, G., 2001. Sleep deprivation blunts the night time increase in aldosterone release in humans. J. Sleep Res. 10, 27–33.

Funder, J.W., Carey, R.M., Mantero, F., Murad, M.H., Reincke, M., Shibata, H., Stowasser, M., Young Jr., W.F., 2016. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 101, 1889–1916.

Gasparini, S., Resch, J.M., Narayan, S.V., Peltekian, L., Iverson, G.N., Karthik, S., Geerling, J.C., 2019. Aldosterone-sensitive HSD2 neurons in mice. Brain Struct. Funct. 224, 387–417.

Gilbody, S., Richards, D., Brealey, S., Hewitt, C., 2007a. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. J. Gen. Intern. Med. 22, 1596–1602.

Gilbody, S., Richards, D., Brealey, S., Hewitt, C., 2007b. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. J. Gen. Intern. Med. 22, 1596–1602.

Gonçalves, M.T., Malafaia, S., Dos Santos, J.M., Roth, T., Marques, D.R., 2023. Epworth sleepiness scale: a meta-analytic study on the internal consistency. Sleep Med.

Johns, M.W., 1992. Reliability and factor analysis of the epworth sleepiness scale. Sleep 15, 376–381.

Murck, H., 2017. Aldosterone action on brain and behavior. In: Pfaff, D.W., Joëls, M. (Eds.), Hormones, Brain, and Behavior, third ed. Academic Press, Oxford, pp. 159–179.

Murck, H., Adolf, C., Schneider, A., Schlageter, L., Heinrich, D., Ritzel, K., Sturm, L., Quinkler, M., Beuschlein, F., Reincke, M., Künzel, H., 2021. Differential effects of reduced mineralocorticoid receptor activation by unilateral adrenalectomy vs mineralocorticoid antagonist treatment in patients with primary aldosteronism - implications for depression and anxiety. J. Psychiatr. Res. 137, 376–382.

Newton, J.L., Pairman, J., Wilton, K., Jones, D.E., Day, C., 2009. Fatigue and autonomic dysfunction in non-alcoholic fatty liver disease. Clin. Auton. Res. 19, 319–326.

Nogueira, I.C., Azevedo, P.O., de Araujo Magalhaes, C.B., Lacerda, V.M.A., de Oliveira Brasil, A.C., Mont'Alverne, D.G.B., 2013. The effectiveness of the epworth sleepiness scale as an auxiliary resource in the diagnosis of obstructive sleep apnea syndrome. Rev. Bras. em Promoção Saúde 26, 56–62.

Reutrakul, S., Van Cauter, E., 2018. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. Metabolism: clinical and experimental 84, 56–66.

Ruiz, M.A., Zamorano, E., Garcia-Campayo, J., Pardo, A., Freire, O., Rejas, J., 2010. Validity of the GAD-7 scale as an outcome measure of disability in patients with generalized anxiety disorders in primary care. J. Affect. Disord.

Sauter, C., Popp, R., Danker-Hopfe, H., Büttner, A., Wilhelm, B., Binder, R., Böhning, W., Weeß, H.-G., the Vigilance Task Group of the German Sleep Research, S, 2007. Normative values of the German epworth sleepiness scale. Somnologie - Schlafforschung und Schlafmedizin 11, 272–278.

Wang, Y., Li, C.X., Lin, Y.N., Zhang, L.Y., Li, S.Q., Zhang, L., Yan, Y.R., Lu, F.Y., Li, N., Li, Q.Y., 2021. The role of aldosterone in OSA and OSA-related hypertension. Front. Endocrinol. 12, 801689.