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Primary Aldosteronism and Obstructive Sleep Apnea: Casual Association or Pathophysiological Link?

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1742433> since 2020-06-29T10:11:59Z

Published version:

DOI:10.1055/a-1133-7255

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**PRIMARY ALDOSTERONISM AND OBSTRUCTIVE SLEEP
APNEA: CASUAL ASSOCIATION OR PATHOPHYSIOLOGICAL
LINK?**

Journal:	<i>Hormone and Metabolic Research</i>
Manuscript ID	Draft
Manuscript Type:	Review
Date Submitted by the Author:	n/a
Complete List of Authors:	Pecori, Alessio; University of Turin, Medical Sciences Buffolo, Fabrizio; University of Turin, Medical Sciences Pieroni, Jacopo; University of Turin, Medical Sciences Forestiero, Vittorio; University of Turin, Medical Sciences Sconfienza, Elisa; University of Turin, Medical Sciences Veglio, Franco; University of Turin, MEDICAL SCIENCES Mulatero, Paolo; University of Turin, Medical Sciences Monticone, Silvia; University of Turin, Medical Sciences
Keywords:	Aldosterone < ADRENAL, Adrenal adenoma < ADRENAL, Renin-angiotensin-aldosterone system; RAAS < HYPERTENSION, Obesity < METABOLIC SYNDROME
Abstract:	The coexistence of aldosterone oversecretion and obstructive sleep apnea is frequently observed, especially in patients with resistant hypertension, obesity and metabolic syndrome. Since aldosterone excess and sleep apnea are both independently associated with an increased risk of cardiovascular disease, to investigate whether their coexistence might be attributed to common predisposing conditions, such as metabolic disorders, or to an actual pathophysiological interconnection appears of great importance. Fluid overload and metabolic abnormalities relating to aldosterone oversecretion may be implicated in obstructive sleep apnea development. Nocturnal intermittent hypoxia may in turn exacerbate renin-angiotensin-aldosterone system activity, thus leading to hyperaldosteronism. Furthermore, fat tissue excess and adipocyte secretory products might predispose to both sleep apnea and aldosterone oversecretion in subjects with obesity. Consistent with these evidences, obstructive sleep apnea frequently affects patients with primary aldosteronism. Conversely, whether primary aldosteronism is more prevalent in individuals affected by obstructive sleep apnea compared to the general population remains controversial.

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3 1 **PRIMARY ALDOSTERONISM AND OBSTRUCTIVE SLEEP APNEA: CASUAL**
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5 2 **ASSOCIATION OR PATHOPHYSIOLOGICAL LINK?**
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19 7 **Key-words:** aldosterone; sleep disorders; obesity; metabolic syndrome; apnea-hypopnea index;
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25 9 **Words count:** abstract: 152; manuscript: 3113 (excluding references)
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Abstract

The coexistence of aldosterone oversecretion and obstructive sleep apnea is frequently observed, especially in patients with resistant hypertension, obesity and metabolic syndrome. Since aldosterone excess and sleep apnea are both independently associated with an increased risk of cardiovascular disease, to investigate whether their coexistence might be attributed to common predisposing conditions, such as metabolic disorders, or to an actual pathophysiological interconnection appears of great importance. Fluid overload and metabolic abnormalities relating to aldosterone oversecretion may be implicated in obstructive sleep apnea development. Nocturnal intermittent hypoxia may in turn exacerbate renin-angiotensin-aldosterone system activity, thus leading to hyperaldosteronism. Furthermore, fat tissue excess and adipocyte secretory products might predispose to both sleep apnea and aldosterone oversecretion in subjects with obesity. Consistent with these evidences, obstructive sleep apnea frequently affects patients with primary aldosteronism. Conversely, whether primary aldosteronism is more prevalent in individuals affected by obstructive sleep apnea compared to the general population remains controversial.

44 **Introduction**

45 Obstructive sleep apnea (OSA), aldosterone excess and resistant hypertension (RH) are common
46 comorbidities, especially in patients affected by obesity[1]. The prevalence of OSA is high in patients
47 affected by RH and even higher in individuals with hypertension refractory to medical therapy[2]. In
48 patients with RH, oversecretion of aldosterone is a frequent finding and primary aldosteronism (PA)
49 has a significantly higher prevalence compared with the general hypertensive population[3]. Patients
50 with RH are significantly more likely to experience adverse cardiovascular outcomes, such as stroke,
51 myocardial infarction, heart failure, renal failure and death, compared with subjects with nonresistant
52 hypertension[4]. Studies performed in the last years suggest that PA is frequent in patients with
53 OSA[5,6] and, on the basis of these evidences, the 2016 Endocrine Society Guideline recommends
54 to screen for PA all patients with hypertension and OSA[7]. The impact of aldosterone excess and
55 sleep apnea on the cardiovascular morbidity and mortality of patients with hypertension is of great
56 importance, as well as the recognition of the interplay between these conditions. Previous studies
57 hypothesized that a bidirectional relationship between aldosterone levels and OSA might be present
58 in patients with RH and PA[8]. Nevertheless, whether the association between PA and OSA is
59 accidental or pathophysiologically-based remains controversial.

61 **Epidemiology**

62 **1.Primary aldosteronism**

63 PA is mostly sporadic, due to unilateral aldosterone-producing adenoma (APA) or bilateral
64 hyperaldosteronism (BHA), and less frequently (1-6%) is a familial condition[9]. Individuals with
65 PA show an increased risk of stroke, coronary artery disease, heart failure, atrial fibrillation, left
66 ventricular hypertrophy, kidney damage, diabetes and metabolic syndrome compared to patients with
67 essential hypertension[10, 11]. The prevalence of PA rates between 5.9% in the general hypertensive
68 population[12] and 11.2% in patients from referral centers[13], and progressively increases with
69 hypertension severity[12].

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70 Two prospective studies suggested a high prevalence of aldosterone excess in patients with sleep
71 disordered breathing (SDB). Calhoun et al. showed that autonomous aldosterone secretion was more
72 frequently observed in patients with RH at high risk of OSA (36%) compared with low-risk patients
73 (19%), defined according to the Berlin Questionnaire results[5]. However, OSA diagnosis was not
74 confirmed by polysomnography and patients with aldosterone oversecretion did not underwent
75 confirmatory testing for PA diagnosis. Di Murro et al. reported a 34% prevalence of PA in patients
76 affected by hypertension and OSA[6]. Nonetheless, polysomnography was performed only in patients
77 showing excessive daytime sleepiness, thus leading to diagnosis of OSA only in a selected subgroup
78 of symptomatic individuals. Therefore, it cannot be excluded that PA prevalence among the overall
79 symptomatic and asymptomatic OSA population would have been different.

80 The recent multicenter multi-ethnic cross-sectional HYPNOS study, reported an 8.9% prevalence of
81 PA in a population of 203 patients with OSA (102 Caucasians and 101 Chinese)[14], a figure that
82 does not significantly differ from the 5.9-11.2% prevalence observed in the PATO and PAPY studies,
83 respectively[12,13]. Moreover, a sub-analysis performed to identify PA prevalence in patients in
84 whom OSA was the only indication to proceed to PA screening, showed that only 1/63 (1.5%) patients
85 displayed confirmed PA. These results provocatively challenge the current Endocrine Society
86 Guideline recommendation to screen for PA all patients affected by OSA and arterial hypertension,
87 irrespective of hypertension severity and the presence of other risk factors.

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89 **2.Obstructive sleep apnea**

90 OSA is a chronic sleep disorder characterized by recurrent episodes of complete (apneas) or partial
91 airflow cessation (hypopneas) due to obstruction of the upper respiratory tract, leading to intermittent
92 hypoxia, hypercapnia and sleep arousals[15]. OSA is an independent risk factor for hypertension[16-
93 18] and cardiovascular disease [19,20], and a predictor of cardiovascular outcomes, including sudden
94 cardiac death[21]. OSA is frequently diagnosed in patients with various cardiovascular comorbidities,
95 such as stroke, end-stage chronic kidney disease, ischemic cardiomyopathy, heart failure, atrial

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3 96 fibrillation and hypertrophic cardiomyopathy[15]. The prevalence of OSA in the overall adult
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5 97 population varies from 9% to 38%, ranging between 13% to 33% in men and 6% to 19% in
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8 98 women[22]. Advanced age is associated with an elevated prevalence of OSA, up to 90% for all stages
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10 99 in a cohort of elderly men[22,23]. OSA prevalence is high in patients with obesity or metabolic
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12 100 syndrome, ranging from 50% to 60%, and it is even higher in subjects with morbid obesity and
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14 101 diabetes[24]. The prevalence of OSA in patients with hypertension is reported to be 30% to 50%[25]
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17 102 and it has been assessed to be as high as 92%[26] for all stages and 70% for severe OSA[27] in
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19 103 patients with RH. A recent study displayed an even higher prevalence of moderate OSA (95.2%),
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21 104 severe OSA (64.3%) and OSA syndrome (52.4%) in patients with refractory hypertension[2].
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24 105 Some studies showed that OSA is more frequent in patients with than in those without PA. In a
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26 106 retrospective cohort, OSA prevalence was significantly higher in subjects with autonomous
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28 107 aldosterone secretion (18%) compared with patients without it (9%)[28]. However, the lack of PA
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30 108 confirmatory testing and the identification of OSA patients using database records are the major
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33 109 limitations of this study. Indeed, the prevalence of OSA in both PA and non-PA hypertensive patients
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35 110 resulted even lower than the one observed in the general population[22]. In a prospective study, the
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37 111 reported OSA prevalence was 78.1% and 71.0% in patients affected by RH with and without PA,
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40 112 respectively, and OSA severity was shown to be higher in the former group[29]. In a recent study
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42 113 aimed at exploring the effects of PA treatment on OSA severity, a 79% prevalence of OSA was
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44 114 showed in patients with PA[30]. Nevertheless, it should be noted that the study cohort was selected
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47 115 by the presence of at least one risk factor for sleep apnea, such as male gender, obesity, history of
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49 116 snoring or daytime sleepiness, therefore the assessed prevalence might represent an overestimation
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51 117 of the actual OSA prevalence in the overall PA population because of selection bias. In the HYPNOS
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53 118 study, among 207 patients with a confirmed diagnosis of PA, the prevalence of OSA was 67.6%[14].
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58 120 **3.Ethnic differences in primary aldosteronism and obstructive sleep apnea prevalence**

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121 Whether ethnic differences might affect the risk of both OSA and PA onset has been a matter of
122 debate. The prevalence of OSA in the general Caucasian population was estimated to be as high as
123 38% to even more than 90% in selected cohorts[2,22,23] and it was observed to be 64.4% in patients
124 with PA[14]. The prevalence of PA was found to be 5.9% in the general hypertensive population[12]
125 and 11.8% in Caucasian patients with OSA[14].

126 The SDB risk in Asian patients was reported to be higher than in Caucasians[31]. OSA is more
127 frequent in Chinese men than in women, although prevalence discrepancies lower along with
128 age[32,33]. The elevated SDB risk in Asians may be correlated to anatomical factors, such as the
129 higher frequency of craniofacial skeletal anomalies and the different body fat distribution compared
130 to Caucasians[31]. Asian patients usually display a greater dietary salt intake than Caucasians, and
131 this feature, along with an elevated salt-sensitivity of blood pressure, might contribute to hydrosaline
132 retention and pharyngeal edema[34]. In the HYPNOS study, Chinese patients with PA had a 70%
133 prevalence of OSA, which was not significantly different compared with Caucasians[14], and resulted
134 to be similar to that reported in Chinese with essential hypertension[35]. Moreover, aldosterone
135 positively correlated with apnea-hypopnea index (AHI) in Caucasians with PA, but not in Chinese
136 patients[14]. Hence, it is reasonable to suppose that the pathophysiology of OSA in Asians might be
137 related mostly to anthropomorphic predisposing features and high salt intake than to aldosterone-
138 mediated mechanisms.

139 Current evidences suggest that SDB risk is greater among patients of African descent compared to
140 Caucasians[31,36,37]. SDB predisposition might be correlated to obesity influence and presence of
141 enlarged upper airway soft tissue in blacks, as well as frequent disadvantageous socio-environmental
142 conditions and tobacco smoke[31]. Blacks with hypertension tend to have lower plasma renin activity
143 than whites[38], possibly suggesting a greater frequency of aldosterone-dependent hypertension [3],
144 though no differences in PA prevalence have been observed[3,39]. Moreover, blacks tend to be more
145 salt-sensitive and to display lower responsiveness to angiotensin-converting enzyme inhibitors and
146 beta-blockers compared to whites[40]. These evidences possibly suggest that aldosterone excess

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147 might play a relevant role in the pathophysiology of OSA in African-Americans, as supported by a
148 study reporting a higher prevalence of both OSA and PA compared with Caucasians, Hispanics, and
149 Asians[28].

The pathophysiological link between aldosterone and OSA

1. Obstructive sleep apnea effects on the renin-angiotensin-aldosterone system

153 Several pathophysiological mechanisms relating OSA to hypertension have been proposed, including
154 intermittent hypoxia, hypercapnia, intrathoracic negative pressure changes and nocturnal arousals.
155 Blood pressure increase due to intermittent hypoxic events has been associated to sympathetic
156 nervous system hyperactivity, renin-angiotensin-aldosterone system (RAAS) overstimulation,
157 oxidative stress, endothelial dysfunction, endothelin overproduction and pro-inflammatory state[41].
158 OSA severity might correlate with aldosterone oversecretion, thus leading to water and sodium
159 retention, and subsequent rise in blood pressure. Indeed, patients with OSA and RH with normal
160 plasma renin activity, plasma aldosterone concentration and aldosterone-to-renin ratio displayed a
161 reduced aldosterone response to saline load along with increasing severity of OSA[42].

162 Is aldosterone excess a result of RAAS hypoxia-induced activation in patients with OSA, or does it
163 represent a contributing factor to OSA pathophysiology? To assess causality of OSA and aldosterone
164 excess relationship, a number of clinical studies were performed and evaluated the impact of
165 continuous positive airway pressure (CPAP) treatment on aldosterone levels in patients with OSA.
166 The results of a meta-analysis of 5 studies indicated minimally yet significantly reduced aldosterone
167 levels after at least one month of CPAP therapy. Nonetheless, a sub-analysis including only
168 randomized controlled trials indicated no significant aldosterone changes in the CPAP-treated
169 patients compared to controls[43]. However, the study performed by Møller et al., showing no
170 significant decrease of aldosterone levels after CPAP therapy, might be limited by the lack of an
171 appropriate BMI-matching of enrolled subjects, thus leading to biased results due to obesity influence

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3 172 on CPAP effects[44]. Of interest, all included studies were performed in Europe and enrolled patients
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5 173 were predominantly male, thus ethnicity and gender influence on aldosterone response to CPAP
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8 174 treatment could not be assessed.
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11 175 A recent study showed that also short-term CPAP treatment might be able to lower plasmatic
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13 176 aldosterone and renin levels in moderate-severe OSA patients with type 2 diabetes[45]. Conversely,
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15 177 a recent randomized controlled trial reported that only optimal CPAP treatment - at least 4 hours per
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18 178 night during the entire 6-month study period - significantly decreased urinary aldosterone excretion
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20 179 in RH patients with moderate-severe OSA compared to controls[46]. Another study displayed that
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22 180 CPAP therapy was able to significantly decrease aldosterone levels and blood pressure in OSA
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25 181 patients with day-and-night sustained hypertension compared to controls, but not in those with
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27 182 isolated nocturnal hypertension[47]. Lastly, aldosterone levels were not significantly decreased by
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29 183 angiotensin receptor-blocker treatment in a cohort of subjects with hypertension and OSA compared
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32 184 to those without OSA, while add-on CPAP therapy in the former group tended to lower aldosterone
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34 185 excess and sympathetic activity. These results support the hypothesis of a subclinical form of
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36 186 hyperaldosteronism in patients with hypertension and OSA[48].
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41 188 **2.Overnight rostral fluid shift as a pathogenetic feature predisposing to obstructive sleep apnea**

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43 189 Several evidences support the importance of volume overload and nocturnal rostral fluid shift in the
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45 190 pathogenesis of OSA. This latter phenomenon is due to redistribution of fluid, accumulated during
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48 191 daytime in the lower extremities because of gravity, from legs to neck upon lying down at night. Fluid
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50 192 displacement into neck structures promotes upper respiratory tract soft tissue edema, which in turn
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52 193 causes airway resistance increase and airflow obstruction[49].
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55 194 Targeting fluid overload in hypervolemic patients might be effective to reduce AHI and upper airway
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57 195 collapsibility in subjects with OSA[49]. A 2-week course of intensified diuretic treatment was
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3 196 reported to be effective in improving OSA severity in patients with uncontrolled hypertension and
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5 197 moderate-severe OSA[50].

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8 198 Aldosterone excess, along with increased dietary sodium intake, leads to fluid overload[1,51]. A
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10 199 meta-analysis showed that aldosterone and angiotensin II are significantly higher in OSA-affected
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12 200 patients with hypertension than in normotensive individuals[52]. Therefore, it has been hypothesized
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14 201 that aldosterone excess might be implicated in volume overload predisposing nocturnal rostral fluid
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16 202 shift in patients with OSA[51]. Conversely, in a large cross-sectional study plasma aldosterone levels
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18 203 and plasma renin activity were not significantly different in RH patients with no or mild OSA
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20 204 compared with patients with moderate-severe OSA[53].
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26 206 **3.Aldosterone blockade and obstructive sleep apnea**

28 207 Several studies documented a positive correlation between aldosterone levels and OSA severity.
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30 208 Plasma and urinary aldosterone levels significantly correlated with AHI in subjects with RH, but this
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32 209 correlation was not observed in normotensive individuals nor in patients with treatment-controlled
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34 210 hypertension of similar age, BMI and OSA severity[46,54]. Nevertheless, a study reported a positive
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36 211 correlation between aldosterone levels and AHI in patients affected by essential, but not secondary,
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38 212 RH[29]. Some studies reported that plasma and urinary aldosterone levels positively correlate with
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40 213 AHI in patients with RH and autonomous aldosterone production. Conversely, no significant
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42 214 correlation between aldosterone levels and AHI was observed in patients with normal aldosterone
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44 215 secretion, suggesting that the role of aldosterone in OSA pathogenesis and severity might be relevant
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46 216 only in subjects displaying a status of aldosterone excess[55,56].
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51 217 A number of clinical studies evaluated the effect of aldosterone blockade on airway obstruction. Two
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53 218 small observational studies reported a significant reduction of AHI after a 2-month treatment with
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55 219 spironolactone in patients with RH and moderate-severe OSA[57], and a 3-month treatment with
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57 220 eplerenone in patients with essential RH and OSA, respectively[58]. Likewise, a small randomized
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59 221 blank-controlled prospective trial showed a significant reduction of OSA severity, blood pressure and
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3 222 aldosterone levels in patients affected by RH and moderate-severe OSA after a 3-month
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5 223 spironolactone therapy on top of preexisting antihypertensive treatment compared to controls[59].
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8 224 Furthermore, AHI and neck circumference were reduced by PA medical or surgical therapy in patients
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10 225 affected by both PA and OSA[30].
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12 226 Aldosterone excess might concur to airway obstruction pathogenesis not only by fluid overload-
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14 227 mediated mechanisms, but also through direct impairment and deregulation of central ventilatory-
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17 228 control[41,60]. Nowadays, targeting aldosterone excess has not yet been defined as an effective
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19 229 treatment for patients with OSA. Notwithstanding, mineralocorticoid receptor-antagonist treatment
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21 230 should be considered in patients with OSA and RH[41].
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26 232 **4.Primary aldosteronism, obstructive sleep apnea and obesity**

28 233 The coexistence of high aldosterone levels and OSA might also be attributed to the presence of
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30 234 common predisposing conditions, such as obesity and metabolic disorder[61]. OSA prevalence is
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33 235 elevated in individuals affected by obesity or metabolic syndrome, and it is even higher in subjects
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35 236 with diabetes and morbid obesity[24]. Furthermore, OSA is associated with insulin resistance
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38 237 independently of concomitant obesity[62] and abnormal glucose metabolism may be attributed to
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40 238 hypoxemia-induced sympathetic nervous system and RAAS activation[63]. Diabetic neuropathy may
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42 239 in turn affect central control of respiration promoting sleep apnea development, leading to a vicious
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44 240 cycle[64].
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47 241 Obesity is common in patients with both OSA and RH[1]. Interestingly, aldosterone levels appear to
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49 242 be higher in patients with OSA and metabolic syndrome compared to those without metabolic
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51 243 alterations[65]. Several studies observed high aldosterone levels in obese subjects, especially in those
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53 244 with visceral obesity[66]. Both adolescents and women with obesity displayed significantly higher
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55 245 aldosterone levels than lean individuals, and weight loss led to significant aldosterone
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57 246 reduction[67,68]. A recent study demonstrated that urinary aldosterone levels were positively
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59 247 correlated with BMI in RH patients, especially in men and regardless of ethnicity[69]. Moreover,
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3 248 BMI was directly correlated to aldosterone levels in postmenopausal Chinese women with obesity
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5 249 and hypertension but not in premenopausal women, possibly because of the role of endogenous
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8 250 estrogens as a regulator of aldosterone secretion before menopause[70].
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10 251 The pathophysiological pathways linking obesity to aldosterone excess still have to be fully
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12 252 elucidated. Adipose cells are able to produce angiotensinogen and angiotensin II; studies on animal
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15 253 models showed that angiotensinogen might be released into circulation by adipose tissue and its levels
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17 254 might correlate with systolic blood pressure[71]. Animal model studies suggested that high
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19 255 concentrations of fatty acids in portal venous blood of obese individuals might be metabolized by the
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22 256 liver to oxidized products, such as linoleic acid derivatives, which could stimulate aldosterone
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24 257 secretion[72]. Adipocyte secretory products, such as adipokines and adipocyte-derived hormones,
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26 258 may directly stimulate adrenocortical aldosterone secretion, independent of angiotensin II[73].
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28 259 Complement-C1q TNF-related protein-1 (CTRP1) was found to be overexpressed in both patients
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31 260 with obesity and hypertension, and to act as an endogenous aldosterone-stimulating factor[74]. Other
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33 261 adipokines such as tumor necrosis factor- α and interleukin-6 have also been shown to be involved in
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35 262 aldosterone secretion[75]. *In vitro* and *in vivo* studies on animal models showed that the adipocyte-
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38 263 derived anorectic hormone leptin could directly promote aldosterone secretion independently of
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40 264 potassium, angiotensin II and adrenocorticotrophic hormone levels[75,76]. Recent findings suggest
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42 265 that leptin-mediated pathway leading to hypertension development in patients with obesity might be
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45 266 mostly dependent to aldosterone oversecretion in women, and predominantly related to hypothalamic
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47 267 receptor activation and consequent sympathetic nervous system stimulation in men[77]. Interestingly,
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49 268 the role of obesity in the pathogenesis of aldosterone hypersecretion appeared to be relevant in
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52 269 patients with BHA, but not with APA[78,79]. These observations suggest that, while aldosterone
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54 270 overproduction is determined by a hormone-secreting tumor in APA patients, obesity might play an
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56 271 important role in aldosterone excess by adipokine-driven pathways in subjects with BHA[78,79].
57
58 272 Vice versa, aldosterone excess might contribute to obesity development through adipose tissue
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60 273 maturation by means of mineralocorticoid receptor activation, thereby leading to a vicious cycle[80].

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3 274 Higher prevalence of metabolic syndrome and diabetes has been shown in patients with PA compared
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5 275 with essential hypertension[81]. Insulin secretion might be impaired by either aldosterone-induced
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7 276 hypokalemia, and direct aldosterone effects resulting in pancreatic beta-cell dysfunction and
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10 277 apoptosis. Furthermore, hyperaldosteronism-related insulin resistance might be explained by
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12 278 defective expression of glucose transporter 4, insulin receptor and its related signal transducing
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14 279 factors in skeletal muscle and adipose tissue, as well as increased hepatic gluconeogenesis and
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17 280 endothelial remodeling affecting insulin and glucose peripheral delivery[82]. Finally, recent findings
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19 281 support the coexistence of mild glucocorticoid excess and aldosterone overproduction in PA,
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21 282 suggesting a role for cortisol-driven pathways in the determination of metabolic risk in a proportion
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24 283 of patients with PA[83].
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28 285 **Conclusions**

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30 286 Aldosterone excess, OSA and obesity could be interconnected within the context of metabolic
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33 287 syndrome through vicious cycle pathogenetic mechanisms. Obesity leads to OSA development
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35 288 through fat deposition within the neck, while OSA could in turn promote obesity. Adipokines released
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38 289 by visceral fat might induce aldosterone overproduction, which could in turn stimulate fat cell
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40 290 differentiation. Moreover, aldosterone excess-induced volume overload contributes to OSA
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42 291 pathogenesis, and intermittent hypoxia might in turn exacerbate RAAS activation. OSA and
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44 292 hyperaldosteronism might both lead to oxidative stress and inflammation, thus favoring the
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47 293 production of oxidized lipidic derivatives which could in turn aggravate aldosterone
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49 294 oversecretion[72]. Furthermore, hyperaldosteronism-related glucose metabolism dysregulation and
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51 295 diabetes[82] might lead to diabetic neuropathy development, which may consequently affect upper
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54 296 airway neural reflexes, thus favoring OSA[64]. Consistent with these evidences, OSA is frequently
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56 297 observed in patients with PA. Conversely, whether PA is more prevalent in patients with OSA
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58 298 compared with the general population remains controversial.
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