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RESEARCH

Isolated hypoaldosteronism is a cause of hypovolemic but not euvolemic hyponatremia

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Abstract

Introduction: Hypoaldosteronism is characterized by hyperkalemia, and/or hypovolemic hyponatremia (HH), often accompanied by metabolic acidosis. HH is typical of hypoaldosteronism, whereas euvolemic hyponatremia (EH) is not. The purpose of the current study is to describe the characteristics of hyponatremia in hypoaldosteronism and elucidate whether EH can be considered part of the disease's spectrum.

Methods: In a hypoaldosteronism cohort, we analyzed the factors associated with hyponatremia, comparing the characteristics of EH and HH and their associated factors. Correlation analyses of mineralocorticoid biomarkers, such as the transtubular potassium gradient (TTKG), the urinary Na+/K+ ratio (UNa+/UK+) with serum, and urinary electrolytes were performed in both types of hyponatremia.

Results: Of 112 hypoaldosteronism episodes, 77.7% were ≥65 years old, 44.6% were women, and 80 (71.4%) had hyponatremia. Hyponatremia was negatively associated with the presence of chronic kidney disease, and positively with a hypovolemic state, malnutrition, a prior history of hyponatremia, and glucocorticoid therapy. HH: 61/80 and EH: 19/80 episodes. HH was associated with an age ≥65 years and the use of diuretics, as well as factors related to an aldosterone deficit and/or mineralocorticoid resistance. In HH but not in EH, urinary potassium was correlated with the TTKG, and urinary sodium with both the TTKG and the UNa+/UK+.

Conclusion: Both HH and EH can be observed in hypoaldosteronism. However, only the former would be related to insufficient mineralocorticoid activity.

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Significance statement

Isolated hypoaldosteronism is a poorly understood and underdiagnosed endocrinological disorder, classically recognized only when hyperkalemia is present. The development of hypovolemic hyponatremia, however, is also easily explained by the physiopathology of the disorder. The current study addresses the features of hyponatremia when found in the context of mineralocorticoid insufficiency, and confirms an association between hypovolemic hyponatremia and isolated hypoaldosteronism. Thus, the clinical spectrum of hypoaldosteronism is extended to include hypovolemic hyponatremia as a frequent manifestation of the disorder.

Keywords: hypoaldosteronism; isolated hypoaldosteronism; hypovolemic hyponatremia; euvolemic hyponatremia; hyponatremia

Introduction

Aldosterone and cortisol are the two main mineralocorticoids in humans. Under physiological conditions, aldosterone is the chief stimulatory ligand of the mineralocorticoid receptor (MR) in the principal cells of the distal nephron. However, the importance of cortisol progressively increases as levels of the glucocorticoid rise to upper limits of normal (1). MR activation in principal cells leads to the synthesis of amiloride-sensitive epithelial Na+ channels and their insertion into the tubular lumen, as well as stimulation of the capillary-side Na+/K+ ATPase pump. These effects facilitate Na+ reabsorption from the tubular lumen into the bloodstream and its exchange for blood potassium, which is accompanied by H+ secretion into the lumen. In α-intercalated cells, mineralocorticoids facilitate urinary H+ excretion and bicarbonate production (2). Thus, mineralocorticoids are essential for maintenance of the effective circulating volume (ECV), as well as for Na+, K+, and H+ homeostasis.

Hypoaldosteronism is a condition occurring when mineralocorticoid action on the distal nephron is inadequately low and is incapable of assuring physiological responses to stimuli. In other words, it is a state of mineralocorticoid insufficiency. Hypoaldosteronism can be due to low circulating aldosterone levels, resistance to the action of mineralocorticoids, or a combination of both (3, 4). It is clinically characterized by hyperkalemia and/or hypovolemic hypovolemia (HH), each of which can be accompanied by hyperchloremic metabolic acidosis (5, 6). These alterations are secondary to a reduction in urinary potassium (UK+) excretion, together with varying degrees of urinary sodium (UNa+) loss and decreased urinary H+ excretion.

The prevalence and incidence of the acquired forms are currently unknown (7). However, hyperkalemia secondary to hypoaldosteronism was detected in 4% of hospitalized patients in one study and was the cause of 48% of cases of marked hyperkalemia (8). A review by Wilczynski *et al.* found that the etiology of hyperkalemia was in fact hypoaldosteronism in 10–80% of patients with this electrolyte alteration in published series (7). Hyperkalemia is not a constant of hypoaldosteronism, yet is often considered to be its sole electrolytic manifestation. However, prior series (9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22), including the first case reported by Hudson *et al.* (23), detected the presence of hyponatremia in this condition. We have recently reported that HH is not infrequent in isolated acquired hypoaldosteronism, particularly when both factors inducing a low circulating level of aldosterone (such as heparin administration) and factors resulting in a resistance to mineralocorticoid action (such as trimethoprim therapy) coincide (6). Yet the same study of 112 episodes of hypoaldosteronism also revealed that euvolemic hyponatremia (EH) was present in 19/112 (16.9%) of episodes. The fact that the volemic status of patients with hyponatremia and hypoaldosteronism can vary directly leads to the question of whether hypoaldosteronism can in and of itself lead to either type of hyponatremia.

HH in hypoaldosteronism is a consequence of renal salt-wasting, which induces hypovolemia. When the renin–angiotensin–aldosterone system (RAAS) responds normally to a decrease in ECV and the consequent reduction of renal perfusion, renin levels rise, leading to an increment in angiotensin II production. The latter both augments Na+ reabsorption at the level of the proximal tubule and stimulates aldosterone secretion by the adrenal gland. Increased aldosterone levels in turn boost Na+ reabsorption by principal cells in the distal nephron through stimulus of the MR within these cells. As a consequence of a higher degree of Na+ reabsorption, water is also retained and volemic status restored. However, when aldosterone levels are low or the hormone's action is impaired, the expected rise in renin and angiotensin II levels can be insufficient to compensate for this loss in mineralocorticoid function. UNa+ loss ensues, and marked hypovolemia can develop. As a low ECV stimulates baroreceptor-mediated release of arginine vasopressin (AVP), hyponatremia will follow.

HH can thus be considered emblematic in hypoaldosteronism, and its physiopathological mechanisms clear. Yet, as mentioned above, EH can

also be detected in patients with hypoaldosteronism. EH could be the consequence of a physiological non-osmotic stimulus of AVP release (as occurs in nausea) or secondary to an increase in fluid intake (e.g. primary polydipsia) or fluid administration (e.g. iatrogenic hypotonic fluid therapy) that exceeds the renal capacity to excrete free water. It can also be induced by inappropriate AVP secretion, such as what is seen in the syndrome of inappropriate antidiuresis (SIAD), which is, in fact, the most frequent cause of euvolemic hyponatremia (24). As we have previously reported that close to one-sixth of hypoaldosteronism cases can present with euvolemic hyponatremia, the question arises as to whether hypoaldosteronism per se can justify its presence.

The purpose of the current study is two-fold. The first aim is to describe the characteristics of hyponatremia detected in cases of hypoaldosteronism as a function of the patients' volume status. The second is to elucidate whether hypoaldosteronism per se can be associated with EH, as well as seeking to confirm its relationship with HH.

Methods

This is a retrospective analysis of hyponatremic patients with a diagnosis of hypoaldosteronism, following assessment by the Endocrinology and Nutrition Department of the Hospital Clínico San Carlos, Madrid, Spain. The methodology and design of our hypoaldosteronism registry have already been described (6). Briefly, we conducted a study with the data of adult patients diagnosed with hypoaldosteronism on hospital wards or at the outpatient clinic from January 2012 to August 2019, following consultation for hyponatremia and/or hyperkalemia. When the same patient was assessed more than once, with a minimum of 6 months elapsing between evaluations and confirmation of interim eunatremia and eukalemia, each episode was considered to be a different case and will be referred to as episodes here. The study complied with accepted standards of good clinical practice according to the Helsinki Declaration and was approved by the Ethical Committee of the HCSC (Code 20/714-E_BS, December 14, 2020). Written informed consent was waived.

The general characteristics of the episodes of hypoaldosteronism seen in the patients studied have been published (6), and in the current study we solely analyzed those with hyponatremia. Hypoaldosteronism was determined according to the criteria established in Supplementary Table 1 (see section on supplementary materials given at the end of this article). Patients with transitory or permanent hypoaldosteronism following adrenal surgery or medical therapy for primary hyperaldosteronism were excluded, as were patients with hypervolemia of any cause or oliguric renal failure. Hyponatremia was defined as a serum sodium (SNa^+) level ≤135 mmol/L following correction for glycemia (25). Hyperkalemia was defined as a serum potassium level (SK^+) ≥5 mmo/L. Hypovolemia was defined as the presence of the maximum height of the internal jugular pulse (HIJP) at or below the sternal angle with the patient reclined at 0–30°, in addition to at least two of the following data: thirst, orthostatic symptoms/signs, blood pressure ≤90/60 mm Hg, heart rate ≥90 bpm, decreased eye tone on palpation, distal venous filling of the upper limbs below the diaphragmatic line in a sitting position, and/or a rise in serum creatinine (SC) accompanying the descent in SNa (26, 27, 28). If HIJP was not measured, hypovolemia was determined by the presence of at least three of the aforementioned symptoms/signs. Patients without symptoms/signs of hypovolemia and with an HIJP at 1–3 cm above the sternal angle were classified as euvolemic. The following mineralocorticoid activity marker was used in the analysis: the transtubular potassium gradient (TTKG) (29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40) and the urinary Na^+/K^+ ratio (32, 41, 42, 43). The TTKG was calculated according to the original formula (33) in which the product of UK^+ and plasma osmolality is divided by the product of SK^+ and urine osmolality.

The description of collected data is available in Supplementary Data. For each patient, clinical data were collected from the moment in which a complete assessment was performed and a diagnosis of hypoaldosteronism was established. We classified the following variables as 'aldosterone-lowering factors' (ALowF): diabetes mellitus with over 10 years of evolution, chronic kidney disease (CKD), renal transplant, chronic synthetic glucocorticoid therapy (initiated ≥6 weeks before the episode), use of heparin, non-steroidal anti-inflammatory drugs, β-blockers, aliskiren, angiotensin-converting enzyme inhibitors (ACEIs), and/or angiotensin II receptor blockers (ARBs). The following variables were classified as 'mineralocorticoid-resistance factors' (ResF): renal transplant, obstructive uropathy, urinary tract infection, use of trimethoprim, cyclosporine, amiloride, tacrolimus, and/or MR blockers (MRB). In the presence of at least one of the aforementioned variables from each group, the patients were considered to have a 'combination of both types of factors' (CombF).

Serum and urinary electrolytes were measured with AU5800® Analyzer (Beckman Coulter) by indirect potentiometry (inter-assay variability coefficient <0.01) or direct whole blood gasometry analysis. Plasma and urinary osmolalities were assessed by A2O® osmometer (Advanced Instruments, Inc., Norwood, MA, USA) by freezing point.

Statistical analysis

We performed an analysis comparing the clinical parameters of the episodes showing hyponatremia with those who did not, dividing the former into hypovolemic or euvolemic hyponatremia.

Endocrine Connections (2024) **13** e230430
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Categorical variables are expressed as frequencies and percentages. Quantitative variables are described as mean ± S.D. or medians and interquartile range (IQR). We used χ^2-squared and Fisher's tests for comparative analysis of categorical variables. The comparison of quantitative variables was performed with Student's *t*-test or ANOVA test if parametric and with Mann–Whitney *U* or Kruskal–Wallis tests if non-parametric. Correlations with Pearson's and Spearman's tests (*r* value) were executed for parametric and non-parametric quantitative variables respectively. R^2 values for linear and logarithmic regression models were calculated in dispersion graphs where the correlations between variables were represented.

For multivariate analysis, logistic regression was performed with the Wald's method of steps forward, including variables with a *P* value < 0.1 in the univariate analysis. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. A *P*-value < 0.05 in two-tailed analysis was considered statistically significant. SPSS, version 25 (IBM Corp.), was used for the analysis.

Results

Of the 112 independent episodes of hypoaldosteronism studied, the patients presented with hyperkalemia in 106 (94.6%) and hyponatremia in 80 (71.4%), the latter the subject of the analyses of the current study. The median age of the patients with hyponatremic episodes was 78 years (IQR: 65–84), and 38/80 (47.5%) were female. Sixty-one of the 80 episodes (76%) had HH whereas 19/80 (24%) had EH, the latter with an additional diagnosis of SIAD. The cause of hypoaldosteronism was primary adrenal insufficiency (PAI) in 7/112 (6.3%) episodes, two of which were due to congenital adrenal hyperplasia. In the remaining 105 episodes, the hypoaldosteronism was isolated, as it did not coincide with primary glucocorticoid insufficiency, and acquired. Hypoaldosteronism was associated with RAAS-interfering medication in over 90, with ACEI/ARB therapy present in 57 episodes, MRBs in 12, heparin in 28, cotrimoxazole in 14, tacrolimus in 5, and cyclosporine present in 1. However, in 66, there was more than one factor that could induce hypoaldosteronism. The clinical characteristics of the 112 hypoaldosteronism episodes at the moment of diagnosis, according to the presence of hyponatremia, are displayed in Table 1.

Factors associated with hyponatremia

We studied the factors associated with hyponatremia irrespective of volemia in all 112 episodes (Table 1). Hyponatremia was more frequent in those with hypovolemia than in those who were euvolemic. Of the comorbidities analyzed individually, the presence of CKD, a history of prior hyponatremia, and malnutrition, as compared with their absence, were associated with different rates of hyponatremia: 56.4% vs 79.5% (P = 0.010), 85.1% vs 51.1% (P < 0.001), and 89.5% vs 62.2% (P = 0.002), respectively. Of the concomitant drug treatments at diagnosis, when analyzed individually, only short-term synthetic glucocorticoid therapy (see in Supplements) during the episode was associated with higher rates of hyponatremia as compared to its absence: 95.2% vs 65.9% (P = 0.007).

Upon analyzing the episodes of hyponatremia as a function of volemia, we found that HH patients had higher rates of an age ≥65 years, CKD, urinary infection, malnutrition, treatment with MRBs, thiazides, or any diuretic (Table 2). Likewise, when all drug treatments were analyzed as a sole group, as well as when the comorbidities and treatment were categorized as ALowF, ResF, or CombF, all of them were associated with HH (Table 2) yet not with EH.

We investigated variables independently associated with HH as compared to EH. We performed two models of multivariable analysis. The first model included the following variables: age ≥65 years, CKD, urinary infection, malnutrition, treatment with MRB, and diuretics. This analysis showed that age ≥65 years and diuretic therapy were associated with HH (Table 3). The second model included variables categorized as ALowF, ResF, or CombF, and age ≥65 years, and showed that only the presence of CombF remained associated with HH (Table 3)

Biochemical impact of HH

Hyperkalemia was observed in 74/80 (92.5%) episodes, corresponding with 55/61 (90.1%) of HH episodes and all 19 EH episodes. Acid–base status was evaluated in 38/80 (47.5%) episodes, with metabolic acidosis diagnosed in 23/38 (60.5%) episodes, corresponding to 20 HH and 3 EH episodes. A tendency toward higher rates of metabolic acidosis was observed in HH as compared to EH episodes (69% vs 33.3%, P = 0.058). HH did not condition higher rates of SNa+ ≤130 mmol/L, SNa+ ≤125 mmol/L, SK+ ≥ 5.5 mmol/L, SK+ ≥6 mmol/L, nor HCO_3^- ≤20 mmol/L vis-à-vis EH. Mean levels of SNa+, SK+, and HCO_3^- were similar in HH and EH. A trend toward lower SNa+ levels was observed in HH. Of the additional biochemical parameters evaluated in serum, differences were observed solely in SC and estimated glomerular filtration rate (GFR), with HH episodes exhibiting higher levels of the former and lower levels of the latter. Urine parameters were similar in HH and EH. Biochemical characteristics of both HH and EH are displayed in Table 4.

Biochemical markers of mineralocorticoid activity: comparison of HH and EH

The means or medians of the markers of mineralocorticoid activity as well as biochemical parameters assessed in serum and urine were similar

Endocrine Connections (2024) **13** e230430
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Table 1 Factors associated with hyponatremia.

	TOTAL	Eunatremia	Hyponatremia	
	n = **112**	*n* = **32**	*n* = **80**	***P***
Age, years	77 (65–84)	76 (65–84)	78 (65–84)	0.951
≥ 65 years, *n* (%)	87 (77.7)	25 (78.1)	62 (77.5)	0.943
Female, *n* (%)	50 (44.6)	12 (37.5)	38 (47.5)	0.336
Volemic state:				
Hypovolemia	71 (64.5)	10 (33.3)	61 (76.3)	<**0.001**[a]
Euvolemia	39 (35.5)	20 (66.7)	19 (23.8)	
Comorbidities				
Hypertension, *n* (%)	85 (75.9)	22 (68.8)	63 (78.8)	0.264
Low-sodium diet, *n* (%)	53 (47.3)	17 (53.1)	36 (45)	0.437
DM, *n* (%)	59 (52.7)	20 (62.5)	39 (48.8)	0.188
>10 years	35 (31.3)	13 (40.6)	22 (27.5)	0.176
CKD, *n* (%)	39 (34.8)	17 (53.1)	22 (27.5)	0.010[a]
Obstructive uropathy, *n* (%)	29 (25.9)	5 (15.6)	24 (30)	0.117
Urinary infection, *n* (%)	10 (8.9)	3 (9.4)	7 (8.8)	0.917
Renal transplant, *n* (%)	5 (4.5)	2 (6.3)	3 (3.8)	0.623
History of prior hyponatremia, *n* (%)	67 (59.8)	10 (31.3)	57 (71.3)	<**0.001**[a]
Malnutrition, *n* (%)	38 (33.9)	4 (12.5)	34 (42.5)	**0.002**[a]
Chronic alcoholism, *n* (%)	9 (8)	3 (9.4)	6 (7.5)	0.713
Primary adrenal insufficiency, *n* (%)	7 (7.8)	1 (4.2)	6 (9.1)	0.670
Concomitant pharmacological treatment				
ACEI/ARB, *n* (%)	57 (50.9)	19 (59.4)	38 (47.5)	0.256
MRB, *n* (%)	13 (11.6)	1 (3.1)	12 (15)	0.105
Aliskiren, *n* (%)	0			–
Short-term GC, *n* (%)[b]	21 (18.8)	1 (3.1)	20 (25)	**0.007**[a]
Chronic GC, *n* (%)[c]	16 (14.3)	3 (9.4)	13 (16.3)	0.551
Diuretics, *n* (%)	34 (30.4)	8 (25)	26 (32.5)	0.435
Loop diuretic, *n* (%)	24 (21.4)	6 (18.8)	18 (22.5)	0.662
Thiazide, *n* (%)	11 (9.8)	2 (6.3)	9 (11.3)	0.726
Thiazide + amiloride, *n* (%)	2 (1.8)	0 (0)	2 (2.5)	0.243
Heparin, *n* (%)	28 (25)	4 (12.5)	24 (30)	0.058
Cotrimoxazole, *n* (%)	14 (12.5)	2 (6.3)	12 (15)	0.343
Pentamidine, *n* (%)	0	–	–	–
Tacrolimus, *n* (%)	5 (4.5)	2 (6.3)	3 (3.8)	0.623
Cyclosporine, *n* (%)	1 (0.9)	0 (0)	1 (1.3)	0.411
NSAID, *n* (%)	9 (8)	2 (6.3)	7 (8.8)	0.653
β-blockers, *n* (%)	20 (17.9)	8 (25)	12 (15)	0.212
Compound variables				
Any drug use	90 (80.4)	24 (75)	66 (82.5)	0.367
Aldosterone-lowering factors	87 (77.7)	23 (71.9)	64 (80)	0.351
Mineralocorticoid-resistance factors	83 (74.1)	23 (71.9)	60 (75)	0.733
Combination of both	66 (58.9)	16 (50)	50 (62.5)	0.224

Bold values indicate statistical significance.
[a]$P < 0.05$; [b]Short-term GC: initiated during the episode or the preceding 6 weeks; [c]Chronic GC: initiated ≥ 6 weeks before evaluation of the episode.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; DM, diabetes mellitus; GC, glucocorticoid therapy; ARB: angiotensin II receptor blocker; MRB,: mineralocorticoid receptor blocker; NSAID, non-steroidal anti-inflammatory drugs.

between HH and EH (Table 4). Upon analyzing all hyponatremic patients together, a negative correlation between the TTKG and the urinary Na+/K+ ratio was found ($r = -0.67$, $P < 0.001$) (Fig. 1). When performing correlation analysis per volemia, we detected differences between the two groups (Table 5). In neither hyponatremic group was SNa+ correlated with SK+, UK+, UNa+, the urinary Na+/K+ ratio, nor with the TTKG. However, in both groups, correlations between SK+ and UNa+, UK+ and the urinary Na+/K+ ratio, UK+ and the TTKG, the fractional excretion of K+ (FEK) and the urinary K+/creatinine ratio, as well as the TTKG and the urinary Na+/K+ ratio were detected. In neither group was SK+ correlated with UK+. Yet in HH, and only in HH, was SK+ correlated with the TTKG, UNa+ with the TTKG, and UNa+ with the urinary Na+/K+ ratio (Fig. 2 and 3).

Endocrine Connections (2024) **13** e230430
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Table 2 Comparison of hypovolemic and euvolemic hyponatremia.

	Total	Hypovolemic hyponatremia	Euvolemic hyponatremia	
	n = **80**	*n* = **61**	*n* = **19**	***P***
Age, years	74.7 ± 12.8	76 ± 12	69 ± 17	**0.037**[a]
≥ 65 years, *n* (%)	62 (77.5)	51 (83.6)	11 (57.9)	**0.019**[a]
Female, *n* (%)	38 (47.5)	28 (45.9)	10 (52.6)	0.608
Comorbidities				
Hypertension, *n* (%)	63 (78.5)	49 (80.3)	14 (73.7)	0.536
Low-sodium diet, *n* (%)	36 (45)	31 (50.8)	5 (26.3)	**0.061**
DM, *n* (%)	39 (48.8)	28 (45.9)	11 (57.9)	0.361
>10 years	22 (27.5)	14 (23)	8 (42.1)	0.103
CKD, *n* (%)	22 (27.5)	20 (32.8)	2 (10.5)	0.042[a]
Obstructive uropathy, *n* (%)	24 (30)	19 (31.1)	5 (26.3)	0.688
Urine infection, *n* (%)	7 (8.8)	7 (11.5)	0 (0)	0.045[a]
Renal transplant, *n* (%)	3 (3.8)	3 (4.9)	0	0.197
Prior hyponatremia history, *n* (%)	57 (71.3)	42 (68.9)	15 (78.9)	0.396
Malnutrition, *n* (%)	34 (42.5)	30 (49.2)	4 (21.1)	**0.036**[a]
Chronic alcoholism, *n* (%)	6 (7.5)	4 (6.6)	2 (10.5)	0.624
Primary adrenal insufficiency, *n* (%)	6 (9.1)	4 (7.8)	2 (13.3)	0.612
Treatment				
ACEI/ARB, *n* (%)	38 (47.5)	32 (52.5)	6 (31.6)	0.112
MRB, *n* (%)	12 (15)	11 (19.7)	0 (0)	**0.008**[a]
Aliskiren, *n* (%)	0			–
Short-term GC, *n* (%)[b]	20 (25)	16 (26.2)	4 (21.1)	0.768
Chronic GC, *n* (%)[c]	13 (16.3)	8 (13.1)	5 (26.3)	0.173
Diuretics, *n* (%)	26 (32.5)	24 (39.3)	2 (10.5)	**0.024**[a]
Loop diuretic, *n* (%)	18 (22.5)	16 (26.2)	2 (10.5)	0.214
Thiazide, *n* (%)	9 (11.3)	9 (14.8)	0 (0)	**0.022**[a]
Thiazide–amiloride, *n* (%)	2 (2.5)	2 (3.3)	0 (0)	0.294
Heparin, *n* (%)	24 (30)	20 (32.8)	4 (21.1)	0.401
Cotrimoxazole, *n* (%)	12 (15)	10 (16.4)	2 (10.5)	0.721
Pentamidine, *n* (%)	0	–	–	–
Tacrolimus, *n* (%)	3 (3.8)	3 (4.9)	0 (0)	0.197
Cyclosporine, *n* (%)	1 (1.3)	1 (1.6)	0 (0)	0.460
NSAID, *n* (%)	7 (8.8)	5 (8.2)	2 (10.5)	0.668
β-blockers, *n* (%)	12 (15)	11 (18)	1 (5.3)	0.276
Compound variables				
Any drug use	66 (82.5)	54 (88.5)	12 (63.2)	**0.011**[a]
Aldosterone-lowering factors	64 (80),	52 (85.2)	12 (63.2)	**0.036**[a]
Mineralocorticoid-resistance factors	60 (75)	50 (82)	10 (52.6)	**0.010**[a]
Combination of both	50 (62.5)	43 (70.5)	7 (36.8)	**0.008**[a]

Bold values indicate statistical significance.
[a]$P < 0.05$; [b]Short-term GC: initiated during the episode or the preceding 6 weeks; [c]Chronic GC: initiated ≥6 weeks before evaluation of the episode.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; DM, diabetes mellitus; GC, glucocorticoid therapy; MRB, mineralocorticoid receptor blocker; NSAID, non-steroidal anti-inflammatory drugs.

The hypothalamic–pituitary–adrenal glucocorticoid axis in hyponatremia

Basal cortisol and ACTH were assessed in 66 episodes. HH and EH had comparable values of basal cortisol and ACTH: 15.9 ± 6 vs 17.5 ± 3.9 µg/dL, $P = 0.330$; and 29 (20.1–35.1) vs 38.7 (26–63.2) pg/mL, $P = 0.191$, respectively. Primary adrenal insufficiency was ruled out in 51/80 (63.7%) episodes: 12 EH and 39 HH episodes, and diagnosed in 6/80 (7.5%). In the 23 episodes without available cortisol/ACTH levels, the glucocorticoid axis was not evaluated in 15 due to the interference of glucocorticoid therapy. In the remaining eight episodes, cortisol levels had not been determined.

In the 51 episodes without PAI, the mean levels of basal cortisol were similar in HH and EH: 18.5 ± 4 vs 18.7 ± 3.5 µg/dL ($P = 0.889$). Likewise, the levels of SNa+ (129 ± 5.1 vs 131 ± 4.7mmol/L, $P = 0.330$), and SK+ (5.3 ± 0.5 vs 5.3 ± 0.3 mmol/L, $P = 0.806$) were also similar. Mean HCO_3^- levels tended to be lower in HH than EH (21.9 ± 2.7 vs 24.2 ±1.7 mmol/L, $P = 0.096$), and the rate of metabolic acidosis was higher in HH than in EH (76.5% vs 20%,

Table 3 Multivariable analysis for HH.

	OR	95% CI	*P*
Model 1			
Presence of an age ≥65 years	3.4	1.045–11.06	0.042[a]
Presence of any diuretic use	5.1	1.055–24.745	0.043[a]
Model 2			
Presence of combF	4.095	1.387–12.088	0.011[a]

[a]$P < 0.05$.
CombF, combination of both factors associated with deficit of aldosterone and associated with mineralocorticoid resistance.

$P = 0.039$). We did not find correlations between cortisol and SK+, SNa+, HCO_3^-, UNa+, UK+, urinary Na+/K+ ratio, nor TTKG in the entire cohort of hyponatremia. However, when analyzed according to volemic status, we found a negative correlation between cortisol and SNa+ in HH ($r = -0.338$, $P = 0.038$) and a positive correlation in EH ($r = 0.678$, $P = 0.015$).

Additionally, we compared all 20 episodes receiving glucocorticoid therapy during the hyponatremic hypoaldosteronism episode (either short-term or chronic) with the 60 episodes who did not. We found that those receiving glucocorticoid therapy had higher mean SK+ values (5.6 ± 0.7 vs 5.3 ± 0.5 mmol/L, $P = 0.042$) and lower basal cortisol values (10.5 ± 5.7 vs 17.2 ± 5 µg/dL, $P = 0.001$). The rate of a SK+ ≥6 mmol/L was also higher in the former than the latter (25% vs 5%, $P = 0.021$). SNa+, HCO_3^-, TTKG, or urinary Na+/K+ ratio values were not statistically different between the analyzed groups. In the group of the 20 episodes treated with GC, we compared the 16 HH with the 4 EH episodes, finding no statistical differences in the levels of SK+, SNa+, HCO_3^-, TTKG, and urinary Na+/K+ ratio.

When the 61 HH episodes were independently analyzed according to the presence/absence of glucocorticoid therapy, we found that the 16 episodes receiving GC had higher levels of SK+ (5.6 ± 0.7 vs 5.3 ± 0.5 mmol/L, $P = 0.035$) and lower cortisol levels (10.3 ± 6 vs 16.9 ± 5 µg/dL, $P = 0.003$) than those without glucocorticoid therapy. No other significant differences were detected. In the 19 episodes of EH, we compared the 4 episodes receiving glucocorticoid therapy with those 19 not administered glucocorticoids. HCO_3^- values were available in 2/4 episodes of EH with glucocorticoid therapy, and in 7/19 without it. The former showed significantly lower levels of HCO_3 than the latter (17.3 ± 1.5 vs 24.8 ± 1.8 mmol/L, $P = 0.001$). However, the low number of episodes analyzed reduces the intrinsic value of the analysis. The other biochemical parameters analyzed did not show significant differences.

Discussion

Characteristics of hyponatremia in hypoaldosteronism

Hyponatremia was detected in over 70% of episodes of hypoaldosteronism. The presence of hyponatremia

Table 4 Biochemical parameters at diagnosis in episodes with hyponatremia according to volemia.

	Total (*n* = 80)	**Hypovolemic hyponatremia** (*n* = 61)	**Euvolemic hyponatremia** (*n* = 19)	*P*
Serum Na+, mmol/L	129 ± 5	128.7 ± 5	131 ± 4	**0.088**
Nadir serum Na+	124.4 ± 5	124 ± 5	125.4 ± 5	0.310
Posm, mOsm/kg	280 ± 12	281 ± 12	279 ± 11	0.654
Serum K+, mmol/L	5.4 ± 0.5	5.4 ± 0.6	5.4 ± 0.4	0.902
Zenith serum K+	5.7 ± 0.6	5.7 ± 0.6	5.8 ± 0.5	0.690
Serum creatinine, mg/dL	1.1 ± 0.5	1.2 ± 0.5	0.8 ± 0.2	<**0.001**[a]
GFR, mL/min/1.73 m^2	119 ± 40	111 ± 41	146 ± 25	<**0.001**[a]
HCO_3^-, mmol/L	22.2 ± 3.4	21.9 ± 3.3	23.1 ± 3.7	0.353
Cortisol, µg/dL	16.3 ± 5.6	15.9 ± 6	17.5 ± 4	0.330
ACTH	35.2 ± 29	33.9 ± 30.5	42.6 ± 19.8	0.588
Serum K+/urinary K+ ratio	0.19 (0.14–0.23)	0.2 (0.15–0.24)	0.16 (0.12–0.23)	0.233
Fractional excretion of K+	13.2 ± 6.8	14.4 ± 6.8	9.7 ± 5.5	**0.057**
Urine K+/creatinine ratio, mmol/L/mg/dL	64.7 ± 29.1	66.2 ± 30.7	60 ± 25	0.564
Urine Na+, mmol/L	72 ± 37	71 ± 38	77 ± 34	0.588
Urine K+, mmol/L	30 ± 12	30 ± 11	32 ± 13.7	0.485
Urine Na+/K+ ratio	2.7 ± 1.6	2.6 ± 1.6	2.8 ± 1.8	0.657
Uosm, mOsm/kg	406 ± 140	401 ± 138	425 ± 150	0.549
TTKG	3.8 (3.1–4.8)	3.7 (3.4–4.7)	3.8 (2.5–5.4)	0.964

Bold values indicate statistical significance.
[a]$P < 0.005$.
Posm, plasma osmolality; GFR, glomerular filtration rate; Uosm, urinary osmolality; TTKG, trans-tubular potassium gradient.

Endocrine Connections (2024) **13** e230430
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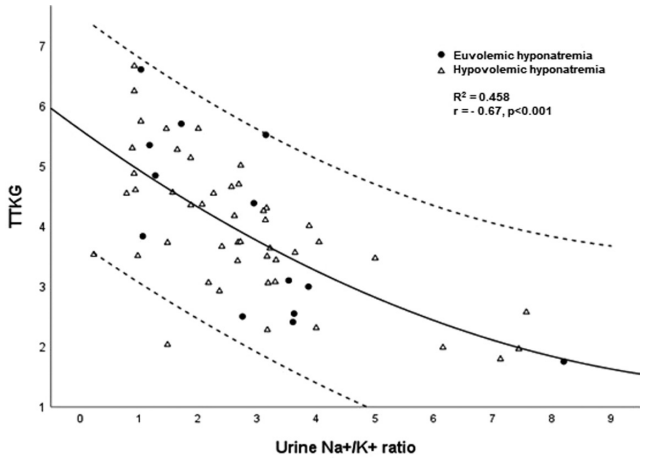

Figure 1

Dispersion graph between trans-tubular potassium gradient and urinary Na+/K+ ratio of hypovolemic and euvolemic hyponatremia episodes. Solid line represents the value of R^2 and the dotted lines its 95% confidence interval.

in and of itself was negatively associated with the existence of CKD and positively associated with a history of a prior hyponatremic episode, malnourishment, and short-term glucocorticoid therapy. The vast majority of episodes were of acquired isolated hypoaldosteronism, with only six corresponding with primary adrenal insufficiency. The current study addresses the features of hyponatremia when found in the context of mineralocorticoid insufficiency.

Table 5 Correlations of mineralocorticoid activity markers with blood and urinary electrolytes according to type of hyponatremia.

	Hypovolemic hyponatremia		Euvolemic hyponatremia	
	r	*P*	*r*	*P*
SK+ with UNa+	0.29	0.029[a]	0.52	0.039[a]
SK+ with UK+	0.16	0.236	0.24	0.375
SK+ with TTKG	−0.34	0.020[a]	−0.24	0.426
FEK with urine K+/creatinine ratio	0.67	<0.001[a]	0.91	<0.001[a]
Urine Na+/K+ ratio with UK+	−0.42	0.001[a]	−0.63	0.009[a]
Urine Na+/K+ ratio with UNa+	0.75	<0.001[a]	0.41	0.115
TTKG with the urine Na+/k+ ratio	−0.63	<0.001[a]	−0.72	0.006[a]
TTKG with UK+	0.53	<0.001[a]	0.59	0.035[a]
TTKG with UNa+	−0.45	0.001[a]	−0.29	0.329

[a]$P < 0.005$.

FEK, fractional excretion of potassium; SK+, serum potassium; TTKG, trans-tubular potassium gradient; UK+, urinary potassium; UNa+, urinary sodium.

Hypovolemia was present in a majority of episodes of hypoaldosteronism (64.5%) and was directly associated with the presence of hyponatremia. Age ≥65 years and diuretic treatment, two factors that can predispose to (44) and induce hypovolemia, respectively, were in turn independently associated with the presence of HH. In fact, more than half of the episodes of hypoaldosteronism studied presented with hypovolemic hyponatremia, with HH three times as frequent as EH, representing a full 76% of hyponatremic episodes. Thus, hypovolemia can be considered to be a predisposing factor for hyponatremia in hypoaldosteronism.

The episodes of HH presented with higher SC and lower GFR values, as a consequence of the low ECV of hypovolemia. No other statistically significant differences in basal serum and urine parameters were observed, as were to be expected, given that all episodes had hypoaldosteronism.

Yet the analysis of elements related to the physiopathology of mineralocorticoid insufficiency revealed differences between the two volume states. In the current study, the presence of factors that are known to impair mineralocorticoid homeostasis (ALowF, ResF, CombF) made HH, but not EH, more likely to occur. Our findings are in accordance with a previous study of hypoaldosteronism, where elements known to interfere with mineralocorticoid physiology were also associated with HH (6) when compared to a group comprised of episodes of euvolemic hyponatremia as well as hyperkalemic non-hyponatremic episodes. Therefore, it appears that hypoaldosteronism itself can readily induce hypovolemic hyponatremia, justifying observations of hyponatremia in prior case series of this disorder (9, 10, 12, 13, 15, 16, 17, 45, 46).

The analysis of the two most emblematic parameters of mineralocorticoid function, the TTKG and the urine Na+/K+ ratio, also sheds light on the relationship between hypoaldosteronism and the two types of hyponatremia under consideration. The levels of both TTKG and the urine Na+/K+ ratio were similar in EH and HH, in accordance with the diagnosis of hypoaldosteronism. Yet SK+ and the TTKG were correlated in HH but not in EH. Additionally, UNa+ was related to the urinary Na+/K+ ratio and to the TTKG in HH but not in EH. The TTKG is a semiquantitative index of mineralocorticoid-dependent K+ excretion (29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40). Its use has been validated in both children (39) and adults (40) and found to be directly related to aldosterone (39, 40) and SK+ levels (30, 37). In normal subjects, both higher aldosterone and K+ levels are accompanied by an elevation of the TTKG. This is not the case in hypoaldosteronism, however, in which the TTKG is characteristically low (30, 32, 40). The urine Na+/K+ ratio is an indirect marker of mineralocorticoid activity that reflects the distal tubular exchange of Na+ for K+ induced by mineralocorticoids. The ratio is negatively correlated with both aldosterone and SK+ levels in healthy children (39) and adults (47). The

Endocrine Connections (2024) **13** e230430
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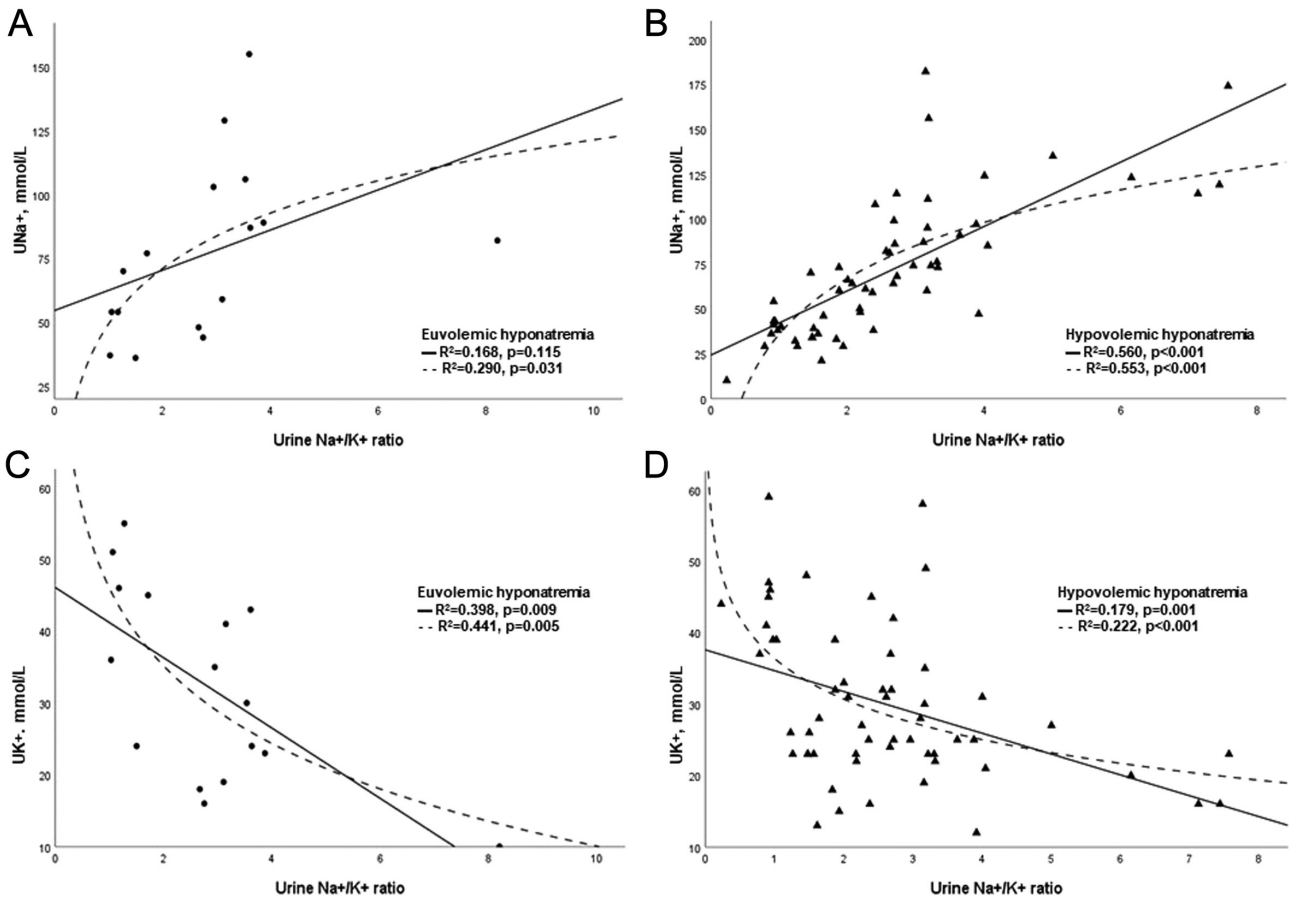

Figure 2

Dispersion graph between urinary Na+/K+ ratios and UNa+ and UK+ according to euvolemic (A and C) and hypovolemic (B and D) hyponatremia. Solid lines represent linear regression and dotted lines logarithmic regression. ●, euvolemic hyponatremia; ▲, hypovolemic hyponatremia. Solid lines represent linear regression and dotted lines logarithmic regression.

more potent the mineralocorticoid stimulus, the greater the principal cell reabsorption of Na+ and excretion of K+, thereby leading to a lower value of the ratio. In fact, when K+ and/or aldosterone levels are elevated, the ratio is normally ≤1 (32, 41, 43). The reverse is the case in hypoaldosteronism, where high ratio values will be found (32, 39, 42). In the current study, these emblematic markers of mineralocorticoid function were only correlated with the aforementioned biochemical parameters in HH and not in EH.

The relationship between HH and both factors that reduce mineralocorticoid action as well as biochemical markers of hypoaldosteronism was absent in the case of EH. Thus, we can extrapolate that, whereas HH can be a direct consequence of hypoaldosteronism, the development of EH in this disease would respond to another physiopathological mechanism altogether. Hypoaldosteronism induces an increase in UNa+ excretion which can cause or facilitate hypovolemia and consequently hypovolemic hyponatremia. Thus, the lower the mineralocorticoid activity, the lower the TTKG and higher the urine Na+/K+ ratio, and the higher the UNa+. In contrast, in an euvolemic state in which non-osmotic AVP secretion is present, the hyponatremia is not secondary to hypovolemia, and a minimum of mineralocorticoid activity could be sufficient to maintain a normal or elevated ECV. UNa+ would therefore be a function of the degree of AVP-induced water reabsorption in the collecting duct and not solely a result of hypoaldosteronism-dependent Na+ loss, thereby rendering the interaction between UNa+ and mineralocorticoid markers irrelevant. Only HH, and not EH, should be considered to be characteristic of hypoaldosteronism.

Role of cortisol in hyponatremia presentation and pathogenesis

We have found adrenal cortisol secretion to be of relevance in the clinical presentation and pathogenesis of hyponatremia in hypoaldosteronism. Hyponatremic episodes on glucocorticoid therapy had higher levels

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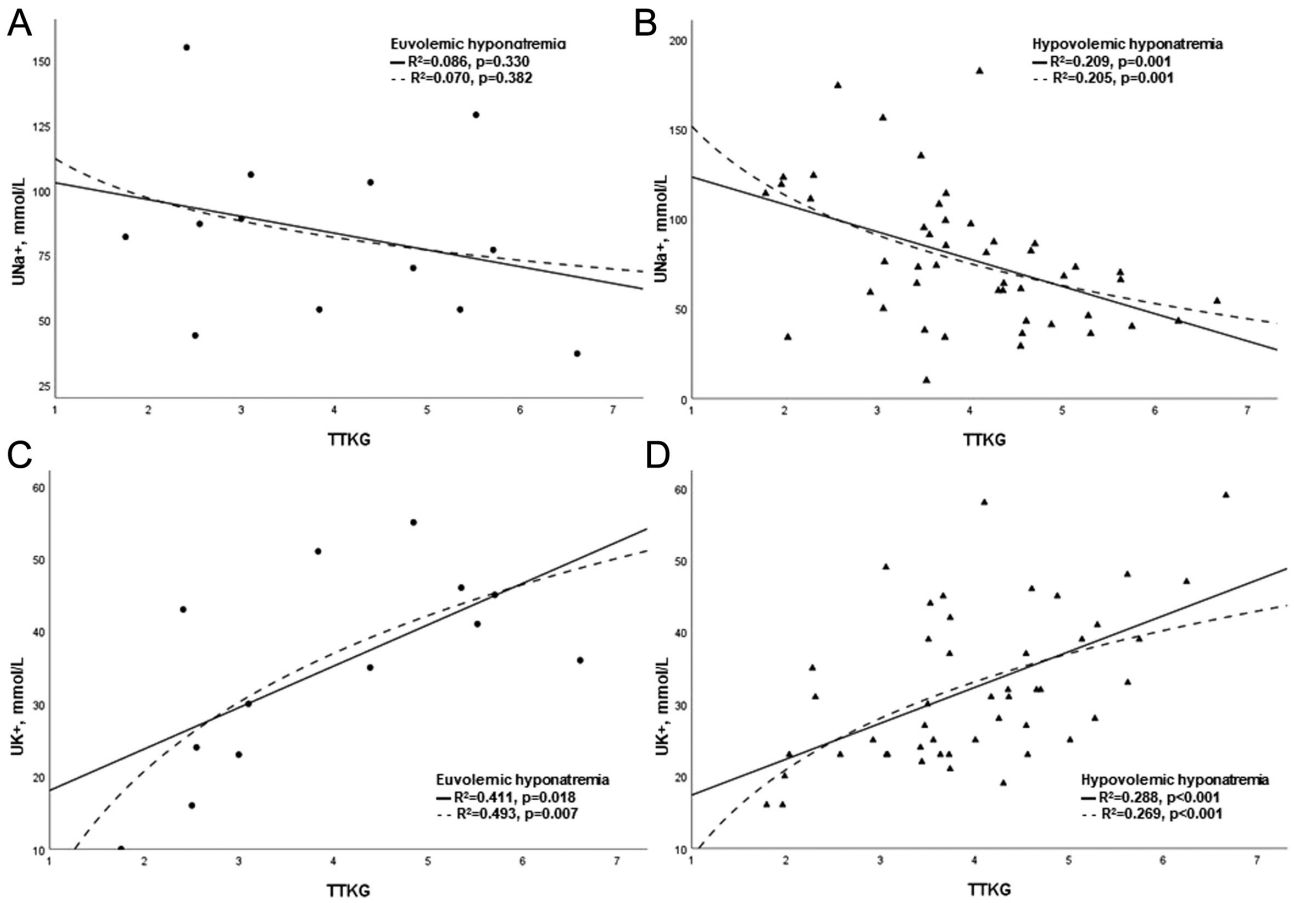

Figure 3

Dispersion graph between urinary trans-tubular potassium gradient and UNa+ and UK+ according to euvolemic (A and C) and hypovolemic (B and D) hyponatremia. Solid lines represent linear regression and dotted lines logarithmic regression. ●, euvolemic hyponatremia; ▲, hypovolemic hyponatremia.

of SK+ and rates of SK+ ≥6 mmol/L than those episodes not receiving steroid treatment, irrespective of volemia. Furthermore, the subanalysis of HH episodes treated vs those not treated with glucocorticoids detected that the former had higher SK+ levels than the latter (the small number of EH episodes receiving steroids impeded a similar subanalysis). These findings can be explained by the fact that, although aldosterone is the principal ligand of the MR in the principal cells of the distal nephron, cortisol acquires a higher relevance in situations in which its levels are in the upper range of normal or elevated (1). The patients studied were receiving synthetic glucocorticoids, known to be weaker mineralocorticoids than cortisol. Thus, through their inhibition of ACTH secretion, cortisol levels would be reduced, and the cortisol boost to mineralocorticoid activity impaired, worsening hypoaldosteronism.

Interestingly, despite the fact that HH and EH had similar cortisolemias, an inverse correlation of cortisol with SNa+ was found in the former, whereas a direct one was detected in the latter. In the case of HH, this finding can be easily explained. A hypovolemic state is known to be associated with an increase in the production of cortisol (48, 49) and AVP. Hypovolemia induces a rapid and marked release of AVP from the neurohypophysis and an increase in magnocellular hypothalamic AVP production. The lower the ECV, the steeper the AVP baroreceptor-mediated rise, and thus, the lower the SNa+. But magnocellular AVP also directly stimulates pituitary ACTH secretion through axons projecting from the supra-optic and paraventricular nuclei to terminate in the medial eminence, thereby providing AVP to the adenohypophysis through the pituitary portal system (50). Furthermore, a recent study suggests that hypovolemia can also stimulate parvocellular paraventricular hypothalamic AVP synthesis (51). Thus, a lower SNa+, reflecting a higher degree of AVP antidiuresis, would be associated with more elevated ACTH-stimulated cortisol levels. This rise, in turn, would help compensate for the loss of aldosterone function. Yet we have detected the opposite in the euvolemic episodes: the lower the SNa+, the lower the cortisolemia. We believe this positive correlation can be explained by the elevation in circulating levels of atrial natriuretic peptide (ANP) observed in SIAD (52, 53, 54), which would be expected whenever, as is common in EH, the ECV is expanded. ANP is a potent inhibitor of pituitary ACTH secretion (55, 56), and consequently,

higher levels of the former would result in a reduction of cortisol secretion. Thus, the higher the AVP and fluid intake, the lower the SNa+, the higher the ECV and ANP, and the lower the cortisol level.

Role of age

The majority of patients in our cohort were ≥65 years of age, in accordance with previously reported case series of hypoaldosteronism. Furthermore, age was independently associated with HH in our cohort. This leads us to hypothesize that older adults could be at a higher risk for the development of hypoaldosteronism. In fact, a more advanced age has been proposed to be a risk factor for hyperkalemia in hypoaldosteronism (57, 58). Lower aldosterone levels (59), a progressive loss of aldosterone synthase activity (60), and reduced TTKG values (37, 38) have all been described in healthy older individuals as compared to young adults. These facts, together with a higher likelihood of receiving RAAS-interfering medication and presenting with comorbidities, underline the need to monitor for alterations in mineralocorticoid homeostasis in the older population. This would be of particular importance when factors that could trigger or exacerbate hypoaldosteronism are present.

Limitations and strengths

Our study has limitations that must be taken into account. First, its retrospective design is associated with the loss of data regarding some of the variables used in the subanalyses, thereby reducing statistical power and impoverishing the interpretation of results. Second, the prescription of drugs that could cause SIAD was not registered. The main strength of our study is that we evaluated a substantial case series from the same cohort, and a thorough classification of volemia was performed. Therefore, homogeneity of criteria used for diagnosis as well as volemic classification was guaranteed, permitting the study to provide new information on the characteristics of hyponatremia in hypoaldosteronism. Furthermore, a direct physio-pathological link between HH with elevated UNa+ and isolated hypoaldosteronism was established.

Conclusion

In conclusion, both hypovolemic and euvolemic hyponatremia can be observed in subjects with hypoaldosteronism. However, the former is more frequent and, in contrast to EH, is directly related to insufficient mineralocorticoid activity. Thus, when EH is detected in hypoaldosteronism patients, other causes of hyponatremia must be sought, such as SIAD. Once the origin of the detected EH is established, hypoaldosteronism and EH must therefore be treated independently, as therapy for hypoaldosteronism will not resolve EH. Furthermore, inhibition of cortisol secretion can directly worsen the clinical characteristics of patients with hyponatremia in hypoaldosteronism, such as hyperkalemia, a fact that highlights the importance of the hormone's role as a mineralocorticoid. We strongly recommend monitoring patients of advanced age receiving drugs interfering with mineralocorticoid homeostasis or with clinical characteristics associated with the latter, given their increased risk for the development of hypoaldosteronism-induced HH.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EC-23-0430.

Declaration of interest
All authors declare that they have no pertinent conflicts of interest for this study.

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Ethical approval
The study was approved by the Ethical Committee of the HCSC (code 20/714-E_BS, December 14, 2020).

Consent to participate
Written informed consent was waived given the registry's anonymized and retrospective nature.

Author contribution statement
Conceptualization: JGR-S, IR; Methodology: JGR-S, ALCP, MPDMN, MARH; Validation: JGR-S, ISR; Formal Analysis: JGR-S; Investigation: JGR-S; Writing – Original Draft Preparation: JGR-S, IR; Writing – Review and Editing: JGR-S, ALCP, MPDMN, MARH, IR; Supervision and Review: IR, ALCP, MPDMN, MARH; Resources: JGR-S, ALCP, IR. All authors read and agreed to the final version of the manuscript.

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