

**Renin concentration indicates the mineralocorticoid activity of fludrocortisone: a 6-year longitudinal study  
in patients with primary adrenal insufficiency**

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***Supplementary Material***

*Supplementary Table 1:* number (n) and percentage (%) of patients divided by months of follow-up from baseline to intermediate visit (T0 → T1) and from intermediate to last follow-up visit (T1→T2).

	Months T0 → T1		Months T1 → T2	
	n	% of 193	n	% of 178
<b>≤ 12</b>	47	24.4	32	18.0
<b>13 - 24</b>	26	13.5	38	21.3
<b>25 - 36</b>	30	15.5	27	15.2
<b>37 - 48</b>	18	9.3	41	23.0
<b>49 - 60</b>	41	21.2	20	11.2
<b>61 - 72</b>	18	9.3	13	7.3
<b>&gt;72</b>	13	6.7	7	3.9

*Supplementary Table 2:* Clinical and endocrine data of 130 patients with Autoimmune PAI (isolated Addison Disease, autoimmune polyendocrine syndrome type 1, 2 and 4) at baseline (T0), intermediate (T1) and last visit (T2). Data are reported as mean  $\pm$  standard error, range in brackets. BMI: Body Mass Index; BSA: Body Surface Area; SBP: systolic blood pressure; DBP: diastolic blood pressure; PRC: Plasma Renin Concentration; Tot Chol: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol.

	T0	T1	T2
Age (years)	43 $\pm$ 1.0 (15-83)	46 $\pm$ 1.0 <sup>a</sup> (16-87)	49 $\pm$ 1.0 <sup>a b</sup> (17-89)
Height (cm)	167.5 $\pm$ 1.3 (150-189.5)	168.3 $\pm$ 1.26 (147-193)	167.6 $\pm$ 1.3 (147-189.5)
Weight (Kg)	64.7 $\pm$ 1.9 (37-100)	68.0 $\pm$ 1.6 (37-106.5)	69.2 $\pm$ 1.6 <sup>c</sup> (38-120)
BMI (Kg/m <sup>2</sup> )	23.54 $\pm$ 0.85 (13.98-35.43)	23.72 $\pm$ 0.6 (16.44-35.08)	24.56 $\pm$ 0.7 (16.00-37.04)
BSA (m <sup>2</sup> )	1.73 $\pm$ 0.04 (1.26-2.22)	1.77 $\pm$ 0.03 (1.26-2.29)	1.78 $\pm$ 0.03 (1.30-2.37)
SBP (mmHg)	115 $\pm$ 2 (80-160)	118 $\pm$ 2 (85-170)	120 $\pm$ 1 (80-160)
DBP (mmHg)	76 $\pm$ 1 (50-110)	78 $\pm$ 1 (40-100)	80 $\pm$ 1 (50-110)
Na <sup>+</sup> (mmol/L)	138.4 $\pm$ 0.35 (123-149)	138.5 $\pm$ 0.3 (127-147)	138.9 $\pm$ 0.3 (130-145)
K <sup>+</sup> (mmol/L)	4.23 $\pm$ 0.0 (2.9-5.6)	4.19 $\pm$ 0.0 (2.9-5.5)	4.2 $\pm$ 0.0 (2.9-5.2)
ACTH (ng/L)	427.2 $\pm$ 72.78 (3.5-2390)	302.9 $\pm$ 52.6 (1.5-1875)	305.1 $\pm$ 43.9 (3.1-1580)
PRC (mIU/L)	223.7 $\pm$ 53.64 (0.6-2933)	154.56 $\pm$ 20.6 (0.2-934.0)	186.25 $\pm$ 39.7 (2-2881)
Glucose (mmol/L)	4.92 $\pm$ 0.25 (3.7-15.87)	5.04 $\pm$ 0.1 (2.7-12.38)	5.09 $\pm$ 0.1 (3.89-9.2)
HbA1c (mmol/mol)	44.46 $\pm$ 3.5 (30-99)	43.3 $\pm$ 2.0 (32-71)	43.97 $\pm$ 2.0 (29-76)
Tot Chol (mmol/L)	5.57 $\pm$ 0.2 (3.32-7.67)	5.64 $\pm$ 0.1 <sup>d</sup> (3.72-8.24)	5.47 $\pm$ 0.1 (2.65-7.90)
HDL (mmol/L)	1.57 $\pm$ 0.1 (0.63-2.87)	1.66 $\pm$ 0.1 (0.78-2.90)	1.62 $\pm$ 0.1 (0.91-2.62)
LDL (mmol/L)	3.15 $\pm$ 0.16 (1.21-4.81)	3.49 $\pm$ 0.14 (1.81-5.44)	3.15 $\pm$ 0.12 (0.85-5.20)
Tryglicerides (mmol/L)	1.38 $\pm$ 0.1 (0.58-3.10)	1.41 $\pm$ 0.1 (0.51-3.56)	1.44 $\pm$ 0.1 (0.6-4.98)

<sup>a</sup> p<0.001 vs T0, <sup>b</sup> p<0.001 vs T1, <sup>c</sup> p=0.047 vs T1, <sup>d</sup> p=0.003 vs. T0.

*Supplementary Table 3:* Clinical and endocrine data of 32 patients with PAI after bilateral adrenalectomy at baseline (T0), intermediate (T1) and last visit (T2). Data are reported as mean  $\pm$  standard error, range in brackets. BMI: Body Mass Index; BSA: Body Surface Area; SBP: systolic blood pressure; DBP: diastolic blood pressure; PRC: Plasma Renin Concentration; Tot Chol: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol.

	T0	T1	T2
Age (years)	52 $\pm$ 3 (15-82)	55 $\pm$ 3 <sup>a</sup> (15-82)	57 $\pm$ 3 <sup>a b</sup> (17-83)
Height (cm)	169.8 $\pm$ 1.9 (156-183.0)	167.13 $\pm$ 1.9 (149-176)	169.3 $\pm$ 2.1 (157-183)
Weight (Kg)	79.9 $\pm$ 7.7 (55-125)	74.8 $\pm$ 4.3 (51-114.5)	79.7 $\pm$ 4.9 (53.5-112)
BMI (Kg/m <sup>2</sup> )	23.9 $\pm$ 2.7 (20.81-43.25)	27.67 $\pm$ 1.8 (20.69-39.10)	27.42 $\pm$ 1.5 (21.43-38.75)
BSA (m <sup>2</sup> )	1.91 $\pm$ 0.1 (1.61-2.32)	1.87 $\pm$ 0.1 (1.49-2.25)	1.87 $\pm$ 0.1 (1.53-2.21)
SBP (mmHg)	125 $\pm$ 4 (100-150)	129 $\pm$ 3 (110-170)	132 $\pm$ 6 (100-185)
DBP (mmHg)	82 $\pm$ 2 (70-100)	82 $\pm$ 2 (60-100)	82 $\pm$ 3 (65-115)
Na <sup>+</sup> (mmol/L)	141.3 $\pm$ 0.6 (135-150)	140.0 $\pm$ 0.5 <sup>c</sup> (132-145)	139.7 $\pm$ 0.5 <sup>d</sup> (134-145)
K <sup>+</sup> (mmol/L)	4.05 $\pm$ 0.07 (3.3-4.9)	4.12 $\pm$ 0.1 (3.3-5.70)	4.3 $\pm$ 0.1 (3.7-5.4)
ACTH (ng/L)	760.2 $\pm$ 402.2 (5.0-9580)	1347.7 $\pm$ 480.0 (15-7000)	895.1 $\pm$ 466.9 (5-11140)
PRC (mIU/L)	50.42 $\pm$ 17.1 (5.4-201)	75.58 $\pm$ 18.7 (0.1-233.0)	127.10 $\pm$ 38.6 (1.6-757)
Glucose (mmol/L)	4.89 $\pm$ 0.3 (3.7-8.71)	5.00 $\pm$ 0.2 (3.40-8.40)	5.49 $\pm$ 0.4 <sup>e</sup> (3.9-11.4)
HbA1c (mmol/mol)	49.00 $\pm$ 12.0 (37-61)	50.3 $\pm$ 4.1 (36-76)	44.38 $\pm$ 3.3 (26-76)
Tot Chol (mmol/L)	5.46 $\pm$ 0.2 (3.69-6.27)	5.41 $\pm$ 0.2 (3.48-7.39)	5.12 $\pm$ 0.37 (3.19-9.04)
HDL (mmol/L)	1.47 $\pm$ 0.1 (0.73-1.84)	1.39 $\pm$ 0.1 (0.68-2.02)	1.54 $\pm$ 0.12 (0.81-2.53)
LDL (mmol/L)	3.12 $\pm$ 0.3 (1.24-4.15)	3.32 $\pm$ 0.2 (2-5.22)	2.97 $\pm$ 0.31 (1.44-5.96)
Tryglicerides (mmol/L)	1.85 $\pm$ 0.4 (0.92-4.49)	1.67 $\pm$ 0.2 (0.70-3.90)	1.50 $\pm$ 0.20 (0.7-3.37)

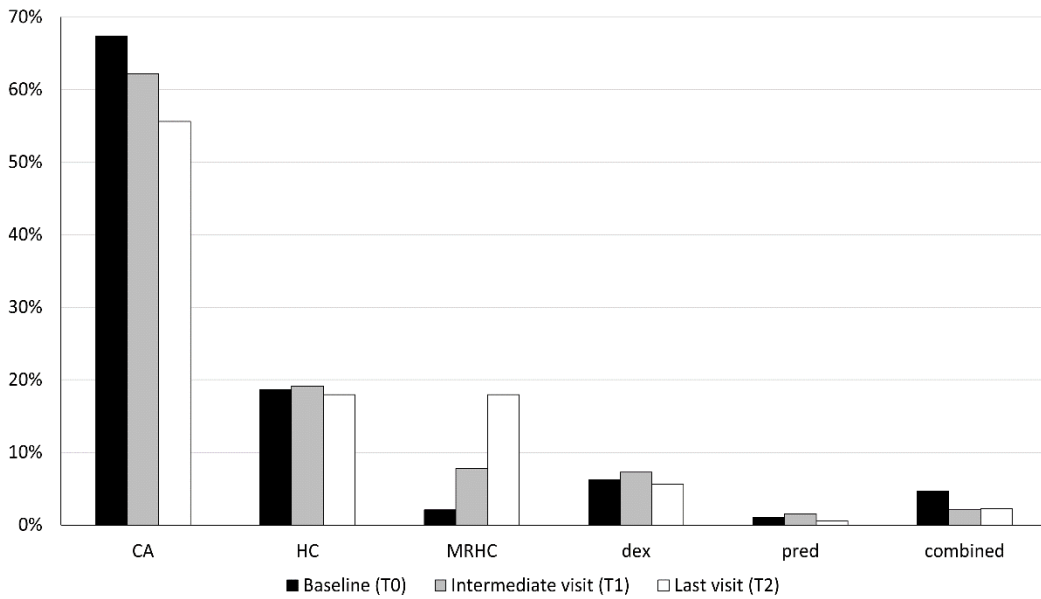
<sup>a</sup> p<0.001 vs T0, <sup>b</sup> p<0.001 vs T1, <sup>c</sup> p=0.002 vs T0, <sup>d</sup> p=0.017 vs. T0, <sup>e</sup> p<0.026 vs T1.

*Supplementary Table 4:* Clinical and endocrine data of 20 patients with salt-wasting CAH at baseline (T0), intermediate (T1) and last visit (T2). Data are reported as mean  $\pm$  standard error, range in brackets. BMI: Body Mass Index; BSA: Body Surface Area; SBP: systolic blood pressure; DBP: diastolic blood pressure; PRC: Plasma Renin Concentration; Tot Chol: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol.

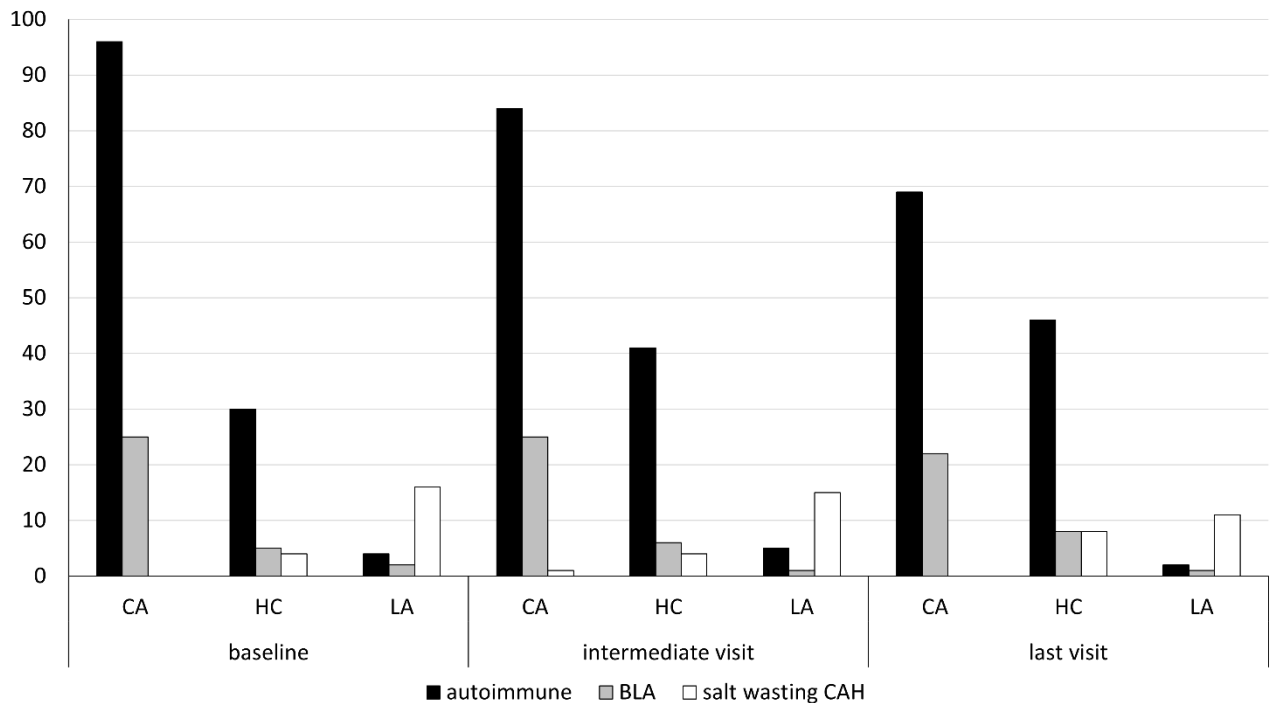
	T0	T1	T2
Age (years)	27 $\pm$ 2 (16-40)	31 $\pm$ 2 <sup>a</sup> (21-42)	35 $\pm$ 2 <sup>a b</sup> (23-48)
Height (cm)	160.7 $\pm$ 4.2 (140-185.0)	163.6 $\pm$ 2.8 (140-184)	164.6 $\pm$ 3.1 (151-185)
Weight (Kg)	59.7 $\pm$ 4.5 (44.5-89)	65.0 $\pm$ 2.4 (51-81.5)	64.7 $\pm$ 3.5 (46-79)
BMI (Kg/m <sup>2</sup> )	23.54 $\pm$ 1.7 (18.12-35.42)	23.87 $\pm$ 1.2 (18.73-38.78)	24.22 $\pm$ 1.3 (19.10-32.89)
BSA (m <sup>2</sup> )	1.63 $\pm$ 0.1 (1.32-2.02)	1.71 $\pm$ 0.04 (1.49-2.0)	1.71 $\pm$ 0.1 (1.41-1.95)
SBP (mmHg)	122 $\pm$ 4 (110-145)	123 $\pm$ 2 (110-145)	117 $\pm$ 3 (98-140)
DBP (mmHg)	78 $\pm$ 3 (60-95)	80 $\pm$ 2 (60-100)	76 $\pm$ 2 (60-90)
Na <sup>+</sup> (mmol/L)	140.3 $\pm$ 0.8 (134-150)	139.5 $\pm$ 0.6 (132-144)	138.4 $\pm$ 0.6 <sup>c</sup> (133-143)
K <sup>+</sup> (mmol/L)	4.04 $\pm$ 0.1 (3.1-4.9)	4.1 $\pm$ 0.1 (3.5-4.5)	4.3 $\pm$ 0.1 <sup>d</sup> (3.8-5.2)
ACTH (ng/L)	46.7 $\pm$ 16.3 (9-210)	185.3 $\pm$ 73.7 (9-1160)	248.4 $\pm$ 83.1 (1.6-1133)
PRC (mIU/L)	64.1 $\pm$ 24.7 (2.8-235.5)	342.1 $\pm$ 189.3 (24.8-1459.0)	526.68 $\pm$ 312.0 (12.9-5144)
Glucose (mmol/L)	4.37 $\pm$ 0.1 (3.8-4.7)	4.73 $\pm$ 0.2 <sup>e</sup> (3.7-5.88)	4.75 $\pm$ 0.1 (3.83-5.6)
HbA1c (mmol/mol)	34.00 $\pm$ 0 (34-34)	35.33 $\pm$ 0.8 (33-37)	34 $\pm$ 1.38 (30-39)
Tot Chol (mmol/L)	4.90 $\pm$ 0.5 (2.28-6.87)	4.57 $\pm$ 0.2 (3.26-5.56)	4.65 $\pm$ 0.3 (4.1-5.78)
HDL (mmol/L)	1.65 $\pm$ 0.2 (1.09-2.71)	1.70 $\pm$ 0.1 (1.2-2.36)	1.69 $\pm$ 0.2 (1.19-2.28)
LDL (mmol/L)	2.91 $\pm$ 0.4 (1.13-4.74)	2.55 $\pm$ 0.2 (1.68-3.97)	2.67 $\pm$ 0.2 (2.13-3.51)
Tryglicerides (mmol/L)	0.81 $\pm$ 0.1 (0.41-1.18)	0.87 $\pm$ 0.1 (0.45-1.6)	1.16 $\pm$ 0.3 (0.6-2.17)

<sup>a</sup> p<0.001 vs T0, <sup>b</sup> p<0.001 vs T1, <sup>c</sup> p=0.002 vs T0, <sup>d</sup> p=0.017 vs. T0, <sup>e</sup> p<0.026 vs T1.

*Supplementary Figure 1:* Substitutive GC treatment according to visits. CA: cortisone acetate, HC: hydrocortisone; MRHC: modified release HC; dex: dexamethasone; pred: prednisolone.

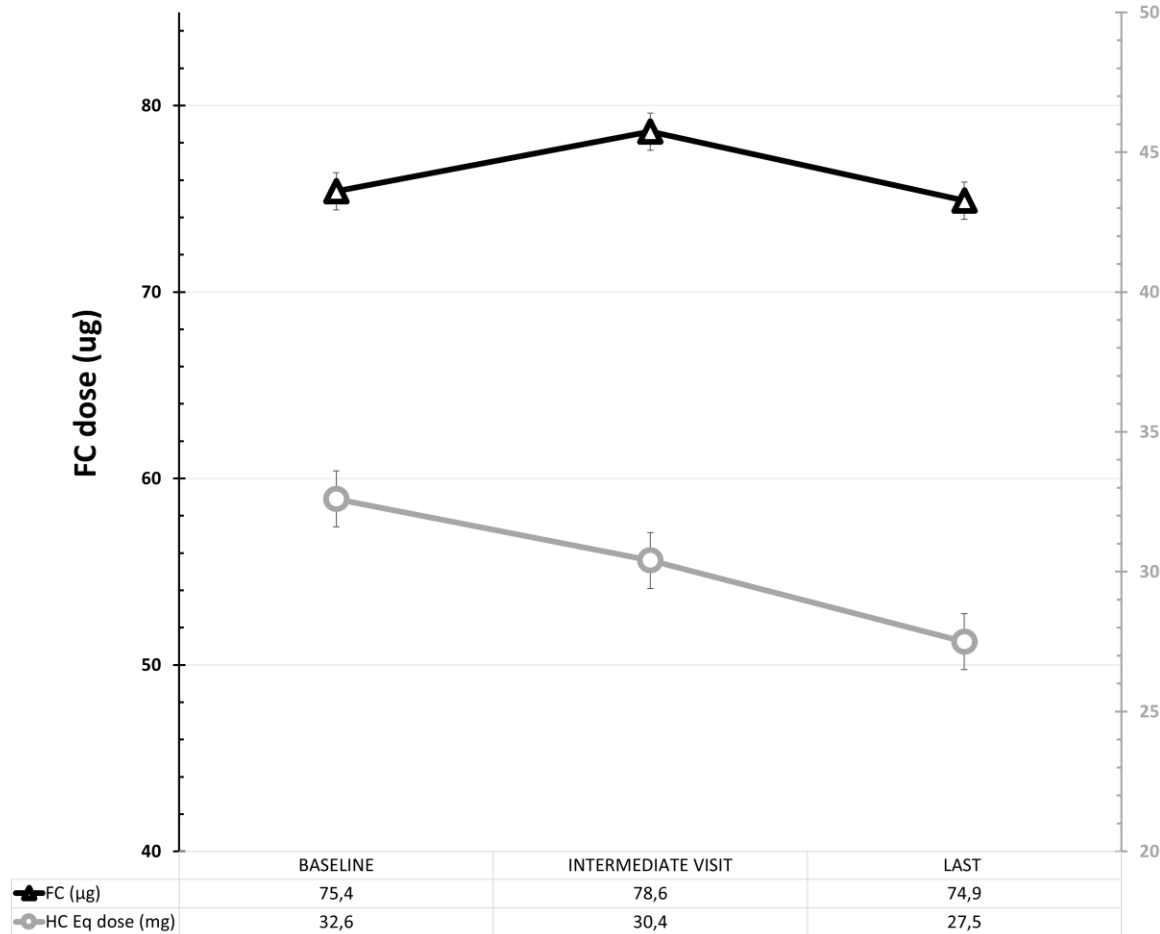


*Supplementary Figure 2:* substitutive GC treatment in different patients with PAI. BLA: bilateral adrenalectomy, CAH: congenital adrenal hyperplasia. CA: cortisone acetate, HC: hydrocortisone; LA: long-acting GC (dexamethasone or prednisolone, either combined).

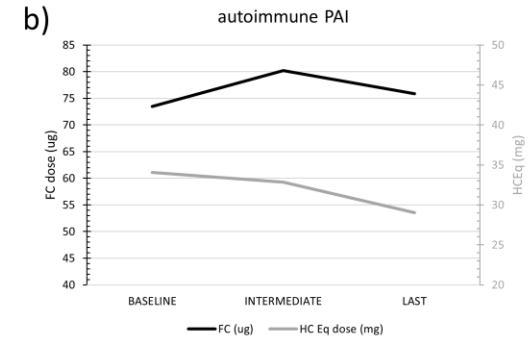


Supplementary Figure 3: mean daily dose of fludrocortisone (FC, black line) and hydrocortisone equivalent (HC Eq, grey line) in the baseline, intermediate and last visit in all patients (panel a), patients with autoimmune PAI (n=130, panel b), after bilateral adrenalectomy (BLA, n = 32, panel c) and with salt-wasting CAH (SW CAH, n = 20, panel d).

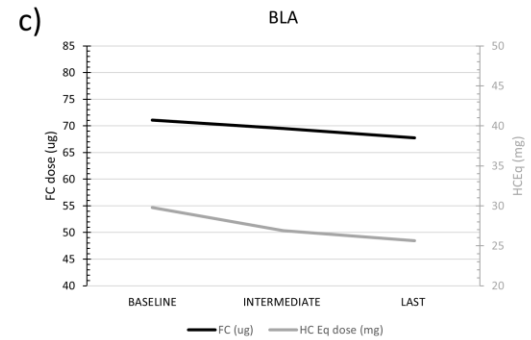
a)



b)



c)



d)

