

Cortisol excess in patients with primary aldosteronism impacts on left ventricular hypertrophy

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1 **Cortisol excess in patients with primary aldosteronism impacts on left ventricular hypertrophy**

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19 **Running title:** Cortisol excess impacts on cardiac structure in PA

20 **Précis:** Left ventricular mass in patients with primary aldosteronism improves after medical and surgical
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33

34 **Abstract**

35 **Context:** Primary aldosteronism (PA) represents the most frequent form of endocrine hypertension.
36 Hyperaldosteronism and hypercortisolism both induce excessive left ventricular hypertrophy (LVH)
37 compared to matched essential hypertensives. In recent studies frequent co-secretion of cortisol and
38 aldosterone has been reported in PA patients.

39 **Objective:** Our aim was to investigate the impact of cortisol co-secretion on left ventricular hypertrophy
40 in PA patients. We determined 24-h excretion of mineralocorticoids and glucocorticoids by gas
41 chromatography-mass spectrometry and assessed cardiac remodeling using echocardiography initially and
42 one year after initiation of treatment for PA.

43 **Patients:** We included 73 patients from the Munich center of the German Conn's registry; 45 with
44 unilateral aldosterone-producing adenoma and 28 with bilateral adrenal hyperplasia.

45 **Results:** At the time of diagnosis, 85% of PA patients showed left ventricular hypertrophy according to
46 left ventricular mass index (LVMI, median 62.4 g/m²). LVMI correlated positively with total
47 glucocorticoid excretion ($r^2=0.076$, $p=0.018$) as well as with tetrahydroaldosterone excretion ($r^2=0.070$,
48 $p=0.024$). Adrenalectomy led to significantly reduced LVMI in aldosterone-producing adenoma ($p<0.001$)
49 while mineralocorticoid receptor antagonist therapy in bilateral adrenal hyperplasia patients reduced
50 LVMI to a lesser degree ($p=0.024$). In multivariate analysis, the decrease in LVMI was positively
51 correlated with total glucocorticoid excretion and systolic 24-hour blood pressure, but not with
52 tetrahydroaldosterone excretion.

53 **Conclusion:** Cortisol excess appears to have an additional impact on cardiac remodeling in patients with
54 PA. Treatment of PA by either adrenalectomy or mineralocorticoid receptor antagonist improves LVMI.
55 This effect was most pronounced in patients with high total glucocorticoid excretion.

56 **Introduction**

57 Primary aldosteronism (PA) is the most frequent cause of endocrine hypertension affecting about
58 5-10 % of patients with elevated blood pressure (1). PA was first described in 1955 by Jerome W. Conn
59 (2) and characterized in its classical form as hypertension, hypokalemia and alkalosis. Patients with
60 bilateral adrenal hyperplasia (BAH), the most common subtype, require lifelong treatment with a
61 mineralocorticoid receptor antagonist (MRA), whereas patients with unilateral aldosterone-producing
62 adenoma (APA) can be cured by adrenalectomy (ADX). Prolonged exposure to elevated aldosterone
63 concentrations causes cardiac and renal damage independently of blood pressure (3). These changes may
64 have adverse impact on clinical outcome.

65 One of the targets of aldosterone action are cardiomyocytes which express mineralocorticoid
66 receptors (MR) (4). Indeed, MR activation has been shown to induce myocardial damage (3), including
67 diffuse myocardial fibrosis, left ventricular hypertrophy (LVH) and left ventricular dilatation (4). In
68 echocardiographic studies, LVH was more frequent and more progressive in PA patients in comparison to
69 matched essential hypertensives (5). Likewise, a number of studies have highlighted an increased risk of
70 stroke, myocardial infarction (MI) and atrial fibrillation in PA patients (6,7). LVH itself is one of the most
71 important predictors for major cardiac events and mortality and is associated with an increased risk of
72 arrhythmia, MI and stroke (8).

73 In a recent study, we identified cortisol co-secretion as a key feature of PA (9) associated with an
74 adverse metabolic risk phenotype, providing a logical explanation for important comorbidities observed in
75 patients with primary aldosteronism more aligned with the effects of glucocorticoid rather than
76 mineralocorticoid excess, such as insulin resistance and type 2 diabetes (10-13), and osteoporosis (14).
77 Interestingly, pronounced LVH has also been described in patients with Cushing's syndrome (CS), who
78 are also afflicted by arterial hypertension, impaired glucose tolerance and serum electrolyte imbalance
79 (15,16). High cortisol levels in patients with CS are associated with an increased mortality rate due to
80 cardiovascular complications (17).

81 Therefore, we hypothesized that cortisol co-secretion observed in PA might have additional
82 adverse effects on cardiac function and cardiovascular outcome in PA patients. Thus, our aim was to
83 investigate the impact of increased cortisol secretion on echocardiographic findings in patients with APA
84 or BAH.

85 **Methods**

86 *Patients*

87 During 2008 and 2013 we consecutively enrolled 210 patients with primary aldosteronism at the
88 Munich center of the German Conn's Registry. In 89 patients a urinary steroid metabolite excretion in
89 24-h urine was performed and of those 89, 73 patients with either APA (n=45) or BAH (n=28) had a
90 technically accurate echocardiography examination, which represents the cohort included in this study.
91 Analysis of urinary steroid metabolite excretion and echocardiography data represented post-hoc analyses.
92 All patients gave written informed consent, and the protocol of the German Conn's registry was approved
93 by the ethics committee of the University of Munich. At each visit, patients underwent standardized
94 clinical phenotyping including collection of anthropometric data and clinical characteristics such as
95 duration of hypertension and current medication.

96 The diagnostic procedures were performed according to the Endocrine Society Practice Guidelines
97 (18,19). In short, PA was diagnosed by an elevated plasma aldosterone to renin ratio (ARR; cut-off 10.0
98 ng/mU, sitting position) and an abnormal confirmatory test (e.g. salt loading test, captopril challenge test).
99 Antihypertensive medication was stopped (n=5) whenever possible prior to testing. Otherwise it was
100 replaced by alpha 1-adrenergic receptor (doxazosin) or calcium-channel blockers (verapamil) (n=68).
101 Subtype differentiation between unilateral and bilateral disease was based on adrenal vein sampling
102 (AVS). In case of APA only patients who underwent ADX were included in the analysis. BAH patients
103 were treated with MRA. In most patients, spironolactone was used at a dose of 25-50 mg per day. All
104 patients were re-evaluated one year after treatment in a standardized fashion.

105

106 *Laboratory analysis*

107 Blood samples were drawn in a fasting state in sitting position at 8.00 a.m. Plasma aldosterone
108 concentration was measured using the radioimmunoassay "aldosterone Coat-a-Count" (Biermann DPC).
109 Active renin concentration was measured by the Liaison chemiluminescence assay (Diasorin). All other
110 analyses were performed in our central laboratory using standard methods. To determine urinary steroid

111 excretion, the patients conducted a 24-hour urine collection. Subsequently, gas chromatography-mass
112 spectrometry (GC-MS) in selected-ion-monitoring (SIM) analysis mode was performed to determine the
113 urinary steroid metabolite excretion as described previously (9), allowing the quantification of 40 different
114 steroid metabolites, including 3 α ,5 β -tetrahydroaldosterone (THAldo), the major mineralocorticoid
115 metabolite. Total glucocorticoid excretion was calculated as the sum of quantified metabolites of cortisol
116 and cortisone, comprising tetrahydrocortisol, 5 α -tetrahydrocortisol, tetrahydrocortisone, α - and β -cortol,
117 α - and β -cortolone, 6 β -hydroxycortisol, and urinary cortisol and cortisone (9).

118

119 *Cardiac ultrasound examination*

120 Comprehensive echocardiographic examination was conducted by experienced sonographers from
121 the department of internal medicine I (cardiology) from the Ludwig-Maximilians-Universität München.
122 The sonographers were blinded with regard to diagnosis and clinical details. Commercially available high-
123 quality ultrasound systems were used (GE Healthcare Vivid 7, Philips iE 33). The patients were lying
124 down in the left lateral decubitus position. Echocardiography included two-dimensional, M-Mode and
125 Doppler ultrasound recordings. Images were obtained in the parasternal (long and short axis) and apical
126 views. The left ventricular internal dimension (LVID), interventricular septum (IVS), posterior wall
127 thickness (PWT) and left atrial dimension in diastole (LAd) were measured via parasternal long axis view.
128 Echocardiographic parameters were measured according to the recommendation of the American Society
129 of Echocardiography (20,21). Echocardiography-based left ventricular mass (LVM) estimation is
130 generally calculated as the difference between epicardium delimited volume and left ventricular chamber
131 volume multiplied by an estimate of myocardial density (22). The LVM was calculated by the Penn
132 Convention formula: $LVM=1.04 \cdot ([LVIDd+PWTd+IVSd]^3-[LVIDd]^3)-13.6g$ (23,24). Obesity is
133 independently associated to LVH (25). Because of higher average values of BMI in our study cohort,
134 LVH was determined as the left ventricular mass index (LVMI). LVM was indexed by height^{2.7} to obtain
135 LVMI. By using the LVMI we minimized the interference of obesity in LVM estimation (26). LVH was
136 prospectively defined as a value of LVMI $\geq 50 g/m^{2.7}$ in males and $\geq 47g/m^{2.7}$ in females (27). Relative wall

137 thickness (RWT) was calculated according to the following equation: $RWT=(IVSd + PWT)/LVIDd$. LVH
138 was separated in concentric hypertrophy with $RWT \geq 0.42$ and eccentric hypertrophy with $RWT < 0.42$
139 (21). Normal LVMI values and RWT values ≥ 0.42 were defined as concentric remodeling (28).

140

141 *Statistical analysis*

142 All values are expressed as median and 25th and 75th percentile if not mentioned otherwise.
143 Within-group changes from baseline to follow-up were calculated by Wilcoxon signed-rank test.
144 Spearman's Rank Order was used to perform bivariate correlation analysis. Stepwise multiple regression
145 analysis was used for multivariate analysis. Two-tailed probability values of $< 5\%$ were considered to be
146 statistically significant. Statistical analysis was performed using standard statistical software (SPSS 23,
147 IBM, Chicago, Illinois).

148 **Results**

149 *Patient characteristics*

150 Clinical characteristics of the total cohort of 73 patients with PA are shown in **Table 1**, the
151 comparison of APA and BAH subgroups in **Table 2**. APA and BAH were diagnosed in 45 and 28
152 patients, respectively. As expected, at diagnosis, patients with APA had higher plasma aldosterone
153 concentration ($p=0.001$), higher urinary THAldo concentrations ($p=0.001$) and lower potassium levels
154 ($p<0.001$), and more pronounced renal impairment according to globular filtration rate (GFR; $p=0.043$).
155 Total glucocorticoid excretion did not differ between groups ($p=0.184$).

156 Patient characteristics one year after initiation of treatment (MRA treatment in BAH, ADX in
157 APA) are listed in **Tables 1+2**. Systolic and diastolic blood pressure and serum potassium levels
158 normalized in both subgroups. As expected, defined daily doses (DDD) of antihypertensive medication
159 decreased significantly in the APA group, whereas in the BAH group there was only a trend towards
160 lower DDDs. BMI remained stable in both groups and both groups had a decline in renal function.
161 Triglyceride levels increased significantly in both groups, whereas HDL cholesterol levels decreased only
162 in the BAH group ($p=0.006$). Pro-BNP, a potential indicator of cardiac preload, improved in both groups.
163 The decline was not due to optimized treatment for heart failure. In fact, DDDs of ACE inhibitors/
164 angiotensin II receptor blockers (1.4 vs. 1.1; $p=0.002$), beta blockers (0.4 vs. 0.2; $p=0.001$) and diuretics
165 (0.4 vs. 0.2; $p<0.001$) have decreased significantly at follow-up.

166

167 *Echocardiographic findings in patients with unilateral aldosteronism and bilateral hyperplasia*

168 **Table 3** summarizes echocardiographic geometric characteristics in APA and BAH patients.
169 LVMI was elevated, the IVS was thickened and the LA was enlarged in both groups at baseline. The
170 overall prevalence of LVH was 85% before initiation of treatment, compared to 66% at follow-up. There
171 was a shift from eccentric and concentric hypertrophy towards normal left ventricular geometry (**Suppl.**
172 **Table 1**). As expected, LVMI improved in both APA ($p<0.001$) and BAH ($p=0.024$) patients with
173 treatment (**Fig. 1**). The reduction of LVMI (Δ LVMI) was numerically greater in APA patients with a

174 significant decrease of LVIDd ($p < 0.001$), PWTd ($p = 0.020$) and IVSd ($p = 0.001$). In BAH patients only
175 LVIDd ($p = 0.001$) improved significantly.

176

177 ***THAldo, total glucocorticoid excretion, urinary sodium excretion and left ventricular structure***

178 As reported previously (9), both THAldo excretion and total glucocorticoid excretion were
179 increased in PA patients (**Table 1**). In univariate analysis THAldo ($p = 0.024$), urinary sodium excretion
180 ($p = 0.044$) and total glucocorticoid excretion ($p = 0.018$) correlated with LVMI at time of diagnosis (**Suppl.**
181 **Fig. 1+2**). In contrast, the relative changes in LVMI in response to treatment (Δ LVMI) correlated with
182 total glucocorticoid excretion ($p = 0.042$), but neither with THAldo ($p = 0.776$) nor with urinary sodium
183 excretion ($p = 0.214$) (**Suppl. Fig. 1+2**). Moreover, when arbitrarily dividing PA patients into low and high
184 steroid secretors, according to whether their THAldo and total glucocorticoid excretion was below or
185 above the median, high total glucocorticoid excretion, but not THAldo, predicted a reduction in LVMI
186 (**Fig. 2**). Similarly, in multivariate analyses, total glucocorticoid excretion and 24-h systolic blood pressure
187 were strong predictors of left ventricular geometry changes, whereas THAldo did not have a significant
188 effect in this model (**Table 4**). One year after treatment we could detect a significant decrease of total
189 glucocorticoid excretion in APA patients. In accordance with our findings in APA patients with complete
190 biochemical remission a higher decrease in total glucocorticoid excretion was followed by a more distinct
191 reduction of LVMI at follow-up ($r^2 = 0.138$, $p = 0.023$).

192

193

194 **Discussion**

195 This is the first study to evaluate the impact of glucocorticoid co-secretion on LVH in patients
196 with PA. PA is characterized by increased aldosterone secretion, but in recent years a relevant cortisol co-
197 secretion has been recognized in several case reports and small case series (29-32). We have recently
198 reported that increased secretion of glucocorticoids is a major biochemical feature in a large proportion of
199 patients with PA, whereas clinically overt signs of Cushing's syndrome are rare (9). We identified cortisol
200 co-secretion in a substantial percentage of patients with APA and BAH and reported its association with
201 parameters of the metabolic syndrome, such as BMI, HOMA-IR, and plasma lipids. Moreover, we found
202 that after unilateral ADX glucocorticoid secretion normalized, followed by postoperative tertiary adrenal
203 insufficiency in one third of patients. Based on this observation, we wondered whether total glucocorticoid
204 excretion might also impact on the cardiac phenotype in PA.

205 Previous echocardiographic evaluations have already demonstrated excess LVM and more
206 frequent LVH in patients with PA (5,33,34). Our patients with APA and BAH frequently had LVH
207 according to LVMI; the most common left ventricular adaptation was eccentric hypertrophy. It has been
208 described before, that high plasma aldosterone concentration results in eccentric changes in LV geometry
209 (33,35) and that LVM is reduced by either MRA or ADX in patients with PA (36-39). A meta-analysis of
210 four studies with an average follow-up of four years reported comparable effects for both treatment
211 strategies (40). In line with this literature, our patients responded to treatment with a significant reduction
212 in LVMI and an increase in the percentage of normal LV geometry.

213 At diagnosis, LVMI in the APA group was higher than in the BAH group. At follow-up, our APA
214 patients showed a trend towards a more distinct reduction in LVMI compared to BAH patients without
215 reaching statistical significance. Inhibition of MR-mediated aldosterone effects by specific medical
216 treatment is an explanation for the comparable effects of MRA and ADX in LVM reduction. Our findings
217 mirror previous studies reporting that the response of LVM reduction in adrenalectomized PA patients
218 could occur earlier than in PA patients treated with MRA (36). Persistent hyperaldosteronemia with
219 possible persistence of non-genomic effects of aldosterone has been proposed to potentially explain why

220 MRA treatment takes longer to show comparable effects than surgery (41). The results of our study
221 suppose an impact of cortisol co-secretion on LVH and LV geometry. Total glucocorticoid excretion was
222 positively correlated with baseline LVMI and Δ LVMI at follow-up. Therefore, patients with higher total
223 glucocorticoid excretion showed higher decreases in LVMI after one year of treatment. In line with these
224 findings, the decrease of glucocorticoid excretion correlated with the improvement of LVMI in our APA
225 patients with biochemical remission.

226 Chronic cortisol hypersecretion, e. g. in patients with CS, is known to cause amongst others,
227 truncal obesity, arterial hypertension, impaired glucose tolerance and dyslipidemia (42). However, also a
228 variety of alterations in cardiac structure and function have been reported, including increased LVM,
229 increased interventricular septum thickness and concentric hypertrophy or remodeling (15,16,43,44). CS is
230 known to be associated with elevated cardiovascular morbidity and mortality (45). Cardiac dysfunction
231 itself represents one of the most important cardiovascular complications affecting mortality. The two
232 major forms of cardiac dysfunction in CS are cardiac hypertrophy and congestive heart failure (46,47). It
233 is thought that the main cortisol effects leading to LVH are hypertension, potentiation of noradrenalin and
234 angiotensin II responsiveness of the cardiomyocytes and cardiomyocyte proliferation and hypertrophy
235 (48). MRs have similar affinity for aldosterone and cortisol. Glucocorticoid excess impairs conversion of
236 cortisol to its MR-inactive cortisone by 11β -hydroxysteroid dehydrogenase type 2 (11β -HSDS2) in
237 classical aldosterone target tissues as the distal nephron, leading to glucocorticoid-mediated
238 mineralocorticoid effects (49,50). In the cardiomyocytes, 11β -HSDS2 is not expressed at relevant levels.
239 Therefore, in physiologic circumstances the MR in cardiomyocytes is mostly occupied by cortisol, which
240 circulates in much higher concentrations than aldosterone. In the event of cardiac tissue damage, cortisol
241 acts as an MR agonist as shown by Mihailidou et al. in ischemia-reperfusion studies in rat heart
242 Langendorff preparations (49). This effect can be blocked by spironolactone but not by the
243 glucocorticoid/progesterone antagonist RU486. However, the abnormalities in LV structure and function
244 have been reported to ameliorate (44) or even to be reversible upon normalisation of glucocorticoid excess
245 (51).

246 Therefore, treatment with ADX or MRA should both be effective against the MR mediated effects
247 of glucocorticoid excess on myocardial tissue. To our knowledge no glucocorticoid dependent MR-
248 mediated effects on lipid and glucose metabolism have been reported so far. Therefore, MRA treatment
249 could be inferior in this regard when increased glucocorticoid secretion in BAH remains unblocked during
250 MRA treatment in glucocorticoid target organs, such as the endocrine pancreas, abdominal fat tissue and
251 the liver. In the current study, however, the improvement of glucose metabolism following adrenalectomy
252 was minimal, but a clinical relevant improvement in glucose homeostasis has been shown previously in
253 several cohorts (52).

254 We acknowledge the limitation that steroid metabolite analysis and echocardiography were post
255 hoc investigations and that our study was neither powered nor planned to examine differences between the
256 two treatment strategies of PA, ADX and MRA treatment. However, following one year of MRA
257 treatment, 54% of our BAH patients still had concentric remodeling or concentric hypertrophy as
258 compared to 42% in APA patients. Therefore, this finding might be explained by ongoing glucocorticoid
259 effects in BAH patients or inadequate MRA dosage. Unfortunately, we have only limited data for follow-
260 up of urinary glucocorticoid excretion in BAH patients. In addition, one year of follow-up might be too
261 short to detect full treatment effects of MRA treatment. Therefore, additional studies are required to
262 address this issue.

263 It is known that patients with essential hypertension obtain LVM reduction by treatment with
264 either ACE inhibitor or MRA and that a combination has an additive effect (53). Blood pressure levels and
265 antihypertensive medication according to DDD's were reduced in both groups one year after start of
266 treatment. Although we detected comparable effects on 24-h blood pressure levels, the DDD's showed
267 numerically a greater reduction in adrenalectomized APA patients. A contributing factor can be the rather
268 low dose of spironolactone of an average of 42 mg/d, in accordance with Endocrine Society Practice
269 Guidelines which can be explained by clinical side effects including gynecomastia preventing further dose
270 escalation. Similar to previous studies, most of the patients after ADX (58%) still needed
271 antihypertensives because of residual hypertension (36,54).

272 The strengths of our study include the prospective standardized collection of all data and
273 biomaterial within the context of the German Conn's registry, the homogeneously characterized study
274 population, and the subtyping of all patients by adrenal vein sampling. A major limitation of the study is
275 the very limited follow-up data for urinary steroid excretion (n=5) for BAH patients. Another limitation is
276 the examination of left ventricular geometry by echocardiography. The main limitation of this technique is
277 an inappropriate acoustic window, limiting patient inclusion to suitable candidates. Secondly, left
278 ventricular parameters for estimation of LVM were generated by M-mode measurement. This is less
279 accurate compared to real time three-dimensional echocardiography or 3D imaging by MRI (55). Thirdly,
280 echocardiographic examinations in this study were performed by different experienced investigators,
281 which could have had an influence on wall thicknesses estimation and therefore LVM and LVMI
282 estimation. However, the investigators were blinded with regard to the underlying cause of disease, which
283 we consider a strength of the study approach.

284

285 **Conclusions**

286 In this study, we investigated the effects of increased glucocorticoid secretion in 73 PA patients
287 (45 APA, 28 BAH) on cardiac geometry. Our data show that total glucocorticoid excretion is associated
288 with LVH independent of mineralocorticoid excess. Moreover, high total glucocorticoid excretion, but not
289 THAldo predicted the Δ LVMI after adrenalectomy in APA patients. In summary, our data suggest a
290 relevant role of glucocorticoid secretion in PA on LV geometry, pointing out the relevance of cortisol co-
291 secretion in the context of PA.

292

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319 **Table 1. Baseline and 1 year follow-up characteristics of all patients with primary aldosteronism.**

320 Data are given as median and 25th and 75th percentile in square brackets. Asterisk indicates significance.

321 Comparisons were performed by Wilcoxon signed rank test.

Patient characteristics (n=73)	n	baseline	after treatment	p
Gender [f/m]	73	28/45	--	n.c.
Age [years]	73	53 [43; 58]	--	n.c.
Duration of hypertension [months]	73	129 [52; 267]	--	n.c.
Antihypertensive agents [DDD]	73	3.0 [2.0; 4.3]	2.0 [0.1; 3.7]	0.002*
BMI [kg/m ²]	73	27.7 [24.9; 30.9]	27.5 [24.9; 30.3]	0.705
Aldosterone [ng/l]	73	219.0 [148.0; 346.5]	124.5 [39.8; 198.8]	0.003*
Plasma renin [mU/l]	73	4.9 [2.2; 13.4]	18.9 [8.9; 44.6]	<0.001*
Serum potassium [mmol/l]	73	3.4 [3.0; 3.7]	4.2 [3.9; 4.5]0	<0.001*
Serum creatinine [mg/dl]	73	0.8 [0.7; 1.0]	1.0 [0.8; 1.2]	<0.001*
Serum urea [mg/dl]	73	13 [11; 16]	19 [15; 27]	<0.001*
GFR [ml/min/1.73 m ²]	73	88.4 [72.3; 100.8]	73.9 [56.3; 85.9]	<0.001*
SBP [mmHg]	73	151 [138; 174]	133 [124; 142]	<0.001*
DBP [mmHg]	73	93 [86; 103]	87 [80; 93]	<0.001*
24h-SBP [mmHg]	57	144 [134; 157]	132 [125; 140]	<0.001*
24h-DBP [mmHg]	57	91 [84; 98]	84 [77; 88]	<0.001*
FPG [mg/dl]	73	102 [93; 113]	99 [91; 107]	0.033*
HDL-C [mg/dl]	70	56 [47; 70]	49 [40; 62]	<0.001*
LDL-C [mg/dl]	70	124 [92; 151]	126 [100; 142]	0.740
Triglycerides [mg/dl]	70	105 [72; 134]	114 [86; 178]	<0.001*
Total cholesterol [mg/dl]	70	197 [174; 227]	200 [174; 219]	0.995
Diabetes mellitus [n]	73	8 (11%)	8 (11%)	n.c.
Total glucocorticoid excretion [µg/24h]; median of healthy controls: 8262 [6380; 11044]	73	11807 [8270; 15266]	--	n.c.
	44	12772 [9000; 16131]§	9458 [5578; 13460]§	<0.001*
Tetrahydroaldosterone excretion [µg/24h]; median of healthy controls: 30 [22; 44]	73	82 [52; 128]	--	n.c.
	44	88 [57; 131]§	21 [14; 39]§	<0.001*

322 Abbreviations: FPG: fasting plasma glucose; DDD: defined daily dose; SBP: systolic blood pressure;

323 DBP: diastolic blood pressure; §: dataset of 44 patients with complete follow-up data, n.c.: not calculated.

324 **Table 2. Baseline and 1 year follow-up characteristics of patients with primary aldosteronism according to subtype.**

325 Data are given as median and 25th and 75th percentile in square brackets. Asterisk indicates significance. Comparisons were performed by
 326 Wilcoxon signed-rank-test and by McNemar-test. Differences between baseline values of both group were marked with # for p<0.05 and ## for
 327 p<0.0001.

Patient characteristics	Aldosterone producing adenoma (n=45)		p	Bilateral adrenal hyperplasia (n=28)		p
	baseline	after ADX		baseline	after MRA	
Time of assessment						
Age [years]	54 [46; 60]	--	n.c.	49 [41; 58]	--	n.c.
Sex [f/m]	17/28	--	n.c.	11/17	--	n.c.
Duration of hypertension [months]	130 [55; 250]	--	n.c.	130 [35; 283]	--	n.c.
BMI [kg/m ²]	27.7 [24.9; 32.1]	28.1 [25.2; 30.3]	0.803	27.6 [25.0; 30.7]	27.1 [24.3; 30.4]	0.323
Aldosterone [ng/l]	242.0 [181.6; 427.9]	53.0 [35.0; 129.5]	<0.001*	159.5 [110.5; 247.5]#	216.0 [160.0; 388.6]	<0.001*
Plasma renin [mU/l]	5.5 [2.1; 12.1]	17.0 [9.1 45.1]	<0.001*	4.7 [2.5; 15.8]	19.9 [7.7; 45.0]	<0.001*
Serum potassium [mmol/l]	3.2 [2.8; 3.5]	4.2 [3.9; 4.5]	<0.001*	3.6 [3.2; 3.8]##	4.2 [3.9; 4.5]	<0.001*
Serum creatinine [mg/dl]	0.8 [0.8; 1.0]	1.1 [0.9; 1.3]	<0.001*	0.8 [0.7; 0.9]	0.8 [0.7; 1.1]	0.016*
Serum urea [mg/dl]	13 [11; 16]	22 [16; 29]	<0.001*	13 [10; 17]	16 [13; 24]	0.003*
GFR [ml/min/1.73 m ²]	79.4 [69.9; 99.6]	68.8 [54.5; 77.8]	<0.001*	93.9 [84.1; 104.3]#	81.3 [71.5; 105.9]	0.031*
SBP [mmHg]	152 [139; 172]	133 [126; 144]	<0.001*	146 [134; 175]	132 [123; 137]	0.005*
DBP [mmHg]	93 [87; 105]	87 [80; 94]	0.001*	92 [86; 101]	88 [79; 93]	0.106
24-SBP [mmHg] †	149 [139; 157]	132 [125; 140]	<0.001*	144 [131; 155]	132 [123; 139]	0.032*
24-DBP [mmHg] †	91 [86; 99]	83 [77; 87]	<0.001*	91 [83; 98]	84 [76; 88]	0.007*
FPG [mg/dl]	102 [94; 112]	99 [91; 106]	0.043*	101 [91; 119]	100 [90; 112]	0.692
Diabetes mellitus [n]	5 (11%)	5 (11%)	n.c.	3 (11%)	3 (11%)	n.c.
HDL-C [mg/dl] †	54 [47; 69]	49 [42; 64]	0.076	56 [47; 72]	51 [39; 62]	0.006*
LDL-C [mg/dl] †	133 [92; 151]	126 [97; 145]	0.861	123 [92; 152]	126 [101; 142]	0.409
Triglycerides [mg/dl] †	103 [66; 134]	113 [79; 169]	0.001*	107 [80; 135]	117 [95; 190]	0.005*

Total cholesterol [mg/dl] †	203 [174; 231]	200 [170; 221]	0.480	192 [173; 221]	197 [175; 219]	0.402
Antihypertensive agents [DDD]	3.5 [2.0; 4.7]	1.5 [.0; 3.2]	<0.001*	3.0 [1.6; 3.5]	2.7 [1.0; 4.6]	0.848
Tetrahydroaldosterone excretion [µg/24h]	95 [63; 140]		n.c.	55 [40; 97]#		n.c.
	95 [62; 147]§	18 [13; 31]§	<0.001*	54 [39; 77]§§	60 [38; 70]§§§	n.c.
Total glucocorticoid excretion [µg/24h]	12980 [9200; 15266]		n.c.	9908 [6328; 16109]		n.c.
	12563 [9015; 15516]§	9304 [5522; 11300]§	<0.001*	19943 [8573; 24897]§§	17073 [6603; 17581]§§§	n.c.
Total sodium excretion [mmol/24h]	204 [136; 238]	164 [131; 257]	0.200	186 [150; 224]	196 [115; 240]	0.713
Pro-BNP [pg/ml]	117 [52; 297]	68 [32; 124]	<0.001*	96 [61; 167]	65 [41; 117]	0.023*

328 Abbreviations: ADX: adrenalectomy; MRA: mineralocorticoid receptor antagonist treatment; FPG: fasting plasma glucose; DDD: defined daily
329 dose; SBP: systolic blood pressure; DBP: diastolic blood pressure; §: dataset of 44 patients with complete follow-up data, §§: dataset of 5 patients
330 with complete follow-up data, n.c.: not calculated, †: Due to incomplete data the calculations for 24-SBP and 24-DBP (APA n=35, BAH n=22),
331 and HDL-C, LDL-C, Triglycerides, Total cholesterol (APA n=43, BAH n=27) were performed with a reduced number of patients as listed in
332 brackets.

333 **Table 3. Echocardiographic characteristics of patients with primary aldosteronism according to subtype.**

334 Data are given as median and 25th and 75th percentile in square brackets. Asterisk indicates significance. Comparisons were performed by
 335 Wilcoxon signed-rank-test.

Left ventricular parameters	Aldosterone producing adenoma (n=45)		p	Bilateral adrenal hyperplasia (n=28)		p
	baseline	after ADX		baseline	after MRA	
LVMI [g/m ^{2.7}]	64.6 [54.7; 71.4]	56.5 [42.7; 63.6]	<0.001*	57.8 [50.3; 70.1]	53.5 [42.1; 65.2]	0.024*
ΔLVMI [g/m ^{2.7}]		8.0 [1.5;18.3]	n.c.		6.4 [-2.0; 14.4]	n.c.
LVIDd [mm]	52 [49; 56]	50 [47; 53]	<0.001*	52 [47; 55]	49 [44; 53]	0.001*
LVIDs [mm]	31 [29; 36]	30 [27; 33]	0.128	31 [28; 34]	29 [26; 34]	0.083
PWTd [mm]	10 [9; 12]	10 [9; 11]	0.020*	10 [8; 11]	10 [9; 12]	0.319
IVSd [mm]	12 [11; 13]	11 [10; 13]	0.001*	12 [10; 13]	12 [10; 13]	0.072
RWTd [cm]	0.40 [0.35; 0.47]	0.40 [0.36; 0.46]	0.775	0.39 [0.33; 0.44]	0.43 [0.38; 0.50]	0.014*
LAd [mm]	42 [38; 46]	39 [36; 43]	<0.001*	42 [36; 47]	41 [33; 46]	0.090

336 Abbreviations: ADX: adrenalectomy; MRA: mineralocorticoid receptor antagonist treatment; LVMI: left ventricular mass indexed for height to the
 337 2.7 power; ΔLVMI: reduction of left ventricular mass indexed for height to the 2.7 power after treatment; LVM: left ventricular mass, LVIDd: left
 338 ventricular internal dimension in diastole; LVIDs: left ventricular internal dimension in systole; PWTd: posterior wall thickness in diastole; IVSd:
 339 interventricular septum thickness in diastole; RWTd: relative wall thickness in diastole; LAd: left atrial internal dimension in diastole, n.c.: not
 340 calculated.

341 **Table 4. Uni- and multivariate analyses of the associations with echocardiographic parameters in all**
 342 **patients with primary aldosteronism.**

343 Data are given as p values. Asterisk indicates significance. Correlation analysis was performed using
 344 Spearman's Rank-Order test and stepwise multiple regression analysis.

	THAldo	TGE	24h-SBP	THAldo, TGE, 24h-SBP
Left ventricular parameters	Univariate, p	Univariate, p	Univariate, p	Multivariate
LVMI [g/m^{2.7}]	0.024*	0.018*	<0.001*	24h-SBP*
ΔLVMI [g/m^{2.7}]	0.776	0.042*	0.008*	24h-SBP*
LVIDd [mm]	0.531	0.003*	0.052	TGE*
IVSd [mm]	0.119	0.105	0.003*	24h-SBP*
PWTd [mm]	0.277	0.008*	0.003*	TGE*, 24h-SBP*
LAd [mm]	0.523	0.026*	0.008*	n.s.

345 Abbreviations: LVMI: left ventricular mass indexed for height to the 2.7 power; ΔLVMI: reduction of left
 346 ventricular mass indexed for height to the 2.7 power after treatment; LVM: left ventricular mass,
 347 LVIDd: left ventricular internal dimension in diastole; PWTd: posterior wall thickness in diastole;
 348 IVSd: interventricular septum thickness in diastole; LAd: left atrial internal dimension in diastole;
 349 24h-SBP: 24-hour systolic blood pressure, THAldo: tetrahydroaldosterone; TGE: total glucocorticoid
 350 excretion; n.s.: no significant results.

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352 **Supplementary Table 1. Changes in left ventricular geometry of all patients with primary**
 353 **aldosteronism after one year of treatment.**

Left ventricular geometry	Aldosterone producing adenoma (n=45)		Bilateral adrenal hyperplasia (n=28)	
	baseline	after ADX	baseline	after MRA
Normal (%)	13	22	18	25
Concentric Remodeling (%)	0	11	0	11
Eccentric Hypertrophy (%)	51	36	43	21
Concentric Hypertrophy (%)	36	31	39	43

354 Abbreviations: APA: unilateral disease; BAH: bilateral disease; ADX: adrenalectomy;

355 MRA: mineralocorticoid receptor antagonist treatment.

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357 **Figure Legends**

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359 **Figure 1: LVMI at baseline and after treatment in BAH and APA patients treated with either MRA**
360 **or ADX.**

361 Median and 95 per cent confidence interval of LVMI are shown before (white bar) and after treatment
362 (checkered bar). Asterisk indicates significance.

363 Abbreviations: APA: unilateral disease; BAH: bilateral disease; LVMI: left ventricular mass indexed for
364 height to the 2.7 power.

365 **Figure 2: Reduction of LVMI following specific treatment according to baseline total glucocorticoid**
366 **excretion and THAldo levels.**

367 Median and 95 per cent confidence interval of baseline glucocorticoid and THAldo excretion of PA
368 patients with low and high total glucocorticoid (8390 µg/24h; 15266 µg/24h) or THAldo (52 µg/24h; 121
369 µg/24h) excretion are shown. Asterisk indicates significance.

370 Abbreviations: APA: unilateral disease; BAH: bilateral disease, LVMI: left ventricular mass indexed for
371 height to the 2.7 power; TGE: total glucocorticoid excretion; THAldo: tetrahydroaldosterone.

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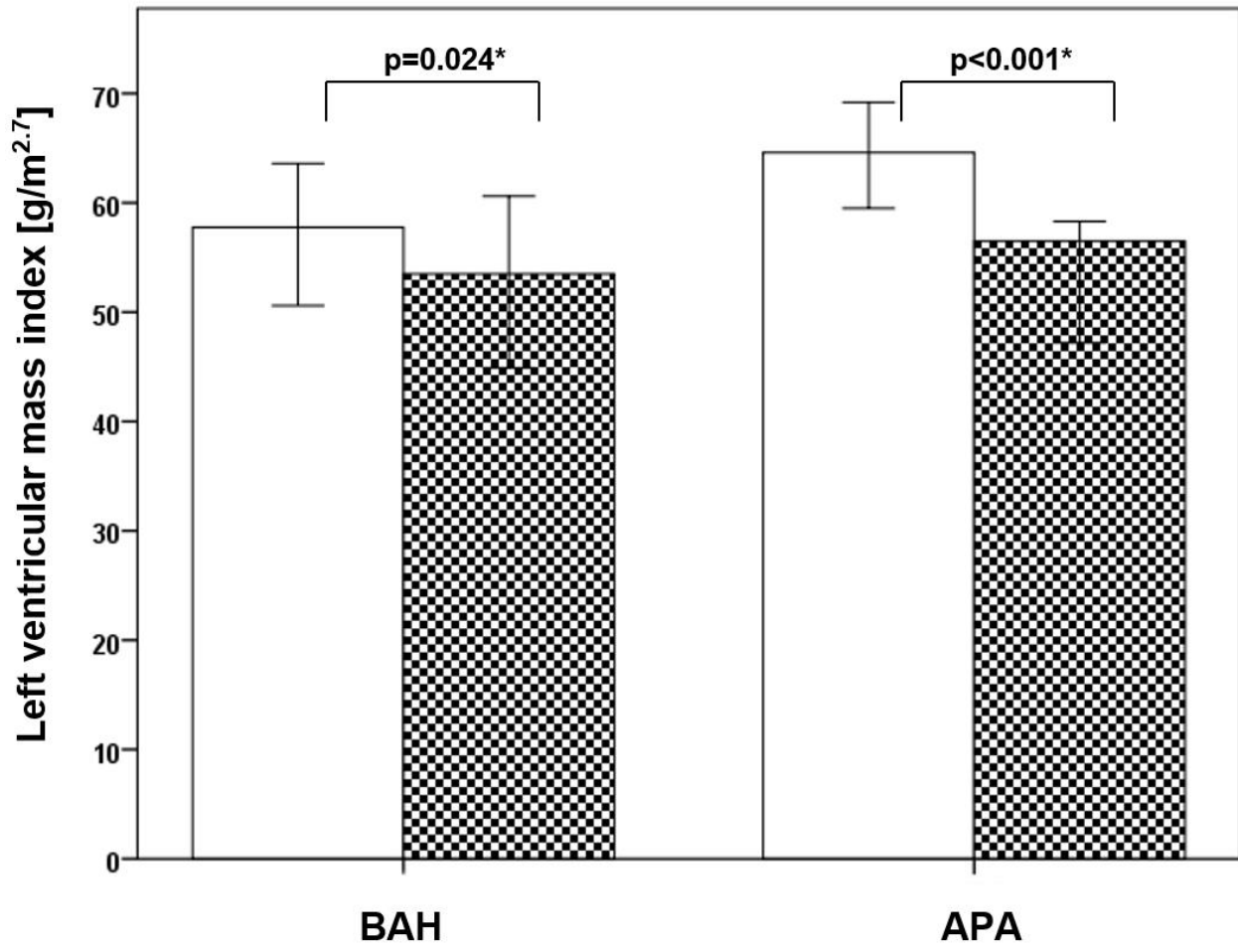
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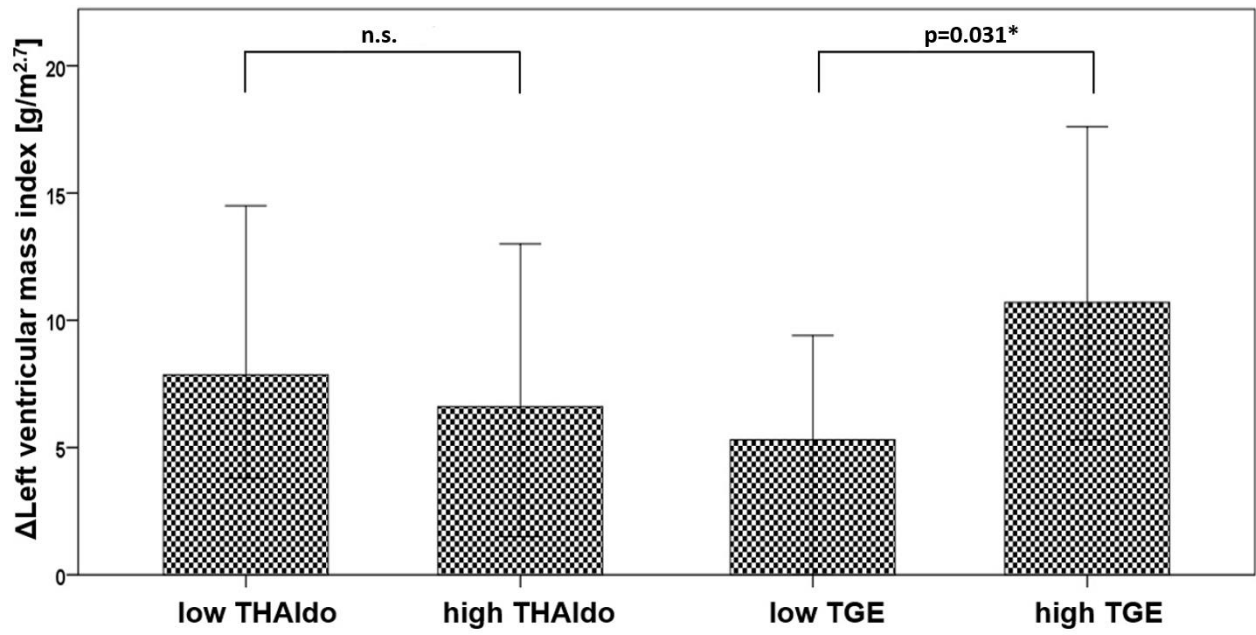
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383 **Figure 1:**
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420 **Supplementary Figure Legends**

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422 **Supplementary Figure 1:** Correlation of total glucocorticoid excretion with left ventricular mass indexed
423 for height to the 2.7 power at baseline in patients with primary aldosteronism.

424 **Supplementary Figure 2:** Correlation of tetrahydroaldosterone excretion with left ventricular mass
425 indexed for height to the 2.7 power at baseline in patients with primary aldosteronism.

426 **Supplementary Figure 3:** Correlation of baseline glucocorticoid excretion with reduction of left
427 ventricular mass indexed for height to the 2.7 power in patients with primary aldosteronism.

428 **Supplementary Figure 4:** Correlation of baseline tetrahydroaldosterone excretion with reduction of left
429 ventricular mass indexed for height to the 2.7 power in patients with primary aldosteronism.

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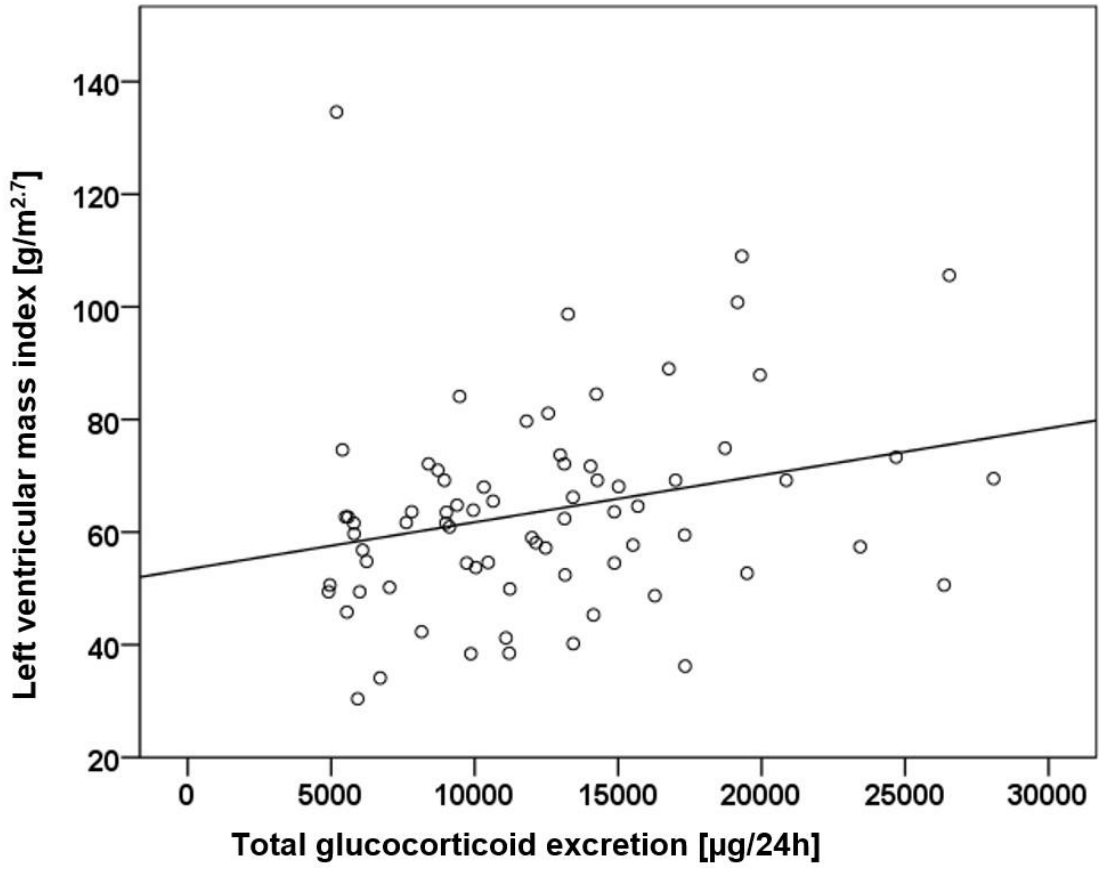
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445 **Supplementary Figure 1:**



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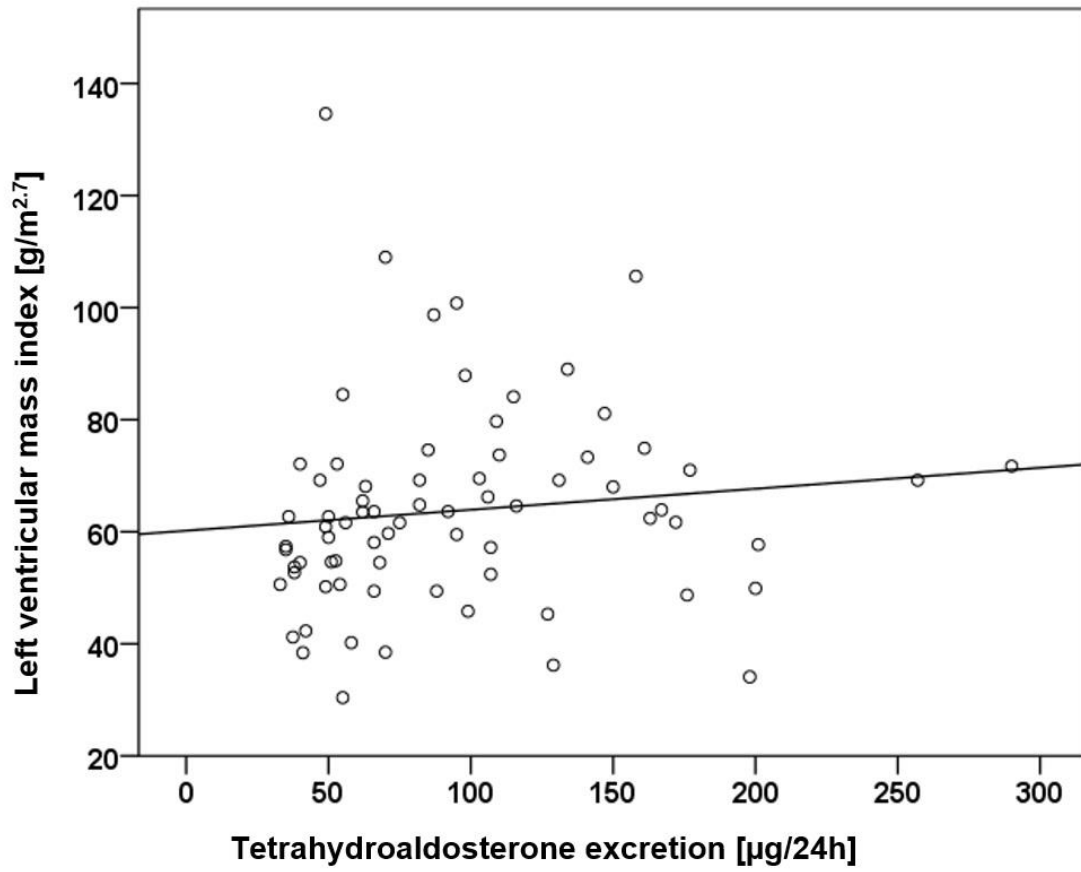
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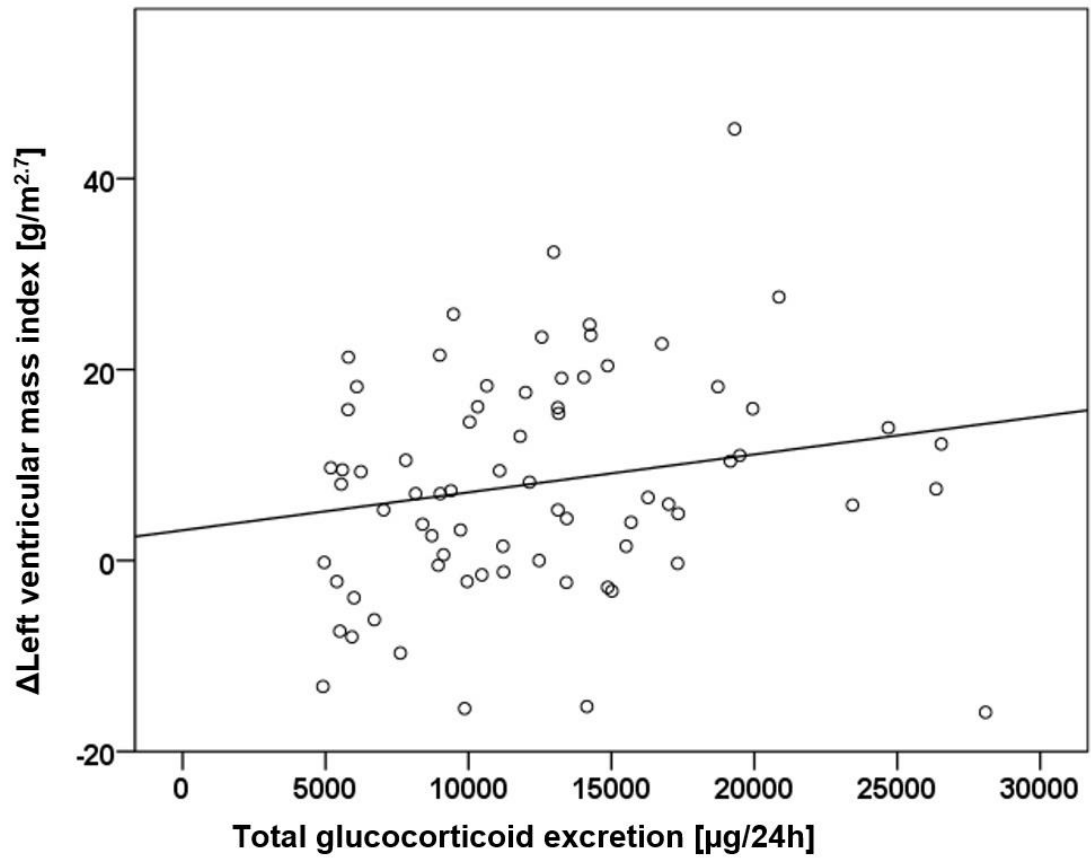
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458 **Supplementary Figure 2:**



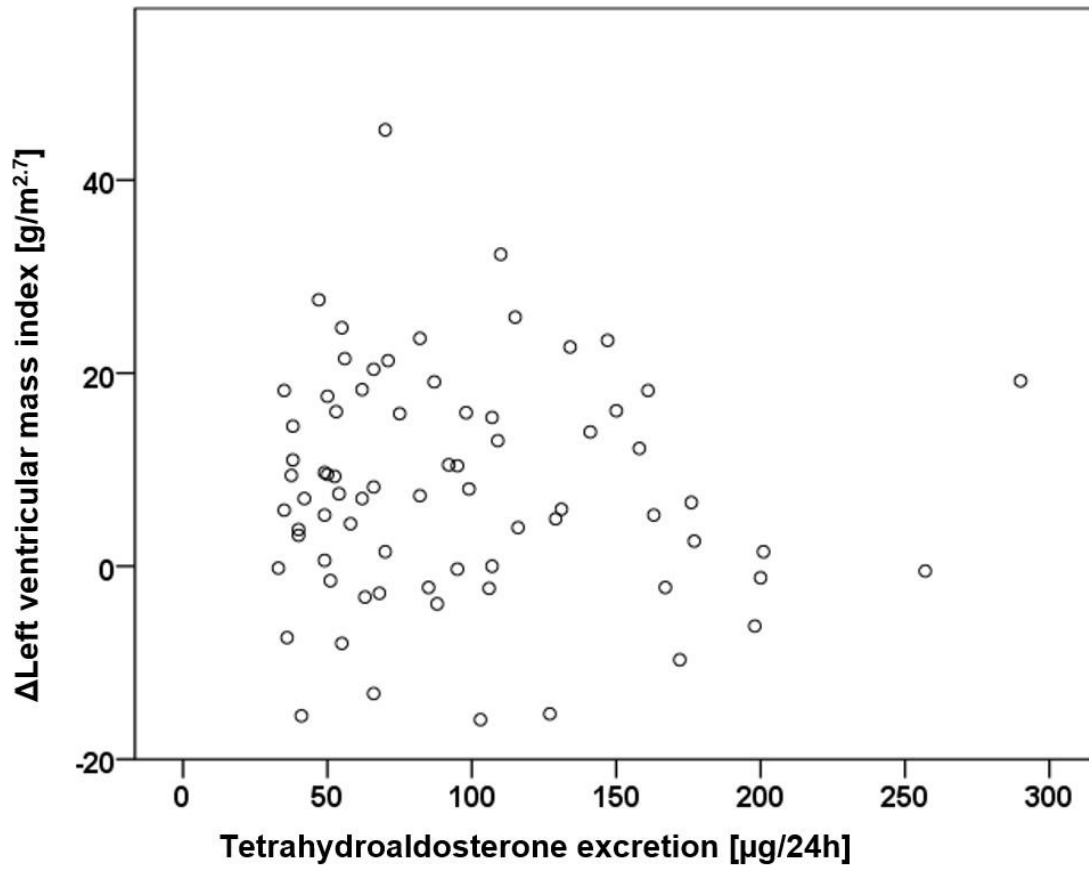
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473 **Supplementary Figure 3:**



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487 **Supplementary Figure 4:**



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