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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33

Abstract

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

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

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

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

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

Introduction

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

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

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

Methods

Patients

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

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

Laboratory analysis

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

excretion, the patients conducted a 24-hour urine collection. Subsequently, gas chromatography-mass

spectrometry (GC-MS) in selected-ion-monitoring (SIM) analysis mode was performed to determine the

urinary steroid metabolite excretion as described previously (9), allowing the quantification of 40 different

steroid metabolites, including 3α,5β-tetrahydroaldosterone (THAldo), the major mineralocorticoid

metabolite. Total glucocorticoid excretion was calculated as the sum of quantified metabolites of cortisol

and cortisone, comprising tetrahydrocortisol, 5α-tetrahydrocortisol, tetrahydrocortisone, α- and β-cortol,

α- and β-cortolone, 6β-hydroxycortisol, and urinary cortisol and cortisone (9).

Cardiac ultrasound examination

Comprehensive echocardiographic examination was conducted by experienced sonographers from

the department of internal medicine I (cardiology) from the Ludwig-Maximilians-Universität München.

The sonographers were blinded with regard to diagnosis and clinical details. Commercially available high-

quality ultrasound systems were used (GE Healthcare Vivid 7, Philips iE 33). The patients were lying

down in the left lateral decubitus position. Echocardiography included two-dimensional, M-Mode and

Doppler ultrasound recordings. Images were obtained in the parasternal (long and short axis) and apical

views. The left ventricular internal dimension (LVID), interventricular septum (IVS), posterior wall

thickness (PWT) and left atrial dimension in diastole (LAd) were measured via parasternal long axis view.

Echocardiographic parameters were measured according to the recommendation of the American Society

of Echocardiography (20,21). Echocardiography-based left ventricular mass (LVM) estimation is

generally calculated as the difference between epicardium delimited volume and left ventricular chamber

volume multiplied by an estimate of myocardial density (22). The LVM was calculated by the Penn

Convention formula: LVM=1.04 ([LVIDd+PWTd+IVSd]^3-[LVIDd]^3)-13.6g (23,24). Obesity is

independently associated to LVH (25). Because of higher average values of BMI in our study cohort,

LVH was determined as the left ventricular mass index (LVMI). LVM was indexed by height$^{2.7}$ to obtain

LVMI. By using the LVMI we minimized the interference of obesity in LVM estimation (26). LVH was

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 ≥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).

Results

Patient characteristics

Clinical characteristics of the total cohort of 73 patients with PA are shown in **Table 1**, the

comparison of APA and BAH subgroups in **Table 2**. APA and BAH were diagnosed in 45 and 28

patients, respectively. As expected, at diagnosis, patients with APA had higher plasma aldosterone

concentration (p=0.001), higher urinary THAldo concentrations (p=0.001) and lower potassium levels

(p<0.001), and more pronounced renal impairment according to globular filtration rate (GFR; p=0.043).

Total glucocorticoid excretion did not differ between groups (p=0.184).

Patient characteristics one year after initiation of treatment (MRA treatment in BAH, ADX in

APA) are listed in **Tables 1+2**. Systolic and diastolic blood pressure and serum potassium levels

normalized in both subgroups. As expected, defined daily doses (DDDs) of antihypertensive medication

decreased significantly in the APA group, whereas in the BAH group there was only a trend towards

lower DDDs. BMI remained stable in both groups and both groups had a decline in renal function.

Triglyceride levels increased significantly in both groups, whereas HDL cholesterol levels decreased only

in the BAH group (p=0.006). Pro-BNP, a potential indicator of cardiac preload, improved in both groups.

The decline was not due to optimized treatment for heart failure. In fact, DDDs of ACE inhibitors/

angiotensin II receptor blockers (1.4 vs. 1.1; p=0.002), beta blockers (0.4 vs. 0.2; p=0.001) and diuretics

(0.4 vs. 0.2; p<0.001) have decreased significantly at follow-up.

Echocardiographic findings in patients with unilateral aldosteronism and bilateral hyperplasia

Table 3 summarizes echocardiographic geometric characteristics in APA and BAH patients.

LVMI was elevated, the IVS was thickened and the LA was enlarged in both groups at baseline. The

overall prevalence of LVH was 85% before initiation of treatment, compared to 66% at follow-up. There

was a shift from eccentric and concentric hypertrophy towards normal left ventricular geometry (**Suppl.**

Table 1). As expected, LVMI improved in both APA (p<0.001) and BAH (p=0.024) patients with

treatment (**Fig. 1**). The reduction of LVMI (ΔLVMI) 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 (ΔLVMI) 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

Discussion

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

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

At diagnosis, LVMI in the APA group was higher than in the BAH group. At follow-up, our APA patients showed a trend towards a more distinct reduction in LVMI compared to BAH patients without reaching statistical significance. Inhibition of MR-mediated aldosterone effects by specific medical treatment is an explanation for the comparable effects of MRA and ADX in LVM reduction. Our findings mirror previous studies reporting that the response of LVM reduction in adrenalectomized PA patients could occur earlier than in PA patients treated with MRA (36). Persistent hyperaldosteronemia with 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 ΔLVMI 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 issues 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 ΔLVMI 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

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/m²]	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 m²]	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.

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
Time of assessment	baseline	after ADX		baseline	after MRA	
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/m²]	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 m²]	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
Time of assessment	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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Supplementary Table 1. Changes in left ventricular geometry of all patients with primary

aldosteronism after one year of treatment.

Left ventricular geometry	Aldosterone producing adenoma (n=45)		Bilateral adrenal hyperplasia (n=28)	
Time of assessment	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

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

MRA: mineralocorticoid receptor antagonist treatment.

Figure Legends

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

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

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

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

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

Abbreviations: APA: unilateral disease; BAH: bilateral disease, LVMI: left ventricular mass indexed for height to the 2.7 power; TGE: total glucocorticoid excretion; THAldo: tetrahydroaldosterone.
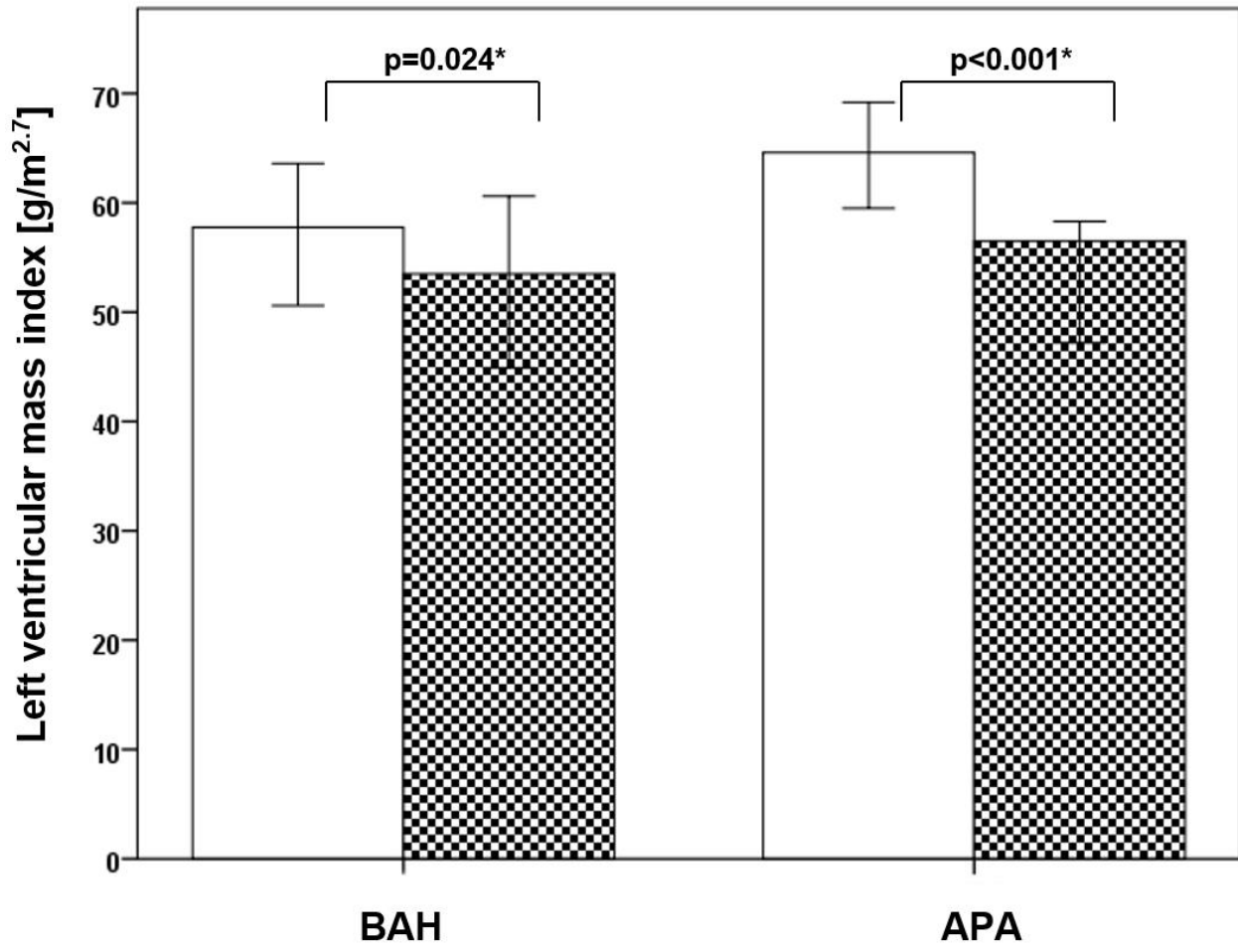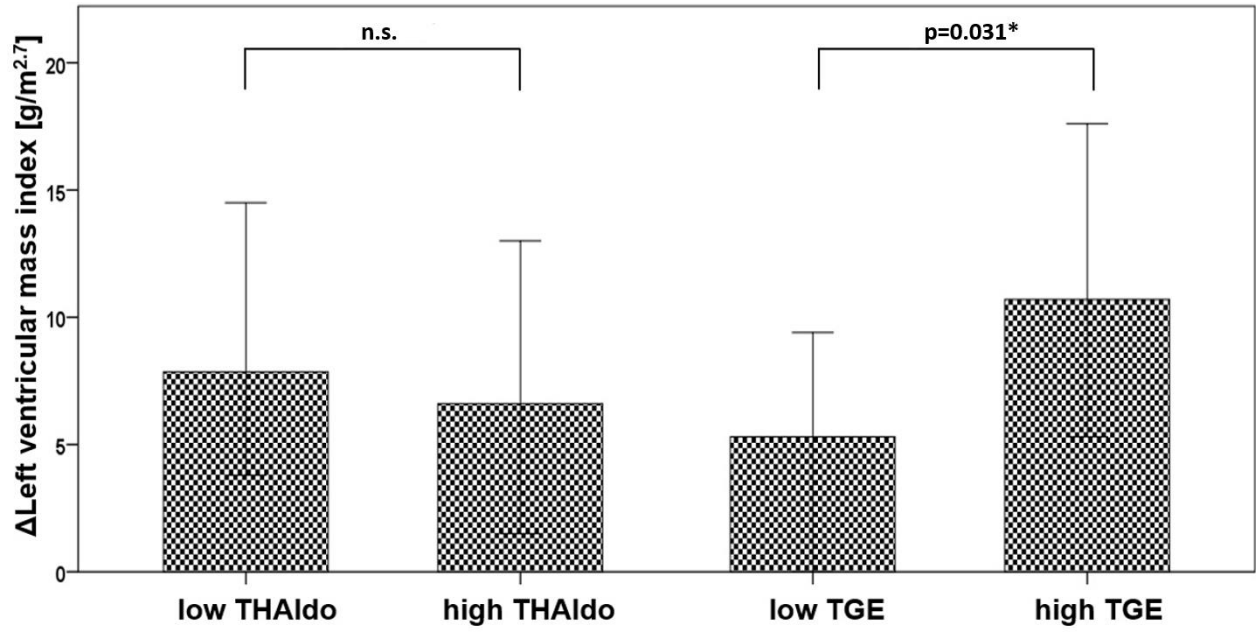
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387   **Figure 2:**
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420   **Supplementary Figure Legends**

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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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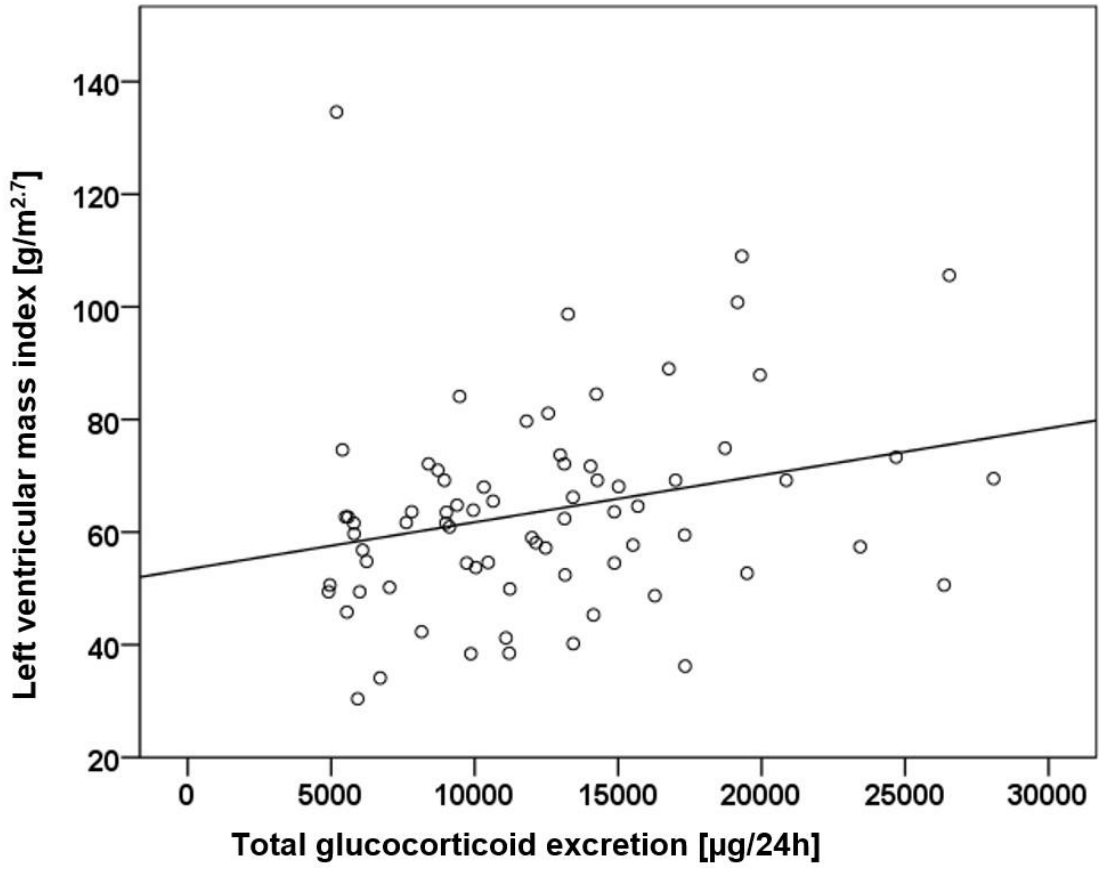444

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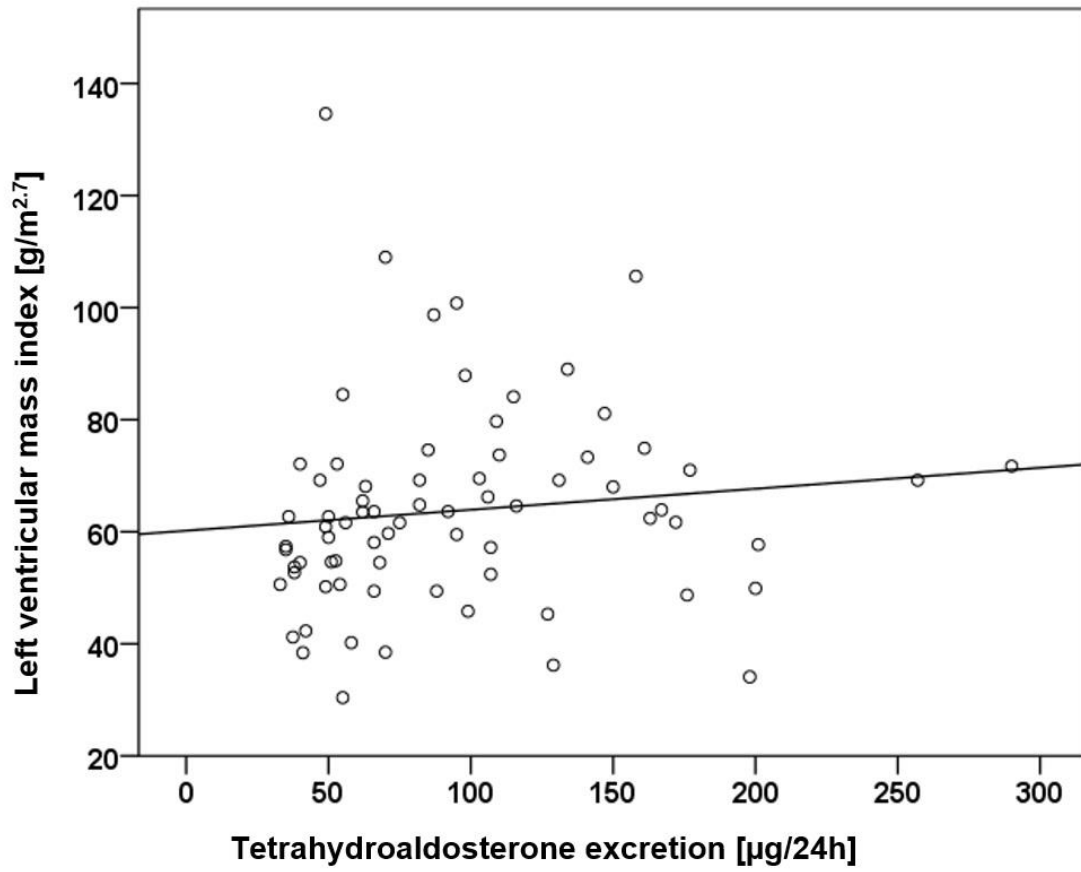
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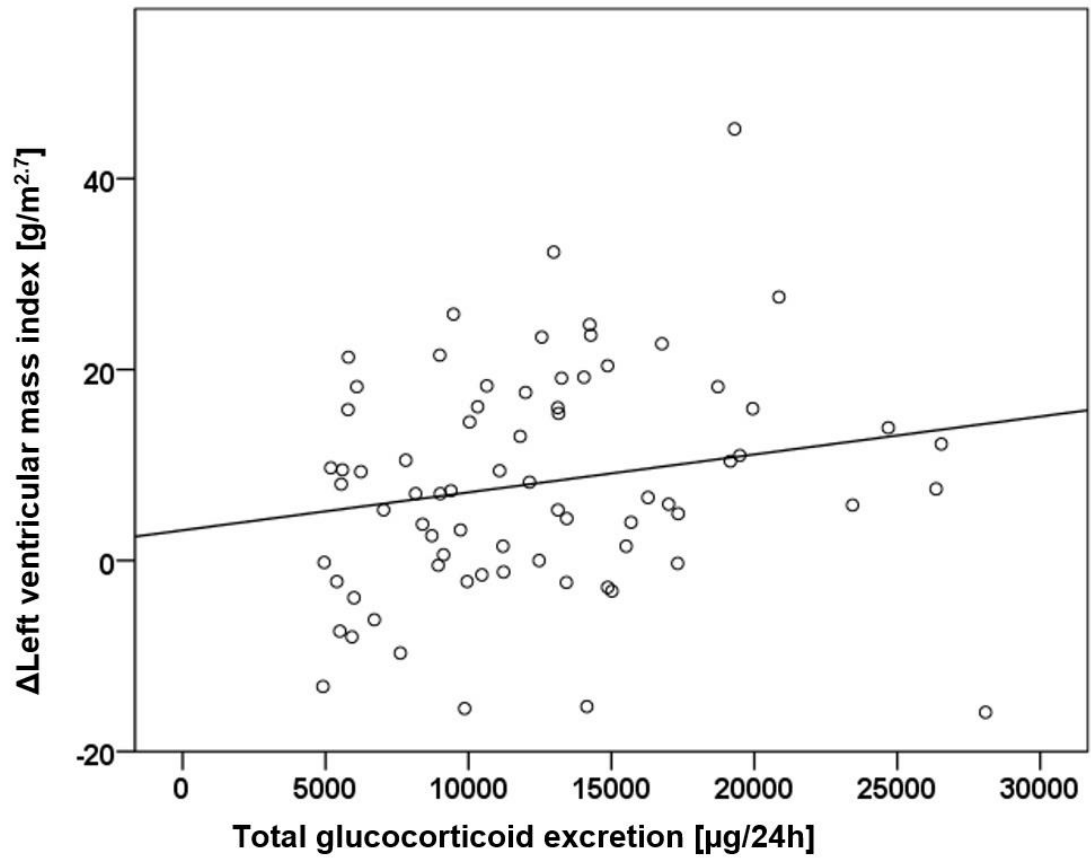
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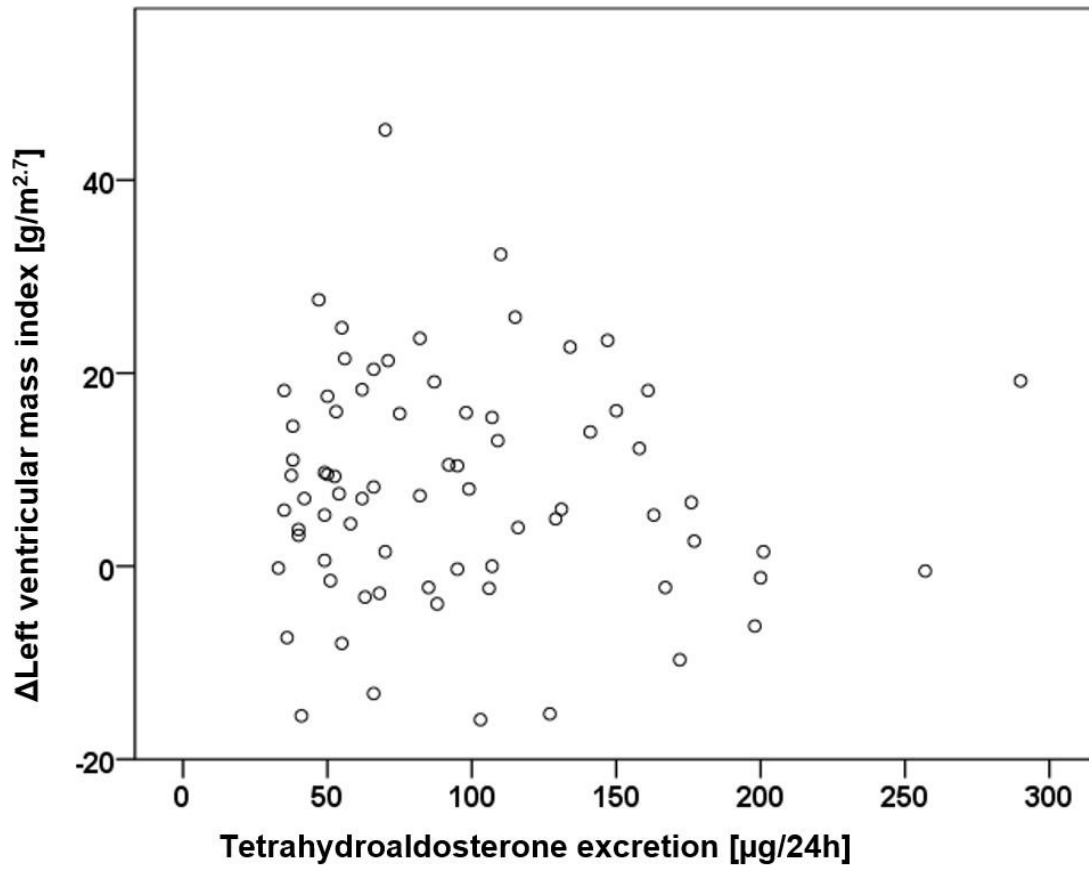

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473 **Supplementary Figure 3:**

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487   **Supplementary Figure 4:**

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