**Supplementary Material**

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**Supplementary table 1.** Plasma glucocorticoids in ADPKD patients versus healthy controls and IgA nephropathy patients

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Groups** | | |  | **p-values for differences** | | |
|  | **ADPKD**  **patients** | **Healthy**  **controls** | **IgA**  **nephropathy** |  | **ADPKD**  **vs HC** | **ADPKD**  **vs IgAN** | **IgAN**  **vs HC** |
| Cortisol  (nmol/L) | 323  [280 – 360] | 314  [238 – 410] | 321  [267 – 394] |  | 0.96 | 0.92 | 0.97 |
| Cortisone  (nmol/L) | 41  [30 – 50] | 55  [45 – 63] | 47  [38 – 55] |  | <0.001 | 0.03 | 0.02 |
| 11-deoxycortisol  (nmol/L) | 0.67  [0.35 – 0.79] | 0.35  [0.22 – 0.56] | 0.88  [0.48 – 1.1] |  | 0.003 | 0.05 | <0.001 |
| Corticosterone  (nmol/L) | 7.7  [4.7 – 12.5] | 6.1  [3.5 – 10] | 5.9  [3.5 – 9.8] |  | 0.23 | 0.40 | 0.98 |
| 11-DOC  (nmol/L) | 0.08  [0.06 – 0.11] | 0.08  [0.05 – 0.11] | 0.10  [0.06 – 0.12] |  | 0.61 | 0.32 | 0.12 |
| 11β-HSD 1 + 2 | 8.1  [6.5 – 11] | 5.8  [4.8 – 7.0] | 6.8  [5.4 – 8.8] |  | <0.001 | 0.06 | 0.04 |
| CYP11B1 | 547  [331 – 896] | 821  [576 – 1122] | 442  [303 – 594] |  | 0.003 | 0.16 | <0.001 |
| CYP11B2 | 84  [51 – 115] | 83  [54 – 116] | 62  [34 – 148] |  | 0.79 | 0.23 | 0.24 |
| Data presented as median [IQR], differences tested with a Mann-Whitney U tests for non-parametric data; 11β-HSD1+2 = cortisol / cortisone, CYP11B1 = cortisol / 11-deoxcycortisol and CYP11B2 = corticosteron / 11-deoxycorticosteron. Abbreviations: 11-DOC,11-deoxycorticosterone; | | | | | | | |

**Supplementary table 2.** Determinants of glucocorticoid production in the overall study population

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Univariate associations** | |  | **Multivariate model 1** | |  | **Model 2** | |  | **Model 3** | |
|  | **R** | **p-value** |  | **St. β** | **p-value** |  | **St. β** | **p-value** |  | **St. β** | **p-value** |
| **Ln Cortisol** |  |  |  |  |  |  |  |  |  |  |  |
| Age | -0.10 | 0.25 |  | -0.11 | 0.20 |  | 0.02 | 0.79 |  | 0.03 | 0.75 |
| Female | -0.11 | 0.21 |  | -0.12 | 0.17 |  | -0.13 | 0.13 |  | -0.11 | 0.21 |
| eGFR | 0.34 | <0.001 |  |  |  |  | 0.36 | <0.001 |  | 0.38 | 0.001 |
| Ln Copeptin | -0.12 | 0.18 |  |  |  |  |  |  |  | 0.07 | 0.53 |
| **Ln Cortisone** |  |  |  |  |  |  |  |  |  |  |  |
| Age | -0.11 | 0.21 |  | -0.13 | 0.14 |  | 0.10 | 0.21 |  | 0.09 | 0.24 |
| Female | -0.15 | 0.08 |  | -0.16 | 0.06 |  | -0.18 | 0.01 |  | -0.18 | 0.02 |
| eGFR | 0.55 | <0.001 |  |  |  |  | 0.60 | <0.001 |  | 0.59 | <0.001 |
| Ln Copeptin | -0.31 | <0.001 |  |  |  |  |  |  |  | -0.03 | 0.73 |
| **Ln Total active pool** |  |  |  |  |  |  |  |  |  |  |  |
| Age | -0.12 | 0.19 |  | -0.13 | 0.13 |  | 0.06 | 0.46 |  | 0.06 | 0.48 |
| Female | -0.13 | 0.14 |  | -0.14 | 0.11 |  | -0.15 | 0.05 |  | -0.15 | 0.07 |
| eGFR | 0.48 | <0.001 |  |  |  |  | 0.51 | <0.001 |  | 0.51 | <0.001 |
| Ln Copeptin | -0.24 | 0.006 |  |  |  |  |  |  |  | 0.01 | 0.91 |
| **Ln Total urinary glucocorticoids** |  |  |  |  |  |  |  |  |  |  |  |
| Age | 0.06 | 0.49 |  | 0.008 | 0.91 |  | 0.09 | 0.29 |  | 0.12 | 0.15 |
| Female | -0.48 | <0.001 |  | -0.48 | <0.001 |  | -0.49 | <0.001 |  | -0.45 | <0.001 |
| eGFR | 0.15 | 0.08 |  |  |  |  | 0.22 | 0.008 |  | 0.33 | 0.002 |
| Ln Copeptin | 0.08 | 0.38 |  |  |  |  |  |  |  | 0.14 | 0.16 |

Univariate and multivariate regression analysis. If applicable, variables were log transformed to meet assumptions for multivariate regression analysis. Total active pool is defined as the sum of urinary cortisol and cortisone excretion.

**Supplementary table 3.** Plasma glucocorticoids in ADPKD patients (n=27) at baseline, 3 weeks of treatment with the vasopressin V2 receptor antagonist tolvaptan and 3 weeks after stopping this treatment (wash-out).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Baseline** | **V2 receptor antagonist** | **Wash-out** | **p-value** |
| Cortisol  (nmol/L) | 323  [280 – 360] | 315  [264 – 346] | 302  [271 – 380] | 0.55 |
| Cortisone  (nmol/L) | 41  [30 – 50] | 39  [[30 – 47] | 38  [28 – 46] | 0.90 |
| 11-deoxycortisol  (nmol/L) | 0.67\*  [0.35 – 0.79] | 0.51  [0.29 – 62] | 0.52  [0.30 – 0.68] | 0.007 |
| Aldosterone  (nmol/L) | 0.26  [0.14 – 0.34] | 0.23  [0.16 – 0.34] | 0.23  [0.13 – 0.38] | 0.57 |
| Corticosterone  (nmol/L) | 7.7  [4.7 – 12.5] | 6.5  [4.7 – 9.8] | 6.8  [5.3 – 10.4] | 0.46 |
| 11-deoxycorticosterone  (nmol/L) | 0.08  [0.06 – 0.11] | 0.07  [0.05 – 0.09] | 0.07  [0.06 – 0.10] | 0.10 |
| 11β-HSD 1 + 2 | 8.1  [6.5 – 11.4] | 8.2  [6.4 – 12.0] | 8.3  [6.9 – 11.4] | 0.32 |
| CYP11B1 | 547\*  [331 – 896] | 766  [382 – 1008] | 722  [403 – 1053] | 0.02 |
| CYP11B2 | 84  [51 – 115] | 85  [71 – 129] | 85  [58 – 121] | 0.46 |
| Data presented as median [IQR], with Friedman’s ANOVA for non-parametric data, with post-hoc test with Bonferroni correction; \*< 0.05 and; \*\*<0.001 compared to on V2 receptor antagonist; 11β-HSD 1+2 = cortisone / cortisol ratio. CYP11B1 = cortisol / 11-deoxycortisol; CYP11B2 = corticosterone / 11-deoxycorticosterone | | | | |

**Supplementary Figure 1.** Schematic representation of the effect of vasopressin on the HPA axis. *Abbreviations: ACTH, adrenocorticotropic hormone; AVP, vasopressin; CRH, corticotropin-releasing hormone, V2R, vasopressin 2 receptor antagonist.*

