**Hypertension and Kidney Dysfunction Despite Long-Term Remission of Cushing’s Syndrome**

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**Supplemental Data:**

**Supplemental Text 1: Treatment of CS**

Almost all patients with CD were treated by transsphenoidal surgical resection (TSS) of the pituitary tumor (n = 51), and one patient received bilateral adrenalectomy (BADX) as first line therapy. From 52 patients with CD, 31 patients had remission after initial therapy, while 21 patients needed additional treatment lines after TSS due to persistent disease. Repeat TSS was applied in 16 patients, radiation in 9 patients, BADX was used in 10 patients and 4 patients received medical treatment as a bridging before finally achieving biochemical control. Removal of the ACTH producing tumor was first-line treatment in 6 patients with ECS while 2 patients underwent first-line BADX before an ectopic tumor was discovered.

In patients with ACS, 17 patients with unilateral adenoma received adrenalectomy. Patients with bilateral hyperplasia received adrenalectomy of the dominant side (n= 2) and BADX (n= 2).

Median duration of uncontrolled hypercortisolism from confirmation of the diagnosis until remission was 10.3 weeks (5.6-42.6). Median time from self-reported first symptoms until remission was 118.4 weeks (53.4-263.7). Median follow-up time was 96 months (80-16).

**Supplemental Text 2: Antidiabetic treatment**

At baseline, prior to the treatment of hypercortisolism, 19.1% of patients were receiving antidiabetic medications. Among them, 70% were treated with insulin, 60% with metformin, 30% with a DPP-4 inhibitor, and only 10% with an SGLT-2 inhibitor. After 7 years, 14.5% of patients were on antidiabetic therapy, with the same distribution: 70% on insulin, 60% on metformin, 30% on a DPP-4 inhibitor, and 10% on an SGLT-2 inhibitor. At 14 years following remission, 9.1% of the patients continued to receive antidiabetic treatment, and all of them received metformin.

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| Baseline (before treatment) | CUSH  n= 81 | KORA  n=283 | P value |
| BP syst. mmHg | 148.0 (130.0-160.0) | 120.0 (108.5-130.5) | <0.0001 |
| BP diast. mmHg | 90.0 (80.0-100.0) | 77.0 (71.0-84.5) | <0.0001 |
| Heart rate bpm | 78.0 (68.0 -84.0) | 72.0 (66.0-79.0) | 0.0070 |
| GFR ml/min/1.73m2 | 86.1 (73.3-100.5) | 97.4 (83.4-106.8) | 0.0052 |
| Prevalence of Hypertension | 84.9% | 23.9% | < 0.0001 |
| Uncontrolled hypertension | 68.7% | 18.5% | < 0.0001 |
| Antihypertensive medication | 60.8 % | 10.7% | < 0.0001 |
| Possible chronic kidney disease (GFR< 60ml/min/1.73m2) | 9.6% | 2.9% | 0.0417 |

**Supplemental Table 2:** Blood pressure data at baseline before treatment of patients with Cushing’s syndrome (CUSH) compared to the control cohort (KORA). Data are reported as median and IQR or in percentage.

Abbreviations: IQR: interquartile range, BP: blood pressure, mmHg: millimeters of mercury, bpm: beats per minute, GFR: glomerular filtration rate.

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| Blood pressure data  7 years | CUSH  n= 81 | KORA  n=243 | P value |
| BP syst. mmHg | 123.5 (110.8-137.5) | 115.5 (104-125.5) | 0.0002 |
| BP diast. mmHg | 80.0 (73.8-90.0) | 72.0 (67.0-79.0) | <0.0001 |
| Heart rate bpm | 75.0 (68.0-83.0) | 72.0 (67.0-78.0) | 0.0771 |
| GFR ml/min/1.73m2 | 81.5 (68.3-91.0) | 93.8 (81.3-103.4) | <0.0001 |
| Hypertension | 52.8% | 26.3 % | <0.0001 |
| Uncontrolled hypertension | 33.8% | 10.3% | < 0.0001 |
| Antihypertensive medication | 40.6% | 20.6% | 0.0018 |
| Possible chronic kidney disease (GFR< 60ml/min/1.73m2) | 17.4% | 2.1% | <0.0001 |

**Supplemental Table 3:** Blood pressure data 7 years after treatment of patients with Cushing’s syndrome (CUSH) compared to the control cohort (KORA). Data are reported as median and IQR or in percentage.

Abbreviations: IQR: interquartile range, BP: blood pressure, mmHg: millimeters of mercury, bpm: beats per minute, GFR: glomerular filtration rate.

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| Blood pressure data  14 years | CUSH  n=42 | KORA  n=243 | P value |
| BP syst. mmHg | 126 (117.0-140.0) | 113.5 (103.5-125.5) | <0.0001 |
| BP diast. mmHg | 84.0 (75.0-88.0) | 70.5 (66.0-77.0) | <0.0001 |
| Heart rate bpm | 74.5 (66.8-84.0) | 71.0 (66.0-78.0) | 0.0375 |
| GFR ml/min/1.73m2 | 74.9 (66.5-85.5) | 82.8 (70.6-93.6) | 0.0359 |
| Hypertension | 48.7% | 32.9% | 0.0669 |
| Uncontrolled hypertension | 38.5% | 9.9% | <0.0001 |
| Antihypertensive medication | 28.9% | 30.0% | 0.9999 |
| Possible chronic kidney disease (GFR< 60ml/min/1.73m2) | 16.2% | 11.5% | 0.4192 |

**Supplemental Table 4:** Blood pressure data 14 years after treatment of patients with Cushing’s syndrome (CUSH) compared to the control cohort (KORA). Data are reported as median and IQR or in percentage.

Abbreviations: IQR: interquartile range, BP: blood pressure, mmHg: millimeters of mercury, bpm: beats per minute, GFR: glomerular filtration rate.



**Supplemental Figure 1:**

BMI (A), systolic (B) and diastolic (C) blood pressure in a subgroup of patient with adrenal insufficiency under standard replacement therapy compared to patients with normal adrenal function at baseline, 7 years (n=36 vs. n= 45, respectively) and after 14 years after biochemical remission of CS (n=20 vs. n= 22, respectively). Box plots are displaying the 90/10 percentile at the whiskers, the 75/25 percentiles at the boxes, and the median in the center line.

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**Supplemental Figure 2:**

BMI (A), systolic (B) and diastolic (C) blood pressure and GFR (D) in subgroup of patient with Cushing’s disease, adrenal Cushing’s syndrome and ectopic Cushing’s syndrome at baseline, 7 years and after 14 years after biochemical remission of CS. Box plots are displaying the 90/10 percentile at the whiskers, the 75/25 percentiles at the boxes, and the median in the center line.