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## Introduction:

- Cushing's disease (CD) results from endogenous excessive glucocorticoid secretion, due to an ACTH-producing pituitary tumour. Medical therapy is necessary to treat severe or persistent hypercortisolism, when surgery is delayed, contraindicated or unsuccessful<sup>(1)</sup>.
- We aim to describe patients undergoing medical treatment for CD in a tertiary hospital in the north of Portugal.

## Methods:

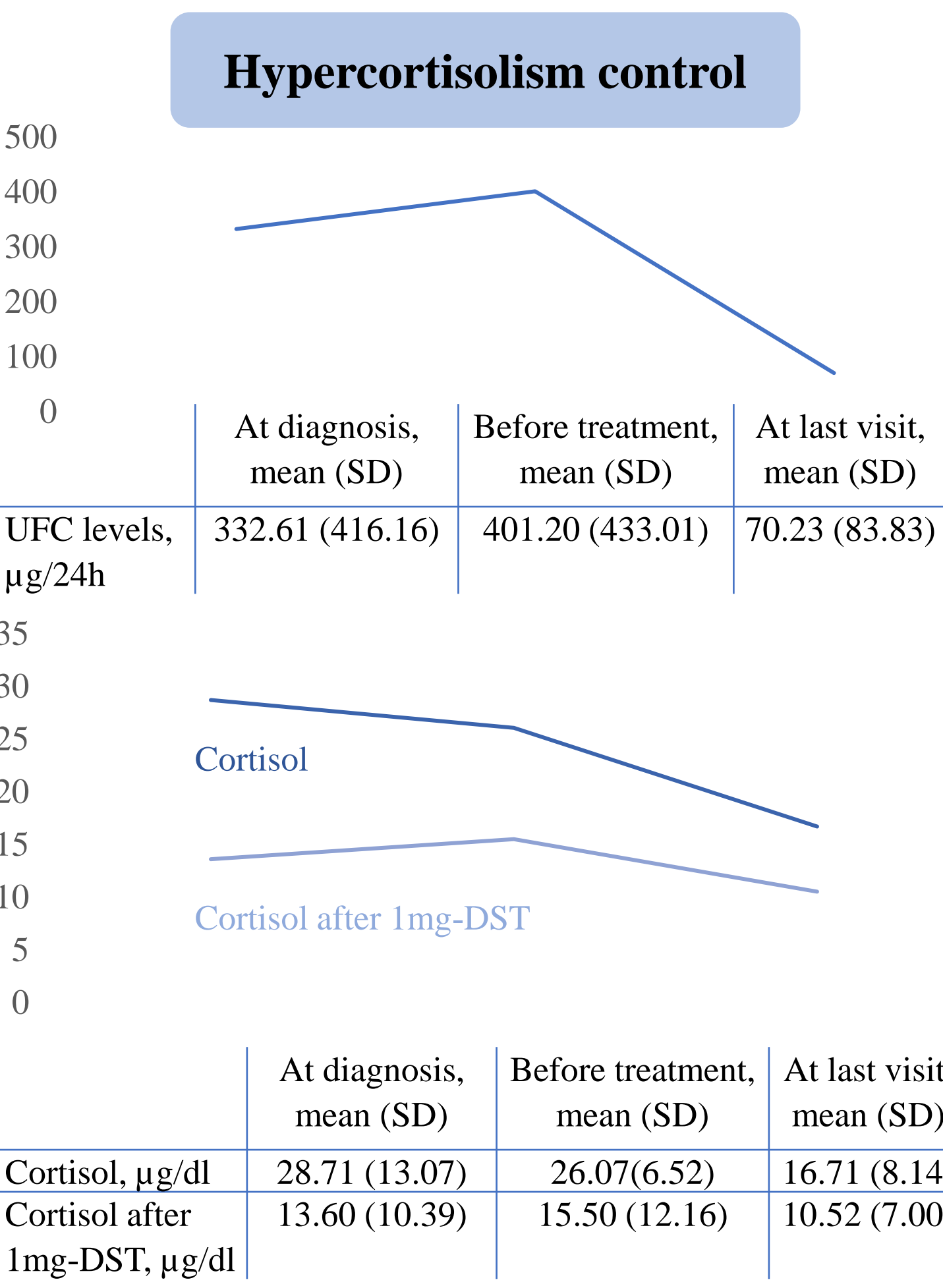
- Retrospective study of adult CD patients followed between October 2016 and December 2021, in a tertiary academic hospital in Portugal. Patients' data was reviewed through medical records.
- Patients were classified as strong or weak responders according to the percentage of decrease in urinary free cortisol (UFC) levels: >50% and <50%, respectively.
- Statistical analysis was made using IBM SPSS Statistics® (version 26).
- Reference range for UFC values, in our laboratory, is 36 -137 µg/24h.

## Results:

- From a total of 48 patients with CD, 14 (29.2%) were medically treated.

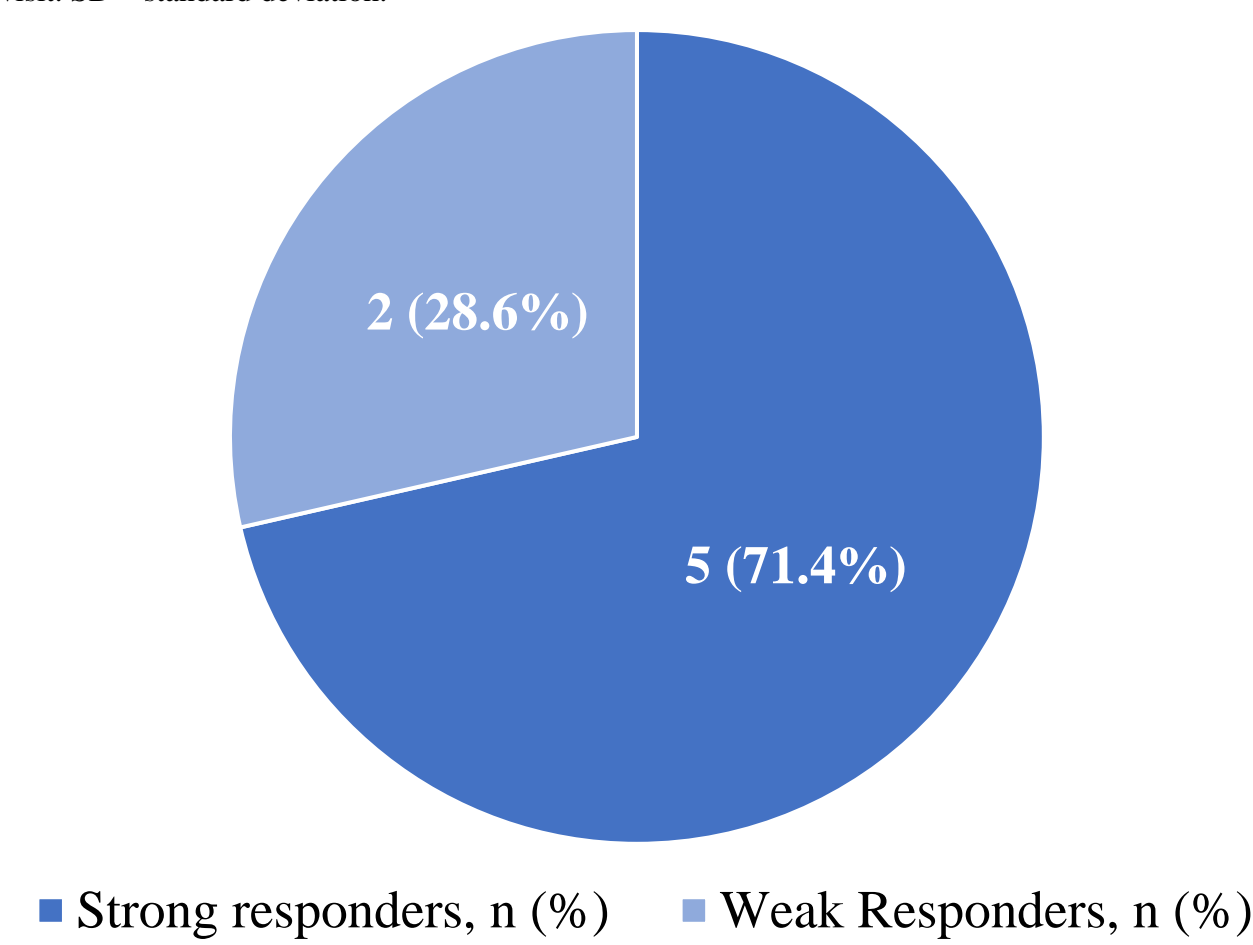
### Ketoconazole

- 7 patients (1 male). MRI: 2 macroadenomas and 5 microadenomas. Mean ACTH at diagnosis: 60.81 (47.74) pg/ml.
- Mean age: 49 ± 15 years; Mean age at diagnosis: 41 ± 15 years.
- Mean treatment's duration: 49 ± 48 months.
- Mean daily dose: 414 ± 146 mg.
- Three patients started treatment before surgery and 4 after surgery + radiotherapy (2 for **tumour relapse** and 2 for **persistent disease**). Cabergoline added in 5 cases.
- Side effects reported in 3 patients (asthenia and liver enzymes elevation < 5 x upper limit of normal).



| Comorbidities                      | Before treatment, mean (SD) | At last visit, mean (SD) |
|------------------------------------|-----------------------------|--------------------------|
| Mean arterial pressure, mmHg       | 104.91 (19.49)              | 95.90 (16.71)            |
| Body mass index, kg/m <sup>2</sup> | 24.72 (4.25)                | 25.07 (3.27)             |
| Potassium levels, mmol/L           | 3.87 (0.64)                 | 4.30 (0.344)             |

Table 1: Comparison of mean arterial pressure, body mass index and potassium levels before treatment with ketoconazole and at last visit. SD – standard deviation.

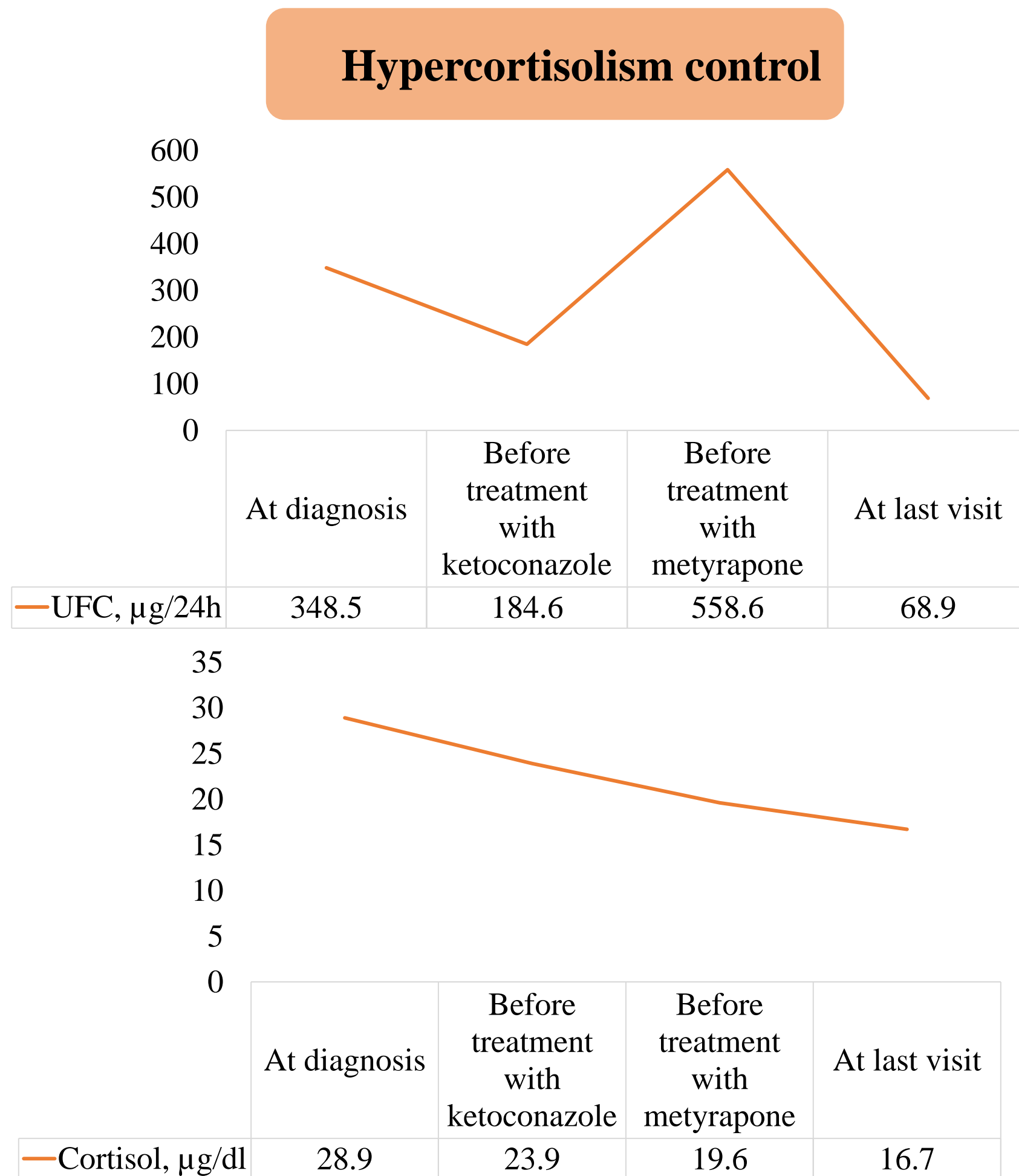


Graphic 2: Rate of strong and weak responders with ketoconazole treatment.

**Six (85.7%) patients showed normalization of UFC**

### Ketoconazole + metyrapone

- 1 patient (male), 30 years old, age at diagnosis: 26 years. MRI: microadenoma. ACTH at diagnosis: 86.10 pg/ml.
- Treatment's duration: 43 months with ketoconazole and 32 months with metyrapone (add-on medical therapy due to disease progression during ketoconazole), after surgery + radiotherapy, for **persistent disease**.
- Daily doses: ketoconazole 600 mg and metyrapone 750 mg.
- No side effects reported.



| Comorbidities                      | Before treatment with ketoconazole | Before treatment with metyrapone | At last visit |
|------------------------------------|------------------------------------|----------------------------------|---------------|
| Mean arterial pressure, mmHg       | 98.67                              | 101.50                           | 127.33        |
| Body mass index, kg/m <sup>2</sup> | 30.49                              | 31.32                            | 35.99         |
| Potassium levels, mmol/L           | 5.10                               | 4.40                             | 4.03          |

Table 2: Comparison of mean arterial pressure, body mass index and potassium levels before treatment with ketoconazole, before treatment with metyrapone and at last visit.

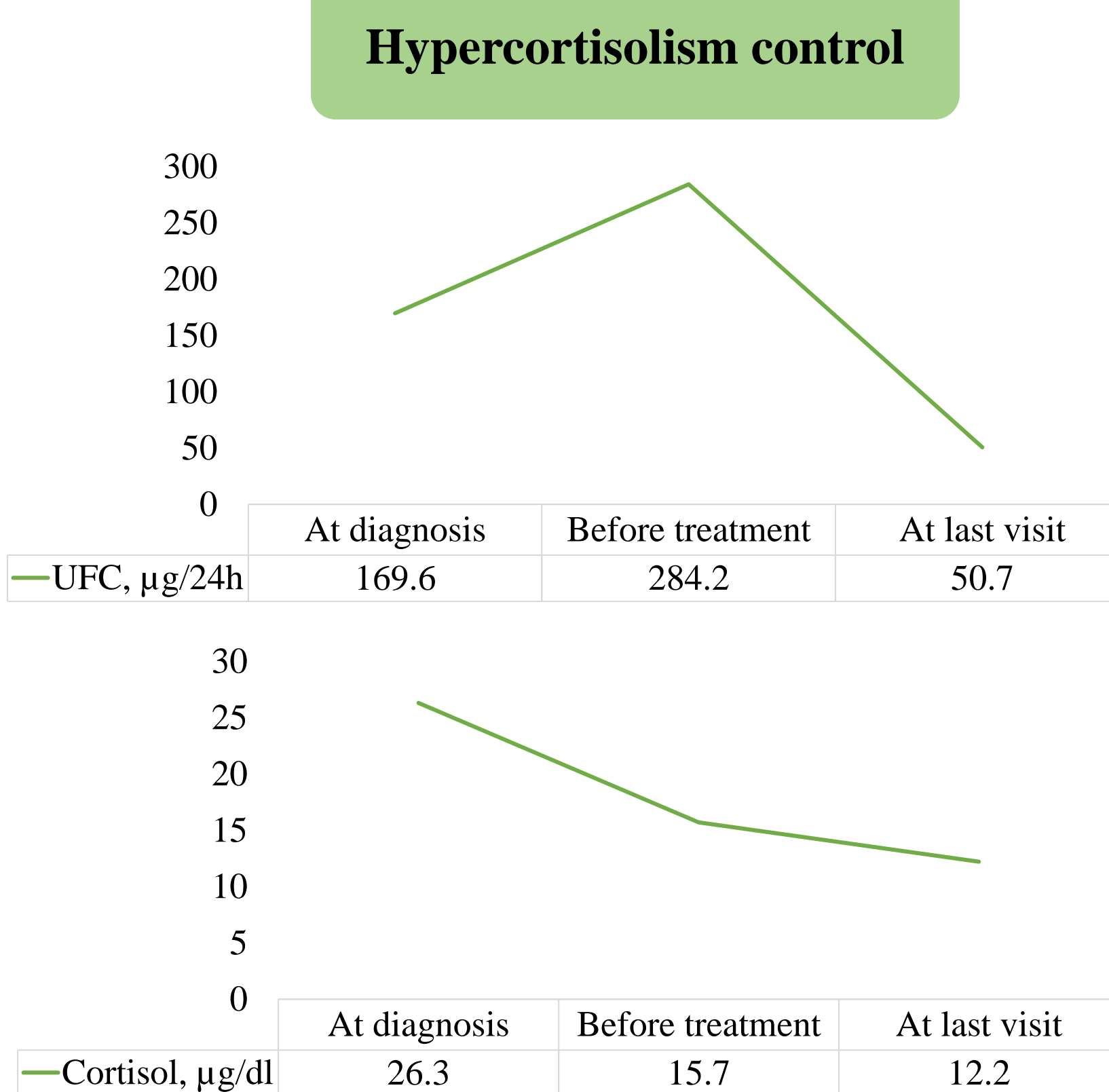
**Strong responder**

**Normalization of UFC**

Graphic 3: Course of mean urinary free cortisol levels (above panel) and mean cortisol levels (below panel), at diagnosis, before treatment with ketoconazole, before treatment with metyrapone and at last visit. UFC – urinary free cortisol.

### Metyrapone

- 1 patient (female), 63 years old, age at diagnosis: 48 years. MRI: microadenoma. ACTH at diagnosis: 19.00 pg/ml.
- Treatment's duration: 12 months.
- Started after surgery + radiotherapy, due to **persistent disease** and previous escape to ketoconazole therapy.
- Daily dose: 1000 mg.
- No side effects reported.



Graphic 4: Course of mean urinary free cortisol levels (above panel) and mean cortisol levels (below panel), at diagnosis, before treatment with metyrapone and at last visit. UFC – urinary free cortisol.

| Comorbidities                      | Before treatment | At last visit |
|------------------------------------|------------------|---------------|
| Mean arterial pressure, mmHg       | 124.00           | 88.33         |
| Body mass index, kg/m <sup>2</sup> | 39.36            | 37.97         |
| Potassium levels, mmol/L           | 3.88             | 4.38          |

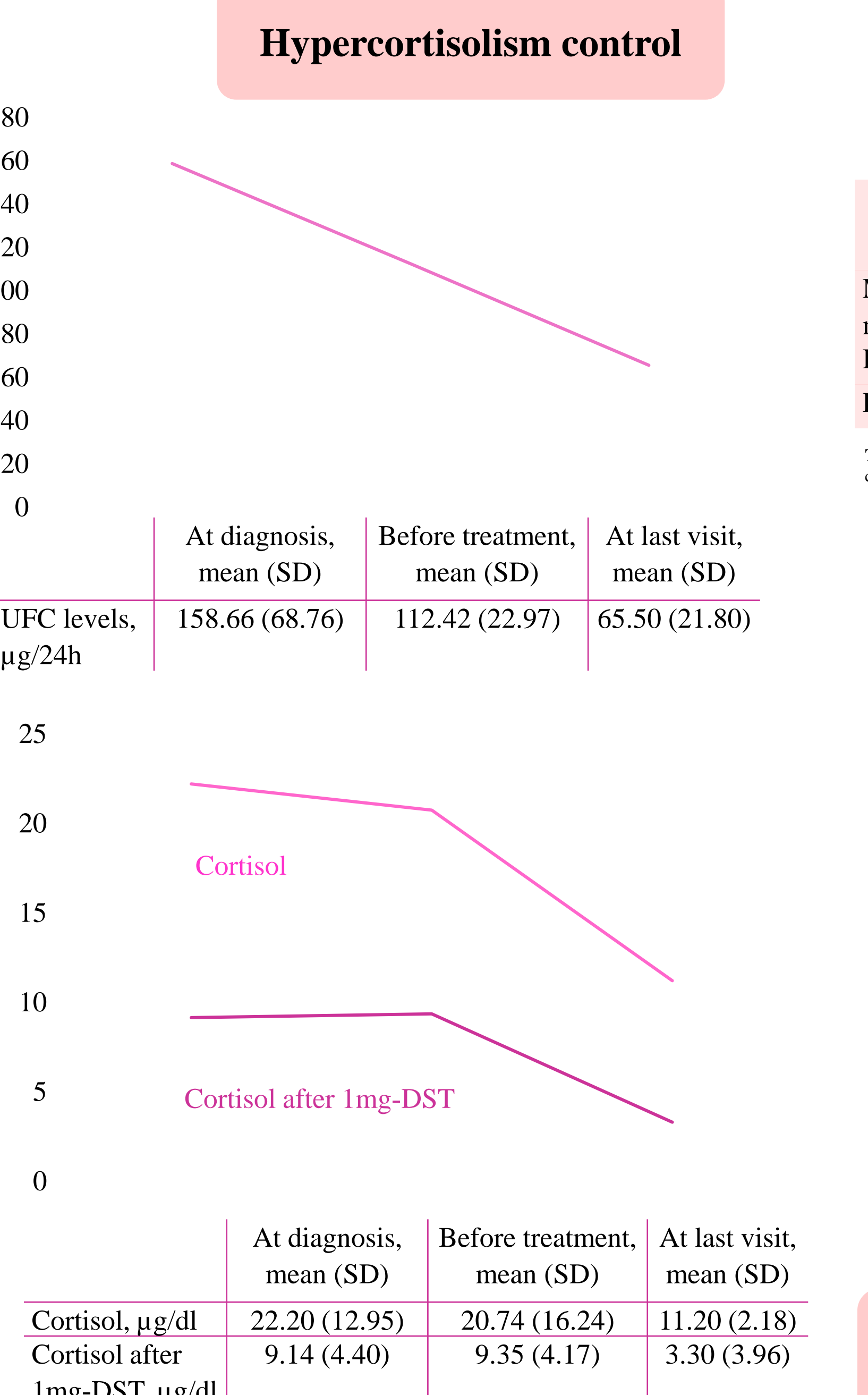
Table 3: Comparison of mean arterial pressure, body mass index and potassium levels before treatment with metyrapone and at last visit.

**Strong responder**

**Normalization of UFC**

### Cabergoline

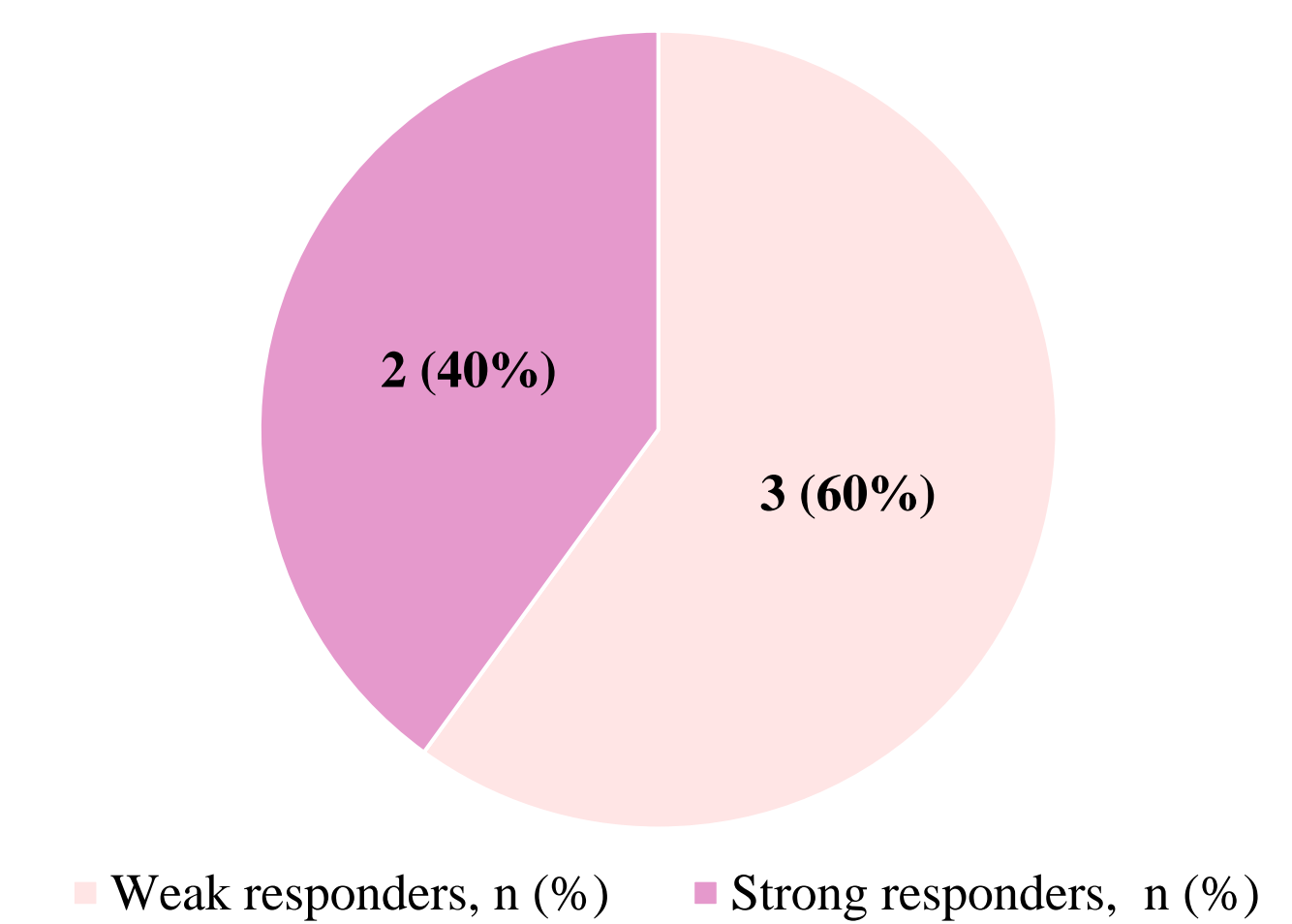
- 5 patients (females). MRI: macroadenomas. Mean ACTH at diagnosis: 89.46 (80.63) pg/ml.
- Mean age: 45 ± 10 years. Mean age at diagnosis 33 ± 9 years.
- Mean treatment's duration: 24 ± 21 months.
- Mean weekly dose: 1.20 ± 0.27 mg.
- Four patients started treatment after surgery (3 for **tumour relapse** and 1 for **persistent disease**), and one is waiting for surgery.
- Side effects reported in 2 patients: orthostatic hypotension.



Graphic 5: Course of mean urinary free cortisol levels (above panel), mean cortisol levels (below panel) and mean cortisol after 1mg dexamethasone test levels (below panel), at diagnosis, before treatment with cabergoline and at last visit. UFC – urinary free cortisol; SD – standard deviation; 1mg-DST – 1 mg dexamethasone test.

| Comorbidities                      | Before treatment, mean (SD) | At last visit, mean (SD) |
|------------------------------------|-----------------------------|--------------------------|
| Mean arterial pressure, mmHg       | 96.27 (13.62)               | 88.80 (9.14)             |
| Body mass index, kg/m <sup>2</sup> | 29.35 (7.44)                | 27.11 (5.76)             |
| Potassium levels, mmol/L           | 4.07 (0.29)                 | 4.36 (0.32)              |

Table 4: Comparison of mean arterial pressure, body mass index and potassium levels before treatment with cabergoline and at last visit. SD – standard deviation.



Graphic 6: Rate of strong and weak responders with cabergoline treatment.

**All patients showed normalization of UFC**

## Conclusions:

- In our patients with CD treated with ketoconazole, metyrapone and/or cabergoline, all show a decrease in hypercortisolism's degree. The rate of strong responders and normalization of UFC values were high with every treatment regimen. Our patients presented few side-effects, underlining that these drugs are a safe choice for CD patients who have relapsing or residual disease.

References: 1 - Fleseriu M. et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 2021 Dec;9(12):847-875.