

## Supplementary data

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#### Supplementary table

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Figure S2. Changes in sHGA & uHGA<sub>24</sub>, and sHPPA & uHPPA<sub>24</sub> in the nitisinone group of the SONIA 2. (p values indicated for comparison between keratopathy and no-keratopathy sampling points where statistical significance was achieved; keratopathy sampling points n = 35; no-keratopathy sampling points n = 272) (data shown as boxplots with median) (statistical significance p expressed \* $<0.05$ , \*\* $<0.01$ , and \*\*\* $<0.001$  respectively).

Figure S3. Changes in sHGA/sTYR & uHGA<sub>24</sub>/uTYR<sub>24</sub>, sHPPA/sTYR & uHPPA<sub>24</sub>/uTYR<sub>24</sub>, and sHPPA/sHPLA & uHPPA<sub>24</sub>/uHPLA<sub>24</sub> in the nitisinone group of the SONIA 2. (p values indicated for comparison between keratopathy and no-keratopathy sampling points where statistical significance was achieved; keratopathy sampling points n = 35; no-keratopathy sampling points n = 272) (data shown as boxplots with median) (statistical significance p expressed \* $<0.05$ , \*\* $<0.01$ , and \*\*\* $<0.001$  respectively).

Figure S4. Changes in uCREAT<sub>24</sub>, uUREA<sub>24</sub>, age and body weight in the male and female subgroups of the nitisinone group of the SONIA 2. (p values indicated for comparison between female pre-nitisinone [n = 24], male pre-nitisinone [n = 45], female nitisinone [n = 120], male pre-nitisinone [n = 225], sampling points where statistical significance was achieved) (data shown as boxplots with median) (statistical significance p expressed \* $<0.05$ , \*\* $<0.01$ , and \*\*\* $<0.001$  respectively).

Figure S5. Changes in sHGA & uHGA<sub>24</sub>, sHPPA & uHPPA<sub>24</sub>, and sHPLA & uHPLA<sub>24</sub> in the male and female subgroups of the nitisinone group of the SONIA 2. (p values indicated for comparison between female pre-nitisinone [n = 24], male pre-nitisinone [n = 45], female nitisinone [n = 120], male pre-nitisinone [n = 225], sampling points where statistical significance was achieved) (data shown as boxplots with median) (statistical significance p expressed \* $<0.05$ , \*\* $<0.01$ , and \*\*\* $<0.001$  respectively).

Figure S6. Changes in sHGA/sTYR & uHGA<sub>24</sub>/uTYR<sub>24</sub>, sHPPA/sTYR & uHPPA<sub>24</sub>/uTYR<sub>24</sub>, and sHPPA/sHPLA & uHPPA<sub>24</sub>/uHPLA<sub>24</sub> in the male and female subgroups of the nitisinone group of the SONIA 2. (p values indicated for comparison between female pre-nitisinone [n = 24], male pre-nitisinone [n = 45], female nitisinone [n = 120], male pre-nitisinone [n = 225], sampling points where statistical significance was achieved) (data shown as boxplots with median) (statistical significance p expressed \* $<0.05$ , \*\* $<0.01$ , and \*\*\* $<0.001$  respectively).

Figure S7. The phenylalanine/tyrosine pathway. The PHE/TYR metabolic pathway highlights the site of the enzyme defect observed in AKU and the site of action of nitisinone, a reversible competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase. The pathway also illustrates the dynamic relationships between HPPA, TYR and HPLA, key interactions after introduction of nitisinone.

Table S1.

| Published cases of corneal keratopathy in AKU nitisinone use (REF 18)   |     |                      |                      |                              |                        |                          |
|---|-----|----------------------|----------------------|------------------------------|------------------------|--------------------------|
| Patient no.   | Sex | Age at onset (years) | Dose nitisinone (mg) | Onset keratopathy (months) ‡ | Slit-lamp confirmation | sTYR $\mu\text{mol/L}$ ‡ |
| NIH Trial   |     |                      |                      |                              |                        |                          |
| 1   | M   | 48                   | 2                    | 1.5                          | Y                      | 600                      |
| NAC   |     |                      |                      |                              |                        |                          |
| 2   | M   | 25                   | 2                    | 36, B                        | Y                      | 964                      |
| 3   | M   | 21                   | 2                    | 1.5, U                       | Y                      | 941                      |
| 4   | M   | 55                   | 2                    | 3, B                         | N*                     | NA*                      |
| SONIA 2   |     |                      |                      |                              |                        |                          |
| 5   | F   | 56                   | 10                   | 3, B                         | Y                      | 1022                     |
| 6   | F   | 69                   | 10                   | 14, U                        | N*                     | 1191                     |
| 7   | M   | 50                   | 10                   | 12, U                        | Y                      | 1236                     |
| 8   | M   | 39                   | 10                   | 6, B                         | Y                      | 1118                     |
| 9   | M   | 54                   | 10                   | 1, U                         | Y                      | 816                      |
| 10  | M   | 44                   | 10                   | 13, U                        | Y                      | 1036                     |
| 11  | M   | 29                   | 10                   | 36, B                        | Y                      | 1149                     |
| 12  | M   | 41                   | 10                   | 30, U                        | Y                      | 976                      |
| 13  | M   | 51                   | 10                   | 24, U                        | Y                      | 934                      |
| 14  | M   | 43                   | 10                   | 6, U                         | Y                      | 609                      |
| ‡ Last serum tyrosine value before onset of keratopathy or withdrawal of nitisinone; serum tyrosine not always measured at diagnosis of keratopathy |     |                      |                      |                              |                        |                          |
| * U – unilateral; B – bilateral; following nitisinone in months   |     |                      |                      |                              |                        |                          |

| Table S2. Dates of start and end of 10mg and 2mg in patients developing keratopathy |                   |                |                |               |
|---|-------------------|----------------|----------------|---------------|
| Patient No.   | First dose (10mg) | Last dose 10mg | First dose 2mg | Last dose 2mg |
| 1   | 6/2014            | 6/2015         | 8/2015         | 10/2016       |
| 2   | 9/2014            | 12/2015        | 2/2016         | 9/2018        |
| 3   | 11/2014           | 11/2015        | 2/2016         | 11/2017       |
| 4   | 11/2014           | 1/2016         | -              | -             |
| 5   | 2/2015            | 4/2015         | 6/2015         | 12/2018       |
| 6   | 2/2015            | 3/2016         | 6/2016         | 4/2017        |
| 7   | 6/2014            | 5/2017         | 7/2017         | 5/2018        |
| 8   | 9/2014            | 4/2017         | 7/2017         | 11/2018       |
| 9   | 10/2014           | 10/2016        | -              | -             |
| 10  | 5/2014            | 5/2015         | 7/2015         | 1/2018        |
| Cells with no dates represent withdrawal from study                                 |                   |                |                |               |

Figure S1.

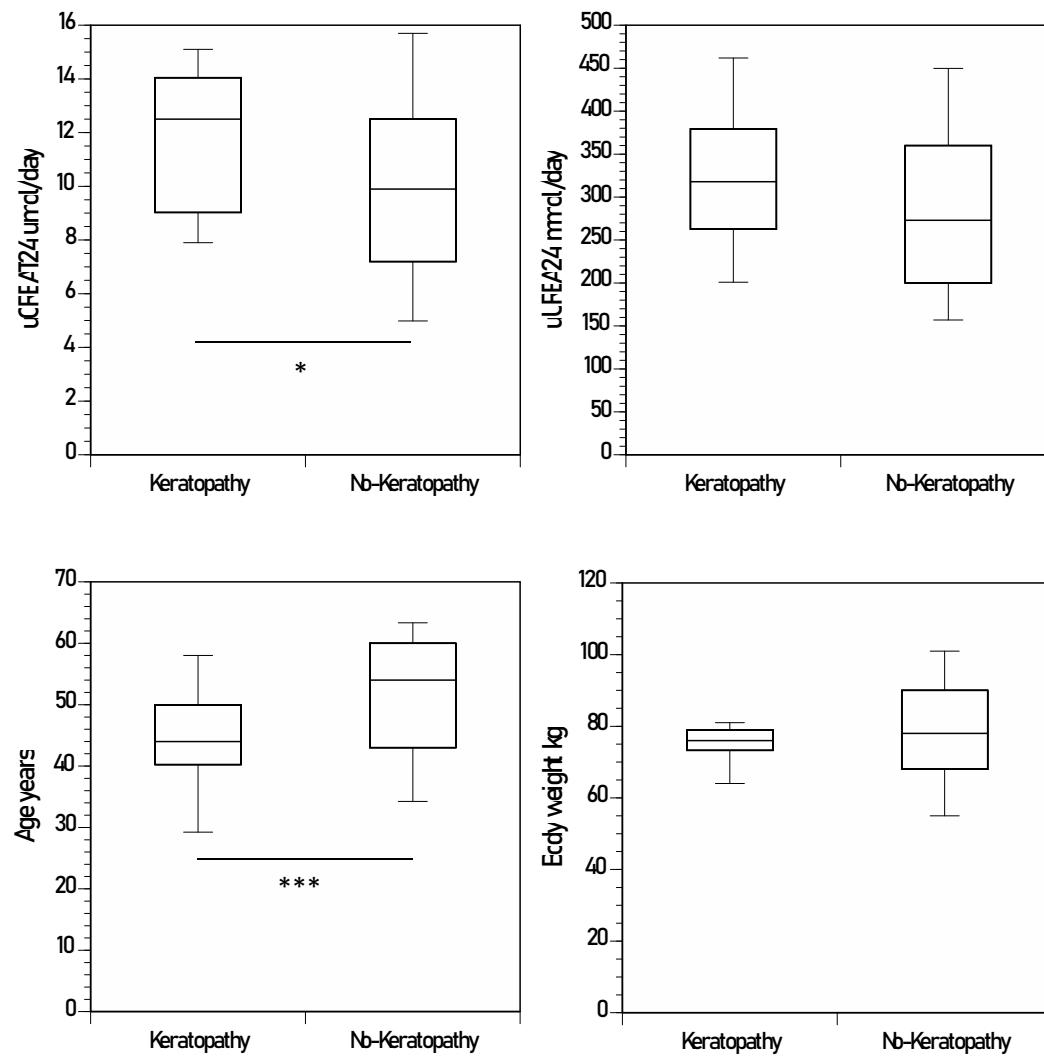


Figure S2.

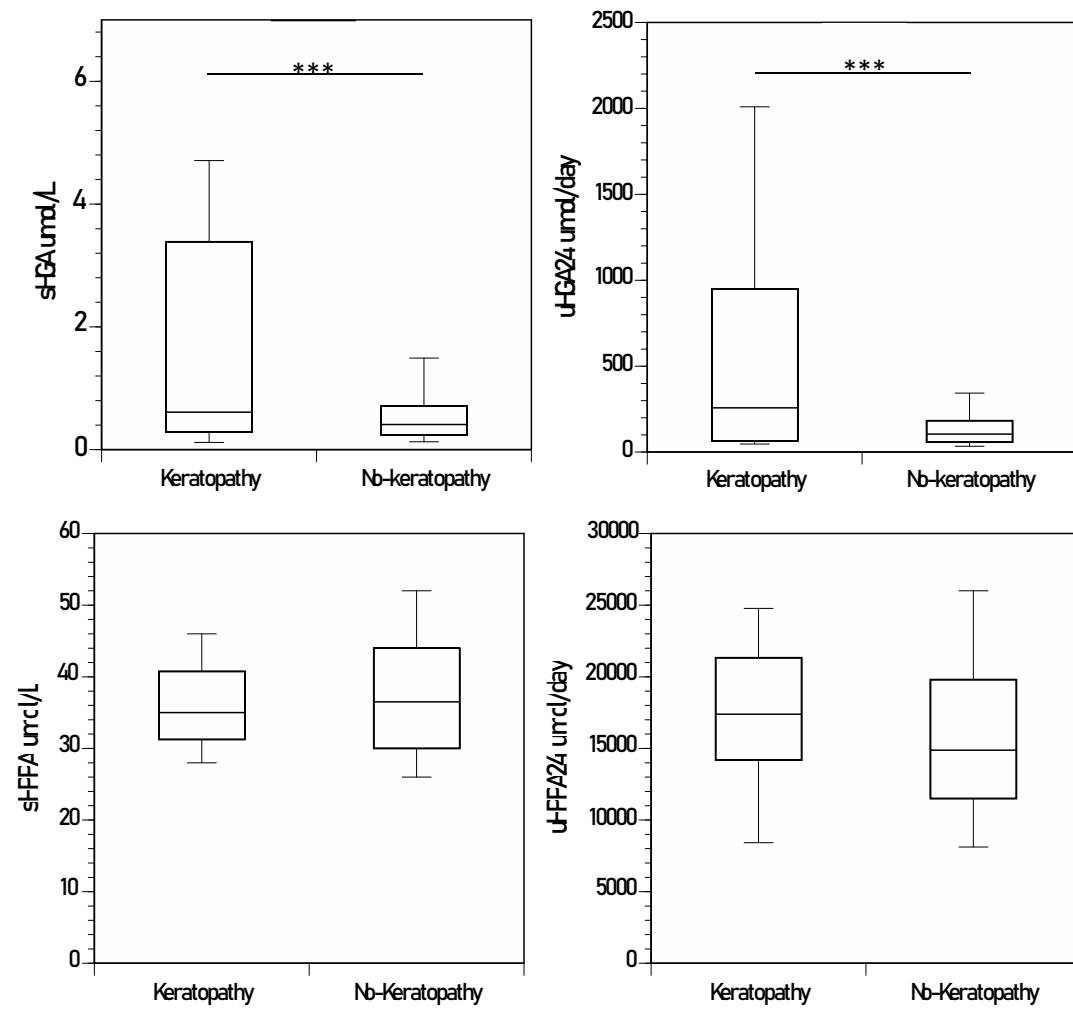


Figure S3.

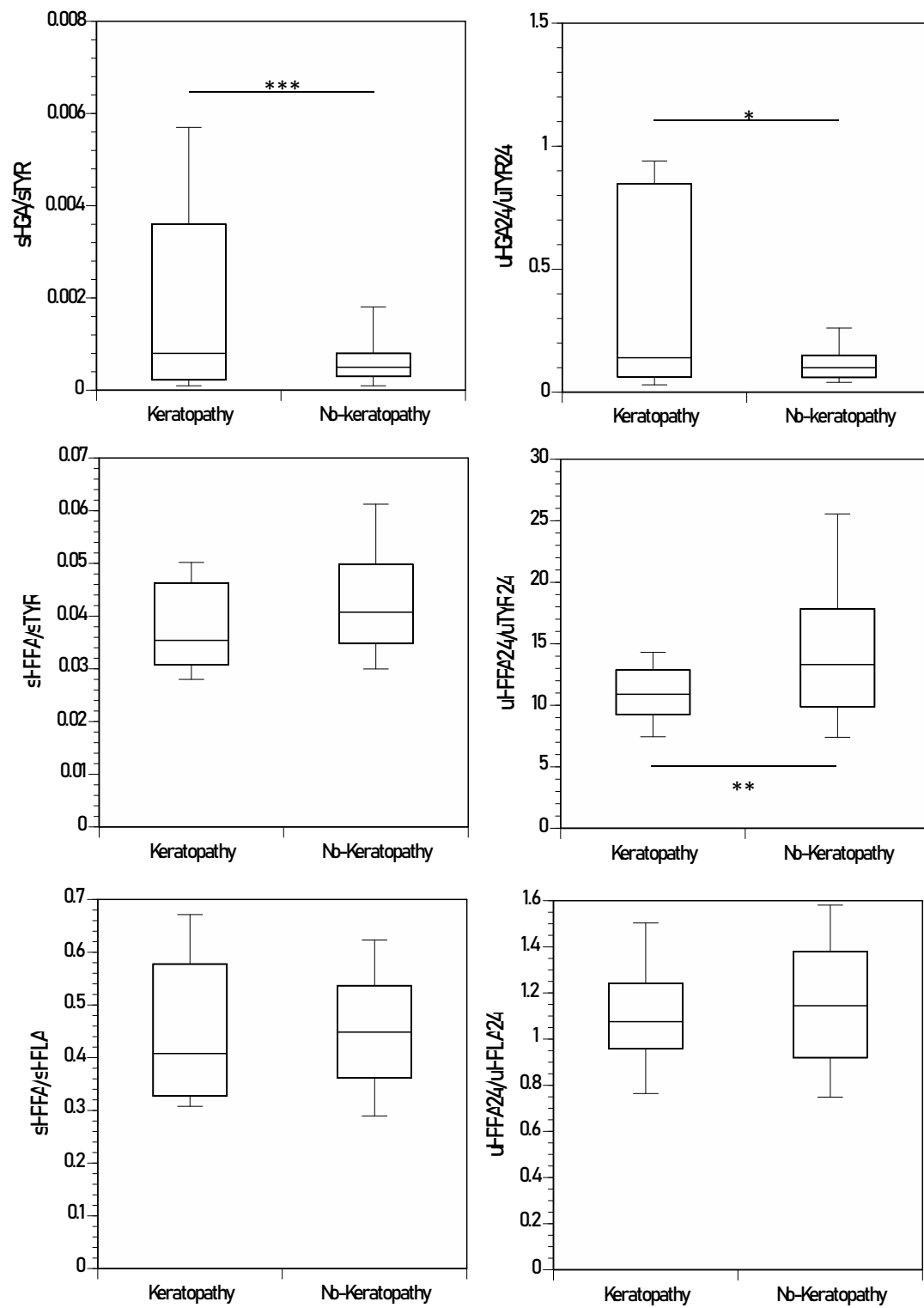


Figure S4.

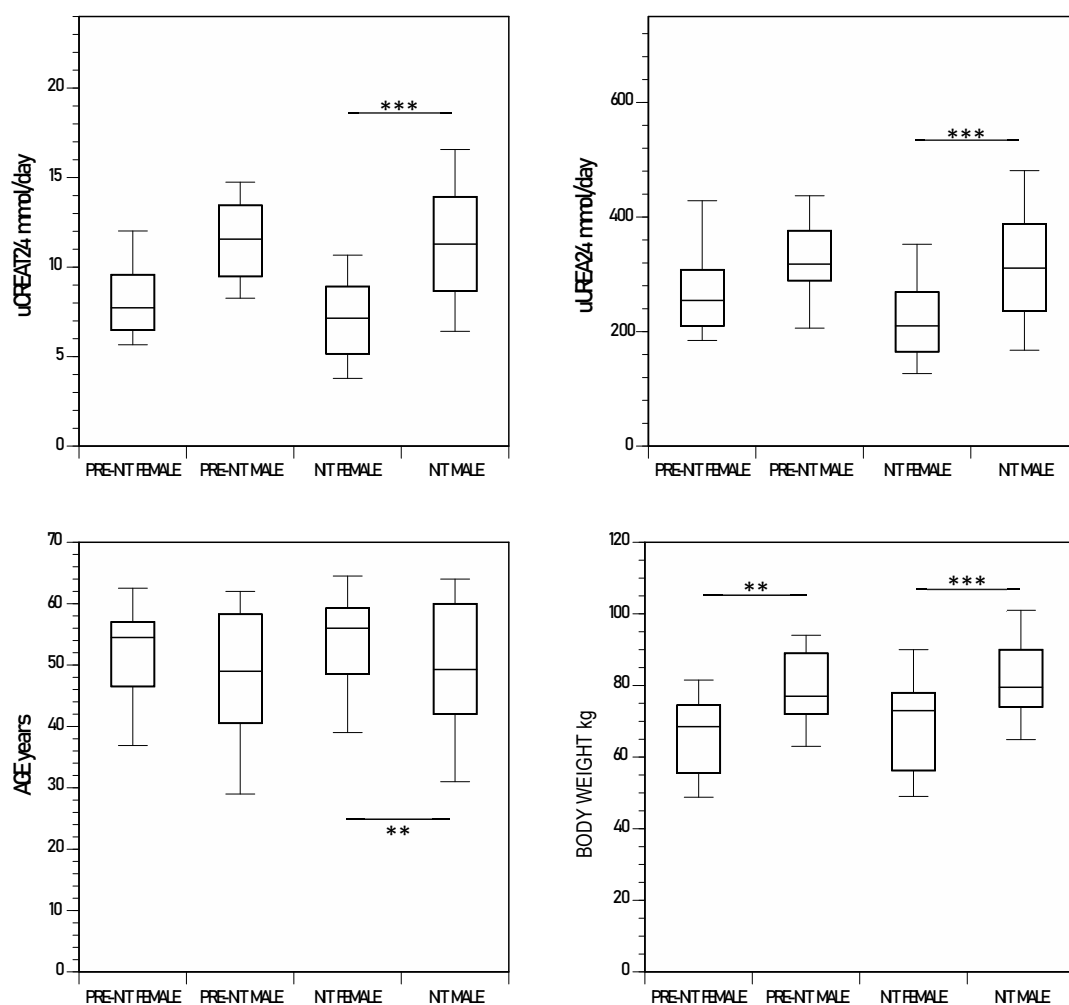


Figure S5.

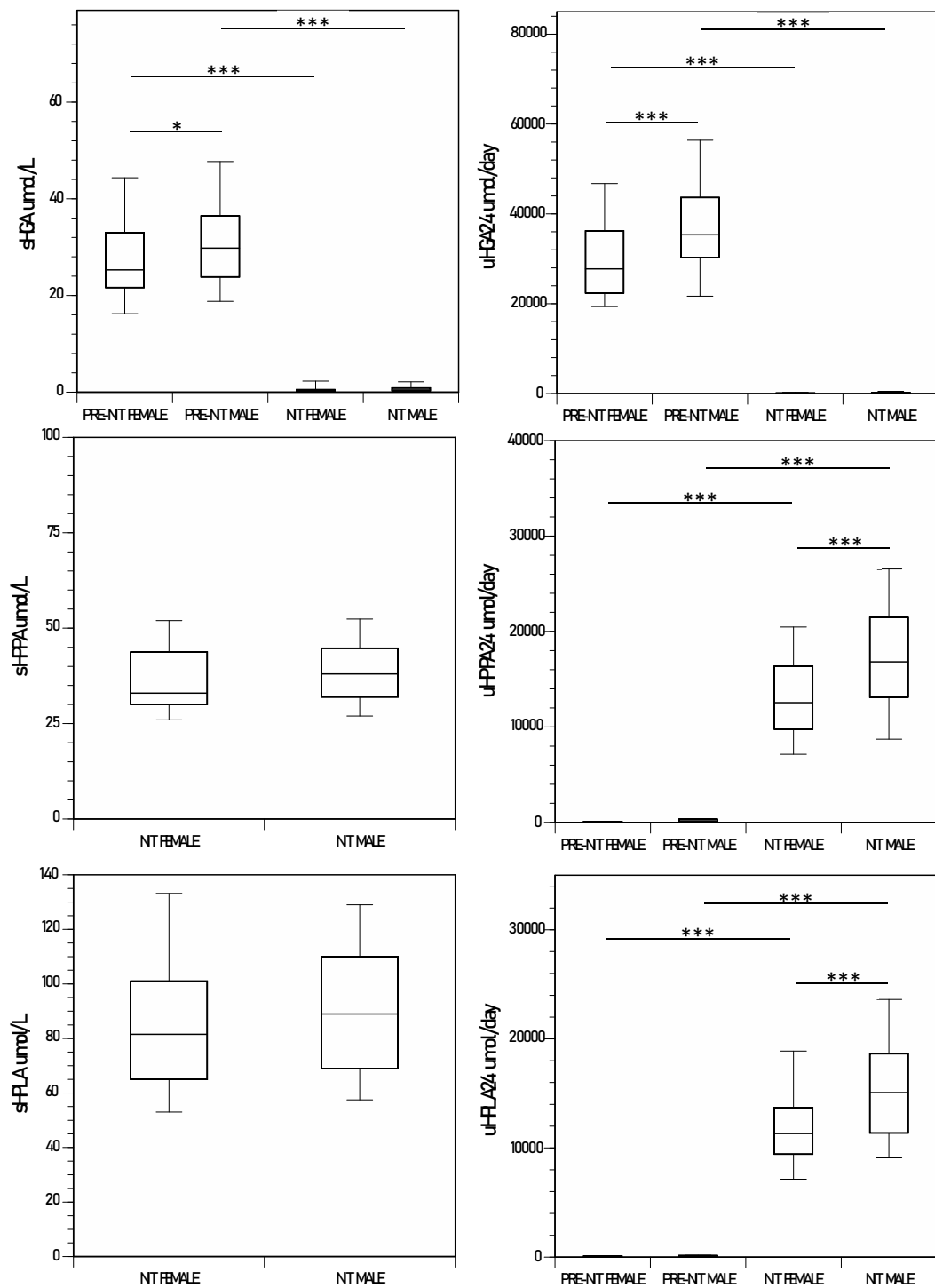




Figure S6.

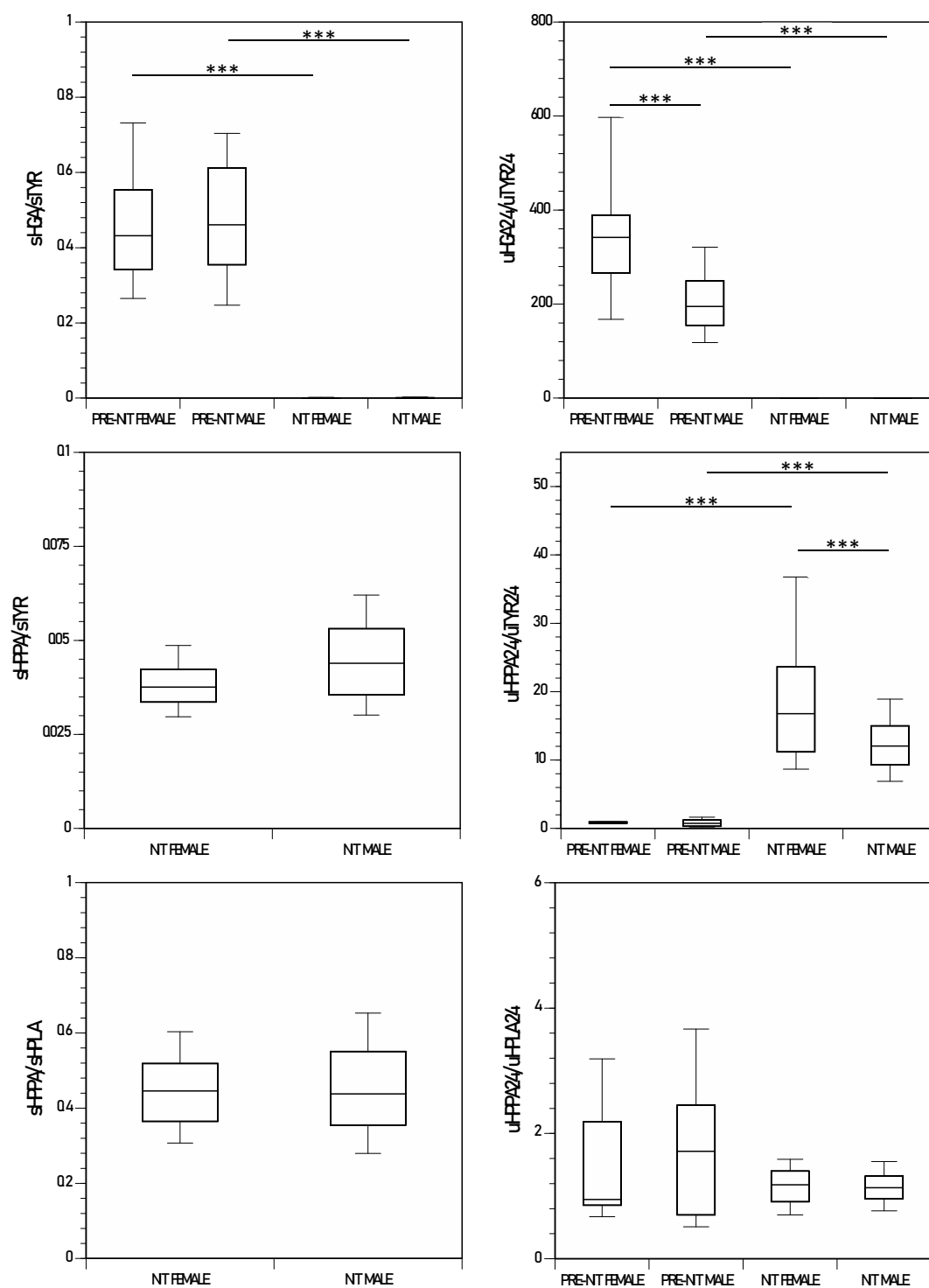


Figure S7.

