

## 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) <sup>‡</sup>	Slit-lamp confirmation	sTYR $\mu\text{mol/L}$ <sup>‡</sup>
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
<sup>‡</sup> Last serum tyrosine value before onset of keratopathy or withdrawal of nitisinone; serum tyrosine not always measured at diagnosis of keratopathy <sup>‡</sup> 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.

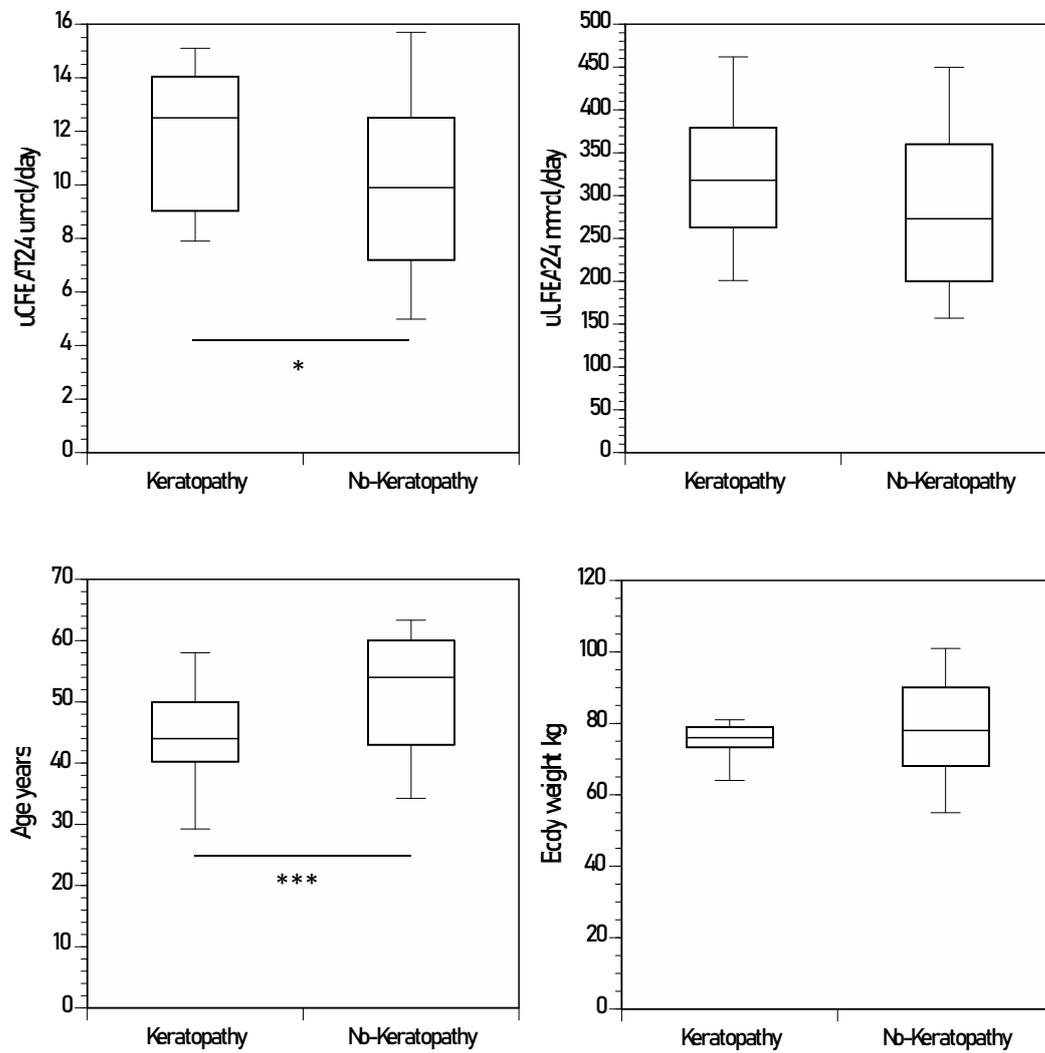


Figure S2.

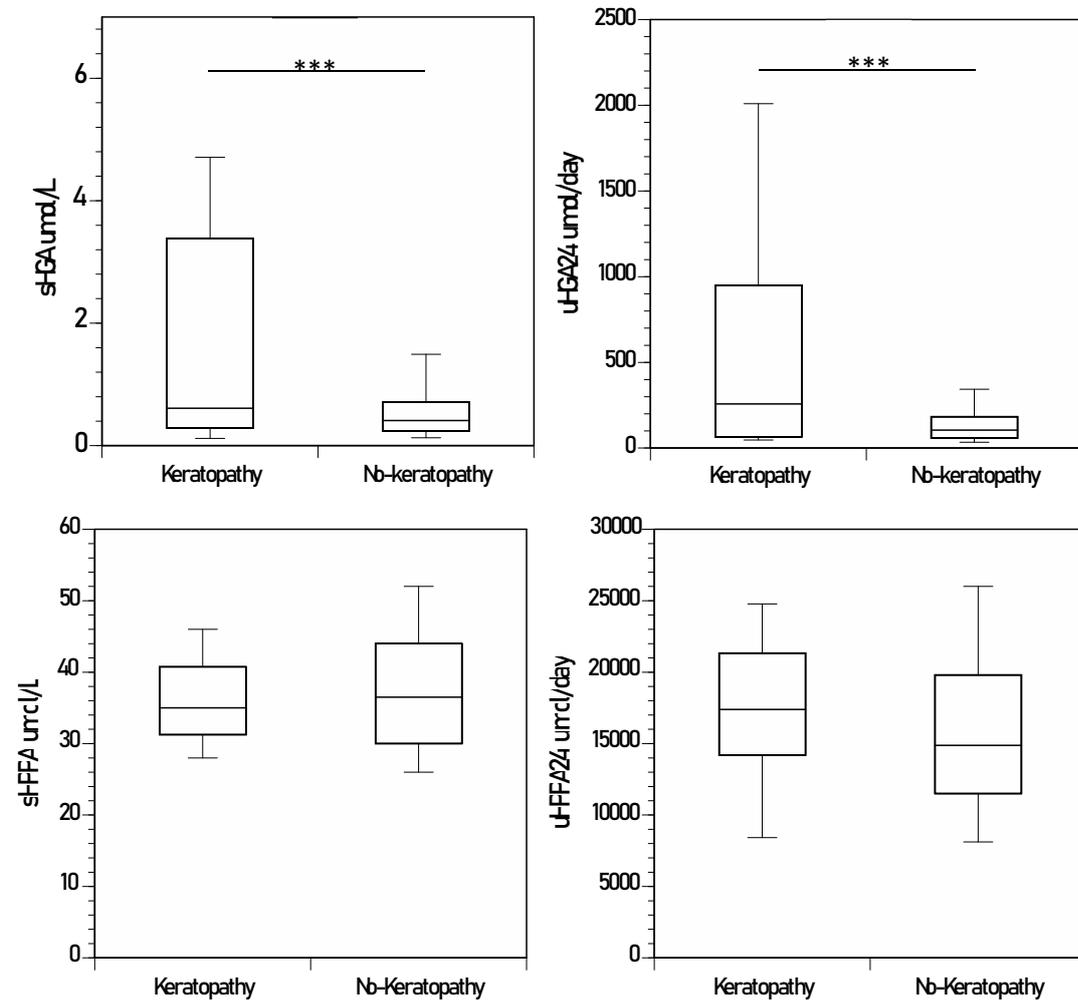


Figure S3.

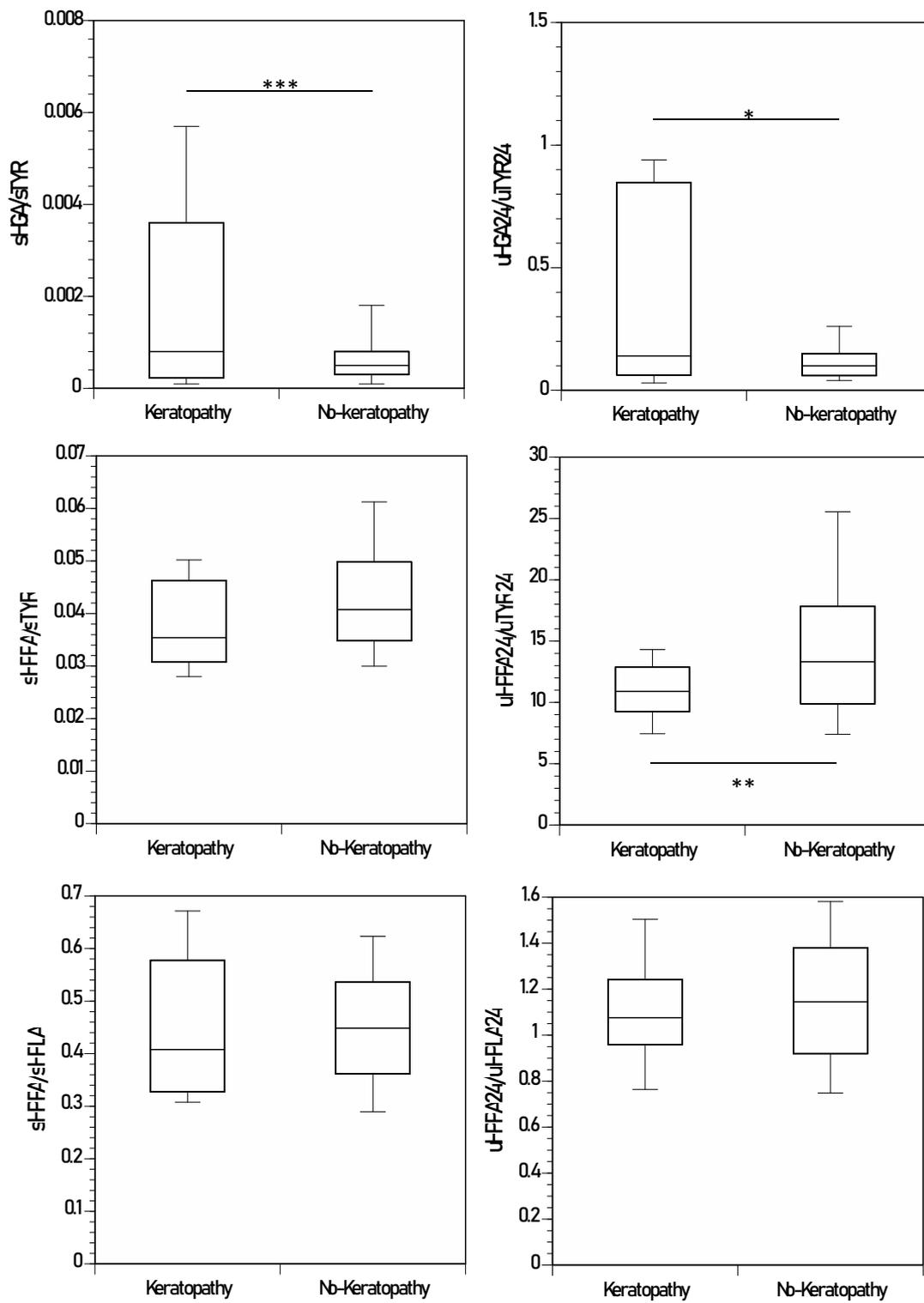


Figure S4.

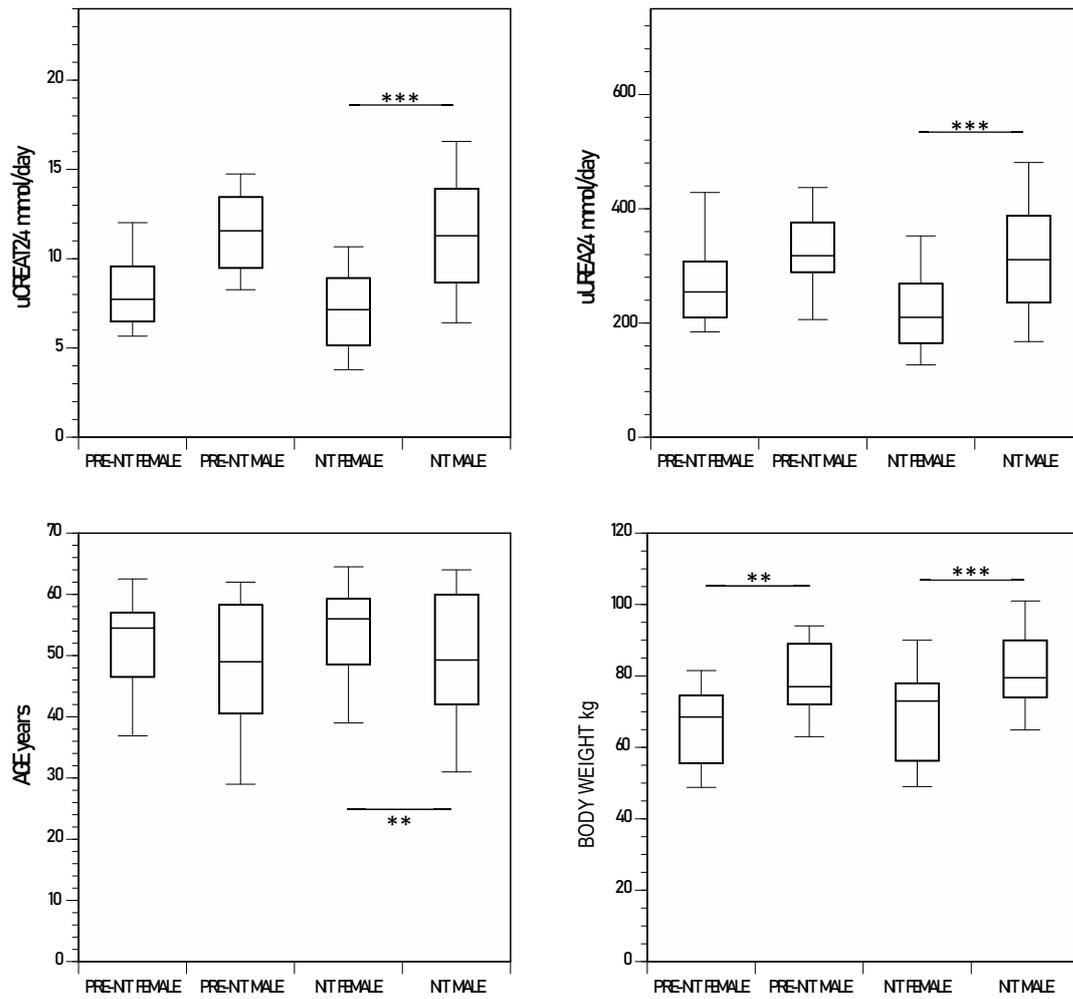


Figure S5.

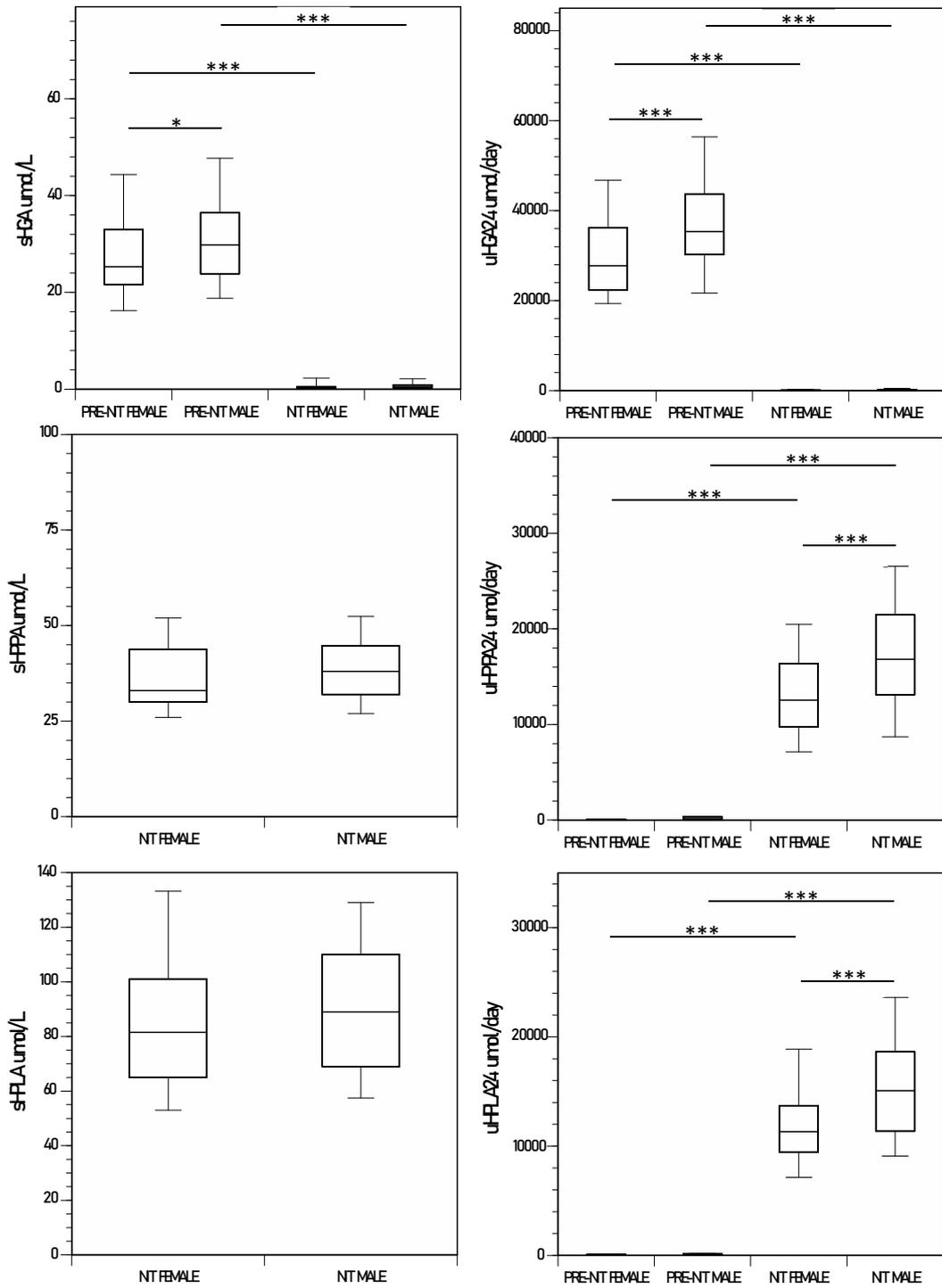


Figure S6.

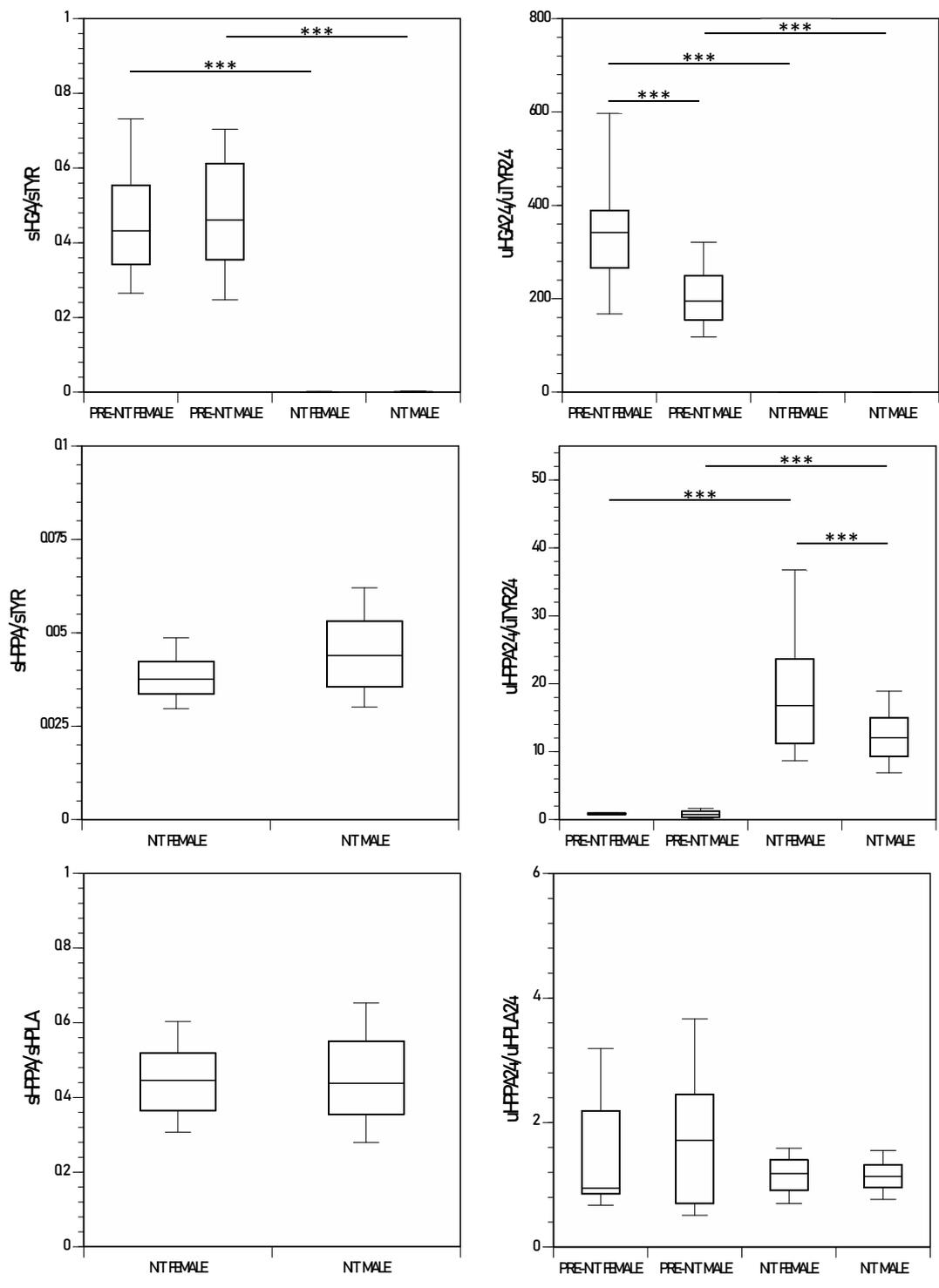


Figure S7.

