

Supplemental Tables and Figures

Supplementary Tables

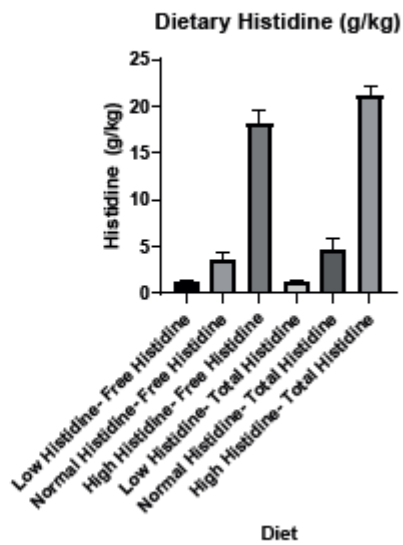
Ingredient	Low Histidine Diet	Normal Histidine Diet	High Histidine Diet
L-Histidine (g)	1.08	4.6	21
L-Histidine (g/kg)	1.28	5.47	25
Protein (g)	175.4	178.9	195.3
Protein (kcal)	7.02	7.16	7.18
Protein (%/total kcal)	18	18	20
Carbohydrate (g)	349.1	345.6	329.2
Carbohydrate (kcal)	13.96	13.82	13.17
Carbohydrate (%/total kcal)	36	35	34
Fat (g)	202.5	202.5	202.5
Fat (kcal)	18.23	18.23	18.23
Fat (%/total kcal)	46	46	46

Supplementary Table 1. Overview macronutrients in murine diets. Kcal: kilocalories, g: grams

Control	Study visit						
	Baseline	2 weeks	p_value	Post AB	p_value	Post recovery	p_value
n	19	19		19		19	
BMI (kg/m ²)	25.49 (2.75)	25.40 (2.75)	0.916	25.49 (2.80)	0.998	25.28 (2.71)	0.81
Waist/Hip ratio	0.90 (0.05)	0.90 (0.05)	0.837	0.90 (0.05)	0.974	0.90 (0.06)	0.90
Weight (kg)	72.95 (13.13)	72.72 (13.43)	0.957	64.07 (41.75)	0.382	72.34 (12.93)	0.89
REE (kcal)	1362.11 (247.70)	1361.93 (224.05)	0.998	1286.69 (194.65)	0.304	1305.53 (303.93)	0.53
Total body fat (%)	27.16 (7.61)	27.87 (8.08)	0.782	20.97 (29.94)	0.401	12.79 (40.11)	0.14
eGFR (mL/min/1.73m ²)	83.56 (7.11)	83.94 (6.09)	0.861	84.94 (6.53)	0.546	86.78 (4.14)	0.106
Type 2 diabetes	Study visit						
	Baseline	2 weeks	p_value	Post AB	p_value	Post recovery	p_value
n	20	20		20		20	
BMI (kg/m ²)	29.56 (2.87)	29.32 (3.29)	0.806	29.32 (2.74)	0.787	21.86 (32.36)	0.295
Waist/Hip ratio	0.98 (0.08)	1.76 (3.13)	0.287	1.00 (0.08)	0.592	-4.30 (22.93)	0.322
Weight (kg)	87.08 (15.01)	66.42 (58.31)	0.133	86.17 (15.04)	0.850	68.02 (59.05)	0.170
REE (kcal)	1549.93 (262.13)	1555.99 (306.33)	0.948	1546.66 (260.33)	0.969	1376.12 (546.96)	0.222
Total body fat (%)	32.42 (7.18)	26.53 (30.50)	0.407	25.90 (30.62)	0.360	20.43 (41.23)	0.208
eGFR (mL/min/1.73m ²)	82.35 (14.10)	84.26 (12.56)	0.658	80.50 (15.49)	0.695	82.39 (14.14)	0.993

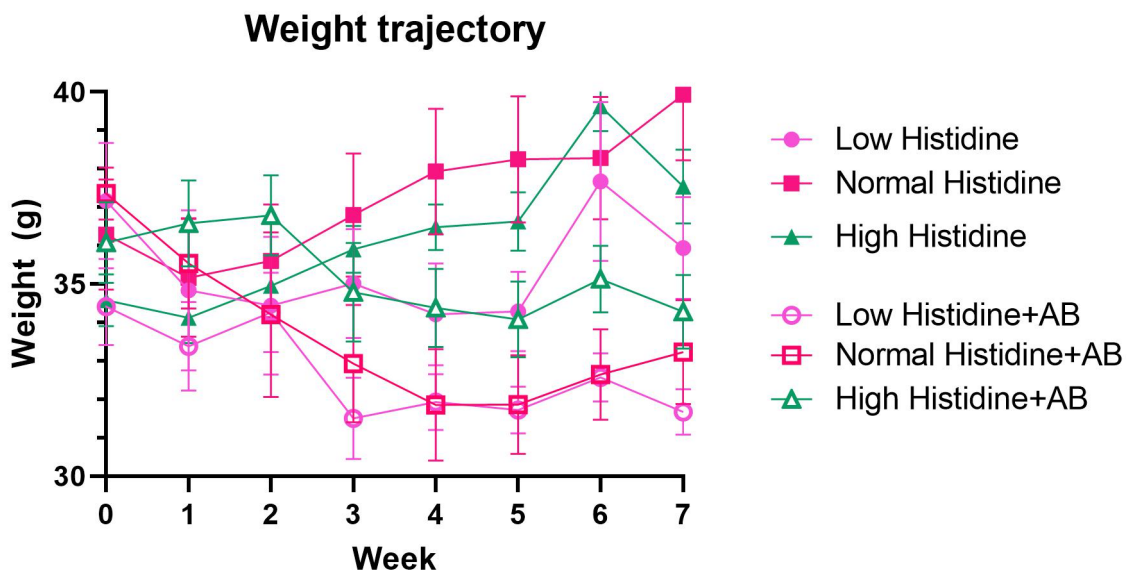
Supplementary Table 2. Anthropometric and biochemical values per visit. Data displayed as mean ±SD or %. t-test for significance. REE: resting energy expenditure . eGFR estimated Glomerular Filtration Rate,

Supplementary Figures



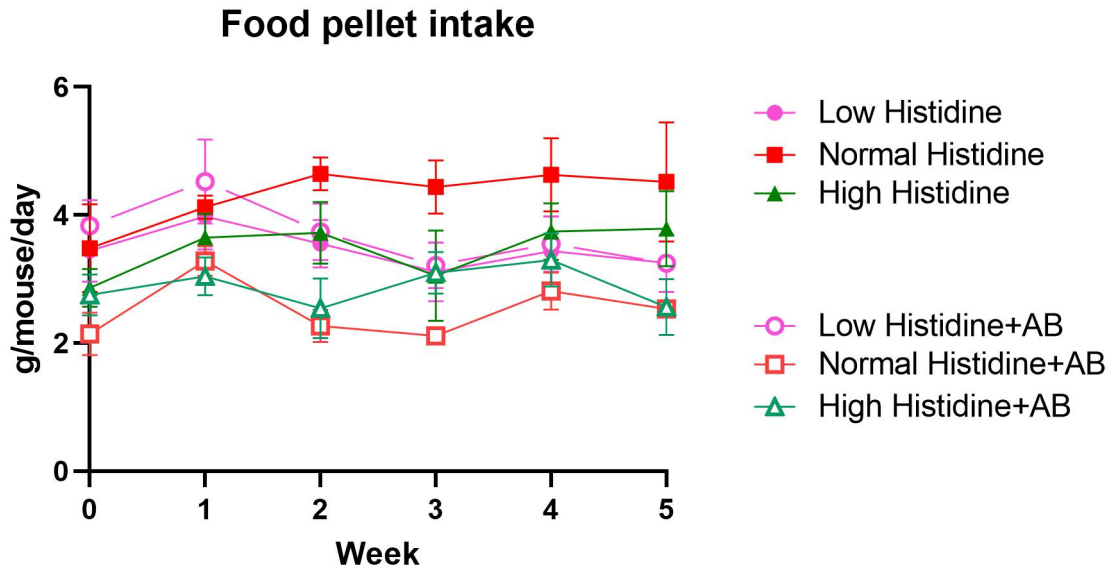
Supplementary Figure 1. Depiction of histidine content in murine diets.

A.



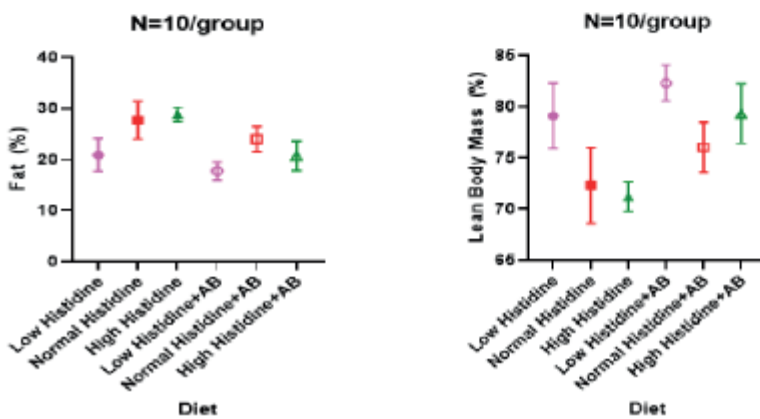
Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
NS	NS	NS	NS	* Normal Histidine-Low Histidine+AB	** Normal Histidine-Low Histidine+AB	* Normal Histidine-Low Histidine+AB
				* Normal Histidine-Normal Histidine+AB	** Normal Histidine-Normal Histidine+AB	* Normal Histidine-Normal Histidine+AB
				* High Histidine-Normal Histidine+AB	** High Histidine-Normal Histidine+AB	* High Histidine-Normal Histidine+AB
					* High Histidine-Low Histidine+AB	* High Histidine-Low Histidine+AB
					* Low Histidine-Normal Histidine	
					* Normal Histidine-High Histidine+AB	

B.



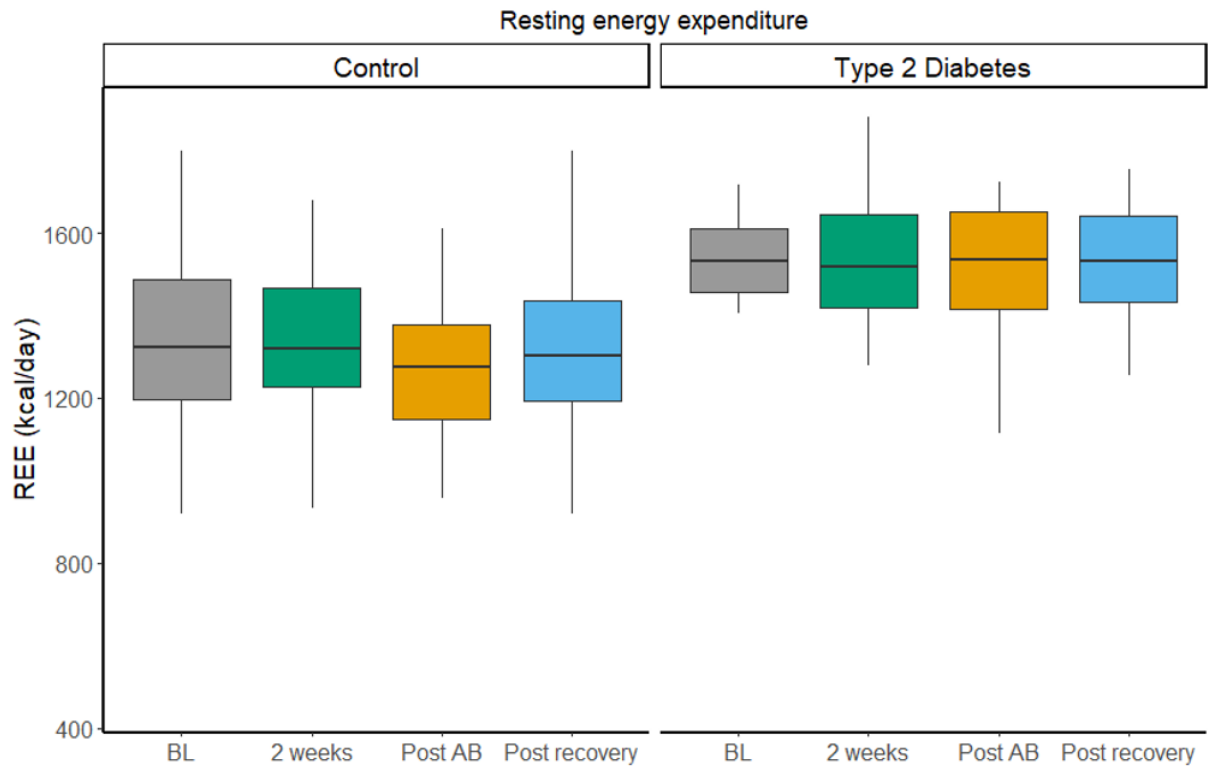
Week 0	Week 1	Week 2	Week 3	Week 4	Week 5
NS	NS	** Normal Histidine-Normal Histidine+AB ** Normal Histidine-High Histidine+AB	** Normal Histidine-Normal Histidine+AB ** Normal Histidine-High Histidine+AB * Normal Histidine-Low Histidine+AB * Low Histidine-Normal Histidine * High Histidine-Normal Histidine+AB	* High Histidine-Normal Histidine+AB	* Normal Histidine-Normal Histidine+AB * Normal Histidine-High Histidine+AB * Low Histidine-Normal Histidine+AB * Low Histidine-High Histidine+AB

C.

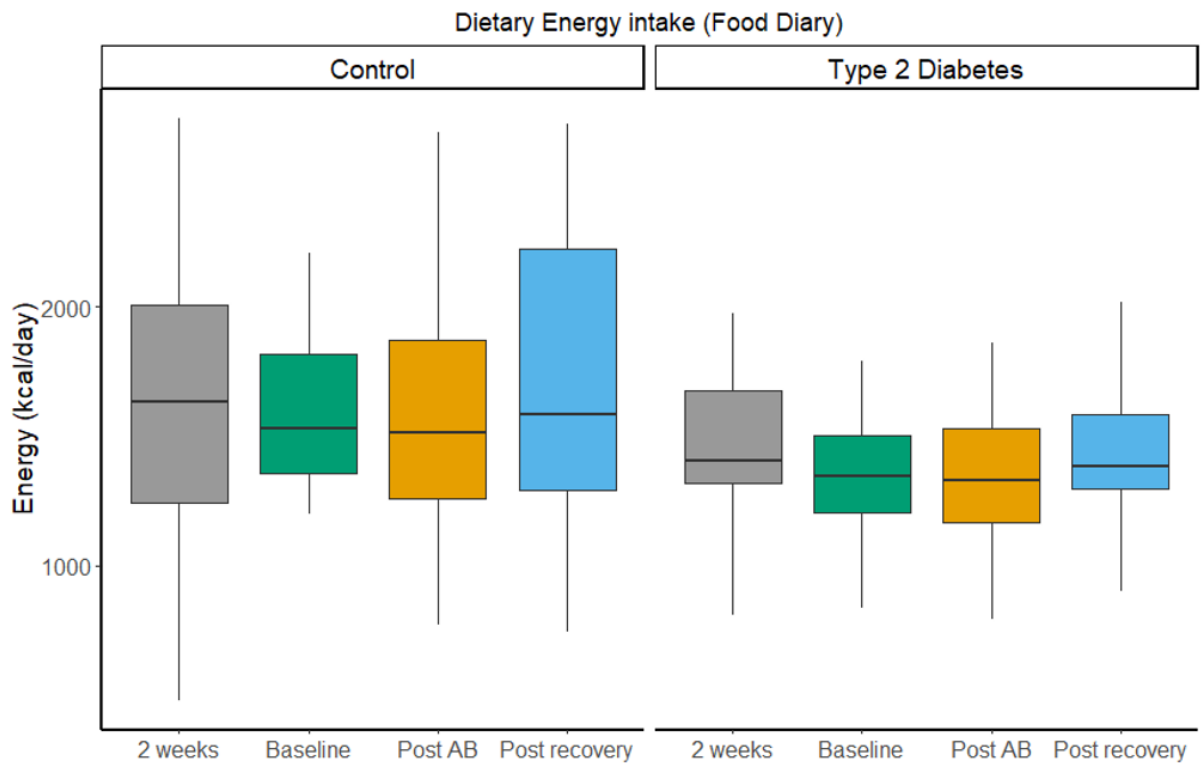


Supplementary Figure 2. Overview measurements during the study. A. Weigh trajectory B. Food pellet intake C. body fat %. Linear mixed effect model with FDR correction. Mouse ID as random effect and diet as fixed effect.

A.

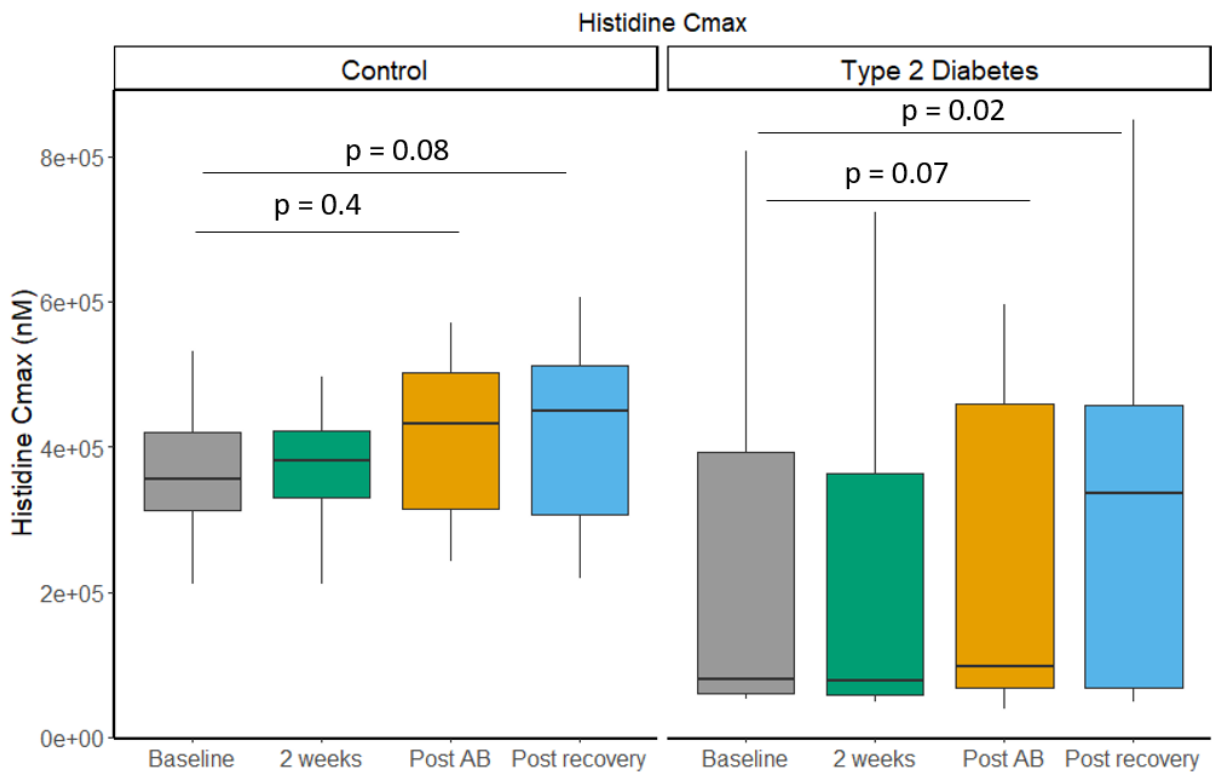


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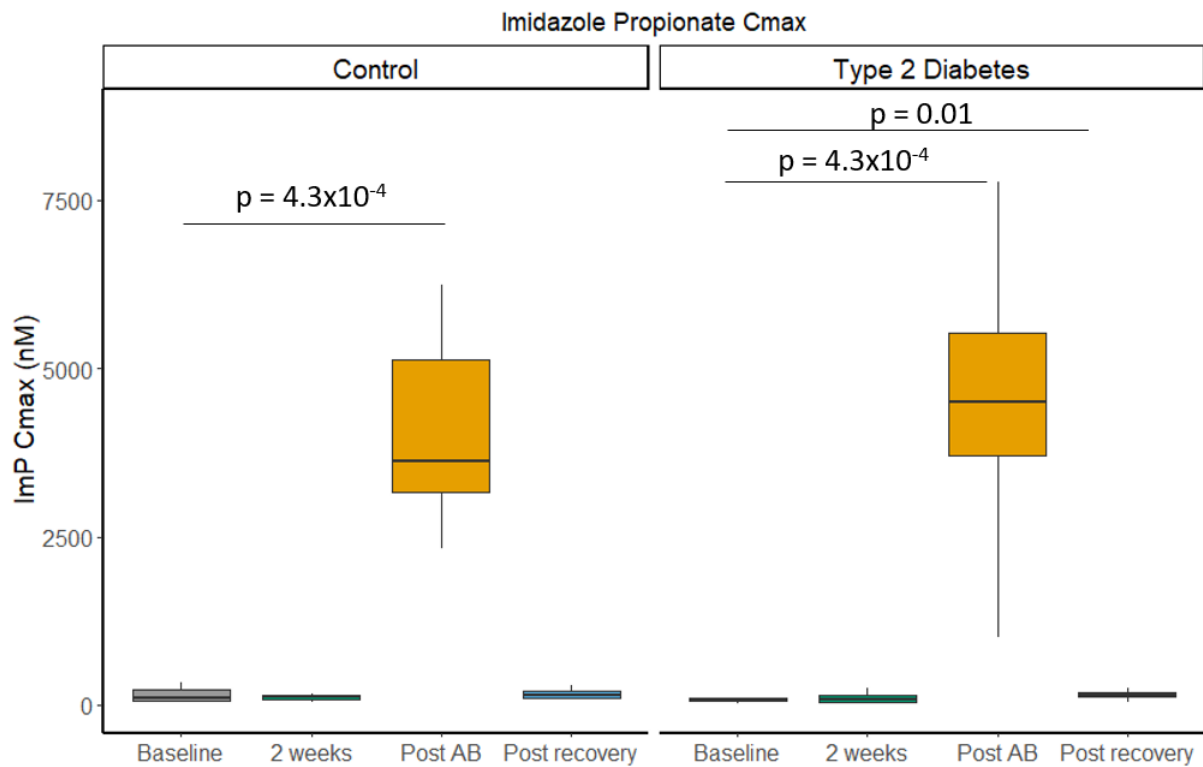


Supplementary Figure 3. Overview energy parameters per visit. A. Resting energy measured by indirect calorimetry. B. Dietary Energy intake measured by food diaries. Paired wilcox testing. FDR corrected p values.

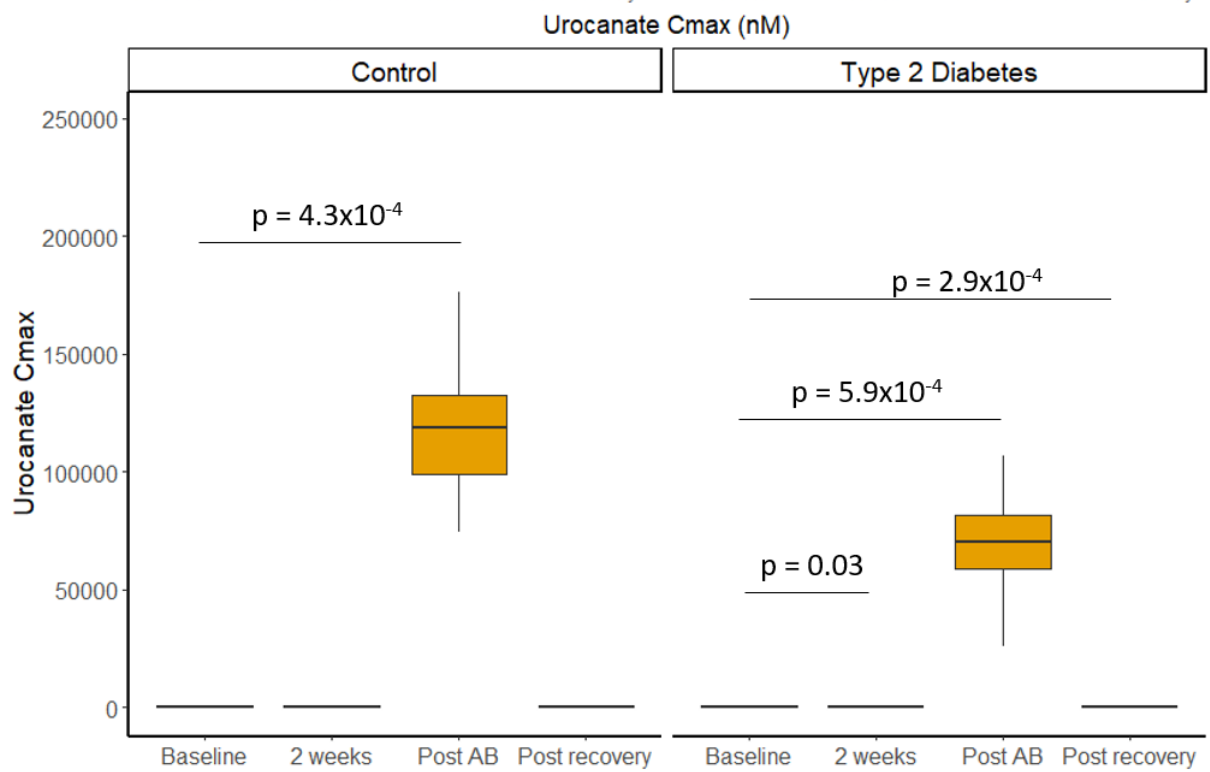
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B.

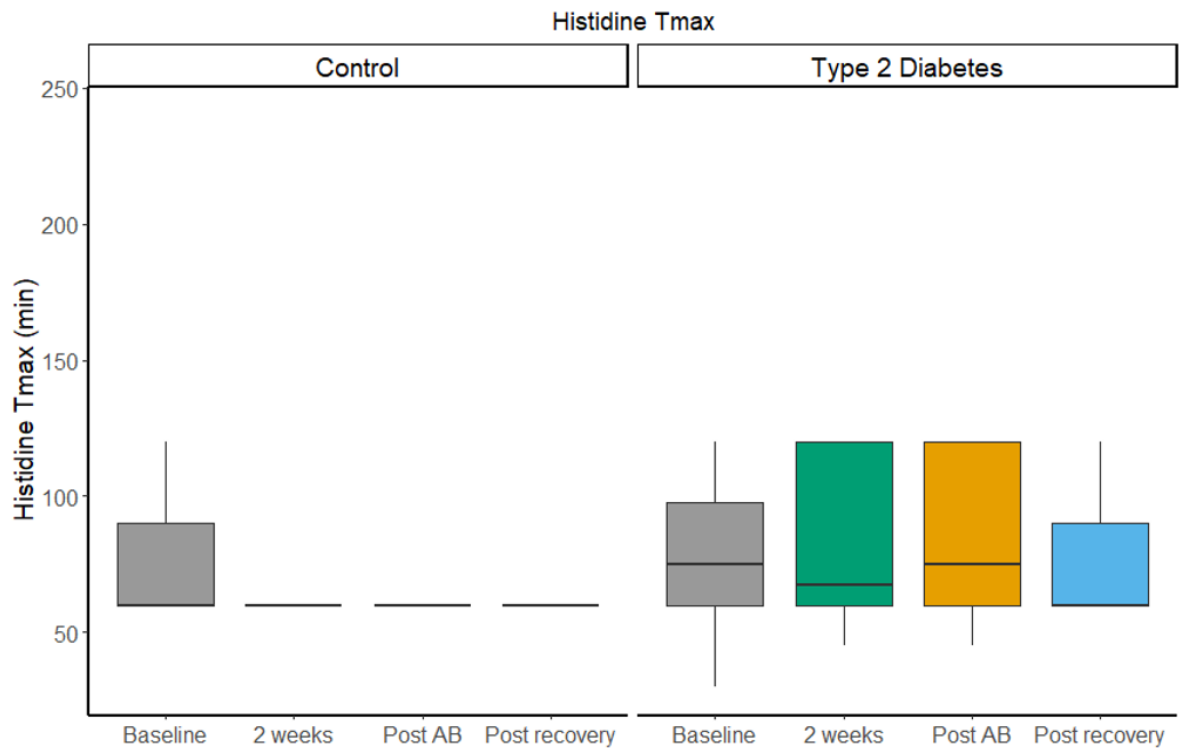


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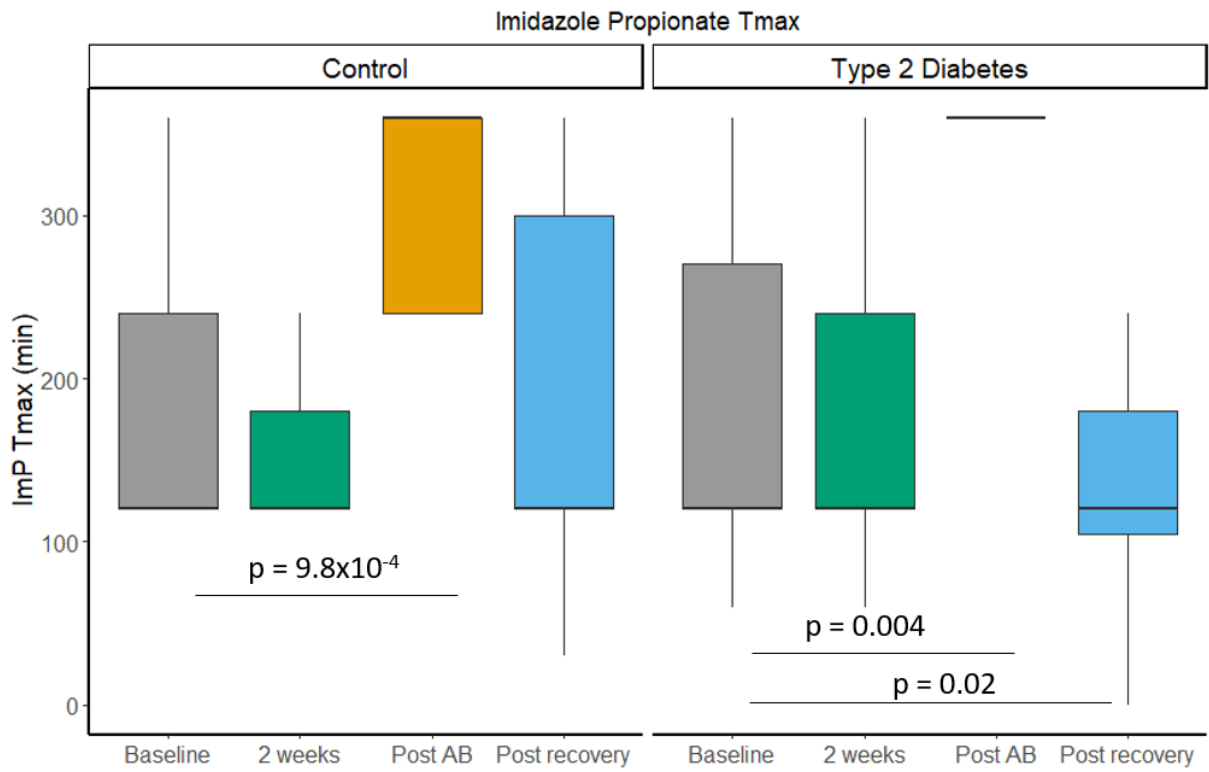


Supplementary Figure 4. Metabolite Cmax concentrations. A. Histidine Cmax. B. Imidazole Propionate Cmax C. Urocanate Cmax. Paired wilcox testing. FDR corrected p values.

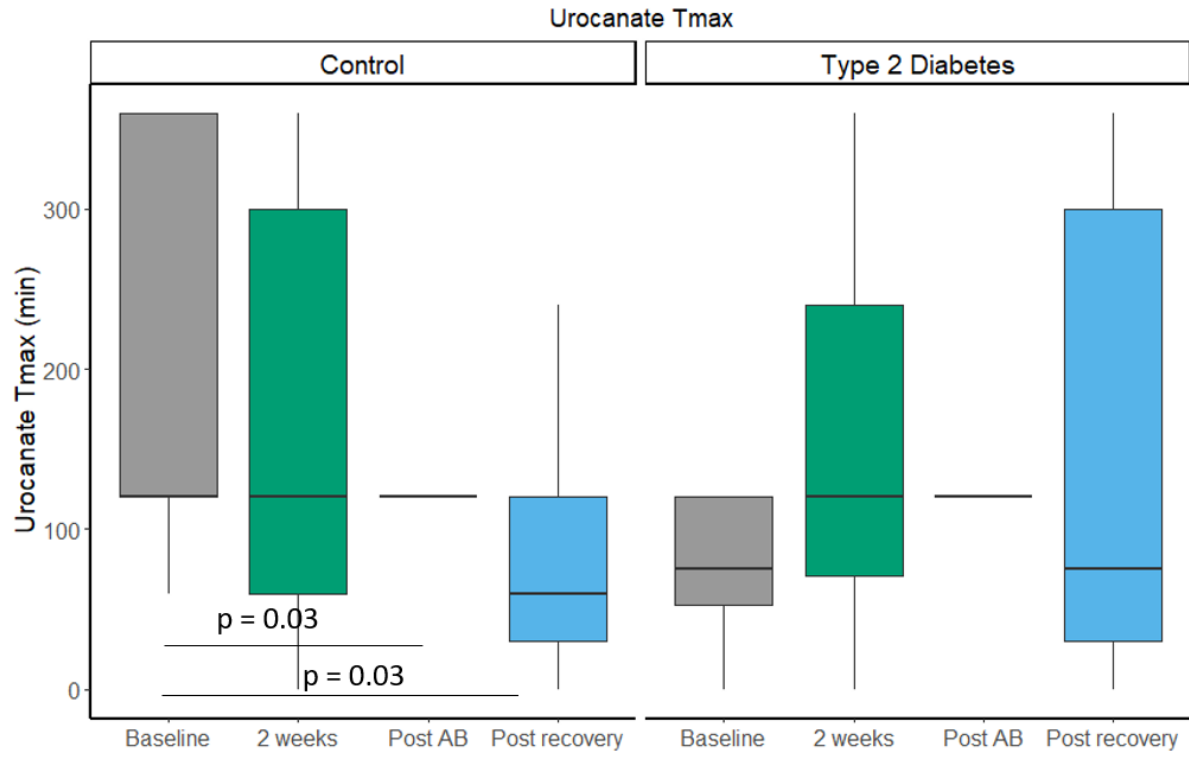
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B.

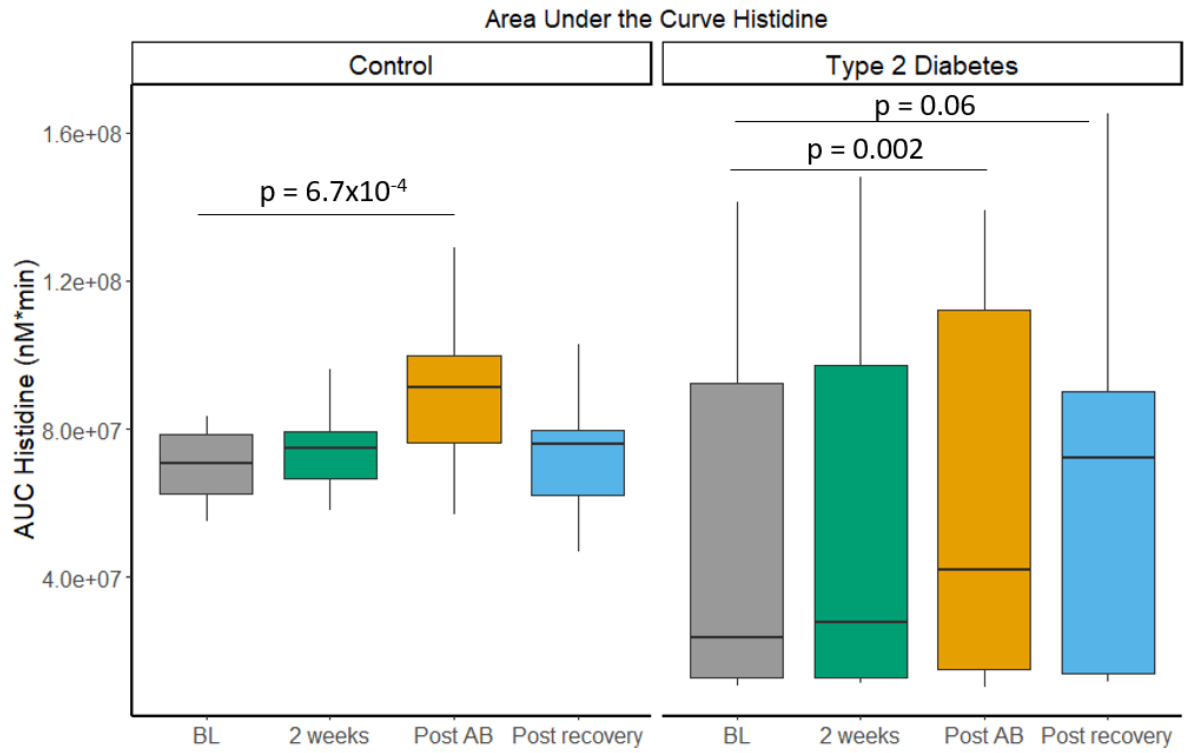


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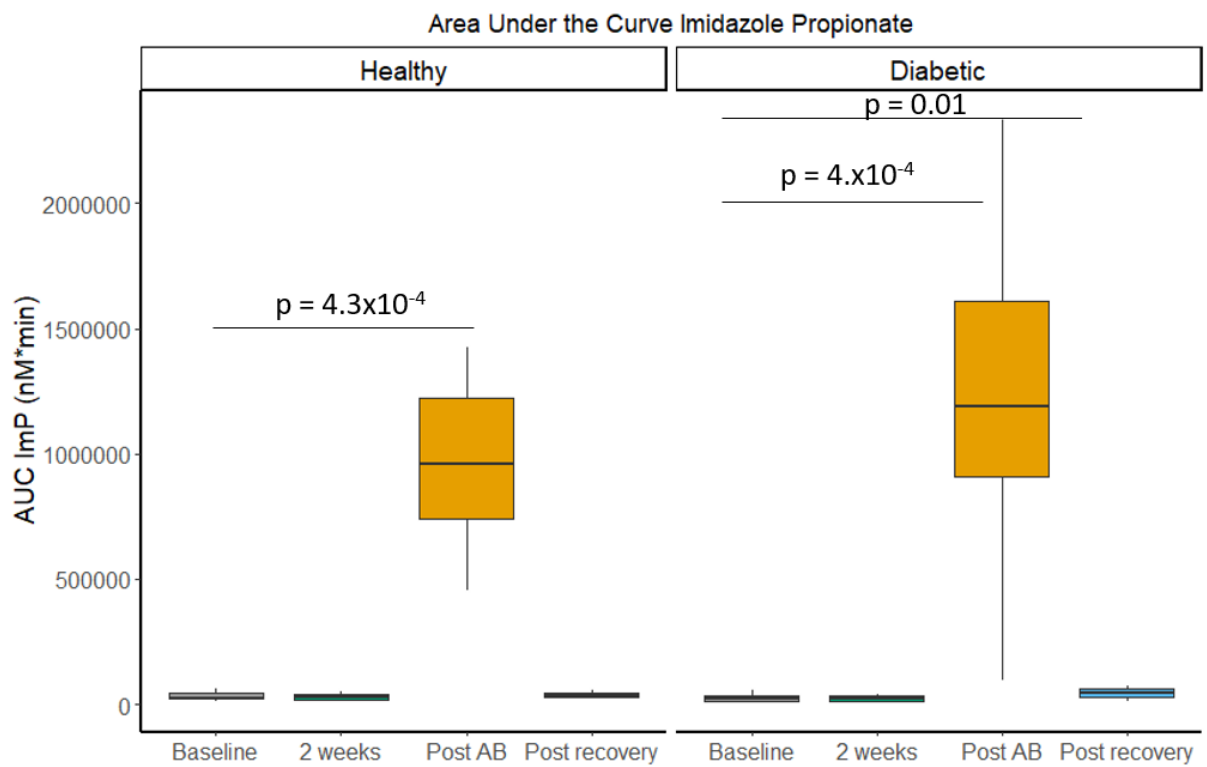


Supplementary Figure 5. Metabolite Tmax concentrations. A. Histidine Tmax. B. Imidazole Propionate Tmax C. Urocanate Tmax. Paired wilcox testing. FDR corrected p values.

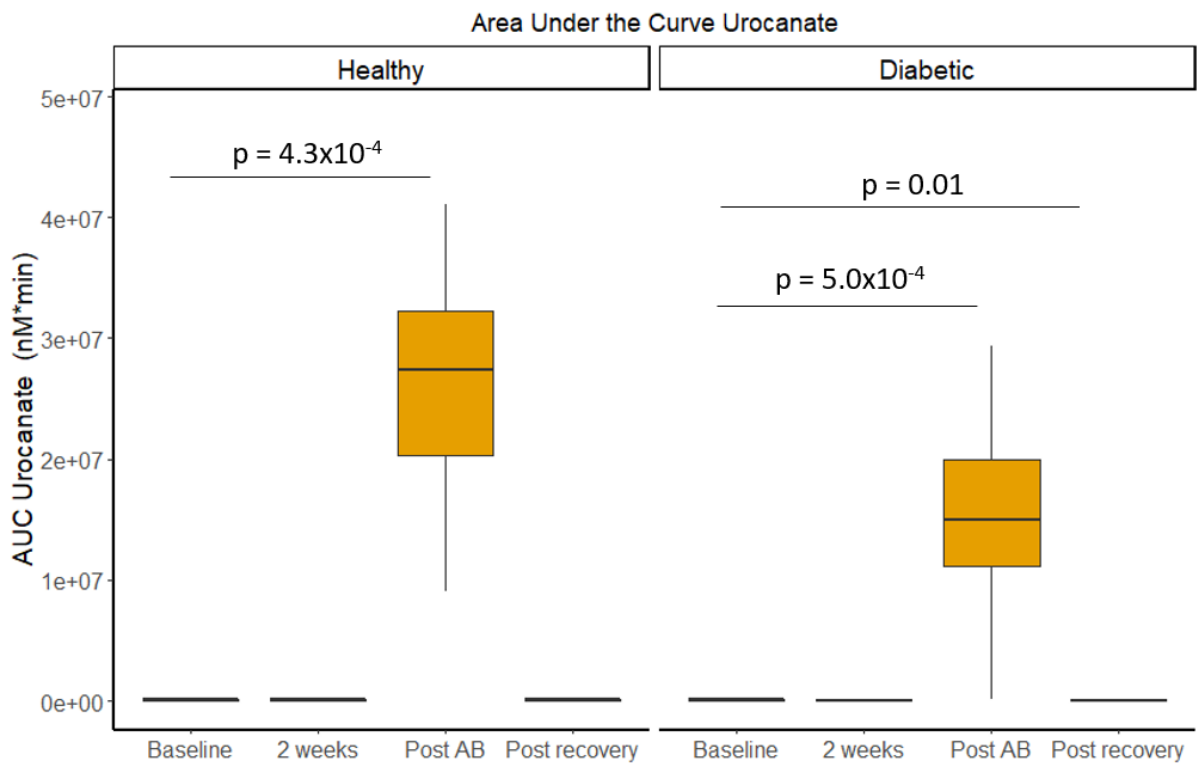
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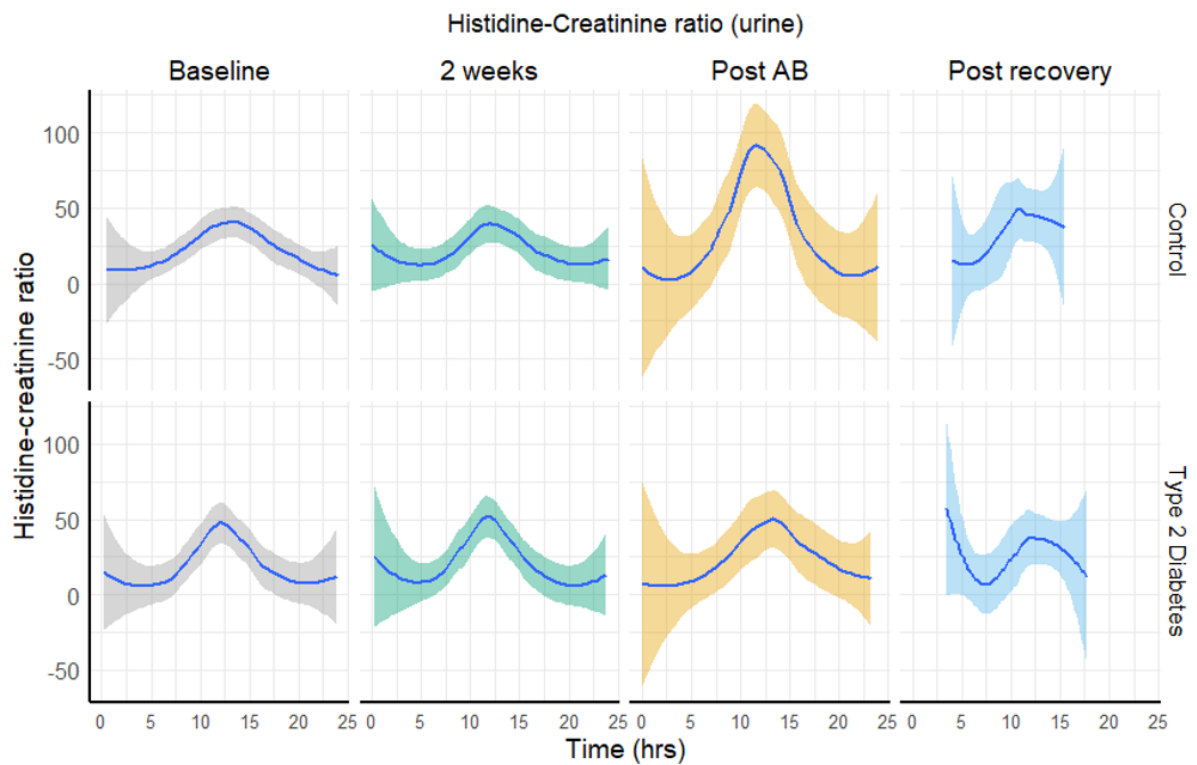


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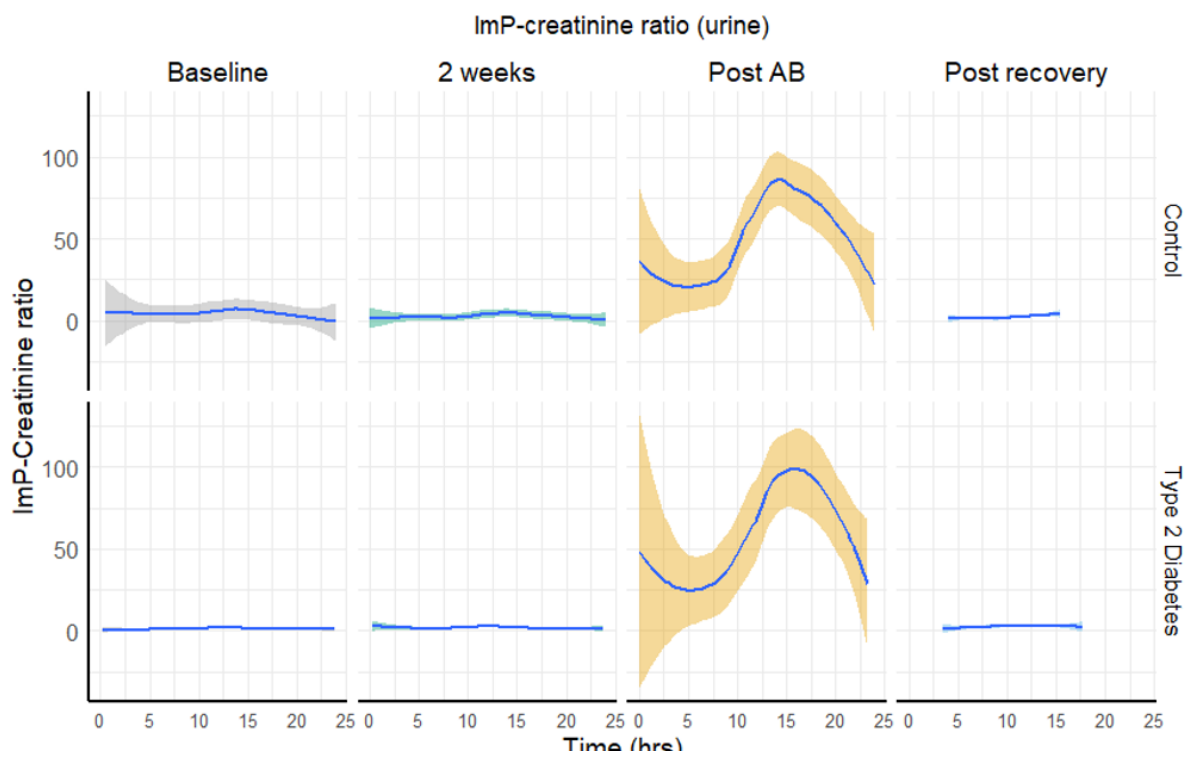


Supplementary Figure 6. Metabolite AUC concentrations. A. Histidine AUC. B. Imidazole Propionate AUC C. Urocanate AUC. Paired wilcox testing. FDR corrected p values.

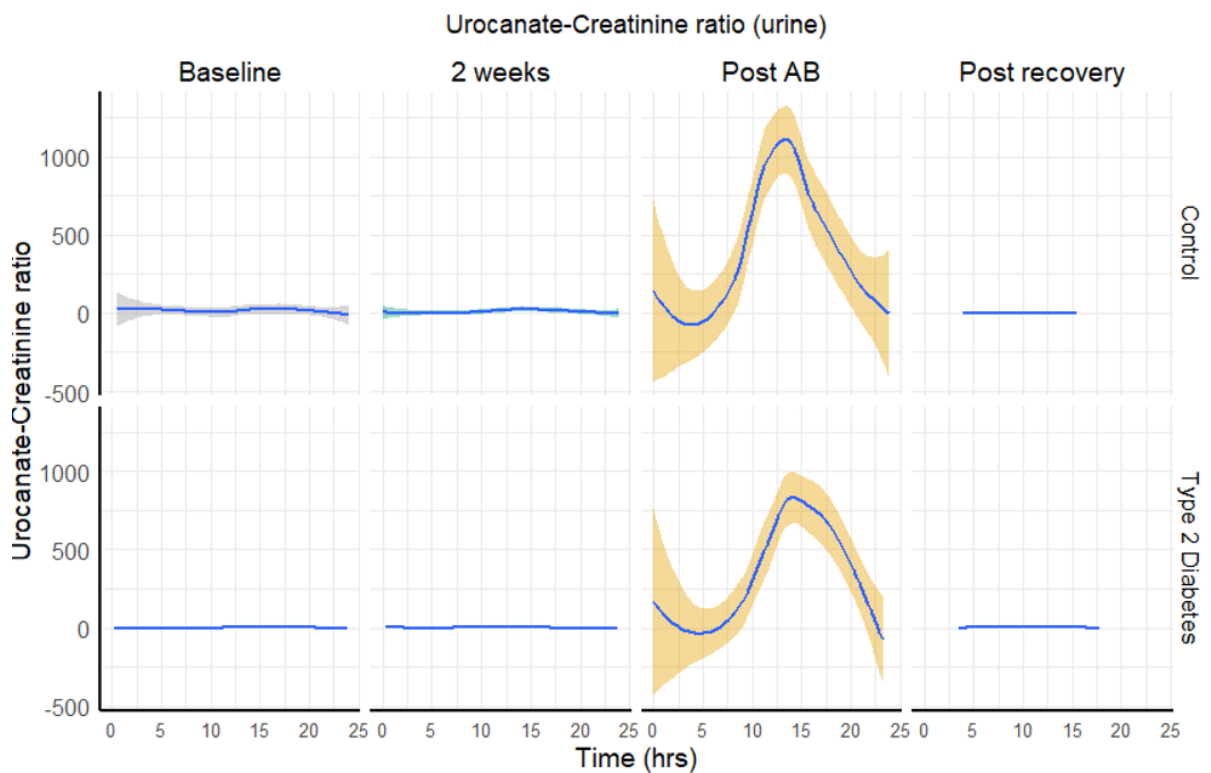
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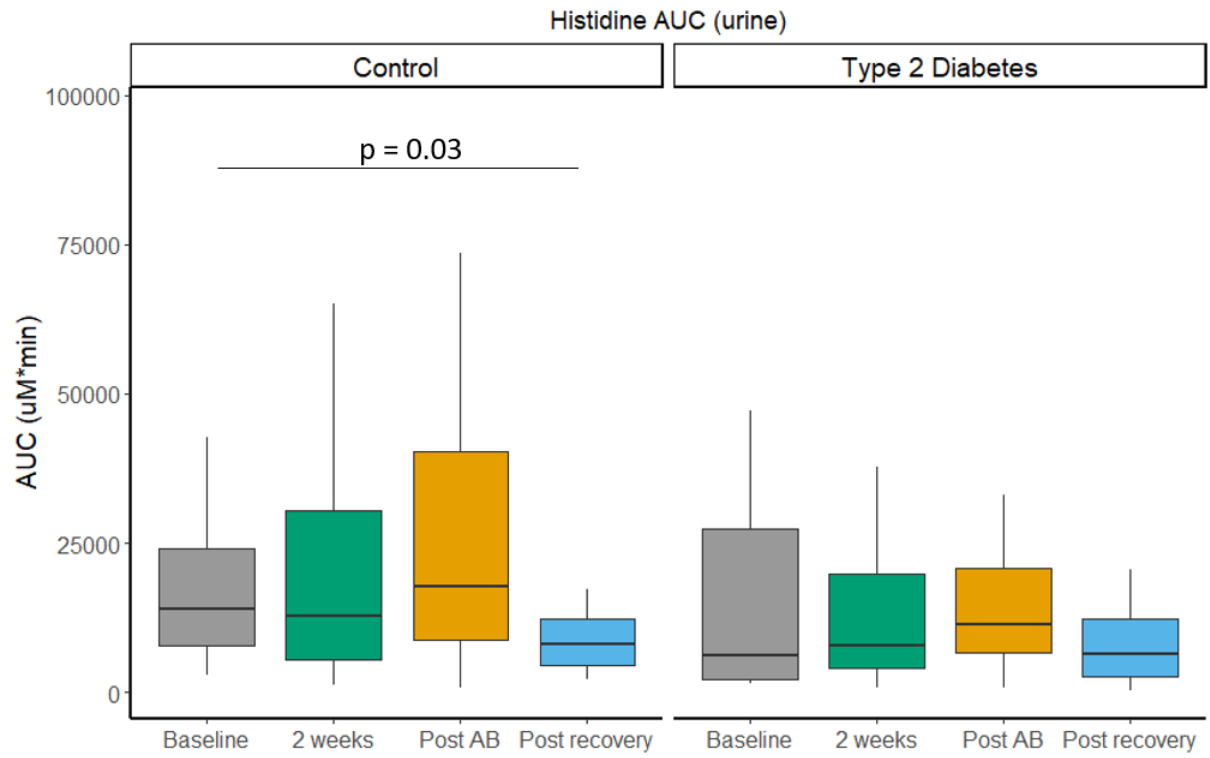


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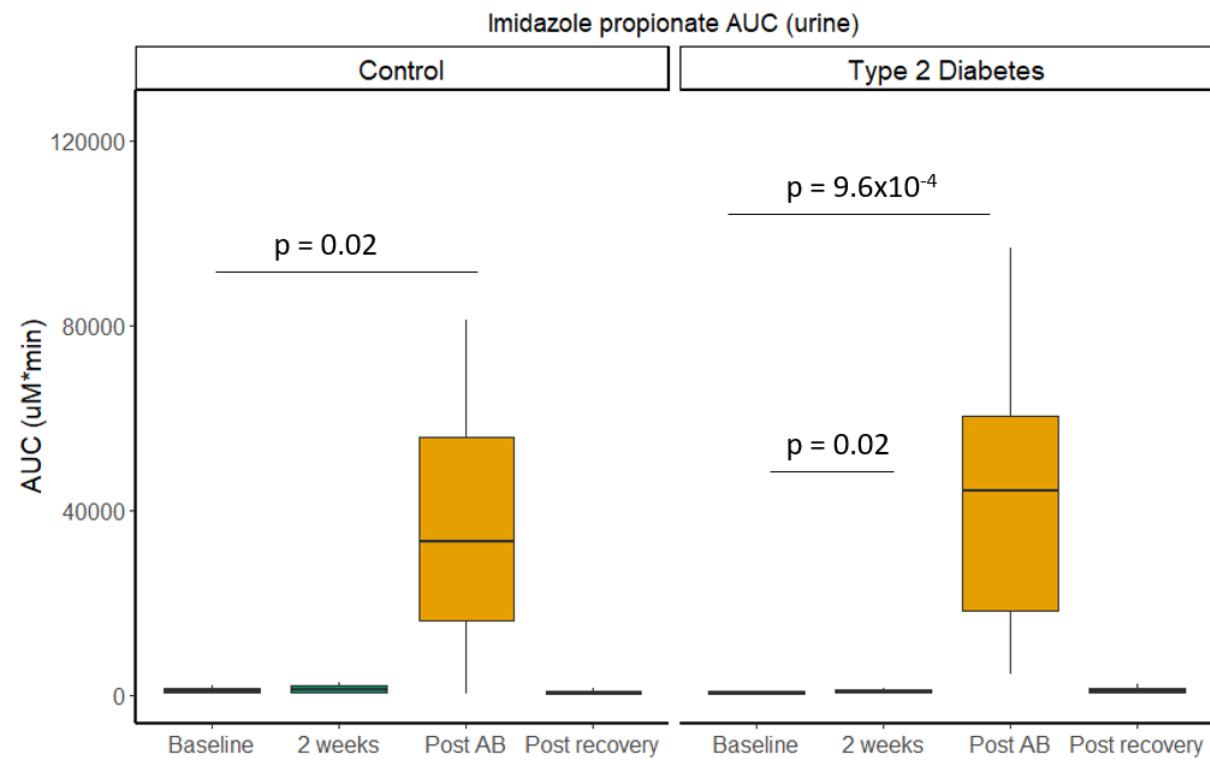


Supplementary Figure 7. Urine metabolite concentrations. A. Histidine-Creatinine ratio. B. Imidazole Propionate AUC C. Urocanate AUC. Data collected during 24 hrs after histidine challenge.

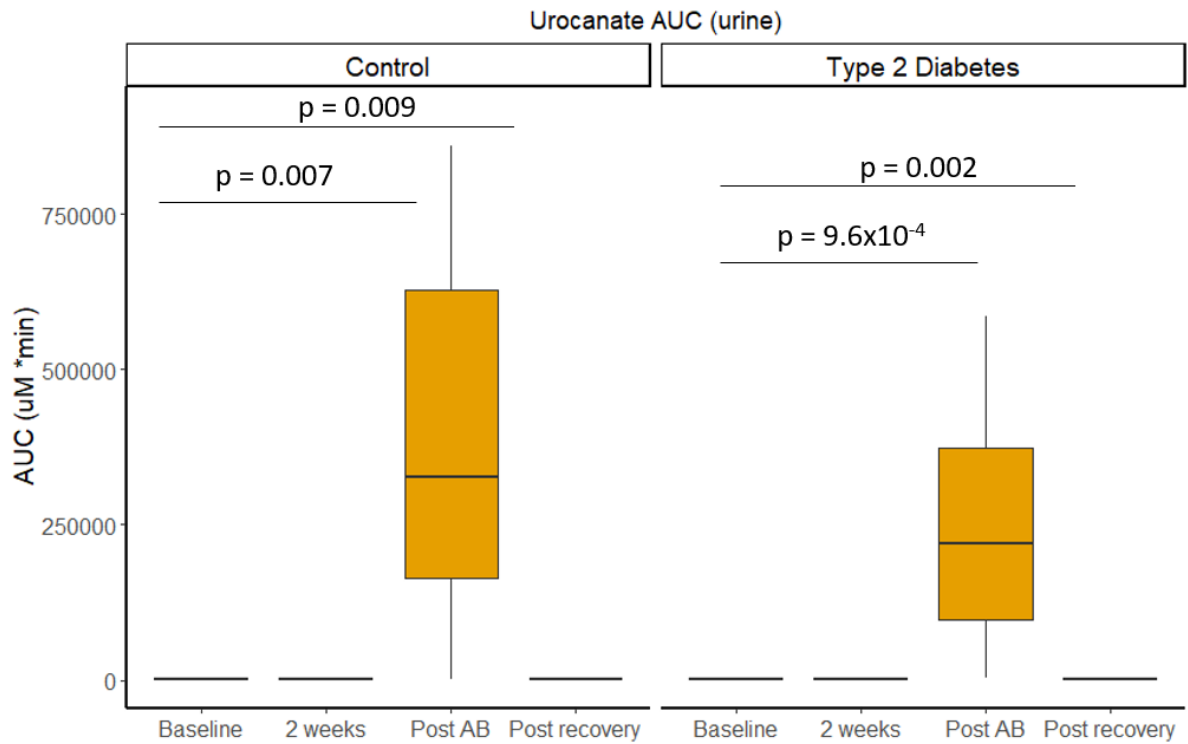
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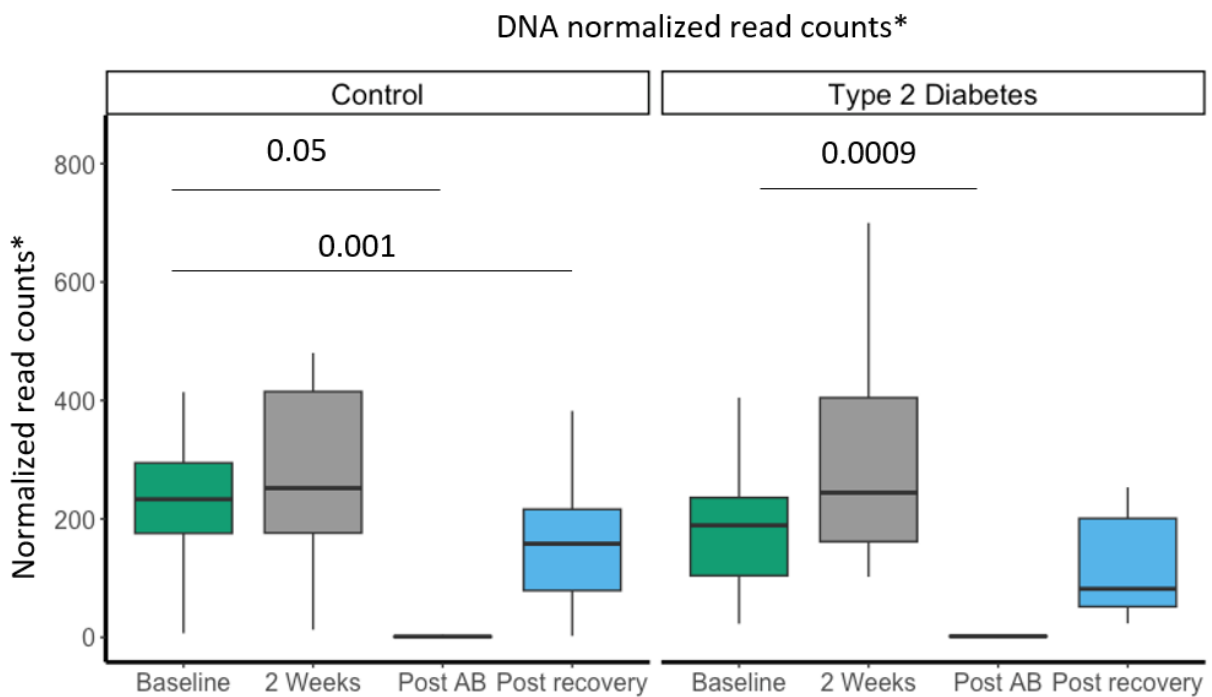


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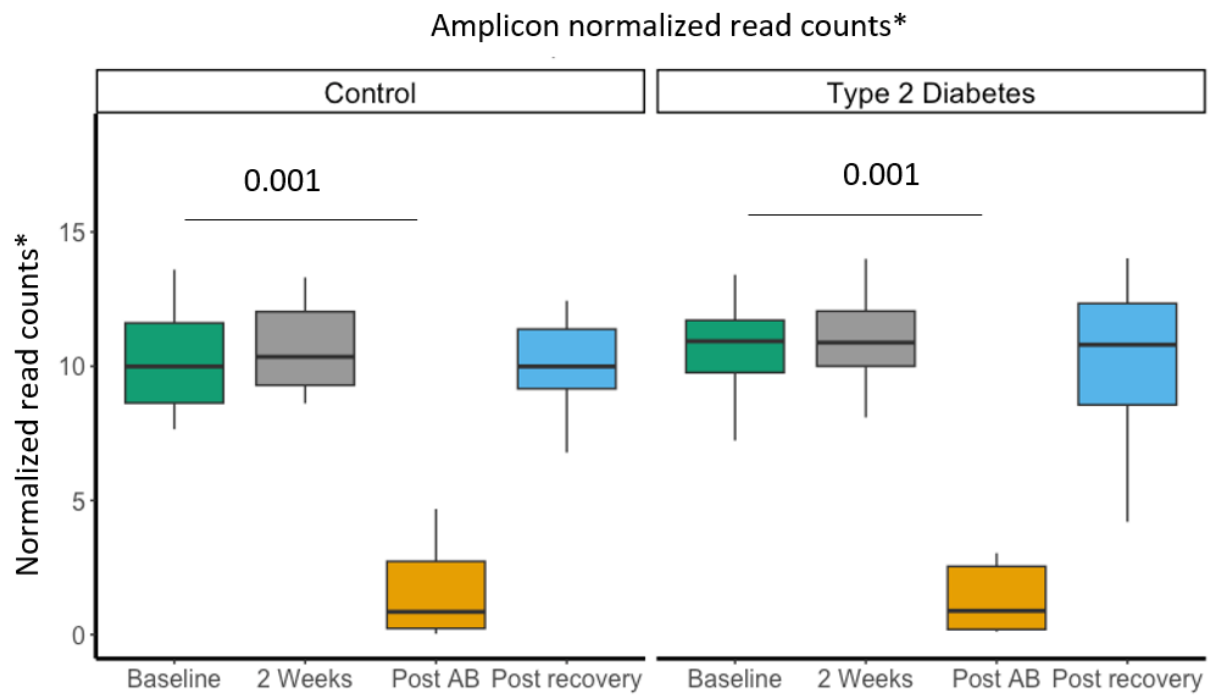
Supplementary Figure 8. Urine AUC metabolite concentrations. A. Histidine-Creatinine ratio. B. Imidazole Propionate AUC C. Urocanate AUC. Data collected during 24 hrs after histidine challenge. Paired wilcox testing. FDR corrected p values.

A.



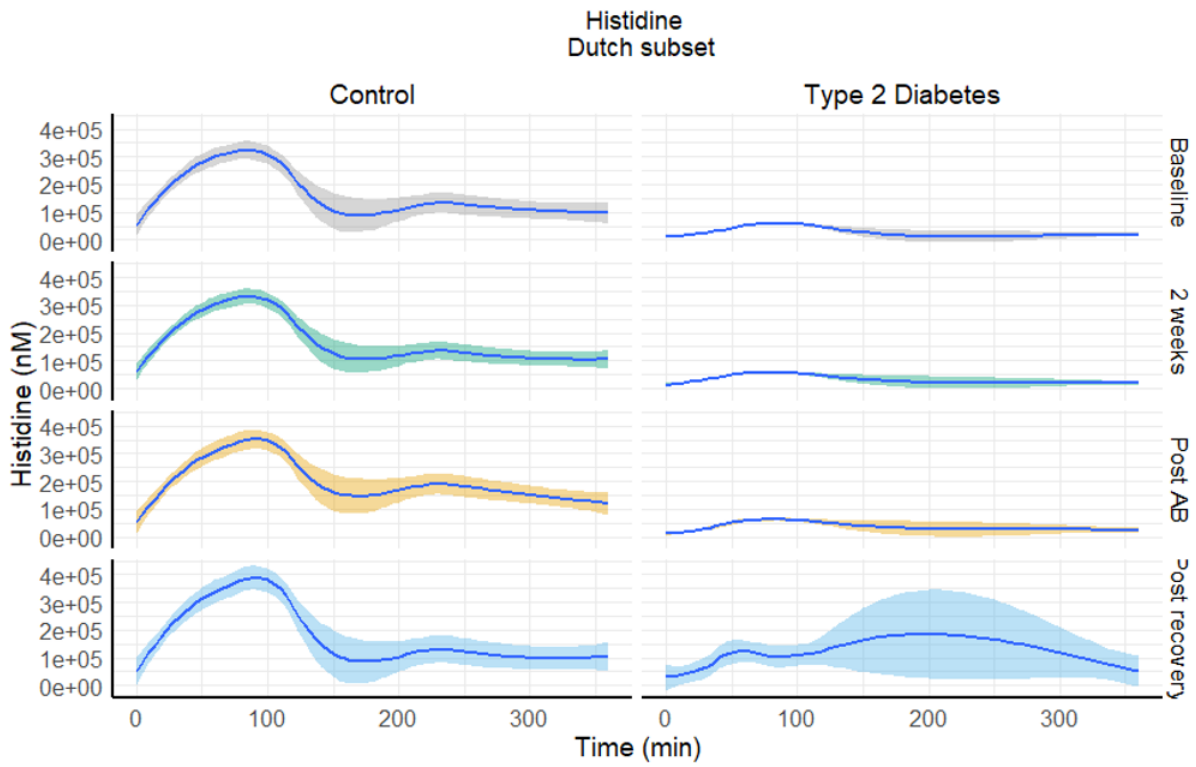
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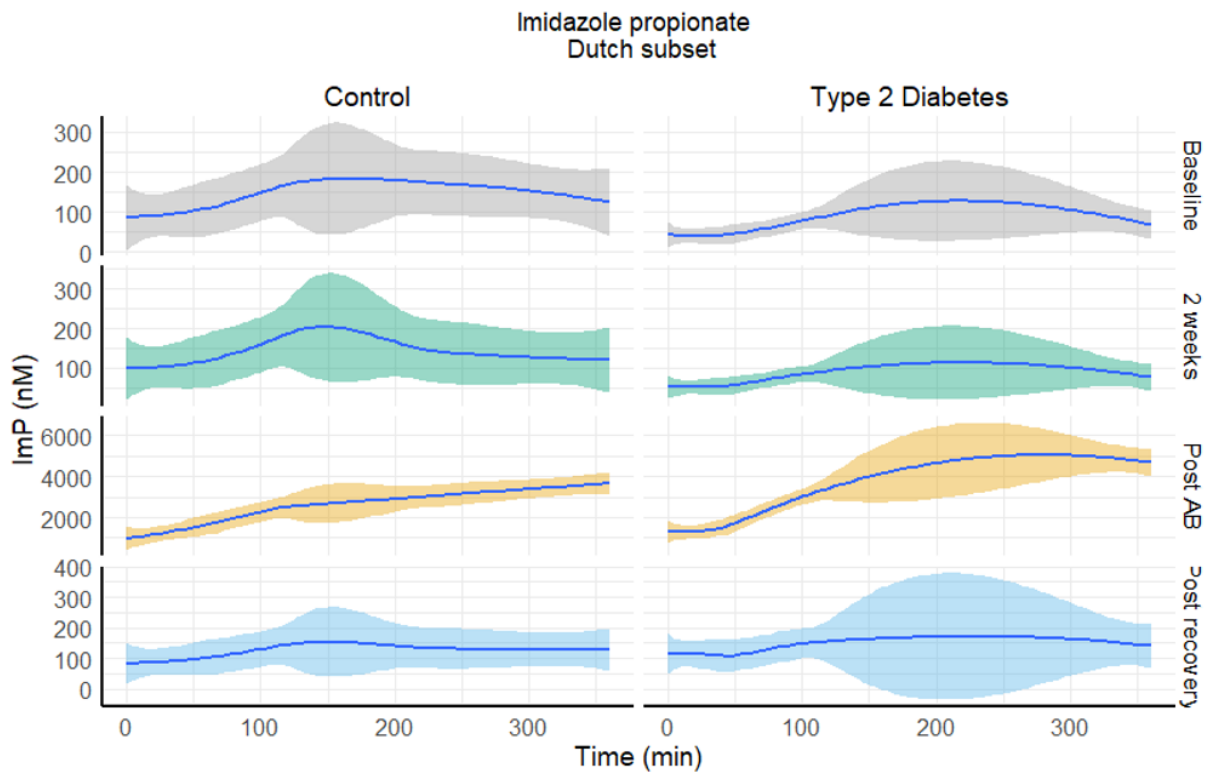


Supplementary Figure 9. Fecal DNA/Amplicon concentrations per visit. A. DNA normalized read counts B. Amplicon normalized read counts. *DNA and Amplicon normalized read counts. Normalized for DNA extraction, amplicon yield and input weight. Paired wilcox testing. FDR corrected p values.

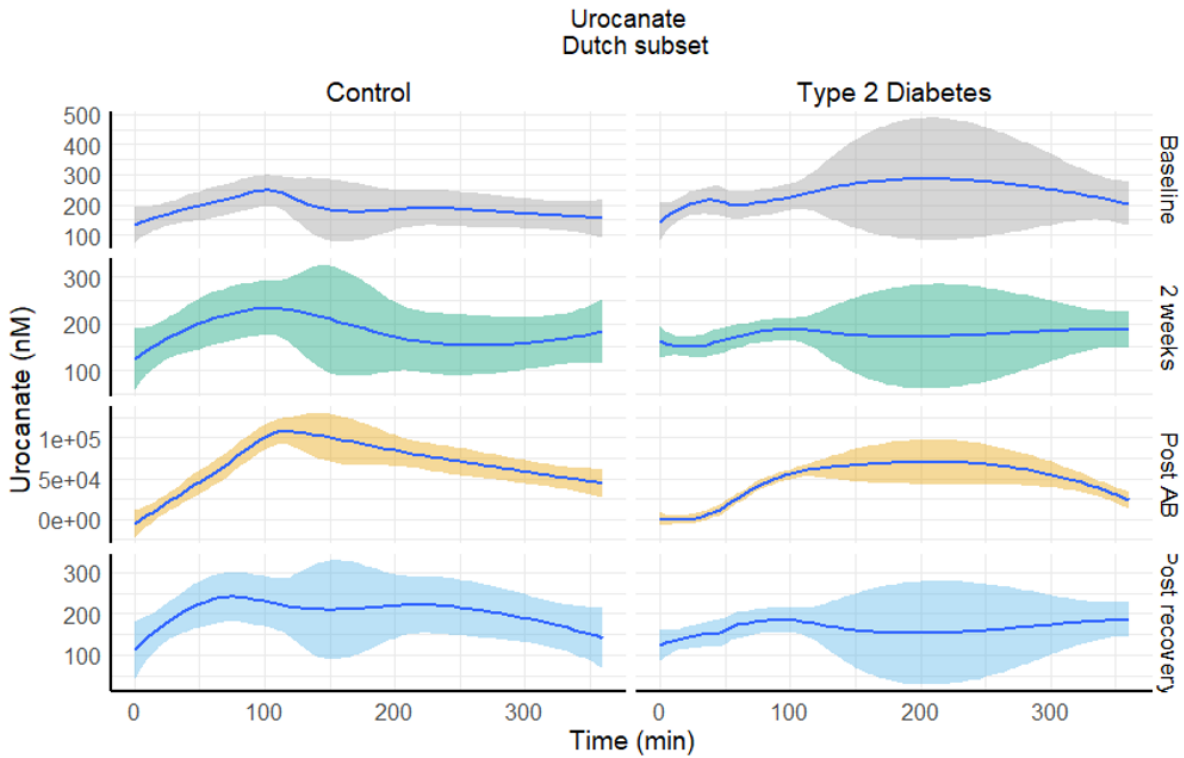
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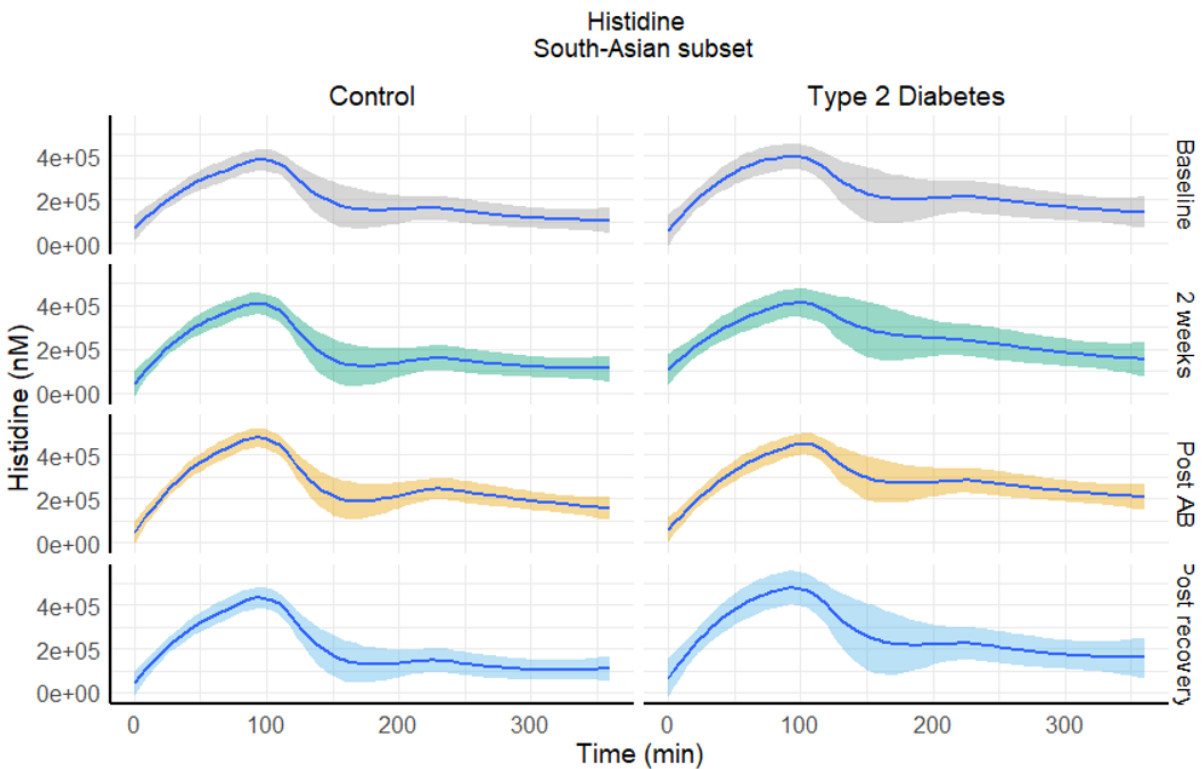


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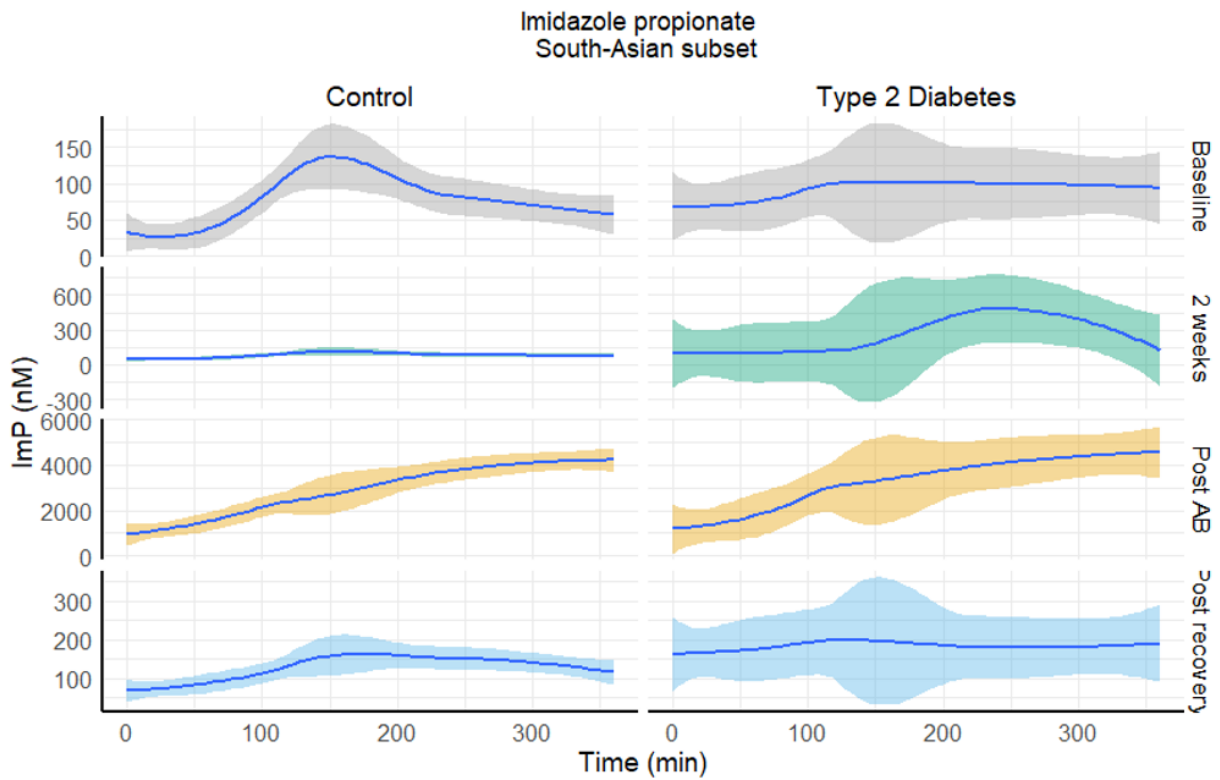


Supplementary Figure 10. Overview Metabolite kinetics in the Dutch subset (T2D: n = 10, control: n = 10) . A. Histidine B. Imidazole propionate. C. Urocanate Kinetics curves during 6 hours after histidine challenge measured by by ultra high performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) .

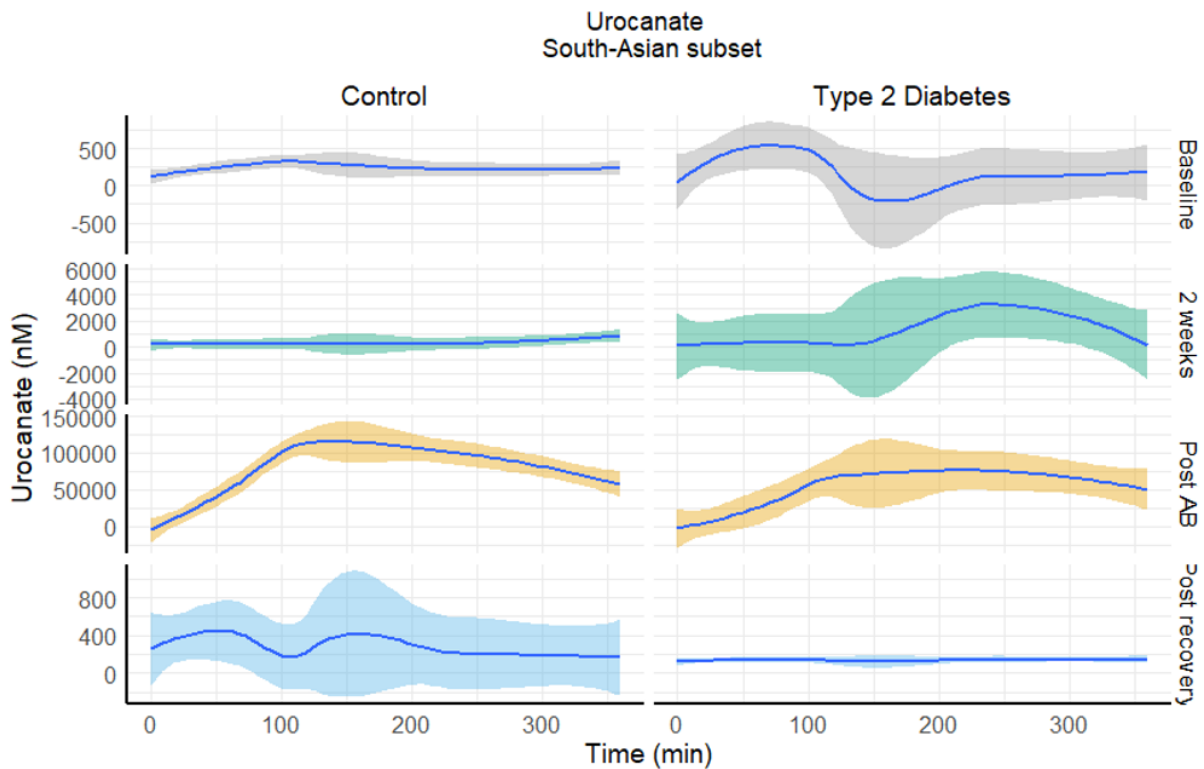
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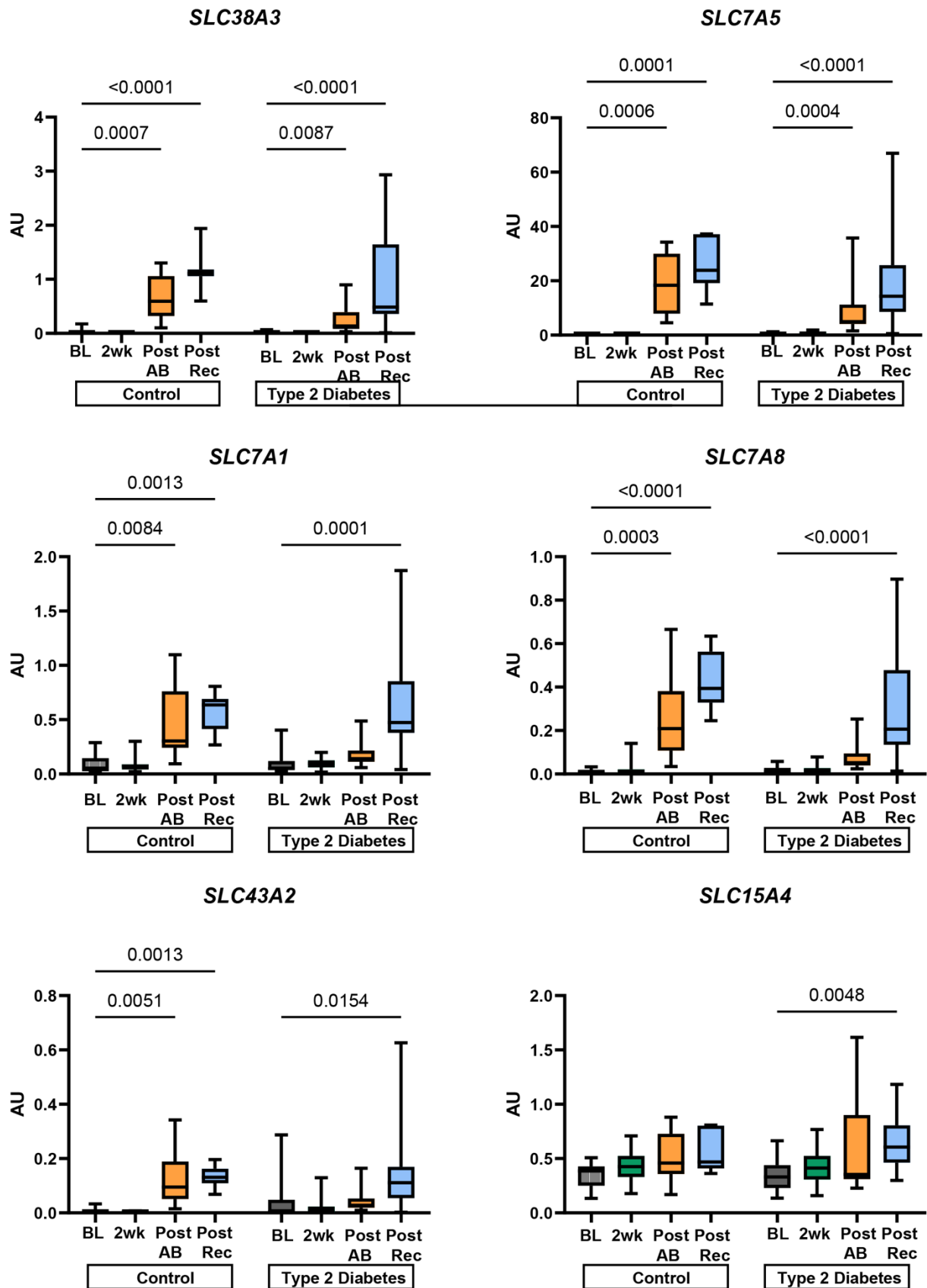
B.



C.



Supplementary Figure 11. Overview Metabolite kinetics in the South-Asian subset (T2D: n = 10, control: n = 9) . A. Histidine B. Imidazole propionate. C. Urocanate Kinetics curves during 6 hours after histidine challenge measured by by ultra high performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) .



Supplementary Figure 12. Amino acid transporters qPCR at baseline (BL), after 2 weeks of histidine (2 wk), Post Antibiotics (Post AB) and Post recovery (Post Rec).

