

Supplemental table 1. Differences in fasting metabolites (all) by CKD status in plasma. Metabolites in bold show hits controlling FDR at 10%, in a model that controls for age, sex, race (white versus not), and weight. Ordered by subclasses of metabolites followed by adjusted percent difference between CKD and controls and adjusted p-value for difference.

Metabolite	% Difference in CKD, compared with controls	p-value	q-value	Pathway
Cystine (241.1 / 120.0)	33	2.60E-09	1.52E-08	Amino Acid
Proline (116.1 / 70.0)	20	0.000195	0.000692	Amino Acid
2-Hydroxyisovaleric Acid (117.0 / 71.0)	47	0.000331	0.001139	Amino Acid
Tyrosine (182.1 / 136.0)	-13	0.000633	0.002014	Amino Acid
Serine (106.0 / 60.0)	-8	0.029507	0.065132	Amino Acid
Glycine (76.0 / 30.1)	13	0.032003	0.06842	Amino Acid
Leucine (132.1 / 86.0)	-5	0.067499	0.139499	Amino Acid
5-Aminovaleric Acid (118.0 / 55.0)	-4	0.127339	0.253324	Amino Acid
Threonine (120.1 / 74.0 (2))	-7	0.145125	0.281179	Amino Acid
Glutamine (147.1 / 84.0)	3	0.169291	0.318061	Amino Acid
Valine (118.1 / 72.0)	-4	0.201091	0.36138	Amino Acid
Arginine (175.1 / 70.0)	5	0.209045	0.362752	Amino Acid
Sarcosine (89.9 / 44.0)	-7	0.209395	0.362752	Amino Acid
Cadaverine (103.0 / 86.0)	4	0.281896	0.459935	Amino Acid
Histidine (156.1 / 110.0)	3	0.319987	0.495386	Amino Acid
Alanine (90.0 / 44.0)	5	0.330111	0.499193	Amino Acid
iso-Leucine (132.1 / 86.0 (2))	-3	0.336431	0.50262	Amino Acid
Phenylalanine (166.1 / 120.0)	2	0.461445	0.61526	Amino Acid
Methionine (150.1 / 61.0)	-3	0.516557	0.681415	Amino Acid
Pipecolate (130.0 / 84.0)	-2	0.633012	0.769544	Amino Acid

Asparagine (133.1 / 74.0)	1	0.718801	0.833003	Amino Acid
Glutamic acid (148.1 / 84.0)	-2	0.775118	0.873769	Amino Acid
Lysine (147.1 / 84.0 (2))	-1	0.854483	0.920769	Amino Acid
Aspartic Acid (134.1 / 74.0)	1	0.861365	0.920769	Amino Acid
Tyramine (138.1 / 77.0)	0	0.911781	0.942174	Amino Acid
3-Methyl-2-Oxovaleric Acid (129.0 / 101.0)	1	0.949731	0.967317	Amino Acid
isoValeric Acid (101.0 / 83.0)	0	0.952419	0.967317	Amino Acid
1/3-Methylhistidine (170.0 / 96.0)	206	1.60E-06	7.33E-06	Amino Acid (Histidine Metabolism)
Erythrose (119.0 / 71.0)	-1	0.69296	0.810632	Amino Acid (Phenylalanine Metabolism, others)
N-AcetylGlycine (116.0 / 74.0)	20	0.18008	0.331568	Amino Acid metabolism
Glycerate (105.0 / 75.0)	-8	0.015263	0.037853	Amino Acid metabolism/Gly, Ser
Guanidinoacetate (116.0 / 74.0 (2))	-15	0.002021	0.005696	Amino Acid metabolism/Gly, Ser,Thr
MethylSuccinate (131.0 / 87.0 (3))	-3	0.458717	0.61526	Amino Acid metabolism/Isoleu
Shikimic Acid (173.0 / 93.0)	99	1.30E-06	6.05E-06	Amino Acid metabolism/Phe, Tyr,Trp
Anthranilate (136.0 / 118.0)	0	0.792699	0.877631	Amino Acid metabolism/Trp, Phe, Tyr
Homogentisate (167.0 / 123.0)	37	2.20E-16	2.75E-15	Amino Acid metabolism/Tyr
Citraconic Acid (129.0 / 85.0)	-17	0.220914	0.375251	Amino Acid metabolism/Val, Leu, IL
Pentothenate (218.1 / 88.0)	41	0.024886	0.057146	Amino acids metabolism/alanine, CoA
Creatinine (114.1 / 44.0)	97	<1 E-16	<1 E-16	Amino acids metabolism/Arg, Gly
Creatine (132.1 / 90.0)	-11	0.32317	0.495386	Amino acids metabolism/Arg, Gly
Cystamine (153.0 / 108.0)	138	6.70E-11	4.4E-10	Amino acids metabolism/Cys
Homocysteine (136.0 / 90.0)	-1	0.670888	0.799905	Amino acids metabolism/Cys, Met
Betaine (118.0 / 58.0)	-11	0.070798	0.143918	Amino acids metabolism/Gly,Ser, Thr metabolism
1-Methylhistamine (126.0 / 96.0)	70	0.001023	0.003171	Amino acids metabolism/His
Carnitine (162.1 / 85.0)	11	0.015197	0.037853	Amino acids metabolism/Lys
2-Aminoadipate (160.1 / 116.0)	17	0.02994	0.065132	Amino acids metabolism/Lys
Hydroxyproline/Aminolevulinate (132.1 / 86.2)	61	5.20E-06	2.23E-05	Amino acids metabolism/Pro

Taurine (126.0 / 108.0)	3	0.61843	0.766853	Amino acids metabolism/Sulfur metabolism
Aminoisobutyrate (104.1 / 86.0)	46	<1 E-16	<1 E-16	Amino acids metabolism/Val, Leu, iso-Leu
OH-Phenylpyruvate (179.0 / 89.0 (4))	100	<1 E-16	<1 E-16	Amino acids metabolites/phe, tyr
Pyroglutamic Acid (130.0 / 83.4)	-3	0.403721	0.56888	Amino acids/Glu
Glutaric Acid (131.0 / 87.0)	0	0.995051	0.995051	Amino Acids/lys, trp, fatty acids
Glucuronate (193.0 / 73.0)	160	<1 E-16	<1 E-16	Amino sugar and nucleotide sugar metabolism
2-Hydroxyglutarate (147.0 / 129.0)	36	3.90E-13	3.03E-12	Amino-acid metabolism & Glycine/Serine/Threonine metabolism
Glycochenodeoxycholate (448.3 / 74.0)	58	0.023639	0.055307	Bile acid metabolism
Adipic Acid (144.9 / 83.0)	71	1.20E-08	6.84E-08	Caprolactam degradation
Margaric Acid (269.1 / 251.3)	32	4.60E-06	2.04E-05	Fatty acid metabolism
Azelaic Acid (187.0 / 125.0)	26	8.50E-06	3.51E-05	Fatty acid metabolism
Acetylcarnitine (204.1 / 85.0)	40	0.000025	0.000101	Fatty acid metabolism
Linoleic Acid (277.1 / 259.0)	6	0.370305	0.540209	Fatty acid metabolism
Linolenic Acid (279.1 / 261.0)	6	0.382243	0.551141	Fatty acid metabolism
Myristic Acid (227.1 / 209.0)	3	0.644233	0.775581	Fatty acid metabolism
G1P/G6P/F6P/F1P (259.0 / 97.0)	-6	0.442312	0.609407	Glycolysis
lactate (89.0 / 43.0)	-2	0.751667	0.855107	Glycolysis
Pyruvate (87.0 / 43.0)	-3	0.610291	0.766853	Glycolysis/amino acids metabolism
Glucose (179.0 / 89.0)	3	0.226124	0.37891	Glycolysis/sugar
Oxalic Acid (89.0 / 61.0)	-7	0.21063	0.362752	Glyoxylate and dicarboxylate metabolism
Hippuric Acid (178.0 / 134.0)	92	0.001118	0.003381	Gut flora metabolism
Trimethylamine-N-oxide (TMAO) (76.1 / 58.0)	87	0.000426	0.001427	Gut flora metabolism / Redox
Trimethylamine (TMA) (60.0 / 44.0)	12	0.015729	0.038243	Gut flora metabolism / Redox
Acetoacetate (101.0 / 57.0)	17	0.035694	0.075018	Ketone
Deoxycarnitine (147.1 / 87.0)	31	0.000041	0.000159	Lipids/phospholipids, ligand
Acetylcholine (146.1 / 87.0)	40	0.001586	0.004574	Lipids/phospholipids, ligand
4-Hydroxybutyrate (105.0 / 77.0)	6	0.287883	0.463603	Lipids/phospholipids, ligand

13-HODE (295.2 / 195.0)	-6	0.448328	0.610909	Lipids/phospholipids, ligand
Arachidonate (303.3 / 59.0)	1	0.897609	0.942174	Lipids/phospholipids, ligand
Propionate (73.0 / 55.0)	44	3.80E-07	2.02E-06	Nicotinate and nicotinamide metabolism
Benzoic acid (121.0 / 77.0 (2))	17	0.013665	0.035302	Nicotinate and nicotinamide metabolism
Hypoxanthine (135.0 / 92.0)	6	0.61812	0.766853	Nucleotide
Xanthine (151.0 / 108.0)	4	0.741114	0.850909	Nucleotide
AMP (346.1 / 79.0)	2	0.904707	0.942174	Nucleotide
Allantoin (157.0 / 114.0)	28	4.70E-07	2.45E-06	Nucleotide Degredation
Oxypurinol (151.0 / 42.0)	6	0.59729	0.763547	Nucleotide metabolism
Inositol (179.0 / 87.0)	95	<1 E-16	<1 E-16	Nucleotide/Purine metabolism
Urate (167.0 / 124.0)	36	2.20E-16	2.75E-15	Nucleotide/Purine metabolism
1-Methyladenosine (282.0 / 150.1)	42	2.20E-16	2.75E-15	Nucleotide/Purine metabolism
Xanthosine (283.1 / 151.0)	74	1.30E-15	1.38E-14	Nucleotide/Purine metabolism
ADP (426.0 / 134.0)	-10	0.39629	0.564827	Nucleotide/Purine metabolism
IMP (347.0 / 79.0)	-8	0.626479	0.769143	Nucleotide/Purine metabolism
Adenylosuccinate (462.1 / 79.0)	2	0.814015	0.887087	Nucleotide/Purine metabolism
Orotate (155.0 / 111.0)	6	0.010402	0.028041	Nucleotide/Pyrimidine metabolism
Cytidine (244.1 / 112.0)	37	0.013231	0.034907	Nucleotide/Pyrimidine metabolism
Uridine (245.1 / 113.1)	-13	0.01946	0.046405	Nucleotide/Pyrimidine metabolism
2/3-Phosphoglyceric Acid (185.0 / 97.0)	-3	0.815548	0.887087	Nucleotide/Pyrimidine metabolism
Ribose-5-P (229.0 / 79.0)	-3	0.529256	0.690818	Pentose phosphate pathway
Sorbitol (183.0 / 91.0)	-12	0.000603	0.001967	Sugar
Sucrose (341.0 / 59.0 (2))	-5	0.181827	0.331568	Sugar
Glyceraldehyde (89.0 / 59.0)	2	0.789328	0.877631	Sugar
Lactose (341.0 / 59.0)	170	0.000084	0.000317	Sugar/Galactose
Mannose (181.0 / 99.0)	0	0.877014	0.929485	Sugar/Galactose Metabolism
Fructose (179.0 / 89.0 (3))	210	7.80E-12	5.35E-11	Sugars
N-Acetylneuraminate (308.1 / 87.0)	79	3.80E-10	2.33E-09	Sugars

Fumaric Acid (114.9 / 71.0)	270	6.70E-16	7.51E-15	TCA Cycle
Oxaloacetate (131.0 / 87.0 (2))	104	7.80E-14	6.92E-13	TCA Cycle
3HBA (103.0 / 59.0)	-14	0.31398	0.495386	TCA Cycle
Succinate (117.0 / 73.0)	3	0.587637	0.759031	TCA Cycle
Alpha-Ketoglutaric Acid (145.0 / 101.0)	1	0.6868	0.810632	TCA Cycle
Malonic Acid (103.0 / 41.0)	1	0.959516	0.967317	TCA Cycle
L-Kynurenine (209.1 / 94.0)	43	9.80E-14	8.08E-13	Tryptophan Cycle
Tryptophan (205.1 / 146.0)	-18	1.00E-06	5.12E-06	Tryptophan Cycle
3-Hydroxykynurenine (225.2 / 110.1)	2	0.419367	0.584287	Tryptophan Cycle
Xanthurenate (204.0 / 160.0)	-13	0.000111	0.000405	Tryptophan Cycle/Amino Acid metabolism
Kynurenate (188.0 / 143.8)	-6	0.250437	0.414056	Tryptophan Cycle/Amino Acid metabolism
Geranyl Pyrophosphate (313.1 / 79.1)	-7	0.128705	0.253324	Ubiquinone and other terpenoid-quinone biosynthesis
Citrulline (174.0 / 131.0)	45	2.10E-14	2.03E-13	Urea Cycle
Ornithine (133.1 / 70.0)	13	0.004032	0.01111	Urea cycle
Choline (104.1 / 60.0)	35	<1 E-16	<1 E-16	Vitamins
Methylmalonate (117.0 / 73.0 (2))	108	<1 E-16	<1 E-16	Vitamins
Ascorbic Acid (Vit. C) (175.0 / 87.0)	94	4.20E-13	3.03E-12	Vitamins
Dimethylglycine (104.1 / 58.0)	-20	0.0013	0.003838	Vitamins
Biotin (243.1 / 200.0)	-12	0.026903	0.060654	Vitamins
Niacinamide (123.0 / 80.0)	-8	0.323599	0.495386	Vitamins
Pyridoxal-5-P (246.0 / 96.9)	-4	0.165999	0.316674	Vitamins/B6
4-Pyridoxic acid (182.1 / 138.0)	-1	0.356444	0.52618	Vitamins/B6

Supplemental table 2. Pathway analysis comparing fasting differences between CKD and controls. Abbreviations: FDR=false discovery rate. Pathways in bold represent pathways involving the mitochondria and NAD synthesis.

	Total Cmpd	Hits	Raw p	-log(p)	Holm adjust	FDR	Impact
Ubiquinone and other terpenoid-quinone biosynthesis	36	3	8.72E-48	108.36	5.06E-46	5.06E-46	0.11976
Tyrosine metabolism	76	8	4.50E-17	37.64	2.56E-15	1.30E-15	0.14651
Arginine and proline metabolism	77	15	9.59E-17	36.883	5.37E-15	1.85E-15	0.55335
Inositol phosphate metabolism	39	1	2.99E-13	28.84	1.64E-11	4.33E-12	0.13703
Citrate cycle (TCA cycle)	20	5	2.74E-12	26.624	1.48E-10	3.18E-11	0.33876
Glycerophospholipid metabolism	39	2	6.63E-12	25.739	3.52E-10	6.41E-11	0.0212
Ascorbate and aldarate metabolism	45	4	3.58E-11	24.053	1.86E-09	2.97E-10	0.13047
Phenylalanine, tyrosine and tryptophan biosynthesis	27	6	2.24E-10	22.218	1.14E-08	1.58E-09	0.1802
Pyrimidine metabolism	60	6	2.46E-10	22.127	1.23E-08	1.58E-09	0.07727
Galactose metabolism	41	7	6.70E-10	21.124	3.28E-08	3.88E-09	0.08046
Tryptophan metabolism	79	5	1.68E-09	20.205	8.06E-08	8.85E-09	0.20303
Butanoate metabolism	40	8	1.93E-09	20.064	9.09E-08	9.34E-09	0.20122
Glycine, serine and threonine metabolism	48	13	7.54E-09	18.703	3.47E-07	3.22E-08	0.53414
Phenylalanine metabolism	45	7	7.76E-09	18.674	3.49E-07	3.22E-08	0.19802
Nicotinate and nicotinamide metabolism	44	5	1.28E-08	18.176	5.62E-07	4.94E-08	0.03827

Supplemental table 3. Associations of plasma (LC-MS) metabolites with insulin/glucose infusion. Results from regressing log-transformed metabolites on sample type (clamp v. fasting), adjusted for age, sex, race (White/non-white), weight, and batch. An FDR of 10% was used to determine significance (in bold). Percent fold change is the adjusted percent change in metabolite associated with the clamp procedure, compared with fasting levels (e.g., a % fold change of -20 would indicate a 20% reduction in metabolite level)

Metabolite	Clamp v. fasting			Metabolite group
	% Fold change (95% CI)	p-value	q-value	
Glycine (76.0 / 30.2)	-7 (-8, -6)	<1 E-16	<1 E-16	Amino Acid
Alanine (90.0 / 44.0)	-9 (-11, -8)	<1 E-16	<1 E-16	Amino Acid
Serine (106.0 / 60.0)	-12 (-13, -11)	<1 E-16	<1 E-16	Amino Acid
Proline (116.1 / 70.0)	-14 (-15, -13)	<1 E-16	<1 E-16	Amino acid
Valine (118.1 / 72.0)	-16 (-17, -15)	<1 E-16	<1 E-16	Amino Acid
Threonine (120.1 / 74.0)	-16 (-17, -15)	<1 E-16	<1 E-16	Amino Acid
Leucine (132.1 / 86.0)	-23 (-24, -22)	<1 E-16	<1 E-16	Amino Acid
iso-Leucine (132.1 / 86.0 (2))	-27 (-28, -26)	<1 E-16	<1 E-16	Amino Acid
Asparagine (133.1 / 74.0)	-18 (-20, -17)	<1 E-16	<1 E-16	Amino Acid
Aspartic Acid (134.1 / 74.0)	-10 (-11, -9)	<1 E-16	<1 E-16	Amino Acid
Lysine (147.1 / 84.0 (2))	-10 (-11, -9)	<1 E-16	<1 E-16	Amino Acid
Glutamic acid (148.1 / 84.0)	-12 (-13, -10)	<1 E-16	<1 E-16	Amino Acid
Methionine (150.1 / 61.0)	-24 (-25, -23)	<1 E-16	<1 E-16	Amino Acid
Histidine (156.1 / 110.0)	-7 (-8, -7)	<1 E-16	<1 E-16	Amino Acid
Phenylalanine (166.1 / 120.0)	-11 (-12, -11)	<1 E-16	<1 E-16	Amino Acid
Arginine (175.1 / 70.0)	-9 (-10, -8)	<1 E-16	<1 E-16	Amino Acid
Tyrosine (182.1 / 136.0)	-21 (-22, -20)	<1 E-16	<1 E-16	Amino Acid
Glutamine (147.1 / 84.0)	-7 (-8, -5)	4.73E-14	8.75E-14	Amino Acid
Cystine (241.1 / 120.0)	-3 (-5, -1)	0.002742	0.003327	Amino Acid

N-AcetylGlycine (116.0 / 74.0)	-12 (-14, -9)	1.52E-13	2.74E-13	Amino Acid metabolism
Glycerate (105.0 / 75.0)	-8 (-10, -5)	5.31E-09	8.36E-09	Amino Acid metabolism/Gly, Ser
Guanidinoacetate (116.1 / 70.0)	-16 (-18, -15)	<1 E-16	<1 E-16	Amino Acid metabolism/Gly, Ser,Thr
MethylSuccinate (131.0 / 113.0)	-18 (-20, -17)	<1 E-16	<1 E-16	Amino Acid metabolism/Isoleu
D-Leucic Acid (133.1 / 87.0)	-12 (-15, -9)	7.01E-13	1.24E-12	Amino Acid metabolism/Leu
Shikimic Acid (173.0 / 93.0)	0 (-2, 1)	0.461029	0.494437	Amino Acid metabolism/Phe, Tyr,Trp
Citraconic Acid (129.0 / 85.0)	3 (-8, 16)	0.572625	0.59682	Amino Acid metabolism/Val, Leu, IL
Pentothenate (218.1 / 88.0)	-13 (-17, -9)	9.27E-10	1.56E-09	Amino acids metabolism/alanine, CoA
Creatine (132.1 / 90.0)	-4 (-6, -3)	1.03E-06	1.47E-06	Amino acids metabolism/Arg, Gly
Creatinine (114.1 / 44.0)	-2 (-3, -1)	0.001222	0.001533	Amino acids metabolism/Arg, Gly
Cystathionine (221.1 / 134.0)	-12 (-15, -8)	1.24E-09	2.04E-09	Amino acids metabolism/cys
Cystamine (153.0 / 108.0)	-6 (-8, -3)	4.97E-05	6.56E-05	Amino acids metabolism/Cys
Betaine (118.0 / 58.0)	-2 (-3, -1)	0.00025	0.000325	Amino acids metabolism/Gly,Ser, Thr metabolism
Carnitine (163.1 / 85.0)	2 (0, 3)	0.004364	0.005209	Amino acids metabolism/Lys
Hydroxyproline/Aminolevulinate (132.1 / 86.2)	-15 (-16, -12)	<1 E-16	<1 E-16	Amino acids metabolism/Pro
Taurine (126.0 / 108.0)	-43 (-46, -41)	<1 E-16	<1 E-16	Amino acids metabolism/Sulfur metabolism
Homovanilate (181.0 / 137.0)	0 (-4, 4)	0.929145	0.929145	Amino acids metabolism/Tyr,ligand
Aminoisobutyrate (104.1 / 86.0)	-2 (-2, -1)	1.72E-07	2.5E-07	Amino acids metabolism/Val, Leu, iso-Leu
Glucoronate (193.0 / 113.0)	-6 (-8, -4)	1.56E-08	2.35E-08	Amino sugar and nucleotide sugar metabolism
2-Hydroxyglutarate (147.0 / 129.0)	-12 (-14, -10)	<1 E-16	<1 E-16	Amino-acid metabolism & Glycine/Serine/Threonine metabolism
Glycochenodeoxycholate (448.3 / 74.0)	-15 (-19, -11)	7.95E-11	1.37E-10	Bile acid metabolism
Chenodeoxycholate (391.0 / 74.0)	-5 (-8, -3)	4.81E-06	6.59E-06	Bile acid metabolism
Glycocholate (464.3 / 74.0)	-14 (-19, -8)	5.25E-06	7.07E-06	Bile acid metabolism
Linolenic Acid (279.1 / 261.0)	-31 (-33, -29)	<1 E-16	<1 E-16	Fatty acid metabolism
G1P/G6P/F6P/F1P (259.0 / 78.8)	-9 (-11, -8)	<1 E-16	<1 E-16	Glycolysis
Glucose (179.0 / 89.0)	-2 (-4, 0)	0.054685	0.061314	Glycolysis/sugar
lactate (89.0 / 43.0)	5 (2, 8)	0.001923	0.002372	Glycolysis/TCA

Hyppuric Acid (178.0 / 134.0)	-31 (-36, -26)	<1 E-16	<1 E-16	Gut flora metabolism
Trimethylamine-N-oxide (TMAO) (76.1 / 58.0)	-12 (-17, -7)	3.22E-06	4.5E-06	Gut flora metabolism / Redox
Trimethylamine (TMA) (60.0 / 45.0)	2 (0, 3)	0.018454	0.021338	Gut flora metabolism / Redox
PGE (351.2 / 315.3)	-41 (-47, -35)	<1 E-16	<1 E-16	Lipids/Arachidonic acid metabolism
Propionate (73.0 / 55.0)	-22 (-25, -18)	<1 E-16	<1 E-16	Nicotinate and nicotinamide metabolism
Xanthine (151.0 / 108.0)	-1 (-4, 3)	0.630052	0.647554	Nucleotide
Hypoxanthine (135.0 / 92.0)	-1 (-5, 4)	0.737351	0.747452	Nucleotide
Allantoin (157.0 / 114.0)	-6 (-9, -4)	3.61E-08	5.34E-08	Nucleotide Degredation
Oxypurinol (151.0 / 42.0)	-20 (-22, -17)	<1 E-16	<1 E-16	Nucleotide metabolism
Adenylosuccinate (462.1 / 79.0)	-17 (-19, -14)	<1 E-16	<1 E-16	Nucleotide/Purine metabolism
GTP (522.0 / 159.0)	-4 (-6, -3)	1.30E-08	2.01E-08	Nucleotide/Purine metabolism
Urate (167.0 / 124.0)	-1 (-2, 1)	0.45612	0.494437	Nucleotide/Purine metabolism
Uridine (245.1 / 113.1)	-14 (-19, -10)	1.98E-09	3.19E-09	Nucleotide/Pyrimidine metabolism
Sorbitol (183.0 / 91.0)	-21 (-22, -19)	<1 E-16	<1 E-16	Sugar
Glyceraldehyde (89.0 / 59.0)	-12 (-14, -9)	<1 E-16	<1 E-16	Sugar
Succinate/Methylmalonate (117.0 / 73.0)	-21 (-23, -19)	<1 E-16	<1 E-16	TCA Cycle
Fumaric Acid/Maleic Acid (115.0 / 71.0)	-1 (-5, 3)	0.556414	0.588209	TCA Cycle
Tryptophan (205.1 / 146.0)	-12 (-13, -11)	<1 E-16	<1 E-16	Tryptophan Cycle
L-Kynurenine (209.1 / 94.0)	-4 (-6, -1)	0.000825	0.001052	Tryptophan Cycle
Melatonin (231.1 / 172.3)	-2 (-3, 0)	0.01064	0.012498	Tryptophan Cycle/Neuroactive ligand
Ornithine (133.1 / 70.0)	-17 (-19, -15)	<1 E-16	<1 E-16	Urea cycle
Citrulline (174.0 / 131.0)	-19 (-21, -18)	<1 E-16	<1 E-16	Urea Cycle
Niacinamide (123.0 / 80.0)	-53 (-56, -50)	<1 E-16	<1 E-16	Vitamin
Choline (104.1 / 60.0)	-2 (-3, -2)	<1 E-16	<1 E-16	Vitamins
Dimethylglycine (104.1 / 58.0)	-11 (-12, -10)	<1 E-16	<1 E-16	Vitamins
Biotin (243.1 / 200.0)	-13 (-16, -10)	<1 E-16	<1 E-16	Vitamins
Pyridoxal-5-P (246.0 / 96.9)	-1 (-2, 0)	0.132492	0.146334	Vitamins/B6

Supplemental Table 4. Modification of association between metabolite level and clamp procedure by CKD status. Results from regressing log-transformed metabolites on sample type (clamp v. fasting), CKD status, and the interaction between CKD status and sample type, adjusted for age, sex, race, and weight. Results are additionally adjusted for batch. Metabolites with a significant CKD interaction (at a nominal 5% level) are in bold. Fold changes compare clamp metabolite levels with fasting levels (i.e., a fold change of 0.4 would indicate an estimated 60% reduction in metabolite level). Metabolites organized by group and p-value. Analysis using mixed model + random intercept accounting for correlation within individual. P-value for interaction. p-value is for heterogeneity in fold change by CKD status (i.e., p-value for interaction of CKD with time trend)

Metabolite	Fold change between clamp/fasting states (95% CI)			
	Control	CKD	p-value	Metabolite group
Clamp vs. fasting	(Time coefficient)	Linear combination		
Arginine	0.89 (0.88, 0.91)	0.92 (0.91, 0.93)	0.0028	Amino Acid
Serine	0.86 (0.85, 0.88)	0.89 (0.88, 0.9)	0.0046	Amino Acid
Glutamine	0.91 (0.88, 0.93)	0.95 (0.93, 0.97)	0.0089	Amino Acid
Phenylalanine	0.87 (0.86, 0.89)	0.89 (0.88, 0.9)	0.028	Amino Acid
¹³ C-Arginine	1.03 (1.01, 1.04)	1 (0.99, 1.01)	0.029	Amino Acid
Valine	0.83 (0.81, 0.84)	0.85 (0.84, 0.86)	0.033	Amino Acid
Threonine	0.83 (0.81, 0.84)	0.85 (0.83, 0.86)	0.099	Amino Acid
Methionine	0.74 (0.72, 0.77)	0.76 (0.75, 0.78)	0.13	Amino Acid
Asparagine	0.8 (0.78, 0.83)	0.82 (0.81, 0.84)	0.2	Amino Acid
Glycine	0.94 (0.92, 0.97)	0.92 (0.91, 0.94)	0.21	Amino Acid
Leucine	0.76 (0.74, 0.78)	0.77 (0.76, 0.79)	0.22	Amino Acid
iso-Leucine	0.72 (0.7, 0.74)	0.73 (0.72, 0.75)	0.23	Amino Acid
Tyrosine	0.78 (0.76, 0.8)	0.8 (0.78, 0.81)	0.25	Amino Acid
Proline	0.86 (0.84, 0.87)	0.86 (0.85, 0.88)	0.55	Amino acid
Histidine	0.92 (0.91, 0.94)	0.93 (0.92, 0.94)	0.65	Amino Acid

Cystine	0.96 (0.93, 1)	0.97 (0.95, 1)	0.67	Amino Acid
Alanine	0.91 (0.88, 0.94)	0.9 (0.88, 0.92)	0.8	Amino Acid
Aspartic Acid	0.9 (0.88, 0.92)	0.9 (0.89, 0.92)	0.91	Amino Acid
Lysine	0.9 (0.88, 0.92)	0.9 (0.88, 0.91)	0.93	Amino Acid
Glutamic acid	0.92 (0.89, 0.95)	0.86 (0.85, 0.88)	< 0.001	Amino Acid
N-AcetylGlycine	0.87 (0.82, 0.92)	0.89 (0.86, 0.93)	0.36	Amino Acid metabolism
Glycerate	0.95 (0.91, 1)	0.91 (0.88, 0.94)	0.085	Amino Acid metabolism/Gly, Ser
Guanidinoacetate	0.83 (0.8, 0.86)	0.84 (0.82, 0.86)	0.53	Amino Acid metabolism/Gly, Ser, Thr
MethylSuccinate	0.79 (0.76, 0.81)	0.83 (0.81, 0.85)	0.0041	Amino Acid metabolism/Isoleu
D-Leucic Acid	0.83 (0.79, 0.88)	0.91 (0.87, 0.95)	0.014	Amino Acid metabolism/Leu
Shikimic Acid	0.98 (0.96, 1.01)	1 (0.99, 1.02)	0.2	Amino Acid metabolism/Phe, Tyr, Trp
Citraconic Acid	1.04 (0.85, 1.27)	1.03 (0.9, 1.19)	0.94	Amino Acid metabolism/Val, Leu, IL
Pentothenate	0.86 (0.8, 0.93)	0.88 (0.83, 0.93)	0.64	Amino acids metabolism/alanine, CoA
Creatine	0.94 (0.92, 0.97)	0.96 (0.94, 0.98)	0.3	Amino acids metabolism/Arg, Gly
Creatinine	0.98 (0.96, 1)	0.98 (0.97, 1)	0.76	Amino acids metabolism/Arg, Gly
Cystathionine	0.86 (0.8, 0.93)	0.9 (0.85, 0.94)	0.38	Amino acids metabolism/cys
Cystamine	0.95 (0.91, 1)	0.94 (0.91, 0.97)	0.62	Amino acids metabolism/Cys
Betaine	0.99 (0.97, 1.01)	0.97 (0.96, 0.99)	0.21	Amino acids metabolism/Gly, Ser, Thr metabolism
Carnitine	1.01 (0.99, 1.03)	1.02 (1.01, 1.04)	0.2	Amino acids metabolism/Lys
Hydroxyproline/Aminolevulinate	0.87 (0.84, 0.91)	0.85 (0.82, 0.87)	0.21	Amino acids metabolism/Pro
Taurine	0.51 (0.48, 0.56)	0.6 (0.56, 0.63)	0.0021	Amino acids metabolism/Sulfur metabolism
Homovanilate	1.02 (0.95, 1.1)	0.99 (0.94, 1.05)	0.56	Amino acids metabolism/Tyr, ligand
Aminoisobutyrate	0.98 (0.97, 0.99)	0.99 (0.98, 0.99)	0.29	Amino acids metabolism/Val, Leu, iso-Leu
Glucoronate	0.94 (0.9, 0.98)	0.94 (0.91, 0.96)	0.9	Amino sugar and nucleotide sugar metabolism
2-Hydroxyglutarate	0.89 (0.86, 0.91)	0.88 (0.86, 0.89)	0.56	Amino-acid metabolism & Glycine/Serine/Threonine metabolism

Chenodeoxycholate	0.93 (0.89, 0.97)	0.95 (0.93, 0.98)	0.35	Bile acid metabolism
Glycocholate	0.89 (0.8, 1)	0.85 (0.78, 0.92)	0.45	Bile acid metabolism
Glycochenodeoxycholate	0.85 (0.78, 0.93)	0.85 (0.8, 0.9)	0.97	Bile acid metabolism
Linolenic Acid	0.68 (0.65, 0.72)	0.69 (0.67, 0.72)	0.72	Fatty acid metabolism
G1P/G6P/F6P/F1P	0.9 (0.88, 0.94)	0.91 (0.89, 0.93)	0.89	Glycolysis
Glucose	1.01 (0.98, 1.05)	0.97 (0.94, 0.99)	0.02	Glycolysis/sugar
lactate	1.07 (1.01, 1.12)	1.04 (1, 1.08)	0.49	Glycolysis/TCA
Hyppuric Acid	0.71 (0.62, 0.81)	0.68 (0.62, 0.75)	0.59	Gut flora metabolism
Trimethylamine-N-oxide (TMAO)	0.91 (0.82, 1)	0.87 (0.81, 0.93)	0.45	Gut flora metabolism / Redox
Trimethylamine (TMA)	1.01 (0.99, 1.04)	1.02 (1, 1.04)	0.67	Gut flora metabolism / Redox
PGE	0.46 (0.39, 0.55)	0.66 (0.59, 0.74)	< 0.001	Lipids/Arachidonic acid metabolism
Propionate	0.77 (0.71, 0.83)	0.79 (0.75, 0.83)	0.59	Nicotinate and nicotinamide metabolism
Xanthine	1.01 (0.96, 1.07)	0.98 (0.94, 1.02)	0.37	Nucleotide
Hypoxanthine	0.99 (0.92, 1.07)	0.99 (0.94, 1.04)	0.93	Nucleotide
Allantoin	0.98 (0.94, 1.01)	0.92 (0.89, 0.94)	0.01	Nucleotide Degredation
Oxypurinol	0.85 (0.81, 0.9)	0.78 (0.75, 0.81)	0.0047	Nucleotide metabolism
Urate	0.98 (0.95, 1)	1 (0.99, 1.02)	0.064	Nucleotide/Purine metabolism
Adenylosuccinate	0.85 (0.82, 0.89)	0.82 (0.8, 0.85)	0.21	Nucleotide/Purine metabolism
GTP	0.96 (0.93, 0.98)	0.96 (0.94, 0.97)	0.93	Nucleotide/Purine metabolism
Uridine	0.83 (0.76, 0.91)	0.87 (0.82, 0.93)	0.38	Nucleotide/Pyrimidine metabolism
Glyceraldehyde	0.84 (0.81, 0.88)	0.9 (0.87, 0.93)	0.019	Sugar
Sorbitol	0.79 (0.76, 0.81)	0.8 (0.78, 0.82)	0.41	Sugar
Succinate/Methylmalonate	0.81 (0.78, 0.85)	0.79 (0.76, 0.81)	0.24	TCA Cycle
Fumaric Acid/Maleic Acid	1 (0.94, 1.06)	0.98 (0.94, 1.03)	0.73	TCA Cycle
L-Kynurenine	0.95 (0.91, 0.98)	0.97 (0.95, 1)	0.23	Tryptophan Cycle
Tryptophan	0.87 (0.85, 0.89)	0.88 (0.87, 0.9)	0.23	Tryptophan Cycle
Melatonin	0.98 (0.96, 1)	0.98 (0.96, 1)	0.8	Tryptophan Cycle/Neuroactive ligand

Ornithine	0.84 (0.82, 0.87)	0.82 (0.8, 0.84)	0.2	Urea cycle
Citrulline	0.79 (0.76, 0.82)	0.81 (0.79, 0.84)	0.26	Urea Cycle
Niacinamide	0.4 (0.36, 0.45)	0.51 (0.47, 0.55)	< 0.001	Vitamin
Biotin	0.82 (0.77, 0.86)	0.89 (0.86, 0.93)	0.0046	Vitamins
Dimethylglycine	0.88 (0.86, 0.9)	0.9 (0.88, 0.91)	0.31	Vitamins
Choline	0.98 (0.97, 0.98)	0.98 (0.98, 0.99)	0.37	Vitamins
Pyridoxal-5-P	1 (0.98, 1.02)	0.99 (0.97, 1)	0.52	Vitamins/B6

Supplemental Table 5. Pathway analysis comparing response to insulin between CKD and Controls.

	Total Cmpd	Hits	Raw p	-log(p)	Holm adjust	FDR	Impact
Nicotinate and nicotinamide metabolism	44	4	0.0011388	6.7778	0.063771	0.033518	0.03827
Arachidonic acid metabolism	62	1	0.0012385	6.6938	0.068119	0.033518	0.0255
D-Glutamine and D-glutamate metabolism	11	2	0.0019416	6.2443	0.10485	0.033518	0.35294
Vitamin B6 metabolism	32	2	0.0023941	6.0347	0.12689	0.033518	0.14449
Nitrogen metabolism	39	10	0.0038156	5.5687	0.19841	0.039164	0.0083
Taurine and hypotaurine metabolism	20	3	0.0041961	5.4736	0.214	0.039164	0.36331
Sphingolipid metabolism	25	1	0.0060013	5.1158	0.30006	0.042009	0
Sulfur metabolism	18	1	0.0060013	5.1158	0.30006	0.042009	0
Biotin metabolism	11	2	0.0084261	4.7764	0.40446	0.052429	0.20325
Pentose phosphate pathway	32	2	0.028756	3.5489	1	0.16103	0.02181

Supplementary Table 6. Correlations of changes in plasma metabolite concentrations (during insulin infusion versus fasting) with glucose disposal during the hyperinsulinemic euglycemic clamp (M/ΔI). Correlations were assessed for each of the metabolites for which change during insulin infusion varied by CKD status.

Δ Analyte	All participants	Participants with eGFR ≥60 mL/min/1.73m²	Participants with eGFR <60 mL/min/1.73m²
Arginine	-0.06	-0.37	0.21
Serine	-0.19	-0.40	0.09
Glutamine	-0.03	-0.17	0.12
Phenylalanine	-0.10	-0.39	0.16
Valine	-0.09	-0.46	0.09
Glutamic acid	-0.19	-0.05	-0.27
Methylsuccinate	-0.14	-0.32	0.05
D-Leucic Acid	-0.05	-0.08	-0.08
Taurine	0.22	0.21	-0.01
Glucose	-0.11	-0.02	0.31
PGE	-0.09	-0.02	-0.04
Allantoin	0.14	-0.26	-0.12
Oxypurinol	-0.13	-0.16	0.12
Glyceraldehyde	-0.11	0.08	-0.16
Niacinamide	-0.15	0.49	-0.18
Biotin	-0.06	-0.34	0.12

Supplementary Table 7. Correlations of changes in plasma metabolite concentrations (during insulin infusion versus fasting) with other metrics of insulin response, evaluated among all study participants (with and without CKD). Other metrics of insulin response include glucose disposal during the hyperinsulinemic euglycemic clamp (M/ Δ I), fatty acid suppression during the oral glucose tolerance test (OGTT NEFA index), and glucose disposal during the oral glucose tolerance test (OGTT Matsuda index). Correlations were assessed for each of the metabolites for which change during insulin infusion varied by CKD status.

Δ Analyte	M/ΔI	OGTT NEFA	OGTT Matsuda index
Arginine	-0.06	-0.23	-0.22
Serine	-0.19	-0.57	-0.45
Glutamine	-0.03	-0.24	-0.23
Phenylalanine	-0.10	-0.38	-0.34
Valine	-0.18	-0.54	-0.53
Glutamic acid	-0.09	0.23	0.19
Methylsuccinate	-0.19	-0.55	-0.49
D-Leucic Acid	-0.14	-0.27	-0.22
Taurine	-0.05	0.03	0.02
Glucose	0.22	0.40	0.38
PGE	-0.11	-0.28	-0.14
Allantoin	-0.09	-0.06	-0.02
Oxypurinol	0.14	0.20	0.13
Glyceraldehyde	-0.13	-0.15	-0.16
Niacinamide	-0.11	-0.06	-0.05
Biotin	-0.15	-0.43	-0.39