Supplementary Materials: Is 3-Carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF) a Clinically Relevant Uremic Toxin in Haemodialysis Patients?

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Table S1. Baseline characteristics of the patient with low and high CMPF.

	CMPF < 2.6 mg/l (n=119)		CMPF ≥ 2.6 mg/l (n=119)		p-value
Clinical characteristics					
Age (years)	65.9	[46.4 - 77.3]	61.5	[51.1 - 73.5]	0.39
Sex male/female	73/46		75/44		0.78
Dialysis vintage (years)	1.8	[1.0 - 4.2]	2.5	[1.1 - 5.3]	**0.08**
BMI (kg/m^2)	24.5	[20.7 - 27.7]	25.8	[23.4 - 29.7]	**0.009**
CI (kg/mg/day)	19.5	[17.2 - 21.5]	20.1	[18.2 - 22.4]	**0.02**
nPCR	1.1	[0.9 - 1.2]	1.1	[0.9 - 1.3]	0.42
spKt/V	1.7	[1.5 - 1.9]	1.6	[1.4 - 1.8]	0.57
Medical history of CV events (%)	31		35		0.49
HTA (%)	89		89		1
Type 1 or 2 Diabetes (%)	34		26		0.20
Dyslipidemia (%)	54		56		0.70
Biological characteristics					
Cr_{pre} (µmol/l)	698	[546 - 864]	796	[628 - 940]	**0.004**
Urea (mmol/l)	19	[16 - 22]	21	[18 - 24]	**0.04**
Hemoglobin (g/dl)	11.3	[10.4 - 12]	11.3	[10.5 - 12.3]	0.55
Ferritin (ng/ml)	368	[176 - 735]	400	[209 - 628]	0.89
Leukocytes (G/l)	6.3	[5.1 - 7.5]	5.8	[4.8 - 7.1]	**0.07**
Platelets (G/l)	226	[182 - 282]	213	[165 - 257]	0.12
Bicarbonate (mmol/l)	21	[19 - 23]	21	[19 - 23]	0.82
Phosphorus (mmol/l)	1.4	[1.1 - 1.8]	1.5	[1.2 - 1.8]	0.93
Calcemia (mmol/l)	2.2	[2.1 - 2.3]	2.6	[2.1 - 2.4]	0.87
PTH (ng/l)	217	[97 - 472]	272	[112 - 514]	0.35
25-OH Vitamin D3 (µg/l)	31	[23 - 37]	35	[25 - 42]	**0.05**
Total cholesterol (g/l)	1.7	[1.4 - 2.0]	1.6	[1.3 - 1.9]	0.31
LDL cholesterol (g/l)	0.93	[0.78 - 1.26]	0.86	[0.61 - 1.10]	**0.04**
HDL cholesterol (g/l)	0.39	[0.30 - 0.49]	0.38	[0.30 - 0.38]	0.27
Triglycerides (g/l)	1.5	[1.0 - 2.1]	1.7	[1.1 - 2.4]	0.26
HbA1c (%)	5.6	[5.0 - 6.6]	5.6	[5.1 - 6.1]	0.80
Albumin (g/l)	38.5	[35.7 - 40.6]	40.0	[37.2 - 41.6]	**0.007**
Prealbumin (g/l)	0.32	[0.27 - 0.38]	0.35	[0.29 - 0.30]	**0.02**
CRP (mg/l)	4.9	[2.0 - 11.2]	5.7	[1.9 - 13.7]	0.47
NT-proBNP (pg/ml)	2590	[910 - 5762]	1619	[725 - 4379]	0.10

Data are expressed as medians [IQR] or percentages (%).
Abbreviations: BMI, body mass index, CI, creatinine index, nPCR, normalized protein catabolic rate, Crpre: pre-dialysis creatinine, HTA, Hypertension, CMPF, 3-Carboxy-4-methyl-5-propyl-2-furanpropionate, PTH, parathyroid hormone, LDL, low density lipoprotein, HDL, high density lipoprotein, HbA1c, glycated haemoglobin, CRP, c-protein reactive, NT-proBNP, N- terminal pro-brain natriuretic peptide, sp Kt/V: single-pool Kt/V

Table S2. Baseline characteristics of the patients without and with PEW criteria.

	0-1 PEW criteria (n=172)		**≥ 2 PEW criteria (n=66)**		**p-value**
Clinical characteristics					
Age (years)	59.2	[44.9 - 72.3]	71.6	[51.8 - 79.3]	**0.009**
Sex male/female	109/63		39/27		0.54
Dialysis vintage (years)	2.3	[1.1 -4.7]	2.0	[1.1 - 4.2]	0.83
BMI (kg/m^2)	25.7	[23.4 - 29.4]	23.7	[20.4 - 27.1]	**0.003**
CI (kg/mg/day)	20.3	[18.3 - 22.4]	17.9	[16.9 - 20.3]	**<0.0001**
nPCR	1.10	[0.96 - 1.30]	0.99	[0.77 - 1.24]	**0.003**
spKt/V	1.6	[1.4 - 1.8]	1.8	[1.5 - 2.0]	**0.009**
Medical history of CV events (%)	31		38		0.95
HTA (%)	87		94		0.14
Type 1 or 2 Diabetes (%)	29		32		0.68
Dyslipidemia (%)	55		55		0.92
Biological characteristics					
Cr_{pre} (µmol/l)	796	[620 - 937]	622	[520 - 788]	**<0.0001**
Urea (mmol/l)	20.8	[18.0 - 23.6]	17.6	[13.3 - 21.6]	**<0.0001**
CMPF (mg/l)	3.3	[1.2 - 6.5]	1.5	[0.8 - 3.2]	**0.001**
Hemoglobin (g/dl)	11.3	[10.5 - 12.2]	11.1	[10.3 - 12.2]	0.46
Ferritin (ng/ml)	407	[194 - 680]	342	[141 - 655]	0.57
Leukocytes (G/l)	5.9	[5.1 - 7.1]	6.3	[4.9 - 7.8]	0.21
Platelets (G/l)	218	[169 - 258]	227	[182 - 285]	0.17
Bicarbonate (mmol/l)	21	[19 - 23]	22	[20 - 25]	**0.01**
Phosphorus (mmol/l)	1.5	[1.2 - 1.8]	1.2	[1.0 - 1.7]	**0.01**
Calcemia (mmol/l)	2.3	[2.1 - 2.4]	2.2	[2.1 - 2.3]	0.12
PTH (ng/l)	260	[120 - 514]	182	[67 - 468]	**0.03**
25-OH Vitamin D3 (µg/l)	34	[26 - 41]	30	[20.3 - 35.8]	**0.02**
Total cholesterol (g/l)	1.6	[1.4 - 1.9]	1.7	[1.3 - 2.0]	0.57
LDL cholesterol (g/l)	0.9	[0.7 - 1.1]	0.9	[0.7 - 1.3]	0.32
HDL cholesterol (g/l)	0.4	[0.3 - 0.5]	0.4	[0.3 - 0.5]	0.97
Triglycerides (g/l)	1.6	[1.0 - 2.3]	1.5	[1.1 - 2.1]	0.58
HbA1C (%)	5.5	[5.0 - 6.1]	5.7	[5.1 - 6.7]	0.31
Albumin (g/l)	40.2	[38.2 - 41.9]	35.6	[25.5 - 37.0]	**<0.0001**
Prealbumin (g/l)	0.36	[0.32 - 0.41]	0.27	[0.23 - 0.29]	**<0.0001**
CRP (mg/l)	4.1	[1.7 - 9,1]	10.5	[3.4 - 19.7]	**<0.0001**
NT-proBNP (pg/ml)	1689	[730 - 4049]	2864	[1215 - 6273]	**0.009**

Data are expressed as medians [IQR] or percentages (%).
Abbreviations: BMI, body mass index, CI, creatinine index, nPCR, normalized protein catabolic rate, Crpre: pre-dialysis creatinine, HTA, Hypertension, CMPF, 3-Carboxy-4-methyl-5-propyl-2-furanpropionate, PTH, parathyroid hormone, LDL, low density lipoprotein, HDL, high density lipoprotein, HbA1c, glycated haemoglobin, CRP, c-protein reactive, NT-proBNP, N- terminal pro-brain natriuretic peptide, spKt/V: single-pool Kt/V

Table S3. Characteristics of patients with bioimpedance measurement (n=66).

Clinical characteristics		
Age (years)	6.33	[47.2 - 74.3]
Male (%)	41	
Women (%)	59	
Dialysis vintage (years)	2.8	[1.1 - 5.0]
BMI (kg/m^2)	25.2	[22.2 - 28.0]
Creatine Index (kg/mg/day)	19.9	[17.5 - 19.9]
BF (%)	38.2	[31.6 - 44.0]
Lean tissue mass (LTM) (kg)	36.9	[28.4 - 43.6]
Lean tissue index (LTI) (kg/m^2)	12.7	[10.6 - 15.4]
Adipose tissue mass (ATM) (kg)	33.9	[20.6 - 47.0]
Fat tissue index (FTI) (kg/m^2)	12.9	[7.6 - 17.8]
Body cell mass (BCM) (kg)	19.0	[14.5 - 25.3]
nPCR	1.07	[0.93 - 1.30]
sp Kt/V	1.6	[1.5 - 1.8]
Medical history of CV events (%)	30	
HTA (%)	88	
Type 2 diabetes (%)	27	
Type 1 diabetes 1	3	
Dyslipidemia (%)	58	
Biological characteristics		
Cr_{pre} (µmol/l)	787	[584 - 943]
Urea (mmol/l)	20.1	[17.5 - 22.2]
CMPF (mg/l)	3.30	[1.40 - 6.93]
Hemoglobin (g/dl)	11.2	[10.7 - 12.1]
Ferritin (ng/ml)	437	[215 - 775]
Leukocytes (G/l)	5.9	[5.0 - 7.0]
Platelets (G/l)	218	[175 - 262]
Bicarbonate (mmol/l)	21	[19 - 23]
Phosphorus (mmol/l)	1.5	[1.2 - 1.8]
Calcemia (mmol/l)	2.2	[2.1 - 2.4]
PTH (ng/l)	367	[192 - 588]
25-OH Vitamin D3 (µg/l)	31	[21 - 38]
Total cholesterol (g/l)	1.70	[1.39 - 2.16]
LDL cholesterol (g/l)	0.86	[0.70 - 1.26]
HDL cholesterol (g/l)	0.35	[0.3 - 0.49]
Triglycerides (g/l)	1.60	[1.04 -2.20]

HbA1c (%)	5.4	[5.0 - 6.0]
Albumin (g/l)	39.5	[36.4 - 42.1]
Prealbumin (g/l)	0.34	[0.29 - 0.40]
CRP (mg/l)	4.7	[2.1 - 11.4]
NT-proBNP (pg/ml)	1379	[662 - 2840]

Data are expressed as medians [IQR] or percentages %.
Abbreviations: BMI, body mass index, BF, body fat percentage, nPCR, normalized protein catabolic rate, Crpre: pre-dialysis creatinine, HTA, Hypertension, CMPF, 3-Carboxy-4-methyl-5-propyl-2-furanpropionate, PTH, parathyroid hormone, LDL, low density lipoprotein, HDL, high density lipoprotein, HbA1c, glycated haemoglobin, CRP, c-protein reactive, NT-proBNP, N- terminal pro-brain natriuretic peptide, sp Kt/V: single pool Kt/V

Table S4. Effect of CMPF in different cellular models.

References	Type of cells used for in vitro experiments	CMPF actions	CMPF concentration
Niwa et al [1]	Isolated mitochondria	Inhibition of ADP-stimulated oxidation of NADH-linked substrates.	48 mg/l (200 μM)
Lim et al. [2]	Rats hepatocytes	Inhibition of iodide production (deiodination of T4).	2,4 mg/l (10 μM)
Everts et al. [3]	Anterior pituitary cells	Increased concentrations of T4. Reduced T4 uptake. No effect on TSH released.	4,8 mg/l (20 μM) 48 mg/l (200 μM)
Sun et al. [4]	Rats hepatocytes	CMPF reduced hepatocyte uptake of erythromycin Inhibition of the enzymatic metabolism of erythromycin by demethylation.	6 mg/l (25 μM) 48 mg/l (200 μM)
Volpe et al. [5]	Human liver microsomes	Effect of CMPF on drug metabolism: CMPF inhibited CYP3A4 metabolism (testosterone metabolism).	20,7 mg/l (86 μM) (IC50 value)
Prentice et al. [6]	β cells and mice islets	CMPF impairs glucose tolerance and utilization. Reduction in high glucose-stimulated secretion.	36 mg/l (150 μM) and 48 mg/l (200 μM)
Miyamoto et al [7]	Proximal tubular HK-2 cells	CMPF increases active TGF-β1secretion in the presence of Angiotensin II and iron. CMPF in addition of Angiotensin II and iron resulted in a significant increase in ROS production. CMPF directly interacts with superoxide anion radicals and peroxy-radicals to produce CMPF radicals. CMPF itself did not increase intracellular ROS production.	96 mg/l (400 μM)
Itoh et al. [8]	HUVEC	Increase in ROS production in the presence of 4 % HSA. No significant increased ROS production at 21 mg/l (87μM) or without HSA.	47 mg/l (196 μM)
Tsujimoto et al. [9]	Caco-2 cells Hep3B cells	Expression level of MRP2 mRNA tended to decrease. Expression level of OATP1B1 mRNA in Hep3B cells tended to decrease.	9.6 mg/l (40 μM)

Abbreviations: HUVEC, human umbilical vein endothelial cells, NADH, nicotinamide adenine dinucleotide, T4, thyroxin, TGF-β1, Transforming growth factor beta 1, ROS, reactive oxygene species, HSA, human serum albumin.

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