S-adenosyl-homocysteine in CKD-associated cardiovascular disease

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Background / Hypotheses

- Homocysteine has been discussed as a cardiovascular risk factor in patients with chronic kidney disease (CKD).
- However, randomized trials in which homocysteine was lowered *via* vitamin B supplementation failed to demonstrate a survival benefit.
- The homocysteine metabolite S-adenosyl-homocysteine (SAH; Figure 1) is a potent inhibitor of methylation reactions and thus a central epigenetic regulator.
- Vitamin B supplementation, which lowers homocysteine, does not reduce SAH.

Hypothesis 1: SAH accumulates more strongly than homocysteine in CKD.

Hypothesis 2: Compared to homocysteine, SAH is more strongly associated with prevalent cardiovascular disease.

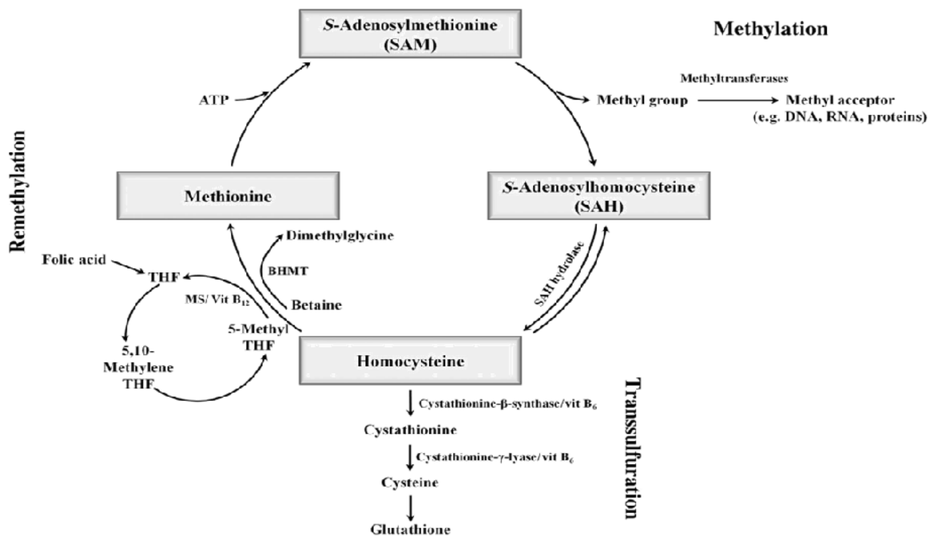


Figure 1: C1 metabolism (schematic overview; Zawada *et al.* NDT 2013)

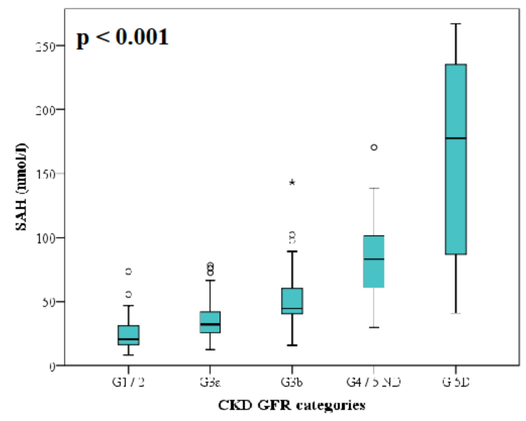
Methods / Results

- Plasma homocysteine (fluorescence polarization immunoassay) and SAH (tandem mass spectrometer) concentrations were assessed among 297 CARE FOR HOMe participants who suffered from CKD (KDIGO G 1- G 5; Table 1).
- Patients with more advanced GFR categories had higher plasma homocysteine and SAH concentrations (Figure 2 & 3).
- eGFR correlated more strongly with plasma SAH (r = 0.497) than with plasma homocysteine (r = 0.424).
- Patients with prevalent cardiovascular disease had higher plasma SAH than patients without prevalent cardiovascular disease (p = 0.007; Figure 4 & 5).
- In logistic regression analyses, however SAH did not independently predict prevalent CVD (Table 2).
- In 24 cases, plasma homocysteine and plasma SAH measurements were repeated one year later, which demonstrated high intraindividual stability of both variables (Figure 6 & 7).

	means ± SD		n (%)
Age (years)	67.0 ± 12.5	**Gender (women)**	117 (39.4 %)
BMI (kg/m²)	30.6 ± 5.6	**Active smoking (yes)**	32 (10.8 %)
Systolic blood pressure (mmHg)	146 ± 21	**Prevalent CVD (yes)**	61 (20.5 %)
eGFR (MDRD) (ml/min/1.73 m²)	44 ± 19	**Diabetes mellitus (yes)**	106 (35.7 %)

Table 1: Baseline characteristics of CARE FOR HOMe participants.

Results



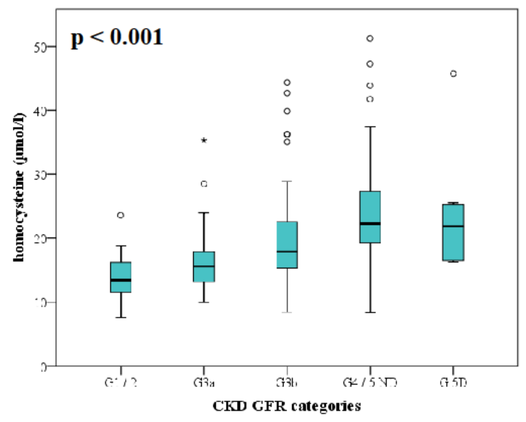
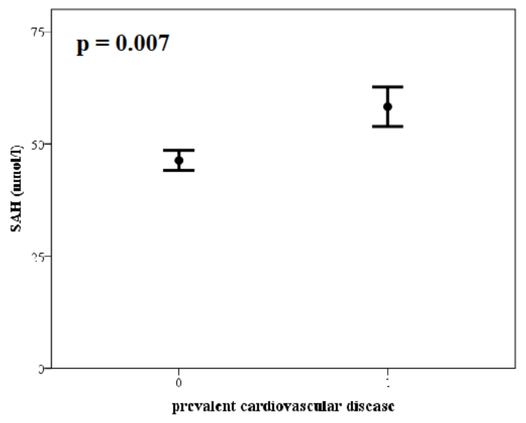


Figure 2 & 3: Plasma SAH and plasma homocysteine in CKD patients stratified for GFR categories. Data are shown as means, 25th / 75th percentile, range, outliers and extreme values. Statistical analysis: one-way ANOVA with p for trend.



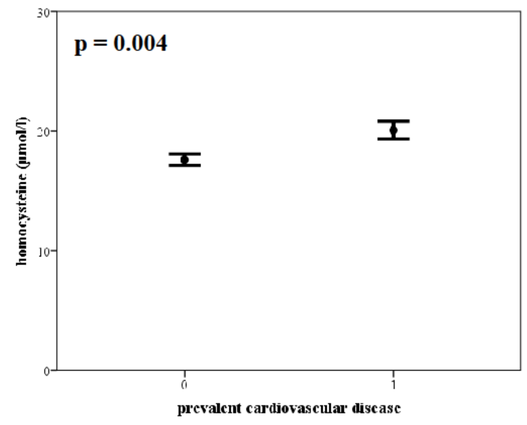
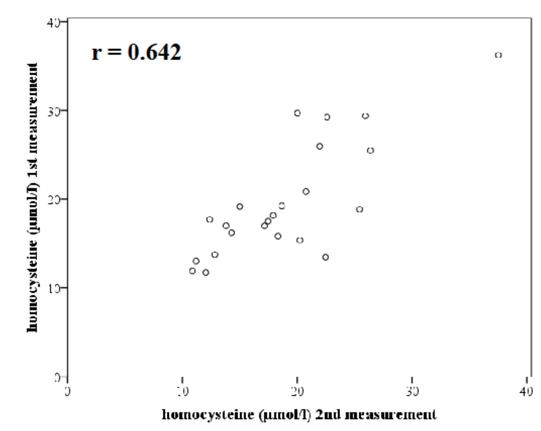


Figure 4 & 5: Plasma SAH and plasma homocysteine in patients without and with prevalent cardiovascular disease (t-test for two independent samples).

	Exp (B)	95% confidence interval	p-value
SAH [nmol/l]	1.003	[0.989; 1.017]	0.658
Age [years]	1.060	[1.029; 1.092]	< 0.001
Active smoking [yes]	0.919	[0.353; 2.393]	0.862
Systolic BP [mmHg]	1.009	[0.996; 1.022]	0.189
LDL-C [mg/dl]	0.995	[0.987; 1.003]	0.238
Gender [female]	0.565	[0.320; 0.999]	0.050
Diabetes mellitus [yes]	1.036	[0.582; 1.844]	0.905
eGFR-MDRD [ml/min/1.73 m²]	1.001	[0.977; 1.026]	0.938

Table 2: Logistic regression analyses: independent variables: SAH, age, gender, eGFR and cardiovascular risk factors; dependent variable: prevalent cardiovascular disease. BP: blood pressure; LDL-C = low density lipoprotein-cholesterol.



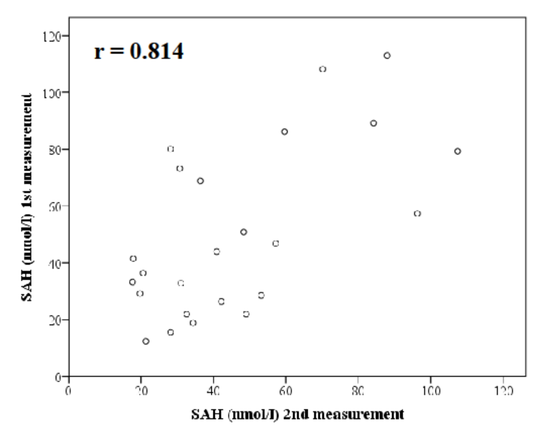


Figure 6 & 7: Intraindividual stability of plasma SAH and plasma homocysteine among 24 patients in whom both variables were re-measured after 12 months.

Discussion

Plasma SAH accumulates to a higher degree than plasma homocysteine in CKD. Follow-up of study participants will reveal whether SAH independently predicts future cardiovascular events. Moreover, additional experimental studies are needed to evaluate SAH as a novel non-traditional cardiovascular risk factor.

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