Online Supplemental Material

Advanced glycation endproducts and dicarbonyls in end-stage renal disease: associations with uremia and courses following renal replacement therapy

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Table of contents

Supplementary Methods

In- and exclusion criteria of the individual studies

Incident dialysis patients were individuals with ESRD who would start with dialysis within one month. Measurements were performed maximum four weeks prior to the first dialysis session. Exclusion criteria for incident dialysis patients were: acute start of dialysis treatment, active symptomatic coronary artery disease or cardiac failure New York Heart Association (NYHA) class III or IV, active malignancies, active infections, and inability to provide informed consent. Incident dialysis patients were recruited from the following dialysis centers in the South East of the Netherlands: Maastricht University Medical Center+ Maastricht, Catharina Hospital Eindhoven, Viecuri Hospital Venlo, Zuyderland Medical Centre Sittard, and St. Laurentius Hospital Roermond (Ethical Committee study number NL33129.068.10).

Kidney transplant recipients were individuals with ESRD receiving a living donor kidney transplant, age ≥18 years, and ability to provide informed consent. These individuals were recruited from the pre-transplantation clinic at the Maastricht University Medical Center+ in the Netherlands (Ethical Committee study number NL43381.068.13). Baseline measurements were performed within five days before kidney transplantation, with the exception of one patient who was examined five weeks before kidney transplantation.

Prevalent dialysis patients participated in the Uremic Toxins, Cardiovascular Effects and Physical Activity in Intensive Hemodialysis (INTHEMO) study, an international multicenter study which has been performed in the southern part of the Netherlands (Maastricht University Medical Center+ and Zuyderland Heerlen Dialysis Unit), Belgium (Jessa Hospital Hasselt Dialysis Unit), and the United Kingdom (Manchester

University NHS Foundation Trust). For the present study, only participants from the Netherlands (Ethical Committee study number NL35039.068.10) were included to improve comparability with the incident dialysis patients, kidney transplant recipients and healthy controls. Prevalent dialysis patients were ≥18 years and treated with hemodialysis (HD) or peritoneal dialysis (PD) treatment for at least six months. Exclusion criteria for the prevalent dialysis patients were similar to those of incident dialysis patients, with the addition of chronic antibiotic use and colectomy.

Healthy donors were individuals who were suitable for living renal donation, for example, no uncontrolled or severe hypertension, and/or diabetes mellitus, and able to provide informed consent. These individuals were recruited from the pre-transplantation clinic at the Maastricht University Medical Center+ in the Netherlands. Baseline measurements were performed within one month before donation.

Healthy controls were non-diabetic, non-smokers, not hypertensive (systolic blood pressure <170 mmHg and/or diastolic blood pressure <100 mmHg), and able to provide informed consent, and were recruited via advertisements at the university hospital.

Dialysis therapy modalities

Detailed data on renal replacement therapy modalities were collected retrospectively and could be retrieved for 16 incident HD patients, 16 incident PD patients, 17 prevalent HD patients and 14 prevalent PD patients.

In both incident and prevalent HD patients, dialysis was performed three times per week for about four hours, using ultrapure dialysates and mostly high-flux dialyzers with synthetic membranes (polysulfone membranes (from Fresenius Medical Care GmbH, Bad Homburg, Germany) in 7 incident HD patients and 11 prevalent HD patients; polyethersulfone membrane (from Nipro, Osaka, Japan) in 5 incident HD patients and 3 prevalent HD patients; polyarylethersulfone/ polyvinylpyrrolidone/ polyamide blend membranes (Gambro, Lund, Sweden) in 2 incident HD patient). In addition, 2 incident HD patients and 3 prevalent HD patients were on low-flux dialyzers with synthetic membranes (polyarylethersulfone/ polyvinylpyrrolidone/ polyamide blend membranes (Gambro) and polysulfone membranes (Fresenius Medical Care), respectively). No patients were treated with hemodiafiltration. Vascular access was via an arteriovenous shunt in 18 incident HD patients and all prevalent HD patients. Three incident HD patients had a central venous catheter (1 of these patients had switched to an arteriovenous shunt after 6 months of follow-up).

In both incident and prevalent PD patients, only PD fluids with low glucose-derived degradation product (GDP) content were used (Physioneal®, Extraneal®, and Nutrineal® from Baxter, Castlebar, Ireland). The glucose concentration was prescribed at the discretion of the treating physician.

During follow-up, three patients changed dialysis modality: 1 from PD to HD from 6 months after dialysis-initiation onwards (first via a central venous catheter, later via

an arteriovenous shunt), 1 from PD to HD at 12 months after dialysis initiation (via a central venous catheter), and 1 from HD to PD at 12 months after dialysis initiation.

Study measurements

Other laboratory measurements

Dialysis adequacy (Kt/V) was retrospectively collected from the electronic medical health record (single-pool Kt/V for HD, weekly Kt/V for PD). In addition, serum creatinine and serum β2-microglobulin were measured with routine laboratory measurements at the time of study participation, except for healthy kidney donors and kidney transplant recipients, for whom these data were retrospectively collected from the health record. In controls and in participants with CKD5-ND, estimated GFR was calculated with the CKD-EPI equation based on serum creatinine ($eGFR_{CKD\text{-}EPI}$).[1] In participants with CKD5-D, residual GFR was estimated with an equation based on serum β2-microglobulin ($eGFR_{residual}$).[2]

Clinical characteristics

Origin of renal disease was based on the diagnosis as reported in the patient's electronic medical health record and categorized as nephrosclerosis, glomerulosclerosis, hypertensive nephropathy, renovascular disease, diabetic nephropathy, polycystic kidney disease, IgA nephropathy, glomerulonephritis, other, and unknown. History of diabetes mellitus and cardiovascular disease, and medication use were based on self-report (for healthy controls) and the health record (for patients). Current smoking was based on self-report. Current dialysis modality, history of kidney transplantation, dialysis vintage and residual urine output were collected from the health record. Body mass index was calculated as weight divided by height squared. Lean tissue index and fat tissue index were calculated as lean tissue mass and adipose tissue mass divided by height squared, respectively. For this purpose, lean tissue mass and adipose tissue mass were determined by

bioimpedance spectroscopy with the Body Composition Monitor (BCM®, Fresenius Medical Care GmbH, Bad Homburg, Germany), which uses a three compartment model (adipose tissue mass, lean tissue mass, and fluid overload).[3] Office blood pressure was measured with an electronic sphygmomanometer (Omron M4-I, Omron, Japan).

References

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3. Chamney PW, Wabel P, Moissl UM, Muller MJ, Bosy-Westphal A, Korth O, Fuller NJ: A whole-body model to distinguish excess fluid from the hydration of major body tissues. *Am J Clin Nutr,* 85**:** 80-89, 2007

Supplementary Tables

Table S1. Courses of (residual) kidney function over time in incident dialysis patients and kidney transplant recipients

Dialysis (overall)*	Time since dialysis initiation (months)			
Biomarkers	Baseline	1	6	12
Serum creatinine (µmol/L)	585.5 [431.0-777.5]	524.0 [390.0-648.8]	613.0 [473.5-791.5]	688.0 [548.0-817.0]
β2-microglobulin (mg/L)	9.9 [7.2-11.9]	9.5 [8.2-13.2]	11.6 [9.0-17.9]	13.2 [9.3-23.1]
$eGFR_{CKD-EPI}$ (mL/min/1.73m^2)	8.1 ±2.8	NA	NA	NA
$eGFR_{residual}$ (mL/min/1.73m^2)	17.6 [10.8-29.8]	16.1 [8.9-26.5]	11.8 [3.8-18.9]	8.3 [2.3-16.2]
Hemodialysis*	Time since dialysis initiation (months)			
Biomarkers	Baseline	1	6	12
Serum creatinine (µmol/L)	598.0 [454.0-804.0]	527.5 [419.8-704.8]	660.5 [575.5-897.5]	699.5 [578.8-975.3]
Serum β2-microglobulin (mg/L)	10.0 [7.3-12.5]	10.2 [8.6-12.8]	16.7 [10.8-21.9]	17.1 [11.1-13.2]
$eGFR_{CKD-EPI}$ (mL/min/1.73m^2)	7.6 ±2.6	NA	NA	NA
$eGFR_{residual}$ (mL/min/1.73m^2)	17.5 [10.1-32.2]	14.7 [8.0-22.0]	5.0 [2.7-12.9]	5.3 [0.9-9.0]
Peritoneal dialysis*	Time since dialysis initiation (months)			
Biomarkers	Baseline	1	6	12
Serum creatinine (µmol/L)	540.0 [423.0-710.0]	520.0 [354.8-611.3]	544.0 [385.0-712.0]	598.0 [432.5-783.5]
Serum β2-microglobulin (mg/L)	9.9 [7.0-11.5]	8.7 [7.0-13.2]	8.9 [7.8-12.7]	10.9 [8.5-16.1]
$eGFR_{CKD-EPI}$(mL/min/1.73m^2)	8.7 ±2.9	NA	NA	NA
$eGFR_{residual}$ (mL/min/1.73m^2)	17.8 [11.0-28.7]	17.0 [9.0-37.8]	16.4 [9.8-23.9]	13.6 [4.4-20.9]

Kidney transplant recipients**	Time since kidney transplantation (months)			
Biomarkers	Baseline	3	6	12
Serum creatinine (µmol/L)	519.0 [431.0-777.5]	129.0 [110.5-156.5]	121.5 [107.0-138.0]	119.5 [101.8-138.5]
$eGFR_{CKD-EPI}$ (mL/min/1.73m^2)	8.7 ±3.6	48.1 ±10.4	51.7 ±9.6	52.7 ±9.7

Data are presented as n (%), mean ± standard deviation, or median [25th percentile - 75th percentile].
Abbreviations: $eGFR_{CKD-EPI}$, estimated glomerular filtration rate based on the creatinine CKD-EPI equation; $eGFR_{residual}$, estimated residual GFR based on β2-microglobulin; NA, not applicable.
* For participants on hemodialysis/peritoneal dialysis, analyses are based on n = 19/17, n = 20/16, n = 18/15, n = 14/13 at baseline, 1 month, 6 months and 12 months after dialysis initiation, respectively.
** For kidney transplant recipients, analyses are based on analyses are based on n = 21, n = 17, n = 18, n = 18 at baseline months, 1 month, 6 months and 12 months after kidney transplantation, respectively.

Table S2. Courses of body mass index, lean tissue index and fat tissue index over time in incident dialysis patients and kidney transplant recipients

Dialysis (overall)*	Time since dialysis initiation (months)			
Body weight measures	Baseline	1	6	12
BMI (kg/m^2)	25.7 ±3.8	25.7 ±6.3	25.6 ±3.7	25.7±3.5
LTI (kg/m^2)	14.5 ±2.5	14.4 ±2.2	14.2 ±2.0	14.5 ±2.3
FTI (kg/m^2)	10.5 ±3.9	10.5 ±4.1	10.7 ±4.4	10.8 ±3.7
Hemodialysis*	Time since dialysis initiation (months)			
Body weight measures	Baseline	1	6	12
BMI (kg/m^2)	27.0 ±3.7	26.8 ±3.7	26.6 ±4.0	26.8 ±3.3
LTI (kg/m^2)	14.7 ±2.3	14.5 ±2.1	14.0 ±1.7	14.5 ±2.3
FTI (kg/m^2)	11.5 ±3.6	11.3 ±4.5	11.8 ±4.5	11.9 ±3.3
Peritoneal dialysis*	Time since dialysis initiation (months)			
Body weight measures	Baseline	1	6	12
BMI (kg/m^2)	24.5 ±3.4	24.7 ±3.4	24.7 ±3.2	24.7 ±3.5
LTI (kg/m^2)	14.4 ±2.7	14.4 ±2.3	14.3 ±2.3	14.5 ±2.4
FTI (kg/m^2)	9.6 ±4.0	9.7 ±3.6	9.8 ±4.2	9.9 ±3.9

Kidney transplant recipients**	Time since kidney transplantation (months)			
Body weight measures	Baseline	3	6	12
BMI (kg/m^2)	24.5 ± 4.5	24.1 ±4.3	24.6 ±4.1	25.4 ±4.8
LTI (kg/m^2)	14.4 ±3.1	14.3 ±2.6	14.2 ±2.0	14.9 ±3.0
FTI (kg/m^2)	9.9 ±4.3	9.4 ±4.3	10.3 ±3.8	10.1 ±5.1

Data are presented as % or mean ± standard deviation.
Abbreviations: BMI, body mass index; FTI, fat tissue index; LTI, lean tissue index.
* For participants on hemodialysis/peritoneal dialysis, analyses are based on n = 21/22, n = 21/22, n = 20/21, n = 18/19 at baseline, 1 month, 6 months and 12 months after dialysis initiation, respectively, for BMI, and n = 19/22, n = 20/22, n = 19/21, n = 17/19, respectively, for LTI and FTI.
** For kidney transplant recipients, analyses are based on analyses are based on n = 21, n = 17, n = 18, n = 18 at baseline, 1 month, 6 months and 12 months after kidney transplantation, respectively, for BMI, and n = 21, n = 16, n = 16, n = 17, respectively, for LTI and FTI.

Table S3. Associations of end-stage renal disease with advanced glycation endproducts and dicarbonyls based on linear mixed models

		CKD5-ND vs. controls*		CKD5-D vs. controls*		CKD5-D vs. CKD5-ND*	
Biomarker	Model	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value
CML_{free}	1	6.13 (3.33; 11.27)	< 0.001	15.89 (8.60; 29.36)	< 0.001	2.59 (1.67; 4.02)	< 0.001
	2	5.99 (3.18; 11.28)	< 0.001	15.81 (8.31 30.09)	< 0.001	2.64 (1.68; 4.14)	< 0.001
$CML_{protein\text{-}bound}$	1	2.50 (2.19; 2.86)	< 0.001	3.14 (2.71; 3.64)	< 0.001	1.26 (1.09; 1.45)	0.002
	2	Does not converge		Does not converge		Does not converge	
CEL_{free}	1	5.86 (2.63; 13.06)	< 0.001	20.17 (9.01; 45.14)	< 0.001	3.44 (2.10; 5.62)	< 0.001
	2	5.73 (2.53; 12.97)	< 0.001	19.69 (8.62; 44.99)	< 0.001	3.44 (2.08; 5.67)	< 0.001
$CEL_{protein\text{-}bound}$	1	Does not converge		Does not converge		Does not converge	
	2	Does not converge		Does not converge		Does not converge	
$MG\text{-}H1_{free}$	1	8.51 (4.83; 14.99)	< 0.001	17.96 (10.11; 31.93)	< 0.001	2.11 (1.92; 3.45)	0.003
	2	8.40 (4.69; 15.03)	< 0.001	17.76 (9.74; 32.40)	< 0.001	2.12 (1.28; 3.51)	0.005
$MG\text{-}H1_{protein\text{-}bound}$	1	1.63 (1.43; 1.85)	< 0.001	1.71 (1.48; 1.96)	< 0.001	1.05 (0.91; 1.20)	0.505
	2	1.64 (1.43; 1.87)	< 0.001	1.72 (1.48; 2.01)	< 0.001	1.05 (0.91; 1.22)	0.471
GO	1	1.92 (1.16; 3.15)	0.011	3.76 (2.28; 6.21)	< 0.001	1.96 (1.42; 2.72)	< 0.001
	2	1.87 (1.18; 2.97)	0.008	3.34 (2.09; 5.35)	< 0.001	1.79 (1.30; 2.46)	< 0.001
MGO	1	2.39 (1.52; 3.73)	< 0.001	4.08 (2.61; 6.40)	< 0.001	1.71 (1.28; 2.28)	< 0.001
	2	2.32 (1.45; 3.70)	< 0.001	3.99 (2.48; 6.40)	< 0.001	1.72 (1.28; 2.31)	< 0.001
3-DG	1	1.23 (0.84; 1.79)	0.287	1.48 (1.01; 2.17)	0.044	1.21 (0.92; 1.58)	0.170
	2	1.21 (0.90; 1.63)	0.194	1.28 (0.95; 1.73)	0.106	1.05 (0.83; 1.33)	0.653
SAF	1	1.24 (0.99; 1.55)	0.057	1.56 (1.24; 1.95)	< 0.001	1.26 (1.07; 1.48)	< 0.001
	2	1.30 (1.15; 1.48)	< 0.001	1.50 (1.31; 1.72)	< 0.001	1.16 (1.02; 1.31)	0.024

Ratios represent the ratio of (geometric mean) levels of the biomarkers in the respective end-stage renal disease group relative to controls and relative to individuals with chronic kidney disease stage 5 non-dialysis.
Model 1: unadjusted; model 2: adjusted for age, sex and diabetes mellitus.
Abbreviations: 3-DG, 3-deoxyglucosone; CEL, N^{ϵ}-(carboxyethyl)lysine; CI, confidence interval; CKD5-D, chronic kidney disease stage 5 dialysis; CKD5-ND, chronic kidney disease stage 5 non-dialysis; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; SAF, skin autofluorescence.
* Analyses based on (Controls/ CKD5-ND/ CKD5-D) n = 40/48/33 for serum AGEs, n = 40/44/33 for dicarbonyls, and n = 42/47/27 for skin autofluorescence.

Table S4. Associations of end-stage renal disease with advanced glycation endproducts and dicarbonyls with additional adjustment for current smoking

		CKD5-ND vs. controls*		CKD5-D vs. controls*		CKD5-D vs. CKD5-ND*	
Biomarker	Model	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value
CML_{free}	1	7.93 (6.38; 9.85)	< 0.001	12.88 (9.90; 16.75)	< 0.001	1.62 (1.29; 2.05)	< 0.001
$CML_{protein\text{-}bound}$	1	2.48 (2.16; 2.86)	< 0.001	3.08 (2.60; 3.65)	< 0.001	1.24 (1.07; 1.44)	0.005
CEL_{free}	1	8.19 (6.46; 10.38)	< 0.001	14.47 (10.85; 19.29)	< 0.001	1.77 (1.37; 2.28)	< 0.001
$CEL_{protein\text{-}bound}$	1	1.12 (0.96; 1.32)	0.155	1.18 (0.97; 1.43)	0.105	1.05 (0.88; 1.25)	0.612
$MG\text{-}H1_{free}$	1	9.87 (7.56; 12.87)	< 0.001	16.01 (11.60; 22.09)	< 0.001	1.62 (1.22; 2.16)	0.001
$MG\text{-}H1_{protein\text{-}bound}$	1	1.67 (1.48; 1.87)	< 0.001	1.75 (1.51; 2.02)	< 0.001	1.05 (0.92; 1.19)	0.450
GO	1	2.26 (1.94; 2.64)	< 0.001	2.82 (2.34; 3.39)	< 0.001	1.24 (1.05; 1.47)	0.011
MGO	1	2.94 (2.56; 3.37)	< 0.001	3.26 (2.76; 3.85)	< 0.001	1.11 (0.96; 1.29)	0.172
3-DG	1	1.35 (1.20; 1.52)	< 0.001	1.20 (1.04; 1.38)	0.012	0.89 (0.78; 1.01)	0.067
SAF	1	1.33 (1.23; 1.44)	< 0.001	1.45 (1.31; 1.61)	< 0.001	1.09 (1.00; 1.20)	0.056

Ratios represent the ratio of (geometric mean) levels of the biomarkers in the respective end-stage renal disease group relative to controls and relative to individuals with chronic kidney disease stage 5 non-dialysis.
Adjusted for age, sex, diabetes mellitus and current smoking.
Abbreviations: 3-DG, 3-deoxyglucosone; CEL, N^{ϵ}-(carboxyethyl)lysine; CI, confidence interval; CKD5-D, chronic kidney disease stage 5 dialysis; CKD5-ND, chronic kidney disease stage 5 non-dialysis; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; SAF, skin autofluorescence.
* Analyses based on (Controls/ CKD5-ND/ CKD5-D) n = 40/48/33 for serum AGEs, n = 40/44/33 for dicarbonyls, and n = 42/47/27 for skin autofluorescence.

Table S5. Association of estimated glomerular filtration rate ($eGFR_{CKD\text{-}EPI}$) with advanced glycation endproducts and dicarbonyls in controls and participants with chronic kidney disease stage 5 non-dialysis

	Controls*		CKD5-ND**	
Biomarker	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value
CML_{free}	0.98 (0.86; 1.13)	0.795	1.08 (1.02; 1.14)	0.008
$CML_{protein\text{-}bound}$	1.05 (0.98; 1.11)	0.150	1.07 (1.04; 1.10)	< 0.001
CEL_{free}	1.00 (0.85; 1.17)	0.976	1.07 (1.01; 1.13)	0.028
$CEL_{protein\text{-}bound}$	0.91 (0.79; 1.04)	0.153	1.03 (0.99; 1.07)	0.097
$MG\text{-}H1_{free}$	1.01 (0.85; 1.21)	0.892	1.08 (1.01; 1.15)	0.021
$MG\text{-}H1_{protein\text{-}bound}$	0.99 (0.92; 1.06)	0.725	1.05 (1.02; 1.08)	< 0.001
GO	1.07 (0.98; 1.17)	0.148	1.04 (1.01; 1.08)	0.013
MGO	1.00 (0.96; 1.04)	0.961	1.04 (1.00; 1.09)	0.030
3-DG	1.02 (0.95; 1.09)	0.548	1.02 (0.99; 1.05)	0.221
SAF	1.03 (0.98; 1.08)	0.252	1.00 (0.98; 1.02)	0.709

Ratios represent the ratio of (geometric mean) levels of the biomarkers per 10 mL/min/1.73m^2 lower eGFR in controls and per 1 mL/min/1.73m^2 lower eGFR in CKD5-ND.

All analyses are adjusted for age, sex and diabetes mellitus (in CKD5-ND only as there were no controls with diabetes mellitus).

Abbreviations: 3-DG, 3-deoxyglucosone; CEL, N^{ϵ}-(carboxyethyl)lysine; CI, confidence interval; CKD5-ND, chronic kidney disease stage 5 non-dialysis; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; SAF, skin autofluorescence.

* Analyses based on n = 40 for serum AGEs, n = 40 for dicarbonyls, and n = 42 for skin autofluorescence.

** Analyses based on n = 42 for serum AGEs, n = 38 for dicarbonyls, and n = 40 for skin autofluorescence.

Table S6. Association of estimated residual glomerular filtration rate ($eGFR_{residual}$) with advanced glycation endproducts and dicarbonyls in participants with chronic kidney disease stage 5 dialysis

Biomarker	Ratio (95%CI)	*P* value
CML_{free}	1.03 (1.02; 1.04)	< 0.001
$CML_{protein\text{-}bound}$	1.02 (1.01; 1.04)	0.003
CEL_{free}	1.03 (1.02; 1.04)	< 0.001
$CEL_{protein\text{-}bound}$	1.00 (0.99; 1.01)	0.859
$MG\text{-}H1_{free}$	1.04 (1.02; 1.06)	< 0.001
$MG\text{-}H1_{protein\text{-}bound}$	1.01 (1.00; 1.02)	0.011
GO	1.03 (1.02; 1.04)	< 0.001
MGO	1.02 (1.01; 1.03)	< 0.001
3-DG	1.01 (1.00; 1.02)	0.168
SAF	0.99 (0.98; 1.00)	0.040

Ratios represent the ratio of (geometric mean) levels of the biomarkers per 1 mL/min/1.73m^2 lower estimated residual GFR.
All analyses are adjusted for age, sex and diabetes mellitus.
Abbreviations: 3-DG, 3-deoxyglucosone; CEL, N^{ϵ}-(carboxyethyl)lysine; CI, confidence interval; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; SAF, skin autofluorescence.
Analyses based on n = 25 for serum AGEs, n = 25 for dicarbonyls, and n = 18 for skin autofluorescence.

Table S7. Association of residual urine output with advanced glycation endproducts and dicarbonyls in participants with chronic kidney disease stage 5 dialysis

Biomarker	Ratio (95%CI)	*P* value
CML_{free}	1.02 (1.00; 1.04)	0.039
$CML_{protein\text{-}bound}$	1.02 (1.01; 1.04)	0.012
CEL_{free}	1.03 (1.01; 1.05)	0.015
$CEL_{protein\text{-}bound}$	1.01 (1.00; 1.02)	0.073
$MG\text{-}H1_{free}$	1.04 (1.01; 1.07)	0.006
$MG\text{-}H1_{protein\text{-}bound}$	1.01 (1.00; 1.03)	0.045
GO	1.03 (1.02; 1.05)	< 0.001
MGO	1.03 (1.02; 1.04)	< 0.001
3-DG	1.01 (0.99; 1.02)	0.370
SAF	1.00 (0.99; 1.01)	0.760

Ratios represent the ratio of (geometric mean) levels of the biomarkers per 100 mL/24h lower residual urine output.
All analyses are adjusted for age, sex and diabetes mellitus.
Abbreviations: 3-DG, 3-deoxyglucosone; CEL, N^{ϵ}-(carboxyethyl)lysine; CI, confidence interval; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; SAF, skin autofluorescence.
Analyses based on n = 33 for serum AGEs, n = 33 for dicarbonyls, and n = 27 for skin autofluorescence.

Table S8. Association of dialysis vintage with advanced glycation endproducts and dicarbonyls in participants with chronic kidney disease stage 5 dialysis

Biomarker	Ratio (95%CI)	*P* value
CML_{free}	1.09 (0.99; 1.19)	0.081
$CML_{protein\text{-}bound}$	1.04 (0.95; 1.13)	0.360
CEL_{free}	1.11 (1.02; 1.21)	0.017
$CEL_{protein\text{-}bound}$	1.04 (0.98; 1.10)	0.169
$MG\text{-}H1_{free}$	1.19 (1.06; 1.34)	0.006
$MG\text{-}H1_{protein\text{-}bound}$	1.07 (1.01; 1.13)	0.028
GO	1.05 (0.97; 1.13)	0.235
MGO	1.05 (0.99; 1.11)	0.126
3-DG	1.05 (0.99; 1.11)	0.126
SAF	1.01 (0.94; 1.08)	0.839

Ratios represent the ratio of (geometric mean) levels of the biomarkers per 1 year longer dialysis vintage.
All analyses are adjusted for age, sex and diabetes mellitus.
Abbreviations: 3-DG, 3-deoxyglucosone; CEL, N^{ϵ}-(carboxyethyl)lysine; CI, confidence interval; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; SAF, skin autofluorescence.
Analyses based on n = 27 for serum AGEs, n = 27 for dicarbonyls, and n = 20 for skin autofluorescence.

Table S9. Cross-sectional comparison of participants on hemodialysis and peritoneal dialysis

	Biomarker level*		PD vs. HD*	
Biomarker	HD	PD	Ratio (95%CI)	*P* value
CML_{free}	1783.3 [1550.2-2382.8]	1558.1 [798.7-2357.4]	0.72 (0.52; 0.99)	0.047
$CML_{protein\text{-}bound}$	268.9 [212.8-326.1]	301.3 [149.0-406.7]	0.95 (0.69; 1.29)	0.716
CEL_{free}	1527.3 [1031.3-1733.5]	1058.8 [664.5-1310.4]	0.74 (0.52; 1.06)	0.096
$CEL_{protein\text{-}bound}$	63.9 [46.9-77.8]	57.6 [53.8-62.5]	0.95 (0.77; 1.16)	0.586
$MG\text{-}H1_{free}$	4312.8 [3326.9-5218.6]	2624.8 [1472.7-4479.1]	0.61 (0.39; 0.93)	0.025
$MG\text{-}H1_{protein\text{-}bound}$	62.7 [54.8-71.5]	53.0 [44.5-73.8]	0.85 (0.68; 1.05)	0.117
GO	2653.8 [1865.0-2952.4]	2096.0 [1361.3-3077.9]	0.85 (0.64; 1.12)	0.246
MGO	1217.0 [1015.6-1479.9]	1139.1 [857.0-1519.2]	0.86 (0.70; 1.07)	0.173
3-DG	1518.7 [1388.2-1946.6]	1717.7 [1408.1-1854.9]	0.99 (0.79; 1.24)	0.933
SAF	3.7 ±0.7	3.4 ±0.7	0.97 (0.81; 1.17)	0.748

Ratios represent the ratio of (geometric mean) levels of the biomarkers in participants on peritoneal dialysis relative to participants on hemodialysis.
All analyses are adjusted for age, sex and diabetes mellitus.
Abbreviations: 3-DG, 3-deoxyglucosone; CEL, N^{ϵ}-(carboxyethyl)lysine; CI, confidence interval; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; SAF, skin autofluorescence.
* Analyses based on (hemodialysis/ peritoneal dialysis) n = 20/13 for serum AGEs, n = 20/13 for dicarbonyls, and n = 13/14 for skin autofluorescence.

Table S10. Course of advanced glycation endproducts and dicarbonyls stratified by dialysis modality

		Ratios of biomarker levels following dialysis initiation relative to baseline levels*						Statistical interaction (month)**
		1 month vs. baseline		6 months vs. baseline		12 months vs. baseline		
Biomarkers	Modality	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value	
CML_{free} (nmol/L)	HD	0.90 (0.72; 1.13)	0.373	1.49 (1.19; 1.89)	< 0.001	1.48 (1.16; 1.89)	0.002	Yes
	PD	0.87 (0.69; 1.08)	0.201	0.87 (0.70; 1.09)	0.225	0.99 (0.78; 1.25)	0.920	6 and 12
$CML_{protein\text{-}bound}$ (nmol/mmol lysine)	HD	0.97 (0.86; 1.10)	0.662	1.25 (1.11; 1.42)	< 0.001	1.33 (1.16; 1.51)	< 0.001	No
	PD	0.88 (0.78; 0.99)	0.039	1.11 (0.98; 1.26)	0.088	1.18 (1.04; 1.33)	0.013	
CEL_{free} (nmol/L)	HD	0.94 (0.73; 1.20)	0.605	1.59 (1.23; 2.05)	< 0.001	1.55 (1.19; 2.03)	0.001	Yes
	PD	0.81 (0.63; 1.04)	0.092	0.76 (0.59; 0.97)	0.027	0.85 (0.66; 1.10)	0.207	6 and 12
$CEL_{protein\text{-}bound}$ (nmol/mmol lysine)	HD	1.15 (0.99; 1.34)	0.066	1.23 (1.06; 1.44)	0.009	1.32 (1.13; 1.55)	< 0.001	Yes
	PD	0.95 (0.82; 1.10)	0.475	1.02 (0.88; 1.18)	0.797	0.95 (0.82; 1.11)	0.528	1, 6 and 12
$MG\text{-}H1_{free}$ (nmol/L)	HD	1.00 (0.75; 1.32)	0.973	1.70 (1.28; 2.26)	< 0.001	1.46 (1.08; 1.97)	0.014	Yes
	PD	0.90 (0.69; 1.19)	0.458	0.78 (0.60; 1.03)	0.084	1.02 (0.77; 1.36)	0.891	6 and 12
$MG\text{-}H1_{protein\text{-}bound}$ (nmol/mmol lysine)	HD	1.04 (0.93; 1.15)	0.519	1.15 (1.03; 1.28)	0.012	1.18 (1.06; 1.33)	0.004	Yes
	PD	0.88 (0.79; 0.97)	0.012	0.94 (0.85; 1.04)	0.231	0.97 (0.88; 1.08)	0.633	1, 6 and 12
GO (nmol/L)	HD	0.84 (0.69l 1.02)	0.077	1.37 (1.13; 1.67)	0.002	1.42 (1.16; 1.73)	< 0.001	Yes
	PD	0.90 (0.75; 1.08)	0.253	1.09 (0.90; 1.31)	0.385	1.11 (0.91; 1.34)	0.294	6 and 12
MGO (nmol/L)	HD	0.77 (0.65; 0.92)	0.004	1.06 (0.89; 1.26)	0.526	1.07 (0.89; 1.29)	0.457	No
	PD	0.89 (0.75; 1.06)	0.188	0.99 (0.83; 1.17)	0.876	1.07 (0.90; 1.28)	0.426	
3-DG (nmol/L)	HD	0.86 (0.76; 0.98)	0.027	0.92 (0.80; 1.04)	0.186	0.96 (0.84; 1.10)	0.530	Yes
	PD	1.02 (0.90; 1.15)	0.774	0.99 (0.87; 1.12)	0.864	0.84 (0.74; 0.95)	0.007	1
SAF (AU)	HD	1.00 (0.93; 1.08)	0.948	0.97 (0.90; 1.04)	0.378	0.96 (0.89; 1.04)	0.329	No
	PD	0.97 (0.90; 1.06)	0.522	1.00 (0.92; 1.08)	0.919	0.98 (0.90; 1.06)	0.556	

Ratios represent the ratio of (geometric mean) levels of the biomarkers at the respective time point after dialysis initiation or kidney transplantation relative to baseline levels based on a linear mixed model containing categorical time, dialysis modality, an interaction term between categorical time and dialysis modality, age, sex, diabetes mellitus, and a random intercept.

Abbreviations: 3-DG, 3-deoxyglucosone; AU, arbitrary units; CEL, N^{ϵ}-(carboxyethyl)lysine; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; NA, not applicable; SAF, skin autofluorescence.

* Analyses based on (baseline/ 1/ 6/ 12 months) n = 41/ 41/ 40/ 35 for serum advanced glycation endproducts, n = 37/ 41/ 40/ 35 for dicarbonyls, and n = 38/ 37/ 40/ 34 for skin autofluorescence, respectively.

** Yes if $P_{interaction} < 0.100$ for the interaction term between categorical time and dialysis.

Table S11. Course of advanced glycation endproducts and dicarbonyls stratified by dialysis modality with additional adjustment for estimated residual glomerular filtration rate

		Ratios of biomarker levels following dialysis initiation relative to baseline levels*						Statistical interaction (month)**
		1 month vs. baseline		6 months vs. baseline		12 months vs. baseline		
Biomarkers	Modality	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value	
CML_{free} (nmol/L)	HD	0.92 (0.79; 1.08)	0.312	1.22 (1.03; 1.44)	0.021	1.19 (0.99; 1.42)	0.064	Yes
	PD	0.81 (0.68; 0.96)	0.014	0.78 (0.66; 0.93)	0.005	0.83 (0.69; 1.00)	0.048	6 and 12
$CML_{protein\text{-}bound}$ (nmol/mmol lysine)	HD	0.96 (0.86; 1.08)	0.532	1.27 (1.12; 1.44)	< 0.001	1.32 (1.16; 1.51)	< 0.001	Yes
	PD	0.87 (0.77; 0.99)	0.038	1.04 (0.92; 1.19)	0.500	1.08 (0.94; 1.24)	0.249	6 and 12
CEL_{free} (nmol/L)	HD	0.97 (0.81; 1.16)	0.728	1.30 (1.01; 1.57)	0.009	1.24 (1.01; 1.52)	0.044	Yes
	PD	0.75 (0.61; 0.92)	0.005	0.73 (0.59; 0.89)	0.002	0.73 (0.59; 0.90)	0.004	1, 6 and 12
$CEL_{protein\text{-}bound}$ (nmol/mmol lysine)	HD	1.16 (0.99; 1.35)	0.062	1.23 (1.05; 1.46)	0.013	1.29 (1.08; 1.54)	0.006	Yes
	PD	0.98 (0.83; 1.16)	0.796	0.97 (0.82; 1.15)	0.696	0.83 (0.70; 1.00)	0.049	6 and 12
$MG\text{-}H1_{free}$ (nmol/L)	HD	1.03 (0.80; 1.32)	0.828	1.40 (1.08; 1.83)	0.013	1.16 (0.87; 1.55)	0.297	Yes
	PD	0.83 (0.63; 1.09)	0.179	0.75 (0.57; 0.99)	0.039	0.86 (0.64; 1.14)	0.287	6
$MG\text{-}H1_{protein\text{-}bound}$ (nmol/mmol lysine)	HD	1.03 (0.92; 1.14)	0.619	1.15 (1.03; 1.28)	0.016	1.17 (1.04; 1.32)	0.010	Yes
	PD	0.89 (0.79; 0.99)	0.038	0.92 (0.82; 1.03)	0.139	0.94 (0.83; 1.06)	0.280	1, 6 and 12
GO (nmol/L)	HD	0.84 (0.73; 0.97)	0.021	1.23 (1.06; 1.43)	0.008	1.23 (1.05; 1.45)	0.012	No
	PD	0.90 (0.77; 1.06)	0.192	1.04 (0.88; 1.21)	0.668	1.03 (0.97; 1.22)	0.726	
MGO (nmol/L)	HD	0.78 (0.68; 0.91)	0.002	0.96 (0.82; 1.13)	0.650	0.94 (0.80; 1.11)	0.464	No
	PD	0.89 (0.76; 1.05)	0.177	0.94 (0.80; 1.10)	0.437	1.02 (0.85; 1.21)	0.863	
3-DG (nmol/L)	HD	0.87 (0.76; 1.00)	0.043	0.91 (0.79; 1.05)	0.193	0.94 (0.81; 1.09)	0.403	No
	PD	0.98 (0.85; 1.14)	0.828	0.98 (0.85; 1.14)	0.822	0.82 (0.70; 0.96)	0.012	
SAF (AU)	HD	1.02 (0.94; 1.10)	0.628	0.99 (0.92; 1.08)	0.875	0.94 (0.86; 1.03)	0.199	No
	PD	0.96 (0.88; 1.06)	0.450	1.00 (0.91; 1.10)	0.949	0.95 (0.86; 1.05)	0.274	

Ratios represent the ratio of (geometric mean) levels of the biomarkers at the respective time point after dialysis initiation or kidney transplantation relative to baseline levels based on a linear mixed model containing categorical time, dialysis modality, an interaction term between categorical time and dialysis modality, age, sex, diabetes mellitus, $eGFR_{residual}$ and a random intercept.

Abbreviations: 3-DG, 3-deoxyglucosone; AU, arbitrary units; CEL, N^{ϵ}-(carboxyethyl)lysine; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; NA, not applicable; SAF, skin autofluorescence.

* Analyses based on (baseline/ 1/ 6/ 12 months) n = 41/ 41/ 40/ 35 for serum advanced glycation endproducts, n = 37/ 41/ 40/ 35 for dicarbonyls, and n = 38/ 37/ 40/ 34 for skin autofluorescence, respectively.

** Yes if $P_{interaction} < 0.100$ for the interaction term between categorical time and dialysis.

Table S12. Course of advanced glycation endproducts and dicarbonyls stratified by dialysis modality with additional adjustment for serum β2-microglobulin

		Ratios of biomarker levels following dialysis initiation relative to baseline levels*						Statistical interaction (month)**
		1 month vs. baseline		6 months vs. baseline		12 months vs. baseline		
Biomarkers	Modality	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value	Ratio (95%CI)	*P* value	
CML_{free} (nmol/L)	HD	0.82 (0.66; 1.01)	0.063	1.04 (0.82; 1.32)	0.762	0.86 (0.65; 1.14)	0.294	Yes
	PD	0.77 (0.61; 0.97)	0.025	0.76 (0.60; 0.96)	0.022	0.79 (0.62; 1.01)	0.064	6
$CML_{protein\text{-}bound}$ (nmol/mmol lysine)	HD	0.93 (0.83; 1.04)	0.193	1.11 (0.97; 1.26)	0.123	1.08 (0.93; 1.26)	0.312	No
	PD	0.85 (0.75; 0.96)	0.009	1.01 (0.90; 1.14)	0.847	1.00 (0.88; 1.15)	0.958	
CEL_{free} (nmol/L)	HD	0.86 (0.68; 1.10)	0.229	1.13 (0.86; 1.47)	0.371	0.92 (0.68; 1.24)	0.579	Yes
	PD	0.71 (0.55; 0.93)	0.012	0.71 (0.55; 0.93)	0.013	0.71 (0.53; 0.93)	0.016	6
$CEL_{protein\text{-}bound}$ (nmol/mmol lysine)	HD	1.13 (0.97; 1.31)	0.128	1.14 (0.95; 1.36)	0.148	1.13 (0.92; 1.40)	0.229	Yes
	PD	0.96 (0.81; 1.14)	0.640	0.95 (0.80; 1.12)	0.547	0.80 (0.67; 0.96)	0.017	12
$MG\text{-}H1_{free}$ (nmol/L)	HD	0.91 (0.69; 1.19)	0.468	1.14 (0.84; 1.54)	0.401	0.78 (0.55; 1.11)	0.167	Yes
	PD	0.78 (0.58; 1.05)	0.103	0.72 (0.54; 0.97)	0.030	0.79 (0.58; 1.09)	0.147	6
$MG\text{-}H1_{protein\text{-}bound}$ (nmol/mmol lysine)	HD	1.00 (0.90; 1.11)	0.970	1.05 (0.93; 1.18)	0.440	1.02 (0.89; 1.18)	0.440	Yes
	PD	0.87 (0.78; 0.97)	0.014	0.90 (0.80; 1.01)	0.061	0.89 (0.79; 1.01)	0.060	1 and 6
GO (nmol/L)	HD	0.78 (0.66; 0.92)	0.004	1.09 (0.91; 1.31)	0.358	0.99 (0.81; 1.21)	0.917	No
	PD	0.88 (0.73; 1.05)	0.161	1.03 (0.86; 1.23)	0.768	1.00 (0.83; 1.22)	0.969	
MGO (nmol/L)	HD	0.73 (0.61; 0.87)	< 0.001	0.88 (0.72; 1.06)	0.168	0.78 (0.63; 0.96)	0.023	No
	PD	0.87 (0.72; 1.05)	0.150	0.92 (0.76; 1.11)	0.395	0.98 (0.80; 1.20)	0.829	
3-DG (nmol/L)	HD	0.86 (0.75; 0.98)	0.025	0.88 (0.75; 1.02)	0.078	0.88 (0.75; 1.04)	0.134	No
	PD	0.98 (0.84; 1.13)	0.754	0.98 (0.84; 1.13)	0.759	0.80 (0.69; 0.94)	0.008	
SAF (AU)	HD	1.02 (0.94; 1.10)	0.693	0.98 (0.90; 1.07)	0.658	0.92 (0.83; 1.03)	0.148	No
	PD	0.96 (0.87; 1.06)	0.402	1.00 (0.91; 1.10)	0.988	0.94 (0.85; 1.04)	0.225	

Ratios represent the ratio of (geometric mean) levels of the biomarkers at the respective time point after dialysis initiation or kidney transplantation relative to baseline levels based on a linear mixed model containing categorical time, dialysis modality, an interaction term between categorical time and dialysis modality, age, sex, diabetes mellitus, serum β2-microglobulin and a random intercept.

Abbreviations: 3-DG, 3-deoxyglucosone; AU, arbitrary units; CEL, N^{ϵ}-(carboxyethyl)lysine; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; NA, not applicable; SAF, skin autofluorescence.

* Analyses based on (baseline/ 1/ 6/ 12 months) n = 41/ 41/ 40/ 35 for serum advanced glycation endproducts, n = 37/ 41/ 40/ 35 for dicarbonyls, and n = 38/ 37/ 40/ 34 for skin autofluorescence, respectively.

** Yes if $P_{interaction} < 0.100$ for the interaction term between categorical time and dialysis.

Figure S1. Flowchart depicting the derivation of the cross-sectional and longitudinal study populations

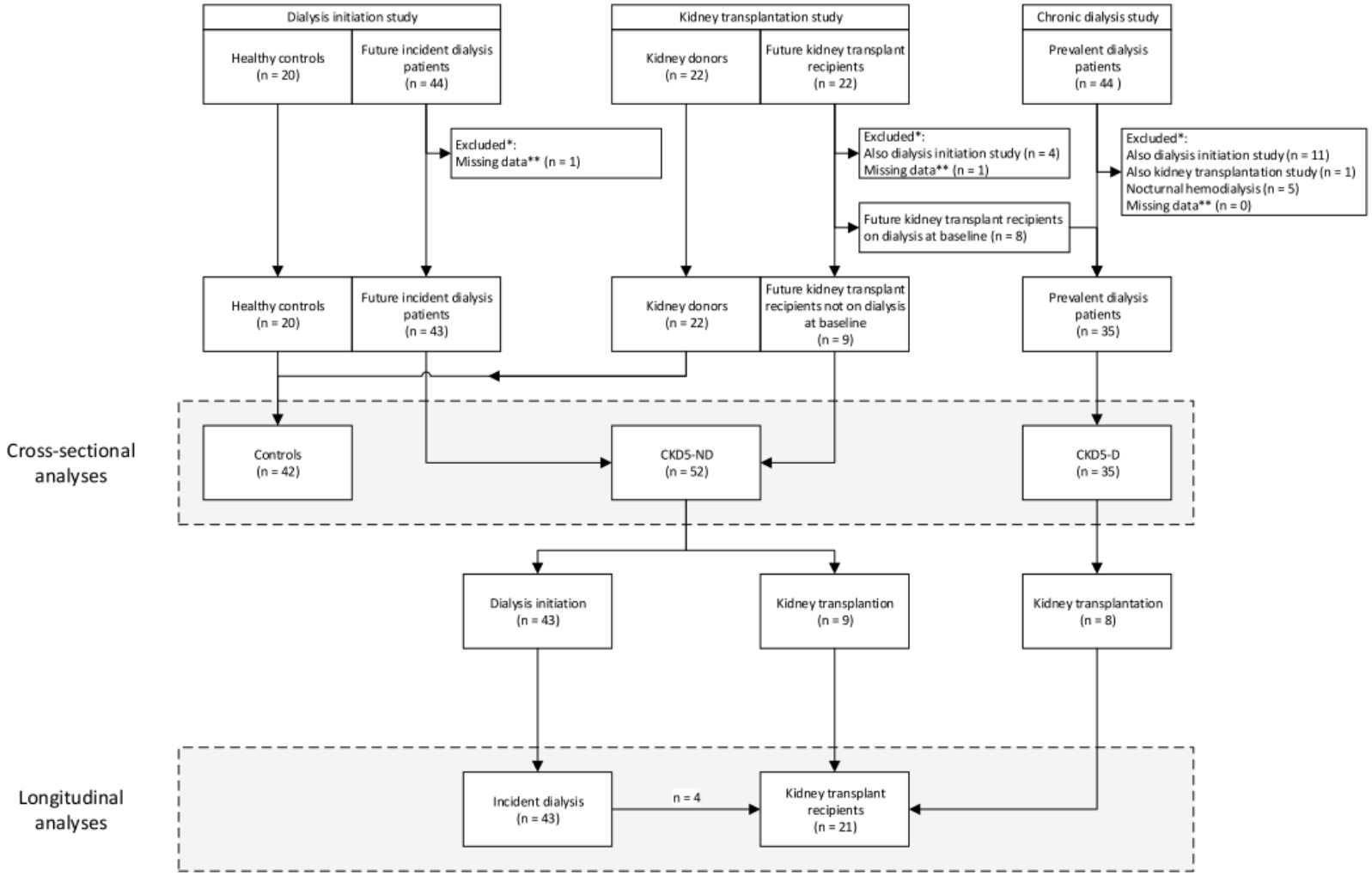
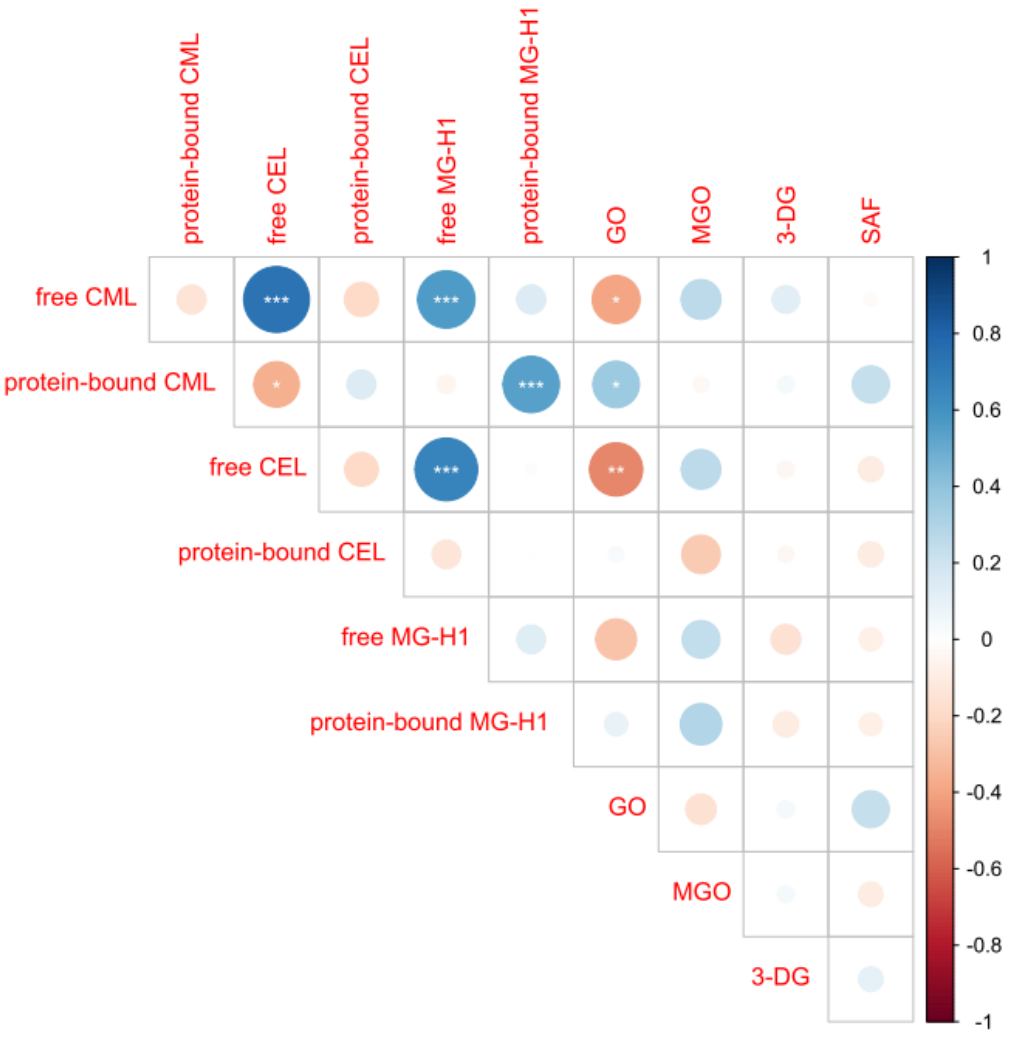


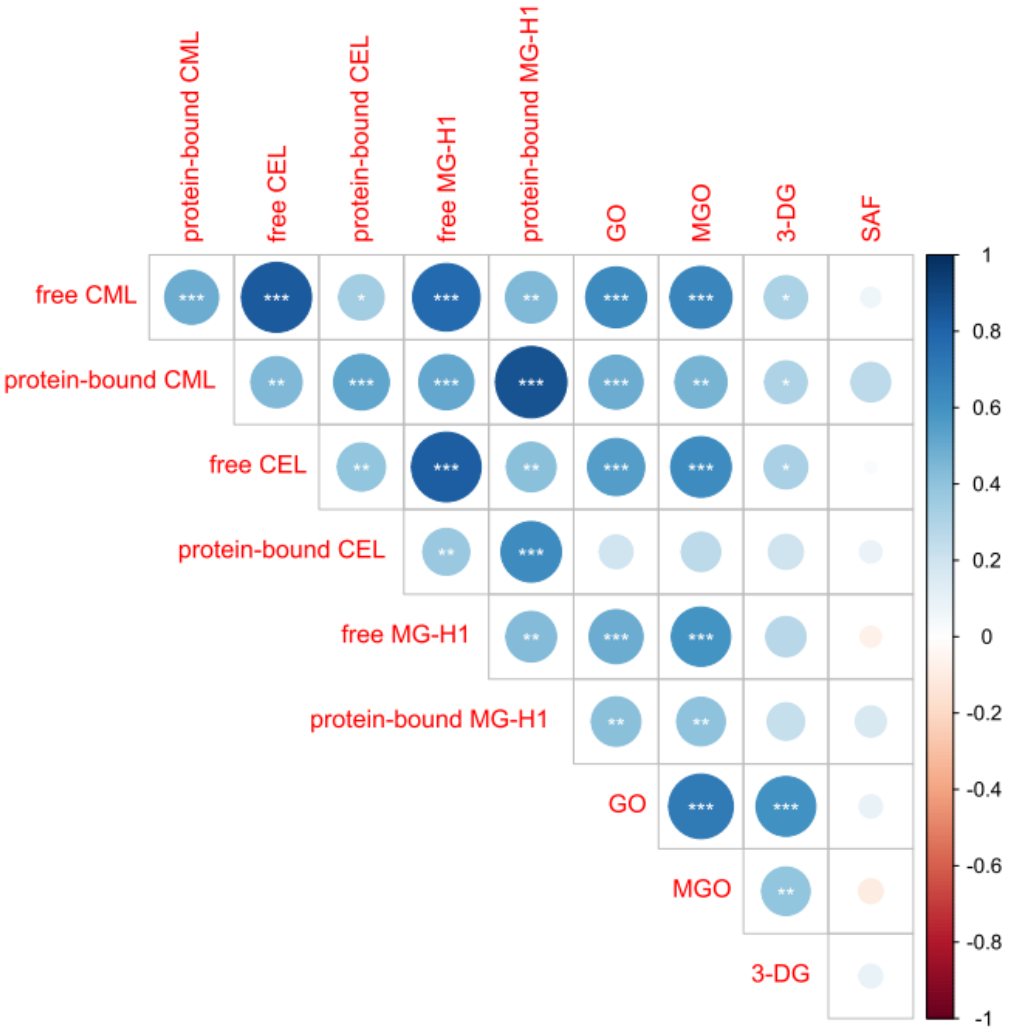
Figure S1. Flowchart depicting the derivation of the cross-sectional and longitudinal study populations. Abbreviations: CKD5-D, chronic kidney disease stage 5 dialysis; CKD5-ND, chronic kidney disease stage 5 non-dialysis. * Participants were sequentially excluded for the reasons described in the figure (*i.e.* counts are mutually exclusive). ** Missing data indicates absence of data on serum advanced glycation endproducts, serum dicarbonyls and skin autofluorescence at baseline.

Figure S2. Correlation matrices between advanced glycation endproducts and dicarbonyls stratified by participant group

A. Controls



B. CKD5-ND


protein-bound CML
free CEL
protein-bound CEL
free MG-H1
protein-bound MG-H1
GO
MGO
3-DG
SAF
free CML
protein-bound CML
free CEL
protein-bound CEL
free MG-H1
protein-bound MG-H1
GO
MGO
3-DG
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

C. CKD5-D

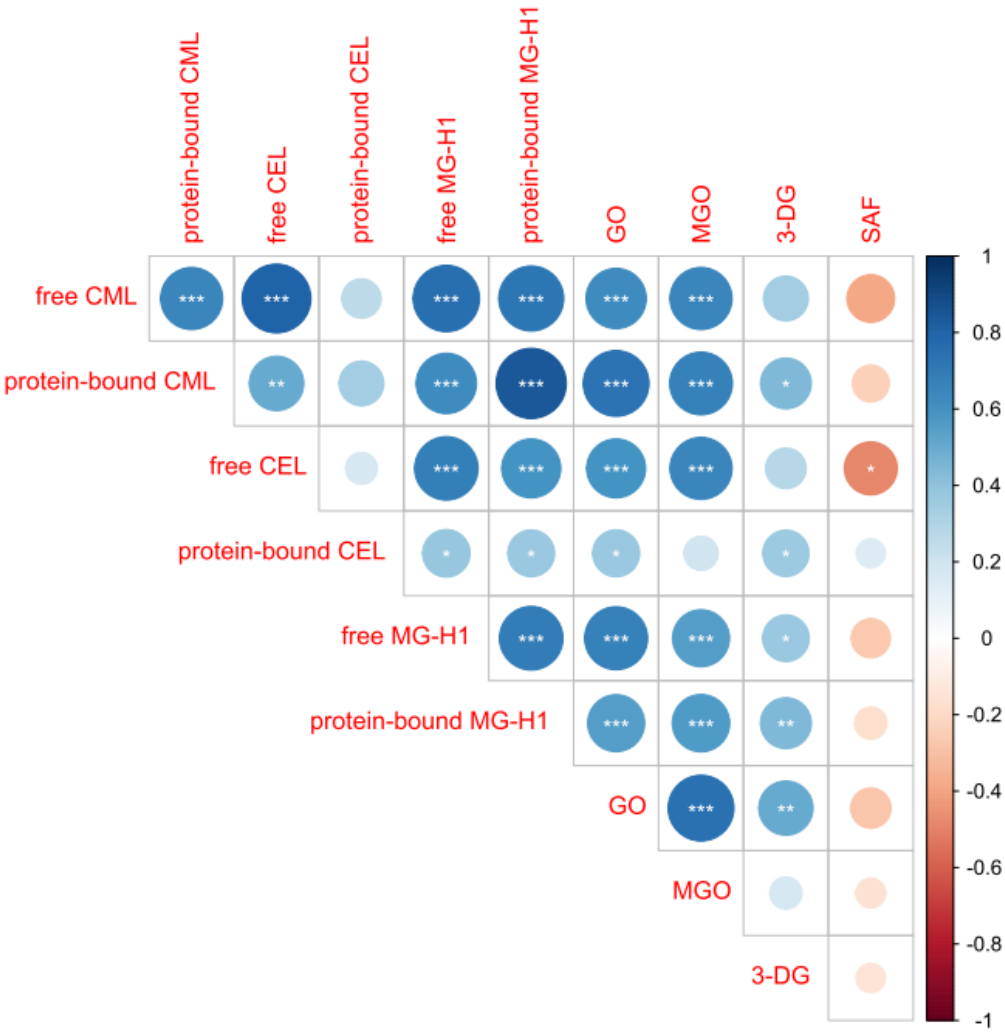


Figure S2. Correlation matrices between advanced glycation endproducts and dicarbonyls stratified by participant group. Circle area and color indicate strength of Spearman's rank correlation coefficients. Abbreviations: 3-DG, 3-deoxyglucosone; CEL, N^{ϵ}-(carboxyethyl)lysine; CKD5-D, chronic kidney disease stage 5 dialysis; CKD5-ND, chronic kidney disease stage 5 non-dialysis; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; MG-H1, N_{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; SAF, skin autofluorescence. * $P < 0.050$, ** $P < 0.010$, *** $P < 0.001$.

Figure S3. Boxplots of serum advanced glycation endproducts, dicarbonyls and skin autofluorescence over time in incident dialysis patients stratified by dialysis modality

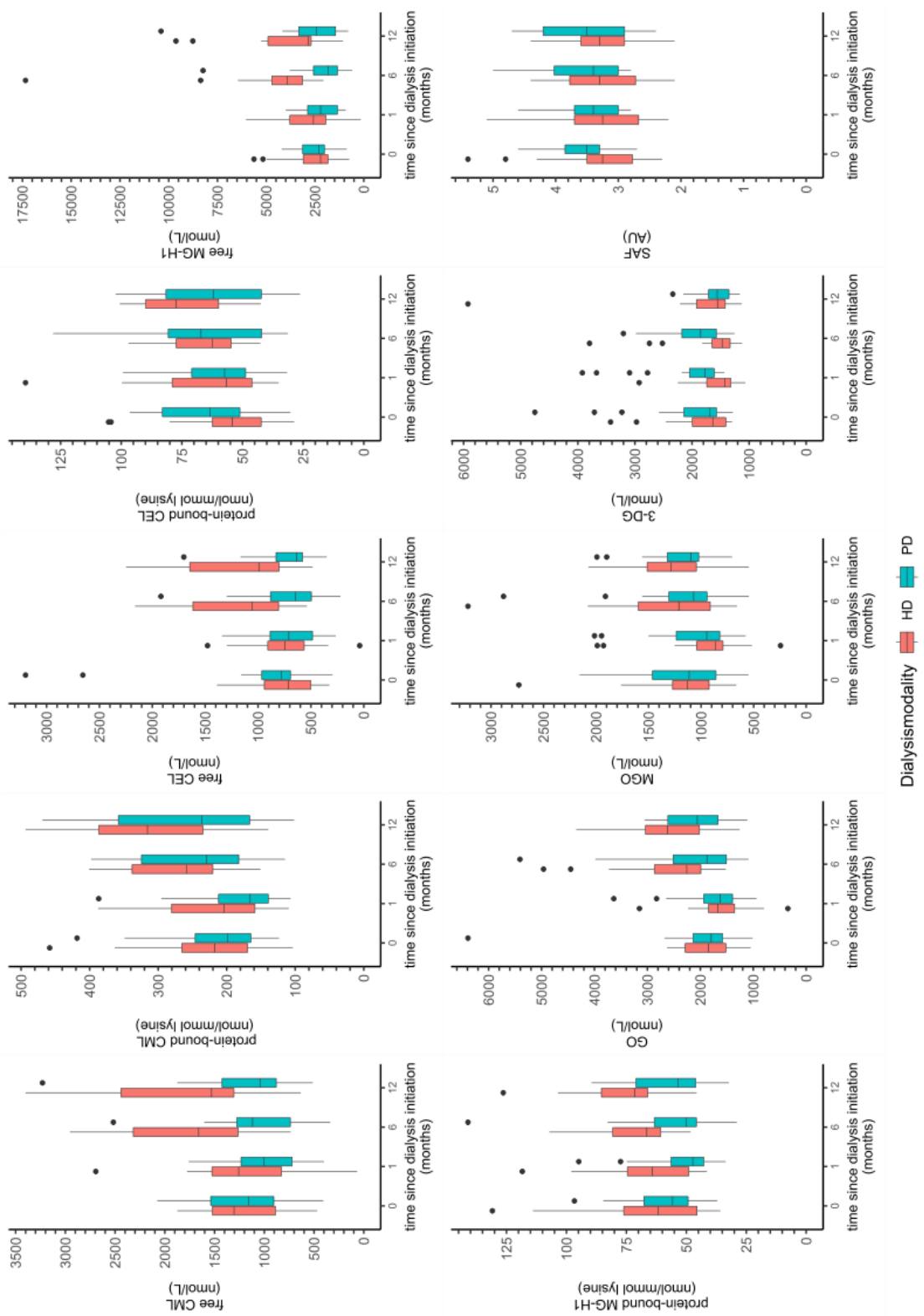


Figure S3. Boxplots of serum advanced glycation endproducts, dicarbonyls and skin autofluorescence over time in incident dialysis patients stratified by dialysis modality. Abbreviations: 3-DG, 3-deoxyglucosone; CEL, N^{ϵ}-(carboxyethyl)lysine; CML, N^{ϵ}-(carboxymethyl)lysine; GO, glyoxal; HD, hemodialysis; MG-H1, $N\delta$-(5-hydro-5-methyl-4-imidazolon-2-yl)ornithine; MGO, methylglyoxal; PD, peritoneal dialysis; SAF, skin autofluorescence.