Supplementary information

Supplementary BOX 1: The ubiquitin–proteasome system and small ubiquitin-like modifiers (SUMO)

The ***ubiquitin–proteasome system*** coordinates covalent lysine 48-linked poly-ubiquitination of proteins, in a process that involves ubiquitin-activating enzyme E1, a ubiquitin carrier protein E2 and a ubiquitin-protein ligase enzyme E3. Such poly-ubiquitination marks the target protein for proteasomal degradation. Of note, protein poly-ubiquitination can also be mediated through other lysines of ubiquitin, which can trigger alterations in protein–protein interactions, rather than induce protein degradation.

SUMOylation involves a covalent protein modification by a small ubiquitin-like modifier (SUMO) peptide as single or multiple monomers or as polymers in an enzymatic process that highly resembles that of ubiquitination, involving an activating E1 enzyme, a conjugating E2 enzyme and an E3 ligase. SUMOylation is highly transient and, like ubiquitination, can have different destination outcomes: it can impact cellular localization or protein–protein interactions, alter protein stability, either by promoting the ubiquitination and proteasomal degradation of its target protein as shown for polymeric SUMOylation, or conversely, by protecting proteins from ubiquitination–proteasomal degradation as shown for SUMO monomers in competition with ubiquitin for binding to lysine in target proteins[1].

Supplementary BOX 2: Vascular calcification

Vascular calcification involves the deposition of calcium phosphate crystals in the vasculature, mainly in the form of hydroxyapatite crystals. This deposition can occur either in atherosclerotic lesions (intimal calcification) or within the medial layer of the arterial wall (medial calcification); aortic valves are also prone to calcification. A complex network of mediators and mechanisms contributes to vascular calcification, driven by an imbalance between calcification inhibitors (for example, fetuin A, carboxylated matrix gla protein, pyrophosphate, uromodulin) and calcification promoters (for example, hyperphosphatemia and uraemic retention solutes in CKD). In the context of medial calcification, vascular smooth muscle cells (VSMCs) undergo a process of osteogenic transition, driven

by master transcription factors (RUNX family transcription factor 2 (RUNX2), Msh homeobox 2 (MSX2), Osterix, SOX9) and characterized by the upregulation of osteochondrogenic proteins (for example, bone morphogenetic protein 2 (BMP2), alkaline phosphatase (ALP)) compared with downregulation of markers of a contractile VSMC phenotype (for example, SM22-α and α-SMA). Osteogenic transition is also observed in valvular interstitial cells in the context of aortic valve calcification. Furthermore, medial calcification has been linked to extracellular vesicle secretion and processes of inflammation, mitochondrial dysfunction, oxidative and endoplasmic reticulum stress as well as cellular apoptosis[2-5], whereas autophagy has a protective role[6].

Supplementary BOX 3: Epigenetics and CKD-associated pathophysiological mechanisms

Nuclear DNA is packaged with histones into chromatin. Epigenetic modifications affect chromatin structure and gene expression through post-translational modifications of DNA and histones or by affecting non-coding RNAs. Epigenetic post-translational modifications include DNA methylation and histone modifications (acetylation, methylation, ubiquitination and phosphorylation).

Nucleic acid methylation represses gene expression when present in gene promoter regions and regulates mRNA transcription, elongation and splicing when present in transcribed regions[7].

Histone deacetylation triggers chromatin compression and thereby reduces gene transcription, in contrast to histone acetylation[7]. Histone deacetylases comprise HDAC1–11, grouped in class I, II and IV, as well as the sirtuins (SIRT1–7) in class III[8]. In addition to histone deacetylation, HDACs and SIRTs are implicated in several (patho)physiological processes through protein deacetylation. Epigenetic mechanisms involved in kidney fibrosis[8], cardiac fibrosis[9] and oxidative stress, inflammation and fibrosis in diabetic kidney disease[7,10] have been reviewed elsewhere.

Supplementary Tables

Supplementary Table 1. Overview of selected clinical studies on non-enzymatic post-translational modifications of lipoproteins and proteins in relation to CKD progression and/or CVD in CKD patients. This table provides full details to the studies summarized in **BOX 1** in the main manuscript.

Modified molecule	Observed association	Patient cohort	Ref
AOPP	Increased plasma AOPP levels as independent risk factor for poor kidney outcome (50% reduction in baseline creatinine clearance or start of dialysis) after a mean follow-up of 5.4 years (Hazard ratio: 1.09 per 10 micromol/L, 95% CI [1.00-1.18]; P= 0.042)	120 patients with IgAN	[11]
AOPP	Significant increase in the severity score of coronary artery disease comparing patients in the highest vs. lowest quartile of plasma AOPP level; Adjusted odds ratio of coronary artery disease per one unit increase of plasma AOPP: 1.02; 95% CI [1.002-1.03]; P=0.026	392 patients who underwent coronary angiography	[12]
AOPP	Serum AOPP levels are an independent predictor of occlusive atherosclerotic cardiovascular events (including coronary, cerebral, or peripheral artery occlusive accidents) in patients with non-diabetic CKD patients in the predialysis phase over a follow-up of 5-8 years (Adjusted hazard ratio: 1.68; 95% CI [1.12-2.51]; P = 0.011)	80 uraemic predialysis patients without diabetes with a creatinine clearance ranging from 20 to 40 mL/min/1.73 m^2	[13]
AOPP	Accumulation of serum AOPP is an independent risk factor for the presence of ischemic heart disease in haemodialysis patients (Adjusted odds ratio: 1.028; 95% CI [1.019–1.036]; P=0.000), but not in patients treated with continuous ambulatory peritoneal dialysis	2095 CKD patients with kidney failure: 1539 on haemodialysis, 556 on continuous ambulatory peritoneal dialysis	[14]
AOPP	L-shaped association between serum AOPP and all-cause mortality in HD patients over a median follow-up of 5.2 years, with a positive association of serum AOPP and all-cause mortality (per SD increment; hazard ratio: 1.24; 95%CI [1.08-1.42]) in patients with AOPP ≥ 87 µmol/L; a similar trend was observed for cardiovascular mortality	1394 patients on maintenance haemodialysis	[15]
Carbonylation of ApoB100 of LDL by malondialdehyde	Malondialdehyde (MDA)-modified LDL as a risk factor for aortic stiffness in patients on haemodialysis (Odds ratio per increase with 1 mg/dL: 1.014; 95% CI[1.007-1.021]; P<0.001); best cut-off serum	155 patients on haemodialysis	[16]

	value of logarithmically transformed MDA-LDL: 80.33 mg/dL with AUC 0.721 (95% CI [0.643–0.790], P<0.001), sensitivity 80.88% (95% CI [69.5%–89.4%]), and specificity 57.47% (95% CI [46.4%–68%])		
Oxidized HDL	A combination of high oxidized HDL (oxHDL) and high interleukin-6 levels was significantly associated with a higher increase in carotid intima-media thickness at 3-year follow-up; oxHDL is a risk factor for cardiovascular events and cardiovascular mortality in CKD patients on haemodialysis, especially with concomitant high levels of interleukin-6	412 patients on haemodialysis	[17]
Carbamylated protein lysine residues (N-ε-carbamyllysine; also termed 'homocitrulline')	Plasma levels of protein-bound homocitrulline predicted cardiovascular events in CKD patients on haemodialysis at five years follow-up (Adjusted hazard ratio: 3.0; 95% CI [1.8-5.0] comparing highest vs. lowest tertiles; P<0.01)	347 patients undergoing maintenance haemodialysis	[18]
	Plasma levels of protein-bound homocitrulline (PBHcit) predicted risk of major adverse cardiac events (MACE) over a 3-year follow up in subjects with largely preserved kidney function (Adjusted odds ratio for incident MACE (revascularization, myocardial infarction, stroke or death) in highest quartile (PBHcit ≥ 0.42 mmol/mol Lys) compared to lowest quartile (PBHcit ≤ 0.12 mmol/mol Lys): 5.0; 95% CI [2.8-8.7])	275 patients who underwent diagnostic cardiac catheterization and experienced MACE in the 3-year period after study enrollment; 275 age- and gender-matched control subjects	[19]
Carbamylated LDL	Increased LDL carbamylation as predictor of cardiovascular events in patients with CKD over a median follow-up of 4.7 years (For carbamylated LDL > 28.1 µg/mg LDL compared to carbamylated LDL ≤ 28.1 µg/mg LDL: adjusted hazard ratio 3.36; 95% CI [1.38-8.18]; P=0.008; adjusted for age, sex, high sensitivity-C-reactive protein, diabetes mellitus, prevalent coronary artery disease and eGFR)	96 patients with proven CKD	[20]
Carbamylated HDL	Independently associated with CKD progression (doubling of serum creatinine and/or initiation of kidney replacement therapy) in diabetic kidney disease after a mean follow-up of 9 years (Adjusted hazard ratio for doubling of serum creatinine: 1.55; 95% CI [1.38-1.73]; P<0.001; adjusted for age, sex, BMI, duration of diabetes, smoking, systolic blood pressure, HbA1c, baseline eGFR, albuminuria status, ACEI/ARB therapy, lipid-lowering therapy, LDL cholesterol and HDL cholesterol)	1320 patients with type 2 diabetes with baseline eGFR ≥30 ml/min per 1.73 m^2	[21]

Carbamylated sortilin	Associated with coronary artery calcification and indicative of a faster calcification progression in CKD over a median follow-up time of 4.4 years	17 CKD patients without sortilin carbamylation and 61 CKD patients with at least one sortilin carbamylation	[22]
Carbamylated albumin	Independent risk factor for CKD progression (progression to kidney failure or 50% reduction in eGFR) in patients with CKD stage 2-4 over an average of 7.9 years of follow-up: compared with quartile 1 (carbamylated-albumin ≤5.80 mmol/mol), those in quartile 4 (carbamylated-albumin >10.71 mmol/mol) had a greater risk for kidney failure (adjusted hazard ratio, 2.29; 95% CI [1.75 to 2.99]	3111 patients with CKD stages 2-4	[23]
Carbamylated albumin	Risk factor of mortality in patients with kidney failure: Baseline % carbamylated-albumin in serum was higher in kidney failure patients who died within 1 year than in those who survived longer than 1 year (1.01% versus 0.77%; P<0.001) and was associated with an increased risk of death within 1 year (hazard ratio of 3.76; 95% CI [2.20–6.43], P<0.0001)	187 CKD participants on haemodialysis	[24]
Guanidinylated apolipoprotein C3 (gApoC3)	Associated with accelerated progression of CKD (50% reduction in eGFR or reaching kidney failure) and increased mortality as well as with an increase in cardiovascular events in CKD over a median follow-up time of 5.3 years For the combined renal endpoint (death, 50% reduction in eGFR or reaching kidney failure): comparing highest with lowest tertile of gApoC3: adjusted hazard ratio: 3.17; 95% CI [1.98-5.06]; P<0.001) For atherosclerotic cardiovascular event and cardiovascular death: comparing highest with lowest tertile of gApoC3: adjusted hazard ratio: 2.08; 95% CI [1.39-3.11]; P=0.001)	543 CKD patients	[25]
Glycated hemoglobin (HbA1c)	Could only be identified as an independent risk factor for CKD progression (reaching kidney failure or 50% reduction in eGFR) in patients with diabetic CKD with low carbamylation but not in those with high carbamylation over a median follow-up of 6.9 years Patients with low carbamylation:	1516 patients with diabetes and CKD	[26]

	Adjusted hazard ratio for every 1% increase in HbA1c: 1.23; 95% CI [1.11–1.36] Patients with high carbamylation: Adjusted hazard ratio for every 1% increase in HbA1c: 0.98; 95% CI [0.89–1.09]		
Accumulation of symmetric dimethylarginine (SDMA) in HDL	Strong, inverse correlation of SDMA serum levels with kidney function (eGFR) Significant positive association between SDMA serum levels und SDMA in the HDL fractions (R^2 = 0.66, P < 0.0001) in patients with kidney impairment In patients with low serum levels of SDMA, higher HDL-cholesterol was associated with a significant, dose-dependent decrease in cardiovascular mortality In contrast, in patients with high serum levels of SDMA, higher HDL-cholesterol was associated with an increase in cardiovascular mortality Hazard ratios for cardiovascular mortality over a median follow-up of 9.9 years comparing highest vs. lowest SDMA quartile and after adjustment for age, sex, high-sensitive CRP, eGFR, body mass index, diabetes, smoking status, acute coronary syndrome, lipid-lowering therapy, Friesinger score, haemoglobin, albumin: For patients with low serum SDMA: ≤0.8 µmol/L (<90th percentile): Adjusted hazard ratio 0.69; 95% CI [0.52–0.92]; P=0.012 For patients with high serum SDMA: >0.8 µmol/L (>90th percentile): Adjusted hazard ratio 1.93; 95% CI [1.11-3.35]; P=0.020	3316 patients undergoing coronary angiography	[27]

AGE, advanced glycation end-products; AOPP, advanced oxidation protein products; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HD, haemodialysis; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Supplementary Table 2. Effect of non-enzymatic post-translational modifications (PTM) on lipoproteins, albumin, collagen and fibrinogen in CKD. PTM identifications in CKD patients or animal models are highlighted in grey. Indicated fold increases of PTMs were extracted from the referenced manuscripts, either from the text, tables or bar graphs, as available. For patient analyses, the modified amino acids have been indicated, whenever available. This table provides full details to the studies summarized in **Table 2** of the main manuscript.

LOW-DENSITY LIPOPROTEIN (LDL): non-enzymatic post-translational modifications in CKD

Modification	Observed effect	CKD Patient population / cell type	Ref
Oxidation	ApoB100 on LDL is oxidized in CKD (>90 oxidative PTMs identified in patients and controls)	CKD patients on haemodialysis with high levels of MPO and circulating MPO-LDL	28
	LDL is increasingly oxidized with CKD progression (1.3-fold upregulation in CKD stage G5 compared to CKD stage G3, *determined by ELISA*)	CKD stage G5 compared to CKD stage G3	29
	Oxidation confers LDL with increased pro-inflammatory properties such as induction of ROS, macrophage foam cell formation and apoptosis, endothelial activation and stiffening through binding to SR-A1, LOX1 and/or CD36	Macrophages, endothelial cells	30,31
Carbonylation	Carbonylation of ApoB100 of LDL by malondialdehyde (MDA-LDL) is a risk factor for aortic stiffness in haemodialysis patients Compared to controls, MDA-LDL was increased 1.2-fold in CKD patients and 1.7-fold specifically in CKD patients with aortic stiffness *(MDA-LDL quantified via ELISA)*	CKD patients on haemodialysis	16
Carbamylation	Carbamylated LDL is increased 3.7-fold in CKD vs. healthy controls *(measured by ELISA)*	CKD patients on haemodialysis	32
	LDL from CKD patients shows in average a carbamylation of 54 ± 4 lysine residues, whereas none were detected in LDL from healthy controls. A higher LDL carbamylation extent predicted increased cardiovascular events in patients with CKD.	CKD patients	20
	The *in vivo* clearance of carbamylated LDL as well as that of LDL isolated from haemodialysis patients is reduced	CKD patients on haemodialysis	33
	Carbamylated LDL induces endothelial cell death	Human coronary artery endothelial cells	32
	Carbamylated LDL (catalyzed by MPO) triggers cholesterol accumulation and foam cell formation in macrophages via SR-A1 but not CD36	Mouse peritoneal macrophages	19

	Increasing urea levels in CKD mice enhance LDL carbamylation along with increasing atherosclerosis	CKD mouse model on high-fat diet	34
	Carbamylated LDL reduces endothelial eNOS phosphorylation, nitric oxide (NO) production and endothelium-dependent vasorelaxation, but induces endothelial ROS production via the LOX-1 receptor and NADPH-oxidase activation	Mouse aortic rings and human aortic endothelial cells	20
Glycation / AGE-modified LDL	CKD patients have higher levels of AGE-modified LDL: The lipid part displayed a 17-fold (CKD stage G5 without diabetes), respectively, 27-fold (CKD stage G5 without diabetes) increase in AGE content compared to controls The protein part (ApoB) displayed a 9-fold (CKD stage G5 without diabetes), respectively, 24-fold (CKD stage G5 without diabetes) increase in AGE content compared to controls *(AGE content determined by ELISA)*	Patients in CKD stage G5	35
	AGE-LDL triggers pro-inflammatory cytokine production in endothelial cells and macrophages AGE-LDL triggers inflammatory signaling via interaction with TLR4, RAGE or CD36	Human coronary artery endothelial cells and human- and mouse-macrophages	36

HIGH-DENSITY LIPOPROTEIN (HDL): non-enzymatic post-translational modifications and other alterations in CKD

Modification	Observed effect	CKD Patient population / cell type	Ref
Oxidation	Oxidized HDL is a risk factor for cardiovascular events and cardiovascular mortality in CKD patients on haemodialysis, especially with concomitant high levels of interleukin-6 *(Oxidized HDL analyzed by ELISA using anti-oxidized ApoA1 antibody; No healthy controls included as comparison.)*	CKD patients on haemodialysis	17
	Oxidized HDL triggers pro-inflammatory signaling (MAPK/NF-kB) and ROS production in kidney proximal tubule epithelial cells via CD36. Oxidized HDL also increases cell apoptosis and reduces cell migration capacity	Human renal proximal tubule epithelial cells (HK-2)	37
	Oxidized HDL triggers endoplasmic reticulum stress, ROS production, lipid accumulation and apoptosis in macrophages via TLR4	RAW264.7 macrophages	38

	Oxidized HDL triggers LOX1 receptor expression as well as pro-inflammatory signaling (NF-kB) and ROS production in endothelial cells	HUVEC-derived endothelial cell line; Human aortic endothelial cells	[39]
	Oxidized HDL triggers the osteogenic differentiation and calcification of valvular interstitial cells along with inducing alkaline phosphatase	Human valvular interstitial cells	[40]
Carbonylation / HDL modification by by-products of lipid peroxidation, e.g. 4-HNE	CKD patients present with increased carbonylation of HDL by 4-HNE, mainly allocated to ApoA1 *(A relative increased presence of HNE-Michael adducts was detected on 48 amino acids (lysine or histidine) from eight constitutive proteins of HDL from haemodialysis patients compared to controls)*	CKD patients on haemodialysis	[41]
	Distinct from the anti-aggregant properties of native HDL, HNE-modified HDL increases platelet aggregation and activation through CD36 and downstream SRC tyrosine kinase signaling	Human platelets	[41]
Carbamylation	Patients with kidney failure display a 2.1-fold increased level of carbamylated HDL *(Carbamylated HDL measured by ELISA)*	Patients with kidney failure on maintenance haemodialysis	[42]
	Patients with kidney failure display a 1.49-fold increased level of carbamylated paraoxonase-1 (an HDL-associated anti-oxidant) in HDL *(Quantified by ELISA)* Carbamylation of lysine 290 (K290) of PON-1, a residue adjacent to the PON-1 activity determining site, was detected in HDL from CKD patients but not detected in control HDL	Patients with kidney failure on maintenance haemodialysis	[43]
	Carbamylated HDL is significantly increased in diabetic CKD patients with CKD stage G3b (4.4-fold increase) and CKD stage G4 (6-fold increase) compared to healthy controls (eGFR>60) Carbamylated HDL is independently associated with CKD progression in diabetic kidney disease *(Carbamylated HDL measured by ELISA)*	Patients with diabetic kidney disease	[21]
	Whereas native HDL has an anti-apoptotic effect via SR-B1, carbamylated HDL (catalyzed by MPO or cyanate) did not or even induced apoptosis (dependent on the used cells)	Bovine aortic endothelial cells and human coronary artery endothelial cells	[19]
	HDL carbamylation reduces endothelial proliferation and migration	Human arterial endothelial cells	[42]

	Carbamylated HDL disturbs the balance in SR-BI-mediated cholesterol uptake vs. efflux, resulting in a net cholesterol uptake in macrophages	Human monocytic THP-1-derived macrophages or mouse RAW264.7 macrophages	44
Accumulation of uraemic retention solutes in HDL, e.g. symmetric dimethylarginine (SDMA)	HDL from CKD patients revealed increased amounts of SDMA (~7.2-fold) but not ADMA compared to controls	CKD patients stage G5	45
	SDMA-enriched HDL abolishes the anti-inflammatory properties of HDL: In contrast to healthy HDL, it reduces endothelial NO production but increases NADPH-oxidase activity and ROS production, fails to reduce endothelial VCAM-1 expression and increases monocyte adhesion to endothelial cells. CKD-HDL and SDMA-enriched HDL trigger pro-inflammatory signaling through TLR2	HDL from CKD patients or enriched with SDMA; Human aortic endothelial cells; Bovine aortic endothelial cells	27,45
Accumulation of pro-inflammatory proteins in HDL of CKD patients, e.g. serum amyloid A (SAA)-1	HDL from CKD patients revealed Increased amounts of SAA1 compared to controls (6.4-fold[46] to 8.2-fold[47] in haemodialysis vs. control)	Patients in CKD stage G4 and CKD stage G5 on haemodialysis	46-48
	SAA-enriched HDL displays increased uptake in macrophages but reduced cholesterol efflux capacity	Mouse J774 macrophages	49
	SAA-enrichment of HDL abrogates the anti-inflammatory action of HDL in LPS-stimulated human monocytes	Human monocytes	48
	HDL-bound SAA triggers pro-inflammatory cytokine expression in vascular smooth muscle cells and aortic tissue by signaling through TLR2 and TLR4	Rat aortic vascular smooth muscle cells and aortic tissue	50

Apolipoprotein C3 as main component of the very-low-density lipoprotein particles (VLDL): non-enzymatic post-translational modifications in CKD

Modification	Observed effect	CKD Patient population / cell type	Ref
Guanidinylation of apolipoprotein C3	ApoC3 is guanidinylated (gApoC3) in a CKD mouse model (2-3 Lysines guanidinylated) and in CKD patients (on Lysine 44), with gApoC3 in CKD patients associated with increased mortality, accelerated progression of CKD and an increase in cardiovascular events	CKD mouse model, CKD patients	25
	Guanidinylation of ApoC3 - but not carbamylation - increases the pro-inflammatory properties of ApoC3: it enhances the release of interleukin-1β and interleukin-6 as well as ROS production in human	Human monocytes	25

	monocytes, with gApoC3 showing an increased binding affinity to the TLR4 receptor compared to native ApoC3.		
	In vivo, gApoC3 but not native ApoC3 enhances kidney fibrosis and inflammatory cell accumulation after unilateral ureteral ligation in mice, and inhibits re-endothelialization after carotid artery injury, revealing a detrimental role of gApoC3 in CKD progression as well as in endothelial regeneration capacity	Mouse model of kidney fibrosis Mouse model of vascular endothelial denudation	[25]

ALBUMIN: non-enzymatic post-translational modifications in CKD

Modification	Observed effect	CKD Patient population / cell type	Ref
Oxidation / AOPP-modification / Carbonylation	Oxidative stress increases the levels of AOPPs (by 4.7-fold in haemodialysis patients), carried to a high degree by the plasma protein albumin, as shown in patients with advanced CKD as well as dialysis patients	Patients with advanced CKD (creatinine clearance < 20 ml/min) and patients on dialysis	[51]
	Albumin is increasingly carbonylated in both non-dialyzed patients and dialyzed CKD patients, which is further increased in individuals with diabetes compared to those without: *Non-diabetic haemodialysis patients: 1.25-increase in carbonyl content in purified albumin vs. controls[52];* *Diabetic haemodialysis patients: 1.35-increase in carbonyl content in purified albumin vs. controls[52];* *CKD stage G3 patients: 1.45-fold increase in albumin carbonylation vs. controls[53];* *CKD stage G4 patients: 1.82-fold increase in albumin carbonylation vs. controls[53]*	CKD patients without or with diabetes	[52,53]
	Albumin from haemodialysis patients is increasingly carbonylated compared to control albumin	CKD patients on haemodialysis	[54]
	A study circumventing lipidic interference confirmed an association of increased serum AOPP levels with increased mortality risk in dialysis patients, with a similar trend for cardiovascular mortality	CKD patients on dialysis	[15]

	AOPP-modified albumin blocks the binding of HDL to SR-B1, which suppresses SR-BI-mediated HDL-cholesterol ester uptake in the liver and thus plasma clearance of HDL-cholesterol ester	Cell culture, BALB/c mice	[54]
	In podocytes, AOPP-modified albumin triggers pro-inflammatory signaling and ROS production via RAGE	Murine podocytes	[55]
	In proximal tubular cells, AOPPs mainly induce ROS via scavenger receptor CD36	Human kidney proximal tubular cells (HK2)	[56]
	In rats subjected to 5/6 nephrectomy, injection of AOPP-modified albumin accelerates kidney hypertrophy, macrophage accumulation and kidney fibrosis	CKD mouse model	[57]
	Carbonylated albumin displays a pro-inflammatory effect by triggering neutrophil ROS production	Human neutrophils	[52]
	AOPP-modified albumin triggers pro-inflammatory chemokine expression via RAGE	Human embryonic kidney 293 cells (HEK293)	[58]
	AOPP-modified albumin impairs endothelial barrier function and induces cellular senescence	Human umbilical vein endothelial cells (HUVECs)	[59]
	AOPP-modified albumin increases plasma TNFα levels and enhances atherosclerosis	Hypercholesterolemic rabbits injected with AOPP-modified albumin	[60]
	AOPP-modified albumin induces endoplasmic reticulum stress and apoptosis in cardiomyocytes	H9C2 rat cardiomyoblast cells	[61]
	Oxidized albumin increases platelet CD40 ligand expression, platelet adherence to endothelium under flow conditions as well as endothelial tissue factor expression through platelet-endothelial interaction	Human platelets and human coronary artery endothelial cells	[62]
	AOPPs isolated from haemodialysis patients as well as albumin-AOPPs promoted platelet aggregation, at least partly through the CD36 platelet receptor	Human platelets	[62]
Carbamylation	Albumin carbamylation is strongly associated with CKD progression (progression to kidney failure or 50% reduction in eGFR) in patients with CKD stage G2-G4 and a risk factor of mortality in patients with kidney failure	Patients with CKD stage G2-G4, patients with kidney failure (CKD stage G5)	[23,24, 63]
	Carbamylated albumin reduces oxidative and signaling responses of neutrophils to collagen I stimulation, but without impact on neutrophil adhesion to collagen	Human neutrophils	[64]

Guanidinylation	Albumin shows increased lysine guanidinylation in CKD, with guanidinylation identified at positions 249, 468, 548, 565 and 588	Patients with CKD stage G5 on dialysis	65
	Guanidinylation of albumin decreases its binding to hydrophobic metabolic waste molecules such as indoxyl sulfate	n.a.	65
Glycation / AGE-modification	Haemodialysis patients displayed increased levels of AGE-modified albumin compared to healthy controls, with a further increase in patients with diabetes compared to those without diabetes: *Non-diabetic haemodialysis patients: 2.95-increase in AGE content in purified albumin vs. controls*[52]*;* *Diabetic haemodialysis patients: 3.90-increase in AGE content in purified albumin vs. controls*[52]	Haemodialysis patients without vs. with diabetes	52
	Glycated albumin stimulates the expression of TGFβ1, fibronectin and collagen-IV	Murine kidney glomerular mesangial cells	66
	Glycated albumin triggers ROS production and pro-inflammatory signaling in macrophages	Macrophage RAW cells; Macrohages derived from human monocyte-derived U937 cells	67,68
	Glycated albumin triggers a pro-inflammatory and pro-thrombotic phenotype but lower metabolic activity in endothelial cells	Human umbilical vein endothelial cells	69
	Glycated albumin stimulated collagen-IV production in glomerular endothelial cells	Murine glomerular endothelial cell line	70
	Glycated albumin increases agonist-induced platelet activation and aggregation, with a stronger effect observed for longer albumin glycation times. In parallel, albumin glycation increases the expression of the glycoprotein IIb/IIIa integrin (CD41, being the platelet receptor for fibrinogen) and the platelet activation marker P-selectin	Human platelets	71,72

COLLAGEN: non-enzymatic post-translational modifications in CKD

Modification	Observed effect	CKD Patient population / cell type	Ref
Carbamylation	In a mouse model fed with cyanate, return to standard diet reduced protein carbamylation in plasma by 99% after 9 weeks, but extracellular matrix proteins such as type I collagen showed only a 45% reduction in carbamylation extent	Mice fed with cyanate (to mimick high uraemic conditions as observed in CKD)	73

	Carbamylated proteins accumulated in plasma as well as in tissue of CKD mice, including in kidney, heart and aorta, with a pronounced progressive accumulation observed for type 1 collagen extracted from tissue (skin, tail) during CKD progression	CKD mouse model (75% nephrectomy)	74
	Carbamylation reduces the capacity of collagen I to trigger intracellular signaling and ROS production by neutrophils	Human neutrophils	75
	Carbamylation of type 1 collagen impairs its capacity to polymerize into fibrils	n.a.	75
	Carbamylation of type 1 collagen induces collagen sensitivity to matrix metalloproteinase (MMP)-mediated proteolysis	n.a.	76
	Carbamylation of type 1 collagen enhanced monocyte adhesion and MMP9 release compared to native collagen	Human blood monocytes	77
Glycation	Treatment of diabetic rats with an AGE inhibitor reduced readouts of collagen cross-linking in parallel to reducing diabetes-induced vascular stiffness	Wistar rats with streptozotocin-induced diabetes	78
	Collagen glycation increases the adhesion of activated monocytes, but decreases the adhesion of non-activated monocytes.	Human monocytes	79

FIBRINOGEN: non-enzymatic post-translational modifications in CKD

Modification	Observed effect	CKD Patient population / cell type	Ref
Carbonylation	Fibrinogen from CKD patients demonstrated a higher degree of carbonylation compared to controls	CKD patients with kidney failure treated with peritoneal dialysis	80
	Carbonylation of fibrinogen did not directly affect coagulation time nor the fibrin fiber thickness in resulting clots	n.a.	80
Carbamylation	Dialysis patients demonstrated enhanced fibrinogen carbamylation: *(quantification of homocitrulline (=carbamylated lysine) in isolated fibrinogen revealed a 2.3-fold increase in haemodialysis patients vs. controls)*	CKD patients on haemodialysis	81
	Carbamylation of fibrinogen resulted in impaired fibrin polymerization and crosslinking, reduced mechanical strength and enhanced clot resistance to fibrinolysis	n.a.	81
Guanidinylation	CKD patients demonstrated guanidinylation of fibrinogen (on lysine)	CKD patients on chronic haemodialysis	82

	Fibrinogen purified from haemodialysis patients triggered the formation of thinner fibers and a reduced clot porosity in an *in vitro* clot formation assay compared to fibrinogen from healthy controls. Similar effects on clot properties were observed when using *in vitro* guanidinylated fibrinogen	n.a.	[82]
Glycosylation	CKD patients demonstrated glycosylation of fibrinogen (on threonine)	CKD patients on chronic haemodialysis	[82]

ADMA, asymmetric dimethylarginine; AOPP, advanced oxidation protein products; eNOS, endothelial nitric oxide synthase; 4HNE, 4-hydroxy-2-nonenal (a reactive carbonyl species); LOX-1, lectin-like- oxidized LDL receptor 1; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form, NADPH); RAGE, receptor for advanced glycation end-products; ROS, reactive oxygen species; SAA, serum amyloid A; SDMA, symmetric dimethylarginine; SR-A1, scavenger receptor (SR)-A1; TLR, Toll-like receptor.

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