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## **Renal insufficiency and chronic kidney disease – promotor or consequence of pathological post-translational modifications**

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## Vitae (100w CV authors)

- **Jonas Laget** is a young researcher investigating CKD pathophysiology, with a background on adipose tissue in type 2 diabetes. Jonas Laget is involved in the pre-clinical evaluation of innovative therapeutic compounds for the prevention of kidney fibrosis and vascular calcification, in terms of pathophysiological, histological, biochemical and molecular aspects.
- **Flore Durantou** is a scientist working on CKD-related questions mainly analysing the performances of diagnostic and prognostic factors, including circulating markers (uremic toxins, proteins, amino acids, lipids) and urinary markers (proteomics) to better understand CKD, improve its detection and limit its impact.
- **Àngel Argilés** is a senior renal physician and research director with high expertise on CKD and bone mineral metabolism. He has been working in clinical nephrology and renal replacement techniques since early eighties mainly in France. After being Research Director at the Centre National de la Recherche Scientifique, he founded the private laboratory RD-Néphrologie where he performs research investigating different CKD aspects.
- **Nathalie Gayraud** is a senior scientist specialised in histology and biochemistry who has devoted her career to study the pathophysiology of CKD. She currently develops drugs that have been proven effective to prevent vascular calcification or fibrosis in preclinical models of CKD.

## Abstract

More than 840 million people, representing almost 10% of world population, were estimated to have chronic kidney disease (CKD) in 2017. In CKD, many systemic changes relative to oxidative stress, inflammation, energy balance or neuroendocrine signalling are observed and can be linked to dysfunctional proteins, including protein post-translational modifications (PTMs). Recent technical advances enabled the detection of PTMs and allowed understanding their participation in CKD pathophysiology and kidney damage. In this review article, the interconnections between CKD and PTMs, both as causes and consequences, are described. PTMs, particularly non-enzymatic PTMs, are frequently observed in CKD, as they are the direct consequence of systemic changes following the decline in kidney function. Other PTMs, mainly enzymatic ones, are critical for proper kidney physiology. Still, both types of PTMs have been shown to induce damage not only in kidney but also in other organs (brain, cardiovascular system). Therapeutic approaches focusing on metabolic changes responsible for PTMs alteration have shown interesting results. Targeting specific PTMs responsible for kidney damage is also being considered, which could lead to the development of innovative treatments.

## Keywords

CKD, ESRD, PTMs, proteins,

## List of abbreviations (excluding protein names\*)

AGE	Advanced glycation end-product
AOPP	Advanced oxidation protein product
ATP	Adenosine triphosphate
CKD	Chronic kidney disease
DMAPT	Dimethylaminoparthenolide
ECM	Extracellular matrix
eGFR	Estimated glomerular filtration rate
EMT	Epithelial to mesenchymal transition
ESRD	End-stage renal disease
GalNAc	N-acetylgalactosamine
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
GlcNAc	N-acetylglucosamine
GPI	Glycosylphosphatidylinositol
HbA1c	Glycated haemoglobin
IMA	Ischemia-modified albumin
Lys	Lysine
NO	Nitric oxide
PTM	Post-translational modification
ROS	Reactive oxygen species
UUO	Unilateral ureteral obstruction

\* Protein abbreviations are detailed in the Table

## 1. Introduction

The synthesis of functional proteins requires polypeptide chains assembly by ribosomes during mRNA translation, followed by chemical modifications often enzymatically driven called post-translational modifications (PTMs). Physiological PTMs mainly involve protein cleavage and amino acid side chain modifications (Knorre, Kudryashova and Godovikova, 2009). PTMs may be necessary for adequate protein binding, for protein function, to regulate protein activity, or inform on protein localization and addressing. PTMs are also involved in pathological processes, a classical example being protein glycation leading to cataract in diabetes (Stevens, 1998).

More than 840 million people, representing over 10% of world population, were estimated to have chronic kidney disease (CKD) in 2017 (Jager *et al.*, 2019). In Western societies with ageing populations, the prevalence of CKD increases, as well as the risk of end-stage renal disease (ESRD), the ultimate and irreversible stage of CKD. ESRD patients depend on costly renal replacement therapies (renal transplantation or regular dialysis) that usually represent 2% of healthcare costs, for less than 0.2% of the population (Vanholder *et al.*, 2017). Preventing ESRD is a public health challenge that requires a thorough understanding of molecular pathways involved in kidney pathophysiology.

The kidney is a central organ in maintaining body homeostasis, mainly blood composition, modifying water, ion and metabolic waste products (McMahon, 2016). Classically, three functions have been identified in the kidneys: filtering through the glomerular membrane, reabsorbing by the tubule and secreting at different levels of the nephron. In addition, an endocrine function has also been described as the kidney synthesises, activates or catabolises a myriad of metabolically active substances exerting local or distant effects. The interrelation between the different functions of the kidney is crucial to the maintenance of the *milieu interieur* described by Claude Bernard (Bernard, 1878). Perturbations in these functions likely result in increased molecular half-life and concentrations in blood and tissues, increased time of contact with endogenous and exogenous toxic agents, and alterations in enzymatically mediated systems, altogether favouring accumulation of enzymatic and non-enzymatic PTMs of proteins. In turn, there are evidence showing that PTMs could induce processes involved in the pathogenesis of CKD, such as the development of persistent fibrosis, possibly involving epithelial to mesenchymal transition (EMT), (Oldfield *et al.*, 2001; Lovisa *et al.*, 2015; Hewitson *et al.*, 2017).

In this review, we evaluated the links between PTMs and CKD, starting from a summary of how CKD may favour the appearance of PTMs, followed by the description of non-enzymatic and enzymatic PTMs associated with kidney diseases, and finally describing ways to prevent or modify the PTMs burden in CKD. A schematic summary of the review is provided in the Figure.

## 2. CKD, a state favouring PTMs generation

### 2.1. Altered tubular metabolism favouring PTMs

The glomerular basement membrane (GBM) is a barrier that has been classically believed to have a cut-off around 50 kDa, meaning that all those compounds of higher molecular weight would not pass through the GBM and remain in the circulation. Although this has been recently challenged, it is clear that most of the proteins and peptides under 40 kDa freely pass the GBM and are presented to the proximal tubules that absorb and catabolize practically all of them. This can be illustrated by serum Beta-2 microglobulin (B2M\*, \*see Table), a 99-amino acid protein of 11.8 kDa, that is filtered by the glomerulus and catabolised by the proximal tubule. Blood B2M levels increase in CKD, reaching levels more than 30 fold higher than normal in patients with ESRD. Renal transplantation results in a decrease in the elevated levels of serum B2M, but seldom succeeds in restoring a normal level (< 3 mg/L). In CKD, the reduction of filtration capacity of the kidneys and the frequent comorbidities add

up and induce elevations in serum level of low molecular weight compounds. The reduced renal catabolism makes low molecular weight proteins and peptide more prone to PTMs. B2M has long been considered a structural protein with no metabolic activity. However, glycated-B2M may have pathological implications in dialysis-related amyloidosis (Miyata *et al.*, 1993). More recently, B2M has also been shown to participate in physiological mechanisms driving the catabolism of proteins at the tubular level. B2M is also the light chain of the neonatal Fc receptor (FcRn\*) heterodimer (Jones and Waldmann, 1972). FcRn has two binding sites, one for albumin and the other one for immunoglobulins (Kuo *et al.*, 2010) and would participate in the transfer of immunoglobulins from the mother to the foetus in the placenta (Story, Mikulska and Simister, 1994). In the proximal tubule, FcRn influences the reabsorption of albumin distributing normal albumin to the basolateral membrane and peritubular vessels while altered albumin will mainly go to the lysosomes and the urinary lumen. This organised triage increases the half-life of normal albumin, while limiting the presence of PTM-albumin which is discarded to final urine. This specific pathway to process albumin by tubules challenges the cut-off concept of the GBM as it was previously understood, since albumin, a 67 kDa protein, was supposed to remain in the blood stream and not pass the GBM reaching the tubules (Dickson *et al.*, 2014).

## **2.2. Altered hormonal and enzymatic activities in CKD**

Resistance to metabolic effects is a general feature of CKD that may favour the generation of PTMs. Resistance can occur at different levels, from an alteration in the synthesis or activity of proteins such as hormones and enzymes, to downstream abnormalities affecting mediators or receptors involved in the solicited pathway. For instance, in CKD, the activity of parathyroid hormone is affected by changes in its fragments displaying opposite effects (Nakajima *et al.*, 2009). In the case of vitamin D, changes in enzymatic activation by 1 $\alpha$ -hydroxylation, or inactivation by 24-hydroxylation as well as in the resultant action of the vitamin D receptor responsive elements in target cells can also modify its activity in CKD (reviewed in (Bikle, 2014)). Another example of an altered enzymatic function in CKD is serum paraoxonase/arylesterase 1 (PON1\*), a key component of the antioxidant activity of high density lipoproteins (Suematsu *et al.*, 2019). In CKD, PON1 activity is reduced, possibly explaining the loss of the protective properties of HDL cholesterol in these patients. Interestingly, PON1 has detoxifying enzymatic activity as it removes N-homocysteinylation from proteins, hence limiting pathological PTMs (Jakubowski, 2019). It has been demonstrated that haemodialysis results in a significant dose- and time-dependent increase in the activity of PON1 (Gugliucci *et al.*, 2007). In conclusion, limited PON1 activity in CKD participates in PTMs accumulation and is prevented by hemodialysis therapy. This highlights that a large array of metabolic modifications occur in CKD which should be taken into account when hoping to decipher mechanisms involved in CKD-related biological changes including PTM generation.

## **2.3. Inflammation and oxidative stress in CKD**

Oxidative stress is an important cause of PTMs (Hawkins and Davies, 2019). In the course of CKD and end-stage renal disease (ESRD), a chronic inflammatory state develops which is characterized by oxidative stress and sustained immune dysregulation (Descamps-Latscha, Drüeke and Witko-Sarsat, 2001). Zimmermann *et al* (Zimmermann *et al.*, 1999) observed that the serum level of C-reactive protein, a marker of inflammation, was a powerful independent predictor of both overall and cardiovascular mortality in hemodialysis patients. In a cohort of CKD patients, inflammation defined by C-reactive protein level over 10 mg/L was observed in 32% of CKD patients and malnutrition in 44% of patients (Stenvinkel *et al.*, 1999). Protein energy wasting or cachexia is frequent in CKD and affects protein metabolism, possibly influencing PTMs generation. In CKD patients, it was shown that sarcopenia and low muscle strength were associated with greater protein carbonylation, a PTM induced by oxidative stress (Song *et al.*, 2020). Interventions targeting the inflammatory state have proven to be successful in CKD (Akchurin and Kaskel, 2015), and are expected to limit pathological PTMs in these patients.

Albumin has the capacity of binding transition metal ions, but this property can be lost after exposure to an ischemic situation turning albumin into Ischemia-Modified Albumin (IMA), (Sinha *et al.*, 2004). IMA is a marker of cardiac ischaemia (Sinha *et al.*, 2004) and could as well be a marker of oxidative stress relevant to other situations (Roy *et al.*, 2006). IMA is increased in CKD and ESRD patients without acute cardiac injury (Turedi *et al.*, 2010). IMA was also reported to increase after dialysis session, but this could also be an artifact due to changes in haemoconcentration (Albarelo *et al.*, 2012; Schneditz *et al.*, 2012). In ESRD patients, IMA was inversely correlated with albumin and haemoglobin levels, and directly with carbonylation (Albarelo *et al.*, 2012). Although the PTM generating IMA is not clearly identified, binding of fatty acids leading to conformational changes has been proposed (Coverdale *et al.*, 2018). Both CKD and chronic inflammation may participate in the increased level of IMA, imposing caution when interpreting rises in this marker.

### 3. PTMs as uremic toxins

CKD is a state favouring PTMs generation, and the limited renal excretion can additionally induce retention of PTM-modified proteins or amino acid residues. The most studied PTMs altered in CKD are discussed below.

#### 3.1. Glycation, glycoxidation and AGEs

Glycation is a non-enzymatic reaction of reducing sugars (mainly glucose) with amino acids, proteins, lipids or nucleic acids. Protein glycation is a PTM corresponding to the Maillard reaction responsible for non-enzymatic food browning. Glycation can occur on N-terminal amino groups of free amino acids and protein-bound amino acid residues to produce fructosamines, which degradation produces advanced glycation end-products (AGEs). The term AGE can refer to glycated proteins covalently binding AGEs adducts (about 95% of total AGE content) or free AGEs (the remaining 5%) (Miyata *et al.*, 1999). Protein glycation can also occur on the side chains of lysine residues to form N $\epsilon$ -1-deoxyfructosyl-lysine which generates AGEs and furosine or, following oxidation (i.e. glycoxidation), carboxymethyllysine. The modification of arginine residues on proteins with reactive dicarbonyl metabolites deriving from oxidative degradation or autooxidation of Amadori products results in AGEs such as methylglyoxal-derived hydroimidazolone adducts, which represents over 90% of AGEs. Pentoses and glucose metabolites can also react with closely located arginine and lysine residues to form the respective cross-linking AGEs pentosidine and glucosepane (Biemel *et al.*, 2001).

It is well known that AGE accumulation occurs in diabetes mellitus and participates in the genesis of its complications (Brownlee, Vlassara and Cerami, 1984; Uchiki *et al.*, 2012). It has also been shown that the blood levels of carboxymethyllysine and other AGEs increase with reducing glomerular filtration rate (GFR) and are even higher in ESRD patients (Floridi, 2002; Semba *et al.*, 2010). In diabetic ESRD patients, Hricik *et al.* reported that, compared to renal transplantation, a combined kidney-pancreas transplantation did not further decrease the level of the AGE pentosidine, suggesting that it is rather the kidney function than the glucose level that is the main factor explaining the formation of AGE adducts in these patients (Hricik *et al.*, 1993). Most likely the decreased metabolism of low molecular weight proteins and peptides is the main factor facilitating this PTM. In patients with normal renal function, the presence of diabetes did not influence free AGE adducts levels while diabetes in ESRD patients was associated with a further increase in free AGE levels (Makita *et al.*, 1994; Floridi, 2002). This confirms that CKD is a major determinant of AGE accumulation and that AGE formation independent of diabetes occurs. During oxidative stress the direct action of reactive oxygen species (ROS) on lipids or carbohydrates produces reactive carbonyl compounds which turn into AGEs (Miyata *et al.*, 1999). This pathway can be further enhanced by reduced concentration and activity of enzymes involved in the detoxification of carbonyl compounds, such as glyoxalase I (Miyata *et al.*, 2001).

Plasma proteins are prone to glycation, which changes their functional and structural properties, notably with the formation of intra- and inter-molecular crosslinking (i.e. polymerisation) leading to protein aggregation and fibril formation. This has been observed for amyloid forming B2M and albumin (Miyata *et al.*, 1993; Bouma *et al.*, 2003). In tissues, extracellular matrix (ECM) proteins such as elastin and collagen are highly susceptible to glycation due to their long half-lives expanding over decades (Toyama and Hetzer, 2013). Glycation of collagen correlates with alterations in mechanical properties of connective tissues (Gautieri *et al.*, 2017). Glycated collagens present differences in charge profiles and a lower solubility (Guitton *et al.*, 1981). Glycation of collagen and laminin induces the formation of intramolecular crosslinks which prevents self-assembly into fibrils (Tsilibary *et al.*, 1988; Charonis *et al.*, 1990). This also prevents fibroblasts from inducing collagen contraction and alters cellular interactions (Haitoglou *et al.*, 1992; Howard *et al.*, 1996). ECM protein glycation is also associated with a reduced production and activation of matrix metalloproteinases (MMPs\*), hereby limiting ECM remodelling (Rittié *et al.*, 1999).

Several receptors binding AGEs have been identified. Receptors can be grouped by effect, some of them inducing cell response, such as the Advanced Glycosylation End Product-specific Receptor (RAGE\*), while others like OST-48\* also referred to as AGER1 participate in AGE turnover (Ott *et al.*, 2014). Because hyperglycaemia promotes AGE generation, the role of RAGE was predominantly studied in models of diabetes mellitus. In diabetic animals, RAGE inactivation with genetic knockout, DNA aptamers and vaccination succeeded in preventing diabetic nephropathy (Reiniger *et al.*, 2010; Matsui *et al.*, 2017; Azegami *et al.*, 2021). These studies confirmed that RAGE is involved in the development of kidney lesions (glomerular hypertrophy, mesangial matrix expansion, thickening of the GBM, altered ECM) leading to clinical signs of renal insufficiency (albuminuria, lower GFR), (Reiniger *et al.*, 2010; Matsui *et al.*, 2017; Azegami *et al.*, 2021). RAGE activation induced the expression of markers of oxidative stress, inflammation (MCP-1\*, ICAM-1\*), fibrosis (TGF- $\beta$ \*, tTG\*, PAI-1\*) and EMT factors (vimentin, e-cadherin, smooth muscle cell  $\alpha$ -actin) in kidneys in vivo and in tubular cells in culture (Oldfield *et al.*, 2001; Reiniger *et al.*, 2010; Sasai *et al.*, 2012).

The AGE-RAGE axis is also relevant to non-diabetic kidney diseases and situations with normoglycemia (Fukami *et al.*, 2015). For instance, in animals with polycystic disease, the administration of anti-RAGE RNA using adenovirus limited cyst growth and loss of renal function (Park *et al.*, 2014). RAGE is expressed on the surface of various cells including endothelial cells, monocytes and macrophages, as well as renal podocytes, mesangial and tubular cells (Fukami *et al.*, 2015). In normal glucose settings, RAGE activation by AGE-proteins induced production of MCP-1 by podocytes (Gu *et al.*, 2006), prooxidative and profibrotic responses (TGF- $\beta$  and fibronectin synthesis, Smad2\* phosphorylation) by mesangial cells via angiotensin II (Fukami *et al.*, 2004) and tubuloepithelial and interstitial lesions with signs of EMT (PDGF\*, TGF- $\beta$ , EGF\*, ET-1\*, CTGF\*, fibronectin, vimentin and e-cadherin overexpression), (Chung *et al.*, 2010; Gross *et al.*, 2011; Huang *et al.*, 2019). The tubular response occurred independently of TGF- $\beta$ , via the RAGE/ERK\*/p38\*/Smad3 cross-talk pathway (Chung *et al.*, 2010). In addition, AGEs-RAGE signalling induced endoplasmic reticulum stress in tubular cells, which was downregulated by calbindin-D28k (Huang *et al.*, 2019). Importantly, kidneys are involved in AGE-proteins catabolism and free AGEs excretion. Mesangial cells present OST-48 on their surface, which binds AGE-proteins and induce their degradation (Lu *et al.*, 2004). Interestingly, in situations with increased AGEs, OST-48 was downregulated and RAGE upregulated (Vlassara *et al.*, 2008). In tubular cells, autophagy participates in AGE degradation and is enhanced by diabetes, but decreased by AGEs overload (Takahashi *et al.*, 2017). Other processes involved in AGE clearance such as ubiquitination are inhibited by glycation (Uchiki *et al.*, 2012). Overall, a positive loop favouring AGE toxicity in pathological state seems to occur. Still, after renal transplantation, a normalization of AGE levels can be observed (Makita *et al.*, 1994).

### 3.2. Carbamylation and homocitrulline



Carbamylation is defined as the non-enzymatic addition of a carbamoyl group (-CONH<sub>2</sub>) on protein or free amino acid functional groups (Kraus and Kraus, 2001). It occurs when isocyanic acid which is produced from urea reacts with amino acids to form covalent bonds. Myeloperoxidase (MPO\*) released from neutrophils and monocytes also produces isocyanate at the site of inflammation, which can induce protein carbamylation. Urea spontaneously dissociates into cyanate which reacts with N-terminal  $\alpha$ -amino groups or  $\epsilon$ -amino groups of lysine side-chains of proteins to irreversibly form carbamylated proteins (Kraus and Kraus, 2001). The latter carbamylation generates  $\epsilon$ -amino-carbamoyl-lysine also called homocitrulline, which is used as a marker of protein carbamylation. Similarly, free amino acids can irreversibly be carbamylated on their  $\alpha$ -amino group, as well as reversibly on side-chain nucleophilic groups, such as hydroxyl groups of tyrosine, serine or threonine and sulfhydryl group of cysteine.

In CKD patients, urea concentration increases exponentially, up to 35 mmol/L or even 60 mmol/L, which is the highest level reported for any uremic toxin (Duranton, Depner and Argilés, 2014). In parallel, the level of cyanate increases from 45 nmol/L in healthy controls to 140 nmol/L in ESRD patients (Nilsson *et al.*, 1996). In ESRD patients, although urea and cyanate blood levels are not correlated, a linear correlation between blood urea levels and protein carbamylation has been reported (Nilsson *et al.*, 1996; Desmons *et al.*, 2016; Kalim *et al.*, 2020). In patients, both carbamylated proteins and free amino acids are observed (Kraus, Jones and Kraus, 1998; Koeth *et al.*, 2013). The importance of plasma carbamylated proteins expressed as a molar ratio of protein-bound homocitrulline to lysine almost doubles in ESRD patients, compared to patients with acute renal failure or controls (Koeth *et al.*, 2013; Desmons *et al.*, 2016). Following the degradation of carbamylated proteins, carbamylated free amino acids cannot be used for protein synthesis, the latter being consequently slowed down by competitive inhibition (Kraus and Kraus, 2001). This mechanism could explain, at least in part, protein wasting observed in CKD patients.

Albumin can be found carbamylated mainly on the lysine (Lys) located on the 549<sup>th</sup> position (Lys-549) of the protein amino acid sequence (Ma *et al.*, 2021). The proportion of carbamylated-albumin found in ESRD patients varies from 1% to 3%, considering modifications of Lys-549 alone and/or on Lys-160, a second carbamylation site (Berg *et al.*, 2013; Ma *et al.*, 2021). In vitro, carbamylation of albumin induced alterations in structure and function, including binding of hydrophobic uremic toxins (Deltombe *et al.*, 2015; Badar *et al.*, 2019). In CKD, carbamylated albumin is associated with adverse outcome including CKD progression, cardiovascular events and mortality (Berg *et al.*, 2013; Kalim *et al.*, 2020). Haemoglobin can be carbamylated on the N-terminal valine residue of globin  $\beta$ -chains. Higher levels of carbamylated haemoglobin have been reported in CKD patients (Smith *et al.*, 1989). Similarly to albumin, carbamylated haemoglobin is directly related to exposure to urea levels and has been proposed as a retrospective index of urea exposure (Kwan *et al.*, 1991). Other blood proteins and lipoproteins including fibrin, fibrinogen, high and low density lipoproteins have been shown to be carbamylated in CKD patients and associated with cardiovascular diseases (Wu, Jankowski and Jankowski, 2021).

Hydroxyhomocitrulline is a recently identified carbamylation product specific to collagen, which has been shown to increase in the blood of uremic patients (Taga *et al.*, 2017). Collagens are the most abundant proteins in the organism and are constitutive of ECM and connective tissues. They are long-lived proteins particularly prone to carbamylation and glycation, which are analogous processes (Kraus and Kraus, 2001; Nicolas *et al.*, 2019). When both PTMs are enhanced by the metabolic state as in CKD with or without diabetes, there is evidence that carbamylation prevails, notably for type I collagen (Nicolas *et al.*, 2019). Although it affects only 1% of available residues, carbamylation of collagen modifies protein structure and function. Carbamylated collagen is less thermally stable and loses the ability to form fibrils and to activate polymorphonuclear leukocytes (Jaisson *et al.*, 2006). Carbamylation inhibited the formation of physiological collagen cross-links (Taga *et al.*, 2017). Carbamylated type I collagen displayed a polyproline II helix structure but did not assembly into triple helix conformation, which prevented degradation by collagenases (MMP1, MMP8, MMP13)

(Jaisson *et al.*, 2007). Still, carbamylated collagen exhibited increased sensitivity to gelatinase MMP2 (Jaisson *et al.*, 2007). In addition, it has been shown that carbamylation inactivates MMP2 produced by mesangial cells, which further participates in altering ECM (Turck *et al.*, 1996). Furthermore, using axolotl kidneys, it was shown that carbamylated albumin promoted tubuloepithelial and interstitial lesions and increased the tubular expression of fibrosis markers (Gross *et al.*, 2011). This is consistent with earlier results showing that exposure of mesangial cells to carbamylated foetal bovine serum proteins increased cell growth and collagen I and IV accumulation (Shaykh *et al.*, 1999). Overall, evidence suggests that carbamylation which occurs because of urea retention in CKD also participates in renal fibrosis progression.

### 3.3. Oxidation, carbonylation and AOPPs

Advanced oxidation protein products (AOPPs) is a term comprising all forms of irreversibly oxidized proteins (Gryszczyńska *et al.*, 2017). AOPPs are characterized by the presence of dityrosine, pentosidine and carbonyl-containing products resulting from oxidative stress, ROS attack, chlorinated stress, or in response to MPO or NADPH oxidase reactions (Witko-Sarsat *et al.*, 1996). Oxidation of lysine, arginine, proline, and threonine residues and reactions with oxidized lipids can also produce carbonylated proteins. Other pathways include protein cleavage,  $\alpha$ -amidation, and oxidation of glutamine side chains. AOPP also induces protein cross-links. Carbonylation of albumin, fibrinogen and haemoglobin have been observed (Witko-Sarsat *et al.*, 1996; Mitrogianni *et al.*, 2009; Madian and Regnier, 2010).

When measured in the plasma, AOPP and carbonylated proteins are shown to increase in CKD patients compared to healthy subjects and even more in hemodialysis patients, notably protein-bound dityrosines and protein carbonyls (Caimi *et al.*, 2013; Colombo *et al.*, 2019). After renal transplantation, carbonylated protein levels were also reduced (Simmons *et al.*, 2005). In fact, AOPP and carbonyls progressively increase with CKD stages (Matsuyama *et al.*, 2009; Azouaou Toulbi *et al.*, 2021). A low-grade inflammation combined with reduced antioxidant protection results in oxidative stress, which directly induces AOPP generation and activates MPO activity resulting in additional AOPP production (Witko-Sarsat *et al.*, 1996; Colombo *et al.*, 2018; Azouaou Toulbi *et al.*, 2021). In a study of 5/6<sup>th</sup>-nephrectomized rats, AOPP administration increased circulating AOPP levels, oxidative stress and macrophage infiltration in the remnant kidney (Li *et al.*, 2007). Chronic administration of AOPPs in diabetic animals increased CKD progression, at the functional (lower GFR, higher albuminuria) and structural (higher hypertrophy, glomerular fibronectin expression) levels, with increased macrophage infiltration, MCP-1 and TGF- $\beta$ 1\* expressions and NADPH oxidase activation in kidneys (Shi *et al.*, 2008). Interestingly, inhibiting NADPH oxidase prevented these signs, suggesting that pro-oxidative effects of AOPP are involved in the progression of CKD (Shi *et al.*, 2008). AOPPs are also known to bind to the RAGE receptor (Guo *et al.*, 2008). By activating the RAGE/Wnt/ $\beta$ -catenin signalling pathway, AOPP promote EMT and consequently renal fibrosis (Feng *et al.*, 2020).

### 3.4. Nitration and nitrotyrosine

Nitration is a chemical process which consists of introducing a nitro group (-NO<sub>2</sub>) into a chemical compound, usually by reaction with peroxynitrite (ONOO<sup>-</sup>). In biological systems, it can affect proteins, lipids and nucleic acids (Pacher, Beckman and Liaudet, 2007). Nitration occurs on transition metal centres of proteins such as haeme in haemoglobin and on amino acid residues cysteine, tyrosine, tryptophan, methionine and histidine. Nitration can modify protein function by gain or inhibition of functions. The most studied nitrated product is nitrotyrosine, which results from the addition of a nitro group to the aromatic ring of tyrosine residues. It can be found in proteins as well as in its free form. Tyrosine nitration occurs on specific sites determined by protein structure and local environment (Barteseaghi *et al.*, 2007). Nonspecific protein nitration and plasma nitrotyrosine are markers of oxidative stress.

Interestingly, in patients with systemic lupus erythematosus, nitration and other oxidative PTMs (i.e. AOPPs and AGEs) levels were higher than in matched controls, and even higher in patients with lupus nephritis (Ene *et al.*, 2021). In CKD patients, increased plasma levels of free nitrotyrosine were reported, as well as higher renal excretion and lower renal clearance, and normalisation after hemodialysis sessions (Agalou *et al.*, 2005). A study comparing the plasma nitroproteome of CKD patients and controls reported a 7 fold increase in the nitrotyrosine to protein ratio in CKD (Piroddi *et al.*, 2011). Many plasma proteins were found nitrated including albumin, fibrinogen, transferrin, and apolipoproteins B and A1 (Piroddi *et al.*, 2011). The relative content of nitrotyrosine in albumin was much lower than for other plasma proteins, suggesting albumin is not a main target of nitration.

In kidneys, nitrotyrosine appears to increase with fibrosis. This was observed in patients with IgA nephropathy and tubulointerstitial fibrosis, in animals models of unilateral ureteral obstruction (UUO), and in kidney epithelial HK2 cells during EMT following TGF- $\beta$  exposure (Fang *et al.*, 2017). This was also observed in a model of ischaemia/reperfusion following unilateral nephrectomy, where animals developed renal lesions (cortical glomerulosclerosis, interstitial fibrosis and myofibroblast accumulation in the medullae of kidneys), (Zhang *et al.*, 2017). Interestingly, renal lesions as well as in situ nitrotyrosine expression and ROS generation could be prevented by post-conditioning (Zhang *et al.*, 2017). Furthermore, the addition of free-radical scavengers limiting ROS production prevented the adverse effects of ischaemia/reperfusion, with no additional benefit of post-conditioning (Zhang *et al.*, 2017), suggesting that oxidative stress is the main mediator of renal fibrosis and post-conditioning in this model. In 5/6<sup>th</sup>-nephrectomized rats, the vascular tissue content in nitrotyrosine increased, while nitric oxide (NO) synthase enzyme levels and NO production decreased, which could be prevented by the antioxidant vitamin E (Vaziri *et al.*, 2002). This suggests that in CKD, NO is inactivated by ROS which leads to accumulation of protein nitration products and NO deficiency. Overall, nitration appears tightly connected to oxidative stress.

#### **4. PTMs as contributors of CKD**

Other PTMs have been involved in the progression of CKD. They are mainly enzymatic modifications of proteins, and can have extensive biological impact. The key enzymatic PTMs involved in CKD pathophysiology are reviewed below.

##### **4.1. Acetylation**

Acetylation is one of the most commonly observed and widely studied PTMs (Khoury, Baliban and Floudas, 2011; Kooistra and Helin, 2012). Acetylation consists in transferring an acetyl group (-COCH<sub>3</sub>) from acetyl coenzyme A to a protein. Acetylation of protein on amino groups can occur in N-terminal position or on lysine residue (Lee, Seo and Kim, 2018). N-terminal acetylation is observed for up to 90% of human proteins and can occur during translation (co-translational modification) or after (post-translational modification). The modification is considered irreversible since no N-terminal deacetylases have been found (Lee, Seo and Kim, 2018). Reversible acetylation is observed on histones lysine residues and is mediated by lysine-specific acetyltransferases (KATs\*).

The balance between histone acetyltransferases (HATs\*) and histone deacetylases (HDACs\*) activities regulates transcription. By neutralising the originally positive charge of histones, lysine acetylation reduces the binding of histones to negatively charged DNA and activates transcription following chromatin opening (Liu, 2021). On the contrary, following HDACs activity, chromatin condensation is enhanced and gene transcription decreases (Seto and Yoshida, 2014). In human, HDACs include 18 enzymes grouped into four classes (I to IV). They have been identified as important regulators for kidney developmental control, especially class I HDACs, and in the pathogenesis and progression of various renal diseases (Liu, 2021). It was established that activation of class I HDACs 1 and 2 was involved in the upregulation of early growth response 1 (EGR1\*) signalling in podocytes and subsequent progression of glomerular disease (Inoue *et al.*, 2019). p300\* and CREB-binding protein (CBP\*) are transcriptional co-activating proteins with histone acetyltransferase activity. In a

mouse model of diabetic kidney disease, Nediani et al. showed that p300/CBP induced NADPH oxidase expression leading to glomerular ROS production with pro-inflammatory and pro-fibrotic consequences (Lazar *et al.*, 2021). This demonstrates that dysregulation of histone acetylation is implicated in renal cell damage.

On the other hand, it has become clear that HATs and HDACs activities are not limited to histones (Seto and Yoshida, 2014). NAD-dependent protein deacetylase sirtuin-1 (SIRT1\*, class III HDACs) presents deacetylase activity and can directly act on transcription factors. It was first observed that SIRT1 regulated the expression of FOXO\* family of Forkhead transcription factors (Brunet *et al.*, 2004). In diabetic nephropathy, acetylation of the transcription factor p65\* (a NF- $\kappa$ B subunit) and Signal Transducer and Activator of Transcription 3 (STAT3\*) is increased in kidney (Liu *et al.*, 2014). In this context, acetylation promoted by STAT3 and p65 was also related to AGEs accumulation and a subsequent decreased expression of SIRT1 in podocytes. Remarkably, in the genetically diabetic leptin receptor-deficient (db/db) mice, the AGE inhibitor pyridoxamine restored SIRT1 expression, reduced p65 or STAT3 acetylation and attenuated proteinuria and podocyte injury whereas SIRT1 deletion in podocytes led to the opposite effects (Liu *et al.*, 2014).

#### 4.2. Methylation

The addition of methyl groups (-CH<sub>3</sub>) to proteins, was first reported in 1959 (Ambler and Rees, 1959) but it is only at the early beginning of the 21st century that advances in molecular biology enabled the effective study and comprehension of protein methylation (Murn and Shi, 2017). Methylation on the side chains of amino acid residues occurs essentially on arginine and lysine. Arginine can present one or two methyl groups whereas lysine can be methylated up to three times. The methylation of arginine has been less studied than for lysine although there may be twice as many methylation sites for arginine compared to lysine (Biggar and Li, 2015). More than 50 lysine-specific methyltransferases (KMTs\*) and nine arginine methyltransferases (PRMTs\*) have been identified (Biggar and Li, 2015). Although it is not limited to this substrate, the methylation of histones is the most described (Biggar and Li, 2015).

Lysine methylation was commonly observed on histone. The turnover of histone methylation is much slower than for acetylation and phosphorylation (other abundant PTMs), (Barth and Imhof, 2010). Also, histone methylation does not affect the charge of the modified residue (Murn and Shi, 2017). For these reasons, it is proposed to be important for genome stability. Still, the crosstalk between methylation and other PTMs, such as acetylation and ubiquitylation, forms a complex network of regulation affecting plenty of biological functions (reviewed in (Biggar and Li, 2015)). Lysine methylation plays a key role for histones interaction and recognition by “effector” proteins which can impact chromatin structure and function. On histone H3\*, it was shown that methylation on Lys-4 leads to transcription activation whereas methylation on Lys-9 induces transcriptional repression (Murn and Shi, 2017). Interestingly, proteins with histone demethylase activity have been identified, for example Lysine-specific histone demethylase 1B (KDM1B\*) is able to demethylate Lys-4 of histone H3, providing dynamic control of transcription (Shi *et al.*, 2004).

In the glycerol-induced rhabdomyolysis model of acute kidney injury, one week after the initial injury an increased methylation of histone H3 Lys-4 was associated with an increased transcription of pro-inflammatory and pro-fibrotic genes (TNF- $\alpha$ \*, MCP-1 and TGF- $\beta$ 1) in the kidney (Zager and Johnson, 2010). Histone H3 Lys-9 was also found tri-methylated in renal tubulointerstitial cells from normal kidneys and methylation was increased in the UUO mouse model of kidney fibrosis (Hewitson *et al.*, 2017). TGF- $\beta$ 1 influenced Histone H3 Lys-9 distribution in fibroblasts with potential effects on fibrosis (Hewitson *et al.*, 2017). Histone H3 Lys-4 methyltransferase SETD7\* expression is positively regulated by the TGF- $\beta$ /Smad3-dependant pathway in UUO and knockdown of SETD7 attenuates kidney fibrosis in this model (Sasaki *et al.*, 2016). It is noteworthy that SETD7 expression is associated with the degree of kidney fibrosis in human (Sasaki *et al.*, 2016). Enhancer of zeste homolog 2 (EZH2\*) is a KMT that induces histone H3 Lys-27 tri-methylation. The latter was increased following EZH2 over-

expression in fibrotic kidney of UUO mice, a finding also observed in CKD patients (Zhou *et al.*, 2016). The increased expression of EZH2 in renal tubular cells and interstitial myofibroblasts induced pro-fibrotic effects following the down-regulation of Smad7 and Phosphatase and tensin homolog (PTEN\*) expressions (Zhou *et al.*, 2016).

#### 4.3. Ubiquitylation

Ubiquitylation is a sequential process involving Ubiquitin-activating enzymes E1\*, E2\* and E3\* leading to the covalent attachment of monomers (mono-ubiquitylation) or chains (poly-ubiquitylation) of ubiquitin to proteins. The highly conserved 76-residue protein ubiquitin is first activated thanks to the single E1 enzyme in an ATP-dependent reaction. After activation, ubiquitin is transferred to a protein substrate by E2 ubiquitin-conjugating enzymes (around 50 identified). Final attachment on lysine of a specific protein is allowed by E3 ubiquitin ligases, a family of more than 1000 enzymes ensuring reaction specificity (Swatek and Komander, 2016; Meyer-Schwesinger, 2019). Ubiquitylation is reversible and ubiquitin removal from target protein can be achieved by de-ubiquitylating enzymes (Mevissen and Komander, 2017).

Ubiquitin contains seven lysine residues (Lys-6, Lys-11, Lys-27, Lys-29, Lys-33, Lys-48, Lys-63) enabling diverse polyubiquitin chain linkage via Lys-Lys attachment with specific effects on substrate proteins. Predominant Lys-48-linking (> 50% of all linkages) leads to proteasomal degradation of proteins (Swatek and Komander, 2016; Meyer-Schwesinger, 2019). In contrast, other ubiquitin modifications can affect the activity, stability, interactions and localization of proteins thereby influencing cellular processes such as endocytosis, epigenetic regulation, NF- $\kappa$ B activation and protein trafficking (Mukhopadhyay and Riezman, 2007; Rape, 2018; Meyer-Schwesinger, 2019).

Ubiquitylation regulation is essential for renal physiology and can be involved in CKD pathophysiology according to ubiquitin-proteasome system dependant and independent effects. TGF- $\beta$  signalling is a key mediator of renal inflammation and fibrosis through interaction with Smads intracellular mediators (Gu *et al.*, 2020). Smad2, Smad3 and Smad4 are involved in pro-fibrotic and pro-inflammatory gene transcription and the inhibitory Smad7 represses this pathway by binding to the TGF- $\beta$  activated receptor (Gu *et al.*, 2020). Smads are the target of the Smad-Ubiquitination Regulatory Factor SMURF1\* and SMURF2\*, that are E3 ligases. Polyubiquitylation and degradation of Smad2, Smad3 and Smad4 lead to anti-fibrotic effects, while that of Smad7 are pro-fibrotic (Meyer-Schwesinger, 2019). A critical role has also been found for the E3 ligase Arkadia that stimulates renal tubular EMT transition in vitro through ubiquitylation and degradation of Smad7 (Liu *et al.*, 2008). Cullin 3 is an E3 ligase essential for cell cycle regulation and KEAP1\*/NRF2\* signalling. Saritas *et al.* showed in a knockout mice model that disrupting kidney tubule-specific Cullin 3 induces interstitial inflammation, renal fibrosis and premature death (Saritas *et al.*, 2019). Interestingly, they also observed decreased expression and nuclear localisation of Cullin 3 in mouse models of CKD and fibrotic human kidney tissue.

PTEN is a phosphatase mainly involved in the regulation of cell cycle. After the addition of Lys-27-polyubiquitin chains on PTEN Lys-80 by the E3 ligase MEX3C\*, PTEN switches from phosphoinositide/tyrosine phosphatase activity to protein serine/threonine phosphatase activity (Hu *et al.*, 2019). This altered enzymatic activity facilitates dephosphorylation and protein stabilisation of TWIST1\*, SNAI1\* and YAP1\* in renal epithelial cells leading to increased EMT and renal fibrosis (Li *et al.*, 2019). Moreover, serum and urine levels in Lys-27-polyubiquitylated PTEN are increased in diabetic kidney disease patients and correlated with estimated glomerular filtration rate (eGFR), (Li *et al.*, 2019).

#### 4.4. SUMOylation

Small ubiquitin-like modifiers (SUMO\*) constitute a family of 4 small proteins, SUMO-1 to SUMO-4, that can be covalently linked to proteins on lysine residues in a 3 steps process similar to

ubiquitylation (Hay, 2005). SUMO proteins (around 12 kDa) can also be detached from proteins by specific proteases such as SENP1\* and SENP2\*. SUMOylation is an important PTM of proteins regulating biological processes such as cell cycle progression, maintenance of genome integrity, protein subcellular transport and stability, apoptosis and transcription (Hay, 2005).

SUMOylation in kidney was first evidenced by the local detection of UBC9\* protein expression, responsible for SUMO-1 binding to protein (Gołebiowski *et al.*, 2003). More recently, the renal specific expression of SUMO-4 with possible implication in diabetic kidney disease were reported (Bohren *et al.*, 2004). SUMOylation has been linked to various kidney diseases such as acute kidney injury, renal carcinoma and nephrolithiasis (Yang, Zhang and Sun, 2019).

The  $\alpha$  subunit of hypoxia-inducible factor 1 (HIF-1 $\alpha$ \*) is a major transcriptional regulator of cellular response to hypoxia which is strongly influenced by SUMOylation (Bae *et al.*, 2004). In kidney, HIF-1 $\alpha$  can be activated following deSUMOylation by SENP1 protease, a mechanism involved in podocyte protective properties against hypoxia (Wang *et al.*, 2015). In the UUO mouse model, HIF-1 $\alpha$  expression facilitated EMT (Higgins *et al.*, 2007). In 5/6<sup>th</sup> nephrectomized mice, animals with higher HIF-1 $\alpha$  protein expression in kidney also presented higher interstitial fibrosis (Kimura *et al.*, 2008). Interacting with TGF- $\beta$  signalling and Smad3, HIF-1 $\alpha$  regulated  $\alpha$ 2(I) collagen expression thus promoting glomerulosclerosis (Baumann *et al.*, 2016). Although the exact role of HIF-1 $\alpha$  in renal fibrosis is still controversial (Liu *et al.*, 2017), its regulation by SUMOylation likely influence renal physiology and CKD susceptibility.

SUMO protease SENP1 inhibited podocyte apoptosis through p53\* deSUMOylation limiting p53 targeted pro-apoptotic genes activation (Wang *et al.*, 2014). Also, TGF- $\beta$  type I receptor is a target for SUMOylation (Kang *et al.*, 2008). SUMOylation of this receptor enhance TGF- $\beta$  signalling, in part through Smad3. PTMs by SUMO are also involved in CKD-associated comorbidities such as vascular calcification. Cai *et al.* showed that SUMOylation of Runx2 transcription factor induced its instability, thus protecting vascular smooth muscle cells against osteoblastic transition and calcification in vivo (Cai *et al.*, 2016).

#### 4.5. Glycosylation

Glycosylation consists in the covalent bonding of sugar moieties (i.e. glycans) onto proteins by specific enzymes. Glycan chains can be attached to nitrogen atoms of amino group of asparagine or to oxygen atoms of hydroxyl groups of serine and threonine, during N-linked glycosylation and O-linked glycosylation, respectively (Reily *et al.*, 2019). Beside the most relevant N- and O-linked glycosylations, other forms of glycosylation exist. For instance, glycosylphosphatidylinositol (GPI)-anchored glycoproteins formation (also “Glypiation”), links proteins to the cell membrane, and C-mannosylation consists in the attachment of an  $\alpha$ -mannose to the second carbon of a tryptophan residue (Reily *et al.*, 2019).

N-glycosylation is initiated in the endoplasmic reticulum by the transfer of a 14 residues glycan comprising 3 glucoses, 9 mannoses and 2 N-acetylglucosamines (GlcNAc). After partial removal of glucose and mannose residues, addition of monosaccharides such as GlcNAc, galactose and sialic acid is performed by GlcNAc-transferases, galactosyltransferases and sialyltransferases, respectively (Reily *et al.*, 2019).

O-glycosylation is viewed as the most diverse form of protein glycosylation. Different sugar moieties can be initially attached to proteins, hereby defining subclasses of O-glycans. An abundant form of protein glycosylation called mucin-type O-glycosylation is tightly controlled by a large family of genes encoding the N-acetylgalactosamine (GalNAc)-transferases that link GalNAc to serine and threonine residues (Bennett *et al.*, 2012). Proteoglycans, another major class of glycoproteins, are long chains of glycosaminoglycans attached to serine through xylose residue (Iozzo, 1998; Reily *et al.*, 2019). The regulation of protein glycosylation is complex and it has been estimated that approximately 700

proteins are required to generate more than 700 different glycans in mammals (Moremen, Tiemeyer and Nairn, 2012).

Protein glycosylation impacts their folding, distribution, stability or activity and participates in many biological processes including cell adhesion, molecular trafficking, endocytosis, receptor activation and signal transduction. Glycosylation strongly influences inflammatory responses and is involved in apoptosis and prevention of cancer cell metastasis, but also affects kidney function and diseases. GlycA is a recently developed nuclear magnetic resonance spectrometry-derived biomarker reflecting the abundance of GlcNAc residues attached onto circulating protein in plasma. GlycA can be influenced by systemic inflammation and was found to be associated with albuminuria and inversely correlated with eGFR (Titan *et al.*, 2017). Also, a potential link between IgG glycosylation and kidney function has been reported (Barrios *et al.*, 2016). From 76 N-glycan traits on IgG studied by Barrios *et al.*, 14 were shown to correlate with eGFR, six in a positive manner and eight negatively. These 14 glycans were related to galactosylation, sialylation and bisecting N-acetylglucosamine (Barrios *et al.*, 2016). In a follow-up study, several N-glycosylation patterns of IgG were associated with a faster decline in eGFR (Singh *et al.*, 2020).

Many glycoproteins, notably proteoglycans, are crucial for proper glomerular filtration and necessary for the structure and function of the GBM, the endothelial glycocalyx and the slit diaphragm (Reily *et al.*, 2019). Indeed, it was shown that altered N-linked glycosylation of nephrin impaired its cellular localisation and perturbed cytoskeleton organisation. This results in alteration of the slit diaphragm structure and favours focal segmental glomerulosclerosis (Esposito *et al.*, 2017). In the proximal tubule, brush border cells present multiple glycoproteins in their apical membrane required for their function. Recently, changes in O-glycans pattern and higher fucosylation levels in the brush border cells were shown in CKD animal models presenting proteinuria (Yu *et al.*, 2021). Polypeptide N-acetylgalactosaminyltransferase 11 (GALNT11\*) is a glycosyltransferase targeting the O-glycosylation of the endocytic receptor LRP2\* in the kidney. GALNT11-deficient mice displayed defects in proximal tubule-mediated reabsorption of proteins associated with proteinuria, which highlights a potential role of GALNT11 in CKD (Tian *et al.*, 2019).

IgA nephropathy is directly linked to O-glycosylation dysfunctions. This disease is characterised by the production of IgG autoantibodies directed against IgA1 containing galactose-deficient O-glycans. Further formation of circulating immune complexes that deposit in the glomeruli leads to mesangial cells activation, inflammation and overproduction of ECM components often resulting in ESRD (Knoppova *et al.*, 2016). Genetic-wide association studies have identified several GalNAc-transferases associated with the production of galactose-deficient IgA1 (Kiryluk *et al.*, 2017).

A strong relationship has been found between glycosylation and EMT (Pucci, Malagolini and Dall'Olio, 2021). CD147\*, for example, is a multifunctional protein with high glycosylation potential affecting its functions (Bai *et al.*, 2014). Interestingly, CD147 is implicated in tubulointerstitial fibrosis (Kato *et al.*, 2011) and promotes EMT (Wu *et al.*, 2011) which makes it an attractive target linking glycosylation regulation and interstitial fibrosis in CKD.

## **5. Targeting PTMs to prevent or improve CKD**

A great effort has been made to decipher the links between PTMs and CKD. From physiopathological changes favouring PTMs generation, to molecular effects of PTMs favouring CKD progression, the connection is multidirectional and proteiform.

Many PTMs observed in CKD are related to oxidative stress attacking amino acids residues of proteins directly or secondary to enzymatic activities leading to production of ROS. Depending on the added residue, PTM-oxidized proteins belong to glycation, nitration, carbamylation, carbonylation, guanidinylation, homocysteination and other PTMs. Many mechanisms and consequences of these PTMs are shared, making the distinction between them a blurred line (Agalou *et al.*, 2005). In

addition, ROS attack on other molecules such as lipids or carbohydrates produces reactive carbonyl compounds which induces protein modifications (Miyata *et al.*, 1999). This pathway can be further enhanced by reduced concentration and activity of enzymes involved in the detoxification of carbonyl compounds, such as glyoxalase I (Miyata *et al.*, 2001). Antioxidative treatments with vitamin E, orally or coated on hemodialysis fibres, were able to reduce AOPP and inflammatory markers (Panichi *et al.*, 2011; Azouaou Tualbi *et al.*, 2021).

PTMs are not only generated by CKD or renal impairment, but also influenced by external sources such as the diet. The consumption of dry heat cooked food (e.g. baking, roasting, grilling) is an important determinant of serum and tissue AGEs (Uribarri *et al.*, 2003). In fact, in dialysis patients, a diet low in AGE resulted in a 30% reduction in circulating AGE levels after one month (Uribarri *et al.*, 2003). Because there is a competition between free amino acids and proteins for carbamylation, a diet low in free amino acids increases protein carbamylation (Berg *et al.*, 2013). In a different approach based on competition for substrate, free amino acids infusion after hemodialysis sessions limited the carbamylation of proteins (Kalim *et al.*, 2015). A clinical trial testing this strategy has recently been completed, although results are not yet available (NCT02472834, 2015).

The performance of dialysis therapies in ESRD also affects circulating PTMs levels. For AGEs, peritoneal clearance and hemodialysis reduction ratios varied from low to high depending on the molecule (Agalou *et al.*, 2005). High flux dialysers and daily hemodialysis improved AGE removal (Makita *et al.*, 1994; Floridi, 2002). In contrast, AOPP and carbonyl residues cannot be normalized by hemodialysis procedures, and are possibly increased by dialysis-induced inflammation, which is probably caused by activation of immune cells in contact with synthetic fibres (Ward, Ouseph and McLeish, 2003; Albarello *et al.*, 2012; Caimi *et al.*, 2013).

Comorbidities can also affect the importance of PTMs in CKD. The widely used glycated haemoglobin (HbA1c) monitoring is a reflect of glycaemic levels over the past 8 to 12 weeks (World Health Organization, 2011). Because diabetic patients with ESRD can have shorter red blood cells survival due to haemorrhages or anaemia, their Hb1Ac level underestimates glucose exposure (Freedman *et al.*, 2010). Glycated albumin is an alternative biomarker, representative of medium-term changes in blood glucose (2-3 weeks), which showed improved results in ESRD (Freedman *et al.*, 2010). This lead the Japanese Society to recommend glycated albumin monitoring in their guidelines for hemodialysis patients (Nakao *et al.*, 2015).

Finally, drugs have shown efficacy in limiting PTMs in CKD, which is followed by beneficial effects. Indeed, it was confirmed in cultured tubular cells that inhibition of the Sodium/glucose cotransporter 2 (SGLT2\*), which prevents glucose tubular reabsorption, limited ROS generation, RAGE expression and AGE-induced apoptosis (Maeda *et al.*, 2013). This suggests that the indirect inhibition of AGE production by SGLT2i, as confirmed by reduced glycated haemoglobin (Bailey *et al.*, 2010), participates in the nephroprotection offered by this drugs (Heerspink *et al.*, 2021). In the past decade, KMTs inhibitors have been developed and their therapeutic potential for the prevention of kidney fibrosis and kidney disease is gaining interest (Yu and Zhuang, 2019). Increasing evidence suggest that HDAC inhibition could also be a promising strategy to tackle renal fibrosis in CKD (Nie *et al.*, 2020). HDAC inhibitors valproic acid and trichostatin A prevented the progression of renal fibrosis in animal models and limited eGFR decline in patients (Pang *et al.*, 2009; Inoue *et al.*, 2019). Another HDAC inhibitor, dimethylaminoparthenolide (DMAPT), showed similar nephroprotective effects in the Ins2Akita mouse model diabetic kidney disease (decreased albuminuria, glomerulosclerosis and tubulointerstitial fibrosis), with a potential add-on effect compared to Angiotensin-Converting Enzyme inhibitors, widely prescribed to patients with diabetic nephropathy (Klein *et al.*, 2020). Finally, the inhibition of enzymes involved in glycosylation can also be beneficial. In glioblastoma multiforme, N-acetylglucosamine glycosyltransferase (MGAT5\*) inhibition prevented tumoral development associated with EMT (Hassani *et al.*, 2017), opening new ways to prevent fibrosis in CKD.



## 6. Concluding remarks

In this review, we provided an overview of the main PTMs involved in CKD pathophysiology, that does not mean to be exhaustive. Amongst other types of PTMs likely involved in CKD, phosphorylation should be mentioned. As the most commonly observed PTM, phosphorylation participates in the regulation more than 30% of proteins (Khoury, Baliban and Floudas, 2011). As such, phosphorylation is likely involved in all biological processes, including renal fibrosis. PTMs involving ubiquitin-like proteins such as NEDD8\* or FAT10\* have been suggested to influence renal inflammation, fibrosis and CKD (Gong *et al.*, 2010). In ischemic acute kidney injury, Peptidyl Arginine Deiminase-4 promotes inflammation in kidneys, by citrullinating NF- $\kappa$ B Essential Modulator (NEMO\*) and consecutively activating NF- $\kappa$ B in renal tubules (Ham *et al.*, 2014; Rabadi *et al.*, 2019). Finally, PTMs involving reactions with lipid derivatives (e.g. palmitoylation, myristoylation) are frequent and their implication in kidney diseases may gain interest in the future (Khoury, Baliban and Floudas, 2011; Roy and Marin, 2018; Yang *et al.*, 2021).

Altogether, there is a large body of evidence that CKD promotes the generation of PTMs, notably non-enzymatic ones. These PTMs have shown toxic properties *in vitro* and *in vivo* that are consistent with the promotion of further renal damage and the setting of fibrosis. Enzymatic PTMs that are essential to normal biological processes have also been shown to be altered in CKD, and again to mediate profibrotic processes in CKD. Interestingly, efforts made to limit the PTMs burden in CKD were found successful and therapies focusing on specific PTMs are promising. In addition, readily available therapies known to be nephroprotective also demonstrate properties of PTM inhibition. PTMs appear to be a central aspect of CKD pathophysiology that deserves attention. Databases gathering and localizing all PTMs are being developed, which will help considering how each PTM can impact protein structure and function, which will likely improve our understanding of the mechanisms driving CKD.

## Declaration of interest

The authors declare that there is no conflict of interest.

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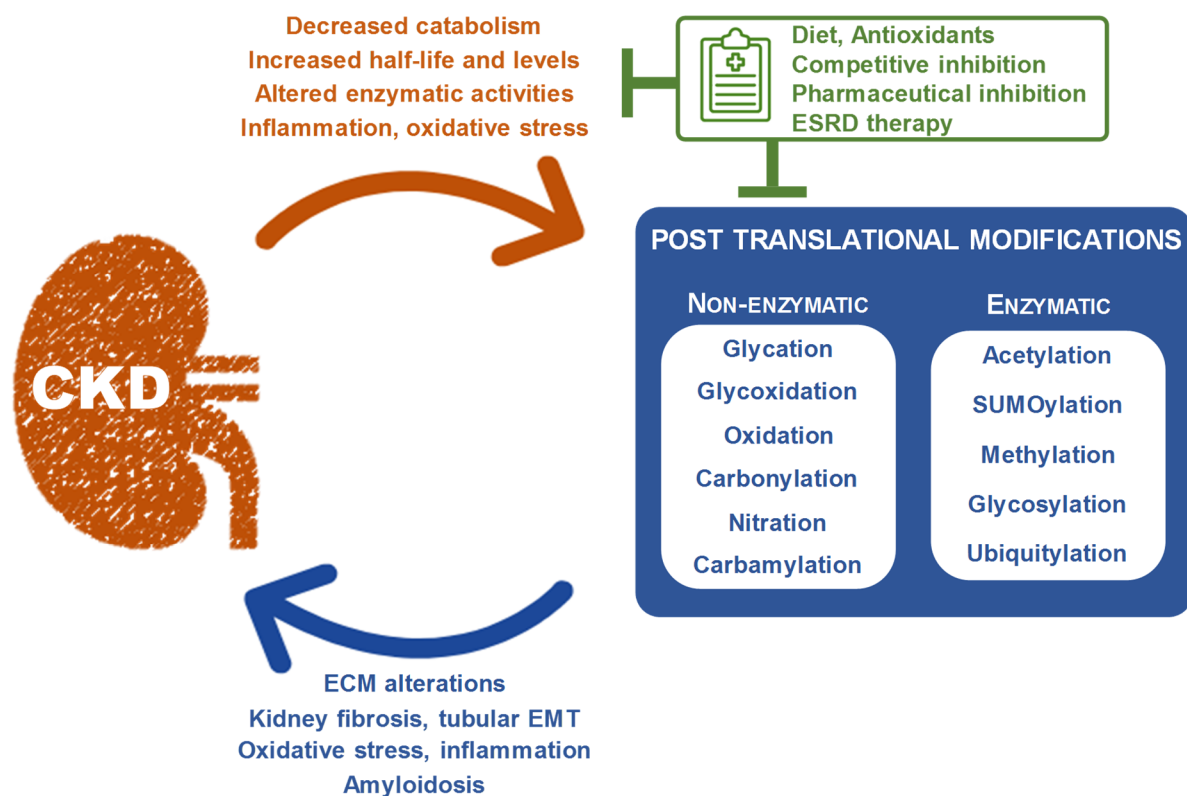
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**Figure.** In Chronic kidney disease (CKD), several mechanisms are involved in the increased generation of protein post-translational modifications (PTMs). PTMs mediate pathological processes of CKD including renal fibrosis. Therapeutic and dietary interventions may prevent or correct these aspects. Abbreviations: EMT, endothelial-mesenchymal transition; ESRD, end-stage renal disease; SUMO, Small ubiquitin-like modifier



**Table. Protein abbreviations, names, coding genes and uniprot IDs of proteins**

Abbreviation	Protein name (alternative name)	Human gene name or family	Uniprot ID
B2M	Beta-2 microglobulin	B2M	P61769
CBP	CREB-binding protein	CREBBP	Q92793
CD147	Basigin (Cluster of differentiation 147)	BSG	P35613
CTGF	Connective tissue growth factor	CCN2	P29279
E1	Ubiquitin-like modifier-activating enzyme 1	UBA1	P22314
E2	Ubiquitin-conjugating enzymes E2	UBE2 family	-
E3	<a href="#">E3 ubiquitin-protein ligases</a>	<a href="#">UBR family</a>	-
EGF	Pro-epidermal growth factor	EGF	P01133
EGR1	Early growth response protein 1	EGR1	P18146
ERK	Extracellular signal-regulated kinase	MAPK family	-
ET-1	Endothelin 1	EDN1	P05305
EZH2	Histone-lysine N-methyltransferase EZH2 (Enhancer of zeste homolog 2)	EZH2	Q15910
FAT10	Ubiquitin D (Ubiquitin-like protein FAT10)	UBD	O15205
FcRn	Neonatal FC receptor	B2M - FCGRT heterodimer	P61769 P55899
FOXO	Forkhead box class O proteins	FOXO family	-
GALNT11	Polypeptide N-Acetylgalactosaminyltransferase 11	GALNT11	Q8NCW6
H3	Histone H3	H3 family	-
HAT	Histone acetyltransferases	HAT family	-
HDAC	Histone deacetylases	HDAC family	-
HIF-1 $\alpha$	Hypoxia-inducible factor 1-alpha	HIF1A	Q16665
ICAM-1	Intercellular Adhesion Molecule-1	ICAM1	P05362
KAT	Histone lysine acetyltransferases	KAT family	-
KDM1B	Lysine-specific histone demethylase 1B	KDM1B	Q8NB78
KEAP1	Kelch-like ECH-associated protein 1	KEAP1	Q14145
KMT	Lysine-specific N-methyltransferases	KMT family	-
LRP2	Low-density lipoprotein receptor-related protein 2 (Megalin)	LRP2	P98164
MCP-1	C-C motif chemokine 2 (Monocyte chemoattractant protein-1)	CCL2	P13500
MEX3C	RNA-binding E3 ubiquitin-protein ligase MEX3C	MEX3C	Q5U5Q3
MGAT5	Alpha-1,6-mannosylglycoprotein 6-beta-N-acetylglucosaminyltransferase A (N-acetylglucosamine glycosyltransferase)	MGAT5	Q09328
MMP	Matrix metalloproteinases	MMP family	-
MPO	Myeloperoxidase	MPO	P05164
NEDD8	NEDD8 (ubiquitin like protein Nedd8)	NEDD8	Q15843
NEMO	NF-kappa-B essential modulator	IKBKG	Q9Y6K9

Abbreviation	Protein name (alternative name)	Human gene name or family	Uniprot ID
NRF2	Nuclear factor erythroid 2-related factor 2	NFE2L2	Q16236
OST-48	Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit (oligosaccharyltransferase 48kDa)	DDOST	P39656
p300	Histone acetyltransferase p300	EP300	Q09472
p38	Mitogen-activated protein kinase	p38 MAPK family	-
p53	Cellular tumor antigen p53	TP53	P04637
p65	Transcription factor p65 (Nuclear factor kappa-B subunit)	RELA	Q04206
PAI-1	Plasminogen activator 1	SERPINE1	P05121
PDGF	Platelet-derived growth factor	PDGFA - PDGFB heterodimer	P01127 P04085
PON1	Serum paraoxonase/arylesterase 1	PON1	P27169
PRMT	Arginine methyltransferases	PRMT family	-
PTEN	Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN (Phosphatase and tensin homolog)	PTEN	P60484
RAGE	Advanced glycosylation end product-specific receptor	RAGE	Q15109
SEN1	Sentrin-specific protease 1	SEN1	Q9P0U3
SEN2	Sentrin-specific protease 2	SEN2	Q9HC62
SETD7	Histone-lysine N-methyltransferase SETD7	SETD7	Q8WTS6
SGLT2	Sodium/glucose cotransporter 2	SLC5A2	P31639
SIRT1	NAD-dependent protein deacetylase sirtuin-1	SIRT1	Q96EB6
Smad	Mothers against decapentaplegic homologs	SMAD family	-
SMURF1	E3 ubiquitin-protein ligase SMURF1	SMURF1	Q9HCE7
SMURF2	E3 ubiquitin-protein ligase SMURF2	SMURF2	Q9HAU4
SNAI1	Zinc finger protein SNAI1	SNAI1	O95863
STAT3	Signal transducer and activator of transcription 3	STAT3	P40763
SUMO	Small ubiquitin-like modifiers	SUMO family	-
TGF-β	Transforming growth factor beta	TGFB family	-
TGF-β1	Transforming growth factor beta-1	TGFB1	P01137
TNF-α	Tumor necrosis factor	TNF	P01375
tTG	Protein-glutamine gamma-glutamyltransferase 2 (tissue transglutaminase)	TGM2	P21980
TWIST1	Twist-related protein 1	TWIST1	Q15672
UBC9	SUMO-conjugating enzyme UBC9	UBE2I	P63279
YAP1	Yes-associated protein 1	YAP1	P46937