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REVIEW

Role of Protein Misfolding in Human Kidney Diseases

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ABSTRACT: Protein misfolding has emerged as a central mechanism in the pathogenesis of human kidney diseases. Normally, proteins achieve their native conformation through highly regulated folding processes in the endoplasmic reticulum (ER) and cytoplasm, assisted by molecular chaperones and quality-control pathways. However, genetic variants, environmental stressors, or cellular overload can destabilize this system, resulting in unfolded or misfolded proteins that trigger aggregation, amyloid formation, endoplasmic reticulum stress, and activation of the unfolded protein response (UPR). These events may ultimately lead to loss of function, gain of toxic function, and apoptosis. This review summarizes the structural basis of protein folding and the mechanisms by which misfolding disrupts renal homeostasis. Special emphasis is given to amyloidogenic pathways and to the contribution of UPR and ER-associated degradation in maintaining proteostasis. We analyze key renal diseases in which protein misfolding plays a causal or contributory role, including amyloidosis, Fabry disease, von Hippel–Lindau syndrome, uromodulin related autosomal dominant tubulointerstitial kidney disease (ADTKD-UMOD-related), Alport syndrome, congenital nephrotic syndrome, diabetic nephropathy, and nephrogenic diabetes insipidus. We also highlight emerging associations in chronic kidney disease and glomerulopathies. Finally, therapeutic strategies directly targeting protein misfolding are reviewed, such as pharmacological chaperones, proteostasis enhancers, and gene-editing approaches. Understanding the interplay between protein misfolding and renal pathology It has translational medical significance, as it may be the future direction towards personalized medicine and/or combination therapies, not only clarifies disease mechanisms but also provides opportunities for innovative, mechanism-based treatments. This study aimed to review current knowledge regarding the role of protein misfolding in human kidney diseases, with the aim of evaluating current therapies available and which mechanisms of protein misfolding could be translated into clinical practice as future therapeutic targets.

KEYWORDS: Protein misfolding; kidney diseases; human; genetic variant; endoplasmic reticulum

1 Introduction

Proteins are essential macromolecules that play critical structural and functional roles in human cells, acting as integral components of the molecular machinery that sustains all vital cellular processes [1]. These molecules are ubiquitously expressed across human organs and tissues, including the kidneys. Disturbances in protein homeostasis—particularly protein misfolding—can directly or indirectly compromise renal structure and function [1].

Misfolded proteins often interfere with cellular functions and have been recognized as a key mediator of pathology [2]. Although traditionally associated with disruptions in protein structure, recent

insights indicate that protein misfolding involves a broader spectrum of biological variables beyond mere conformational changes [1].

Misfolded proteins often aggregate into insoluble deposits that interfere with cellular functions and have been implicated in a range of disorders, including renal diseases in humans [3]. A notable example is the formation of amyloids—protein aggregates characterized by fibrillar morphology (7–13 nm in diameter) and enriched in β-sheet secondary structures. The term "amyloid" was first introduced by Virchow, who observed such deposits in cerebral, splenic, renal, and hepatic tissues [4]. The pathogenic role of amyloids was later elucidated by Alois Alzheimer, who identified senile plaques and neurofibrillary tangles in the brain of a middle-aged woman experiencing progressive cognitive functions decline [3].

As the field evolves, it is increasingly clear that the multifactorial nature of protein misfolding must be fully understood [1]. A comprehensive understanding of its role in kidney disease requires familiarity with normal protein structure and the physiological mechanisms that govern control protein folding [1].

This review critically examines the role of protein misfolding and its downstream consequences in human kidney diseases, with particular attention to the genetic and molecular pathways involved. The purpose of this review is to gather knowledge in this field, to elucidate which mechanisms are common in various human kidney diseases, with the aim of translating these concepts into potential therapeutic targets.

1.1 Protein Structure

Proteins possess a hierarchical three-dimensional structure composed of four organizational levels—primary, secondary, tertiary, and quaternary—that are critical for maintaining their proper function.

- **Primary structure** refers to the linear sequence of amino-acids (AAs) linked by peptide bonds to form a polypeptide chain. A peptide bond is established between the carboxyl group of one AA and the amino group of the next. The side chains of the AAs, not involved in the peptide bond, are known as R-groups [1]. The thermodynamic stability of the primary structure depends on interactions between the polypeptide and its intracellular or extracellular environment, including factors such as pH, temperature, and the presence of other cellular components [3]. This primary sequence is fundamental for directing correct protein folding [5]; alterations in environmental conditions or genetic variants can disrupt this sequence, impairing proper folding, leading to loss of the native conformation, and promoting misfolding and amyloid aggregation [5].
- **Secondary structure** arises from hydrogen bonding between the amide and carbonyl groups within the polypeptide chain [6]. The two principal secondary motifs are α-helices and β-pleated sheets. In α-helices, each AA forms a hydrogen bond with another four residues ahead in the chain, resulting in a right-handed helical structure with 3.7 residues per turn [7]. The R-groups extend outward, enabling interactions with surrounding residues. In β-pleated sheets, two or more segments of a polypeptide chain align side by side and are stabilized by hydrogen bonds, forming either parallel (with aligned termini) or antiparallel configurations. In this structure, the R-groups alternate above and below the sheet plane, facilitating further interactions [8].
- **Tertiary structure** represents the overall three-dimensional conformation of a single polypeptide chain, stabilized by a combination of hydrophobic interactions, non-covalent forces, and covalent disulfide bonds. Hydrophobic AAs residues typically cluster in the protein core, while hydrophilic residues are oriented toward the aqueous environment [9]. Disruption at this level—such as exposure of hydrophobic core regions to the solvent—can initiate misfolding and lead to the formation of insoluble fibrillar aggregates known as amyloid fibrils [3].

- **Quaternary structure** is formed by the assembly of two or more polypeptide subunits into a functional protein complex. Not all proteins exhibit quaternary organization.

Disruptions in any of these structural levels—whether due to environmental changes such as altered pH or osmolarity, or due to mutations in the genetic code—can compromise the thermodynamic stability of the protein. This, in turn, can result in improper folding, loss of function, and the development of misfolding-related pathologies [1]. Fig. 1 illustrates the four levels of protein structure.

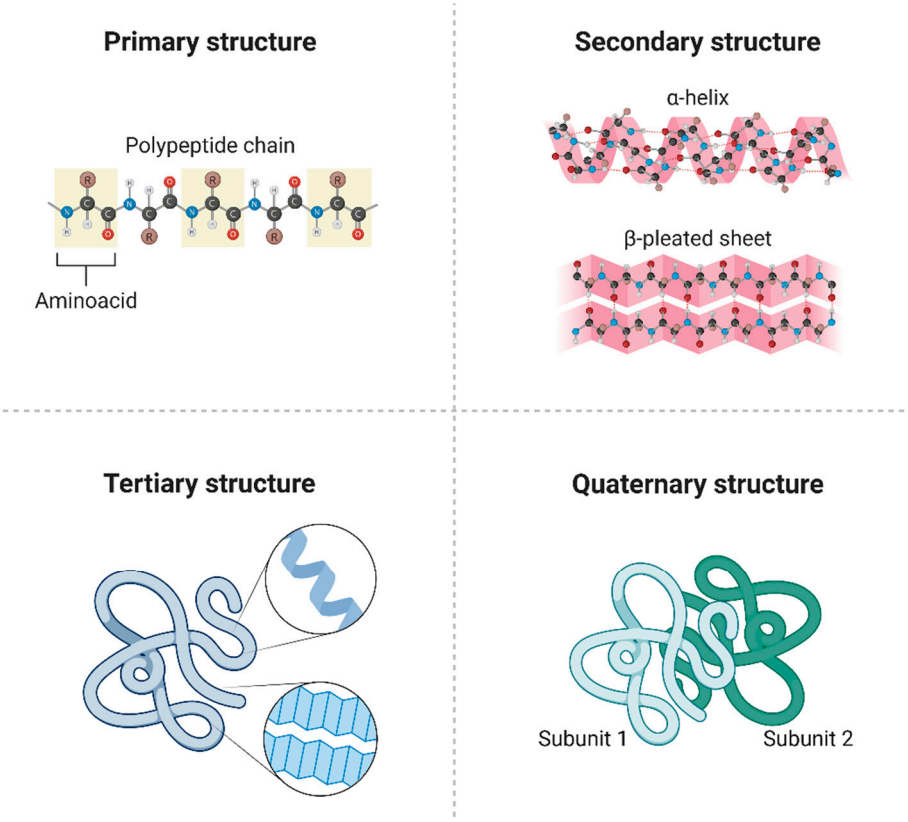

Figure 1: The different structure of the protein. The graphic was created and/or edited at Biorender.com.

1.2 Protein Synthesis

The endoplasmic reticulum (ER) serves as the primary site for the synthesis and folding of secretory, transmembrane, and ER-resident luminal proteins. Protein folding is an inherently error-prone process, with up to 30% of newly synthesized polypeptides undergoing misfolding. This proportion increases significantly under conditions of cellular stress, exposure to toxic agents, or when the nascent protein harbors mutations [10].

Protein folding is a multistep mechanism. Initially, glycoproteins receive an N-linked oligosaccharide, to which two terminal glucose residues are sequentially trimmed by glucosidases I and II [11]. This glycan processing enables recognition by the ER-resident chaperones calnexin and calreticulin, which facilitate proper folding and prevent premature aggregation of glycoproteins. Following removal of the innermost glucose by glucosidase II, the protein is released from the chaperones.

The enzyme UDP-glucose/glycoprotein glucosyltransferase (UGGT) then assesses the folding status of the glycoprotein. If the protein remains misfolded, UGGT re-glucosylates it, thereby promoting its re-binding to calnexin and calreticulin and retaining it within the ER. This cycle persists until UGGT

recognizes the protein as correctly folded, functioning as a critical checkpoint to prevent the export of defective proteins [11].

In addition to calnexin and calreticulin, other molecular chaperones contribute to this process. Glucose-regulated protein 78 (GRP78), a 78-kDa ER chaperone, plays a central role in binding unfolded proteins through its hydrophobic domains. GRP78 activity is modulated by co-chaperones containing J-domains with histidine-proline-aspartate motifs, which facilitate substrate recognition [11]. Among these, ERdj4 is notable for its interaction with the ER-associated degradation (ERAD) pathway and its role in targeting misfolded proteins for elimination [12].

The ERAD process involves retrotranslocation of terminally misfolded proteins from the ER lumen to the cytosol, followed by ubiquitination and subsequent degradation via the proteasome [11].

1.3 Genetics of Protein Misfolding

Only about 2% of the human genome corresponds to coding regions, which provide the sequences translated into proteins. The remaining non-coding DNA, although not directly encoding AAs, exerts critical regulatory functions by controlling gene activation, forming centromeres and telomeres necessary for DNA replication, and contributing to epigenetic regulation of gene expression [13].

Genetic variants in coding regions can impair protein function by altering localization, catalytic activity, hydrogen-bonding networks, stability, and folding; examples include:

Protein mislocalization: Mutations in nuclear localization sequences may prevent proteins from reaching the nucleus, exposing them to inappropriate environments that can trigger unfolding. Environmental changes, such as altered pH or ionic strength between compartments, can also destabilize proteins [14].

Catalytic dysfunction: Variants may disrupt active sites, protein–protein interaction domains, or allosteric regulation sites, thereby compromising enzymatic activity [14].

Disruption of hydrogen-bond networks: Mutations can alter hydrogen bonding, expose hydrophobic cores to aqueous environments, and promote aggregation via misfolding. These changes may also influence catalytic properties, pH sensitivity, and stability.

Altered thermodynamic stability: Protein stability is determined by the difference in the free energy (ΔG) between the unfolded, folded, and misfolded states. Variants may destabilize or, less commonly, excessively stabilize a protein by altering the activation energy required for misfolding, both scenarios potentially impairing function.

Genetic variants may promote protein misfolding through several mechanisms [14,15]:

Stabilization of misfolded intermediates: certain mutations favor partially folded states over native conformations, as in familial amyotrophic lateral sclerosis due to profilin-1 variants [16].

Premature degradation: partially functional misfolded proteins may be erroneously targeted for ER-associated degradation. In Gaucher disease, mutant β-glucosidase retains partial activity but is degraded prematurely, exacerbating disease severity [17].

ER retention: Misfolded proteins may fail to reach their proper cellular destinations, accumulating in the ER. In α-1 antitrypsin deficiency, mutant α-1 antitrypsin is retained in hepatocyte ER rather than being secreted to the lungs [18].

Constitutive activation: Some variants produce continuously active proteins, as in a hereditary form of hypertension caused by a constitutively active mineralocorticoid receptor [19].

Dominant-negative effects: Misfolded mutant proteins can co-aggregate with wild-type counterparts, impairing function even in heterozygous individuals. In epidermolysis bullosa simplex, mutant keratin forms defective intermediate filaments with wild-type keratin, leading to skin fragility and blistering [20].

Toxic aggregation: Misfolded proteins can form toxic oligomers, amyloid pores that mimic ion channels, or insoluble amyloid fibrils, all of which disrupt cellular homeostasis [21–23] (Fig. 2).

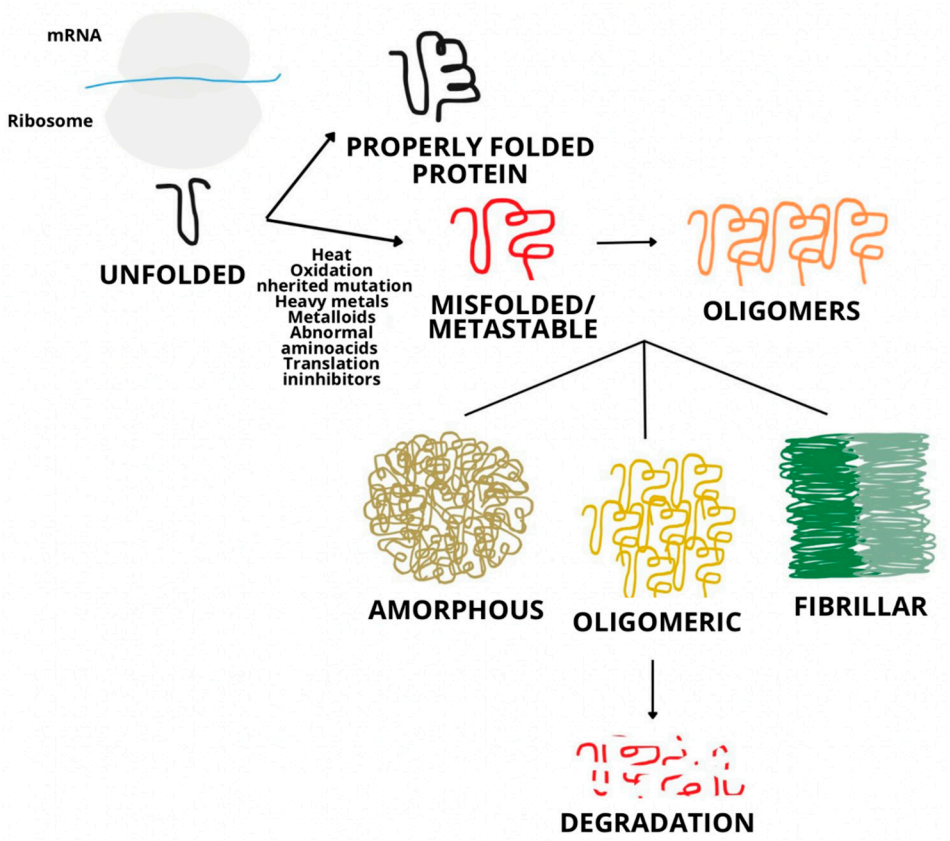

Figure 2: Schematic representation of protein misfolding. The graphic was created and/or edited at Biorender.com.

1.4 Unfolded Protein Response

The ER is a membranous network contiguous with the nuclear envelope that functions as a central site for calcium storage, lipid biosynthesis, and protein homeostasis. Within the ER, newly synthesized proteins undergo folding, post-translational modifications, trafficking, and, when necessary, degradation [23]. Secretory and membrane-resident proteins are synthesized in the ER by ribosomes, producing nascent polypeptide chains that are subsequently folded by ER-resident chaperones. These proteins undergo post-translational modifications such as glycosylation, disulfide bond formation, and lipidation before being transported to their final destinations [23].

A key regulator of ER proteostasis is GRP78 (also referred to as BiP), an ER-resident chaperone, as previously mentioned. Under basal conditions, GRP78 binds to three transmembrane proteins—protein kinase R-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6)—maintaining them in an inactive state [24,25]. When unfolded proteins accumulate, GRP78 dissociates from these transmembrane sensors, activating three distinct Unfolded Protein Response (UPR) signaling branches: PERK, IRE1, and ATF6. Unfolded proteins can also directly bind to IRE1, triggering its activation [26].

PERK pathway: Upon activation, PERK dimerizes, autophosphorylates, and phosphorylates eukaryotic translation initiation factor 2 alpha (eIF2α). This reduces general protein translation, thereby decreasing the ER folding load. PERK activation also induces preferential translation of activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP). These transcription factors upregulate

chaperones (e.g., GRP78), promote protein translation recovery via growth arrest and DNA damage protein 34 (GADD34), or induce apoptosis if PERK signaling remains prolonged [27].

IRE1 pathway: Activated IRE1 exhibits endoribonuclease activity that splices X-box binding protein 1 (XBP1) mRNA, producing XBP1s, a transcription factor that upregulates ER chaperones and ERAD components [28]. IRE1 can also degrade ER-targeted mRNAs to prevent further protein influx [28] and recruit tumor necrosis factor receptor-associated factor 2 (TRAF2), activating apoptosis signal-regulating kinase 1 (ASK1) and c-Jun N-terminal kinase (JNK), leading to apoptosis [29].

ATF6 pathway: In its inactive state, ATF6 contains a Golgi localization signal masked by GRP78. Upon GRP78 dissociation, ATF6 translocates to the Golgi, where it is cleaved by site-1 (S1P) and site-2 (S2P) proteases [24]. The cleaved cytosolic fragment acts as a transcription factor in the nucleus, upregulating genes encoding chaperones, folding enzymes, XBP1, and CHOP [23,29].

In its early phases, UPR activation is adaptive, aiming to restore ER homeostasis by improving folding capacity or promoting the degradation of misfolded proteins. However, persistent or excessive activation shifts the balance toward apoptosis, underscoring the dual nature of the UPR as both a pro-survival and pro-death mechanism [28,30].

1.5 Physiological Anti-Misfolding Mechanisms

The ERAD pathway plays a central role in maintaining protein quality by identifying and removing unfolded or misfolded proteins from the ER. These defective proteins are retrotranslocated to the cytosol, ubiquitinated, and degraded by the proteasome. This process prevents excessive accumulation of misfolded proteins, thereby reducing chronic activation of the UPR. In cells with impaired ERAD, persistent UPR activation is commonly observed [30].

Under normal physiological conditions, most human proteins attain their correct conformation through the coordinated action of folding systems in the ER–Golgi network and cytoplasm. These systems detect abnormal conformations, refold partially misfolded proteins, or target irreversibly defective ones for degradation, thereby avoiding aggregation [31].

Most human proteins are synthesized through the normal folding process, achieving proper structure and function; however, in certain situations, as previously mentioned, this normal process can be altered, and there are mechanisms to try to prevent "misfolding" [3].

Living cells present an active control system for adequate protein folding in the ER-Golgi network and cytoplasm. This system recognizes and degrades proteins which are misfolded to prevent further aggregation. If the quality control system is altered, it could lead to the deposition of misfolded proteins in various tissues and organs [32].

The ER also serves as a reservoir for chaperones and folding catalysts [3]. Chaperones not only facilitate the folding of nascent proteins but can also rescue misfolded proteins, providing them with a "second chance" to reach their native conformation [3]. This rescue process is ATP-dependent, explaining the high energy demand observed in stressed cells [3,31]. Heat shock proteins (Hsp70, Hsp90, Hsp40) are especially relevant, ensuring correct folding under both physiological and adverse conditions [31,32].

In contrast to the UPR, the ER-overload response (ER-OR) activates survival-promoting pathways in response to the prolonged accumulation of properly folded proteins in the ER. This process involves the Ca^{2+}–reactive oxygen species (ROS)–NF-κB pathway, promoting expression of pro-inflammatory mediators, adhesion molecules, and apoptosis regulators [3].

Although numerous structural and functional studies have elucidated the pathways leading from partially folded intermediates to amyloid fibrils, the detailed mechanisms of amyloidogenesis extend beyond the scope of this review.

1.6 Pathological Significance of Amyloids

Protein aggregation is a complex, multistep process involving intermediate states, often referred to as multistate folding. These intermediates are essential checkpoints in the pathway from a newly synthesized polypeptide to a fully folded, functional protein [3]. Under certain conditions, these intermediate states interact abnormally, promoting aggregate formation and shifting the equilibrium toward amorphous protein aggregation and amyloid fibril formation. The transition from native to amyloid structure is influenced by factors such as pH, temperature, protein concentration, and ionic strength. When intermolecular interactions outweigh intramolecular stability, fibrillogenesis is favored [33].

Although amyloid formation is typically associated with disease, evidence also exists for functional amyloids, which participate in physiological processes such as RNA translation [33]. These functional amyloids are rare [33].

1.7 Role of Amyloids Structures and Misfolding in Human Disease

Improper protein folding not only impairs biological function but also increases the likelihood of post-translational modifications that accelerate degradation through the ER–Golgi quality control system [3]. Even if the primary AA sequence is correct, failure to adopt the native conformation can result in pathological states collectively known as protein misfolding diseases or protein conformational disorders.

In the kidney, amyloid deposition alters tissue architecture, disrupts organ function, and activates downstream pathogenic pathways. The consequences of misfolding are diverse and include:

Loss of function: structural distortion leads to inactivation of essential proteins.

Gain of toxic function: misfolded proteins assemble into oligomers or fibrils with cytotoxic activity.

Stress response activation: accumulation of misfolded proteins triggers ER stress and the UPR, which, if sustained, culminates in apoptosis.

Disruption of signaling: aggregates interact aberrantly with membranes or intracellular components, perturbing normal signaling cascades (Fig. 3 summarizes the cellular consequences of protein misfolding).

1.8 Endoplasmic Reticulum Stress in Renal Diseases

When defective proteins accumulate beyond the ER's capacity, the condition known as ER stress arises. Physiological ER stress is transient and adaptive, helping to restore proteostasis, whereas pathological ER stress is sustained and contributes directly to cellular dysfunction and disease [23].

ER Stress and the Kidney

The kidney is particularly susceptible to ER stress due to its high metabolic activity and dependence on specialized protein-handling functions in podocytes, mesangial cells, and tubular epithelial cells. Activation of UPR has been demonstrated in multiple renal pathologies, including acute kidney injury (AKI), chronic kidney disease (CKD), glomerulosclerosis, Heymann nephritis (a rat model of membranous nephropathy), mesangioproliferative glomerulonephritis (MPGN), diabetic nephropathy (DN), and minimal change disease (MCD) [34–37].

Environmental stressors such as glucose deprivation, hypoxia, oxidative stress, lipid imbalance, toxins, and pathogenic genetic variants can all trigger ER stress in renal cells, including podocytes, mesangial cells, and tubular epithelial cells [35].

Protein Aggregation and Proteasome Dysfunction

The accumulation of misfolded proteins not only activates the UPR but also disrupts the ubiquitin–proteasome system (UPS), a central pathway for protein degradation. Impairment of the UPS further exacerbates protein accumulation, amplifying ER stress [5].

For example, in podocyte injury, MPGN, and DN, the retention of misfolded proteins within the ER leads to dysfunction of the podocytes, mesangial cells, and tubulointerstitium, respectively [35].

Role of ER-Associated Degradation

Soluble misfolded proteins are retrotranslocated via the HRD1 (putative human orthologue of yeast Hrd1p/Der3p)–E3 ligase complex, while integral membrane proteins are extracted through ERAD pathways involving E3 ubiquitin ligases. Once in the cytosol, these substrates are ubiquitinated and degraded by the proteasome, preventing excessive ER stress [38].

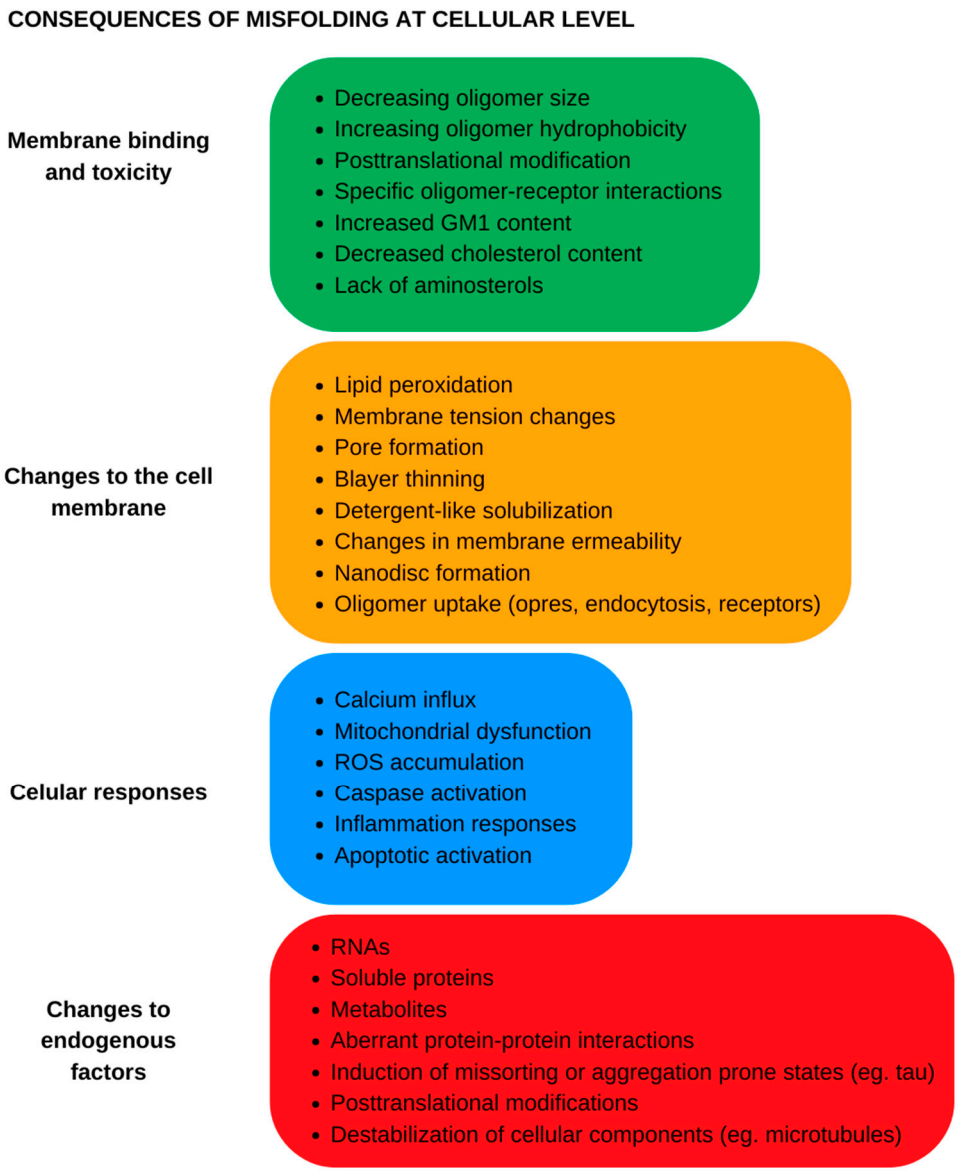

Figure 3: Cellular consequences of protein misfolding. Abb: GM1: monosialotetrahexosylganglioside 1; ROS: reactive oxygen species.

2 Material and Methods

2.1 Literature Search Strategy

A structured literature search was conducted in PubMed, Embase, Scopus, Cochrane Library, and Google Scholar. The following keywords and MeSH terms were applied in different combinations: protein misfolding, amyloid, chaperones, protein quality control, kidney disease, endoplasmic reticulum stress, and unfolded protein response. The search was limited to articles published in English between 1990 and August 2025 in order to capture both seminal and recent contributions. Reference lists of selected articles were also screened to identify additional relevant studies. To search for genetic variants causing human kidney diseases due to protein misfolding, the OMIM® public access database was used.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria:

(i) Articles addressing protein misfolding and its cellular mechanisms;
(ii) Studies linking protein misfolding, ER stress, or amyloid formation to kidney physiology or pathology;
(iii) Research involving human subjects, animal models, or *in vitro* studies relevant to renal biology.

Exclusion criteria:

(i) Publications not available in English;
(ii) Reports focused solely on non-renal diseases without mechanistic overlap;
(iii) Editorials, commentaries, and conference abstracts lacking primary data.

2.3 Data Extraction and Synthesis

Two authors reviewed independently screened the titles and abstracts of retrieved records (GV and CDDlVE). Full texts of potentially eligible studies were assessed, and any discrepancies were resolved through discussion and consensus. Data were extracted regarding study design, molecular mechanisms described, disease models, and reported renal outcomes.

The synthesis of evidence was narrative, with emphasis on:
Mechanisms of protein misfolding and quality control,
The role of ER stress and UPR in renal pathology,
Clinical and experimental evidence linking misfolded proteins to kidney disease progression.

Selection Process

Data extraction, data items and risk of bias: Two investigators (MLB and MVdR) conducted the search independently, and a third investigator (SJ) corroborated the information overlap. Database search results were imported into EndNote (EndNote; X7.1 Clarivate, Philadelphia, PA, USA) and duplicates were removed. Extracted data items included: sample size and characteristics, study design, setting, nature of the included interventions, outcomes measured, and results. Finally, we recorded relevant information in an *ad hoc* database to sort the publications and summarize the main results.

3 Results

3.1 Review of Renal Diseases Associated with Protein Misfolding

In the context of protein misfolding, kidney diseases may arise from (i) functional protein alterations or (ii) the aggregation of amyloid fibrils, both resulting from misfolding. In addition, in the field of nephrology,

amyloidosis can also occur as secondary complications of dialysis treatment. This review focuses on primary causes, with special emphasis on the role of protein misfolding (Fig. 4).

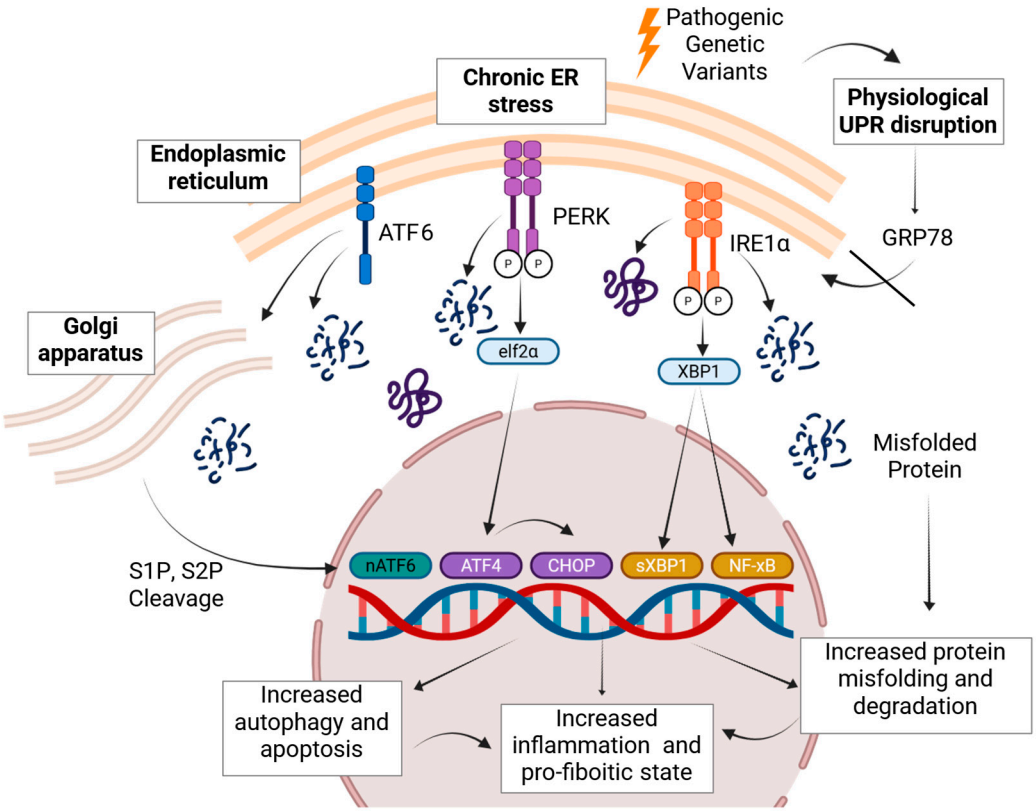

Figure 4: Chronic endoplasmic reticulum stress in renal cells. References: ATF6: activating transcription factor 6; chop: C/EBP homologous protein; elf2α: eukaryotic translation initiation factor 2 α; ER: endoplasmic reticulum; GRP78: Glucose-regulated protein 78; IRE1α: inositol-requiring enzyme 1 α; nATF6, nuclear (N-terminal) activating transcription factor 6; NF-κB: nuclear factor κB; PERK: protein kinase R-like ER kinase; S1P: site-1 protease; S2P: site-1 protease; XBP1: X-box binding protein 1.

3.2 Renal Amyloidosis

Amyloidosis is traditionally classified according to the origin of the precursor protein: acquired (wild type), hereditary (mutant), or iatrogenic [39–41]:

(i) Acquired: the most frequent form, represented by immunoglobulin light chain amyloidosis (AL). Approximately 75% of AL cases involve λ light chains. This form is typically associated with plasma cell clones. Systemic AL typically progresses rapidly and is fatal without treatment, especially in patients with heart involvement. Renal involvement is common (53–67%), presenting with marked proteinuria (3.5–6.1 g/24 h) and mild-to-moderate decline in glomerular filtration rate (GFR); 5% progress to advanced renal failure [42]. It is the only subclass of amyloidosis treated with chemotherapy (e.g., bortezomib, cyclophosphamide, dexamethasone) and autologous stem cell transplantation [43,44]. Lenalidomide, pomalidomide and daretumumab are therapeutics options, the first two for refractory patients [45,46]. In these forms of amyloidosis, the main mechanism that generates the abnormal deposit is hyperproduction but not protein misfolding and its consequences (Table 1).

(ii) Hereditary (mutant): caused by pathogenic genetic variants, which determine a mutant protein (misfolding-ERAD-UPR) and amyloidosis of different types of renal involvement, depending on the form.
(iii) Iatrogenic: recently described in association with injectable medications (which appear as subcutaneous nodules at the injection sites) [45], such as anakinra (Interleukin-1 receptor antagonist), which can produce localized or renal amyloidosis [47].

Table 1: Non-inherited genes associated with protein misfolding in human kidney diseases.

Gene/Locus	Protein Target	Associated Pathophysiological Pathway	Phenotype
TTR/18q12.1	Transthyretin wild type	Chronic infection or chronic inflammation leading to protein misfolding	Systemic amyloidosis with cardiomyopathy and amyloid neuropathy; renal involvement less common
SIRT1/10q21.3	SIRT1	Altered mitophagy/apoptosis	Chronic kidney disease (CKD)

Note: Abbreviations: TTR: transthyretin; CKD: chronic kidney disease; SIRT1: shock gene Sirtuin 1.

A fourth group of amyloidosis of uncertain etiology has been recognized by experts [45]. This group includes Amyloidosis Derived from Leukocyte Chemotactic Factor 2 (ALECT2), a form of renal amyloidosis with increasing frequency and currently one of the most common in certain geographic regions such as Egypt, India, Sudan and China [45]. Said et al. describe ALECT2 as the third most frequent cause of renal amyloidosis in the USA, and the most frequent in the southwest, with Hispanic predominance (88%) [48]. ALECT2 is characterized by an atypical presentation compared to other amyloidosis, with late-onset progressive CKD (average age 70 years), with nephrotic syndrome being rare. The etiology is currently unknown. The strong geographical predominance and evidence of familial involvement suggest a genetic etiology. No pathogenic genetic variants have been detected in the ALECT2 gene, but all patients studied were homozygous for the G-allele (SNP rs31517) at nucleotide 172. This polymorphism is more frequent in Mexican ancestry, so it has been linked to Hispanic origin rather than to the pathogenesis of the disease, and is considered a necessary but not sufficient condition for causing the disease [49].

Forty-two proteins are recognized as amyloidogenic in humans, sixteen of which affect the kidney [41,45]. Some proteins have a natural tendency to misfold, and amyloid formation is enhanced when it is overproduced (acquired) while the amyloidogenicity in others is enhanced by pathogenic genetic variants [45].

The pattern of involvement of amyloidosis is organ/tissue-specific, with the kidney being the organ most commonly affected by severe organ involvement in humans [45].

The diagnosis of renal amyloidosis requires a kidney biopsy. Staining with Congo red allows us to observe common amyloid characteristics on light microscopy, immunofluorescence, electron microscopy [45]. An interesting updated review of the diagnostic techniques and algorithms for renal amyloidosis and its classification was recently written by Leung and Nasr [45], this topic is not the scope of this work.

Certain genes producing misfolding of specific proteins have been linked to the development of hereditary amyloidosis (For more details, see Table 2):

- AD: FGA/4q31.3—Fibrinogen A (α-chain); GSN/9q33.2—Gelsolin; APOA1/11q23.3—Apolipoprotein A-I; TTR/18q12.1—Transthyretin variant; APOA4/11q23.3—Apolipoprotein A-IV.
- AR: APOC2/19q13.3—Apolipoprotein C-II.
- AD and AR: APOA2/1q23.3—Apolipoprotein A-II.
- Undescribed inheritance: LYZ/12q15—Lysozyme (β-domain); APOC3/11q23.3—Apolipoprotein C-III.

Table 2: Inherited genes associated with protein misfolding in human kidney diseases.

Gene/Locus	Inheritance	Protein Target	Associated Pathophysiological Pathway/Clinical Manifestations	Phenotype	Renal Involvement	Recurrence after KT
FGA/4q31.3	AD	Fibrinogen A (α-chain)	Immunodefficiency	*Amyloidosis, hereditary systemic	Nephrotic proteinuria and progressive CKD	Yes
LYZ/12q15	ND	Lysozyme (β-domain)	Immunodefficiency	Amyloidosis, hereditary systemic	ESRD 3th decade	ND
GSN/9q33.2	AD	Gelsolin	Bacteriolytic and macrophage motility disturbances	Amyloidosis, hereditary systemic Finnish type	Later in life with heavy proteinuria (median 5.5 g/d)	Yes
APOA1/11q23.3	AD	Apolipoprotein A-I	Hypoalphalipoproteinemia, primary	Amyloidosis, hereditary systemic	Depends on the genetic variant	Yes
APOA2/1q23.3	AD; AR	Apolipoprotein A-II	Hypercholesterolemia, familial	Renal amyloidosis predominant	Proteinuria and progressive CKD	Yes
APOC2/19q13.32	AR	Apolipoprotein C-II	Hyperlipoproteinemia, type Ib	Renal amyloidosis predominant	Glomerular involvement with or without CKD	ND
APOC3/11q23.3	ND	Apolipoprotein C-III	Apolipoprotein C-III deficiency	Renal amyloidosis predominant	Hypertension and CKD	ND
**TTR/18q12.1	AD	Transthyretin variant	Polyneuropathy and cardiomyopathy frequent	Amyloidosis, hereditary	CKD occasional	
APOA4/11q23.3	AD	Apolipoprotein A-IV	p.L66V pathogenic variant	Amyloidosis, hereditary	Tubulointerstitial kidney disease	ND
GLA/Xq22	X-linked	α-Gal-A	MF-ERAD-UPR	Fabry disease	Determined by gender and phenotype (see section FD)	Not
VHL/3p25.3	AD	pVHL	HIFα-angiogenic factors	VHL syndrome	Multiple cysts and bilateral and multifocal carcinomas	ND
COL4A3/2q36.3	AD/AR	Type-IV collagen Alpha-3 chain	Hearing loss; vision abnormalities; (Goodpasture syndrome?)	AS AD and AR; Hematuria, benign familial AD	Hematuria; proteinuria, CKD; ESRD	Not
COL4A4/2q36.3	AD/AR	Type-IV collagen Alpha-4 chain	Hearing loss; vision abnormalities	AS AR; Hematuria, benign familial AD	Hematuria; proteinuria, CKD; ESRD	Not
COLA5/Xq22.3	X-linked	Type-IV collagen Alpha-5 chain	Diffuse leiomyomatosis; Hearing loss; vision abnormalities	AS X-linked	Hematuria; proteinuria, CKD; ESRD	Not
COLA6/Xq22.3	X-linked	Type-IV collagen Alpha-6 chain	Diffuse leiomyomatosis; Hearing loss; vision abnormalities	AS X-linked	Hematuria; proteinuria, CKD; ESRD	Not

Table 2: *Cont.*

Gene/Locus	Inheritance	Protein Target	Associated Pathophysiological Pathway/Clinical Manifestations	Phenotype	Renal Involvement	Recurrence after KT
NPHS1/19q13.12	AR	Nephrin	GFB disturbance	CNS1; NSSR	Severe proteinuria; Renal biopsy: Glomerulosclerosis and fibrosis	Yes
PDCN/1q25.2	AR	Podocin	GFB disturbance	CNS2; NSSR	Proteinuria; Renal biopsy: Glomerulosclerosis and fibrosis; mesangial IgM deposition	Yes
LAMB2/3p21	AR	Laminin β2 chain	Ocular and neuromuscular symptoms; muscular hypotonia; psychomotor disability	CNS; NSSR; Pierson's syndrome	Proteinuria; Early-onset ESRD; Death in first weeks of life without dialysis; Renal biopsy: diffuse mesangial sclerosis; Decreased or absent laminin β2 in GBM	ND
PLCE1/10q23.33	AR	Phospholipase C epsilon 1	Male pseudohermaphroditism, and Wilms tumor	CNS3; NSSR; Denys-Drash syndrome.	Proteinuria; Renal biopsy: Glomerulosclerosis and fibrosis	Yes
PDSS2/6q21	AR	Decaprenyl diphosphate synthase, subunit 2	Coenzyme Q10 primary deficiency; encephalomyopathy	CNS; NSSR; Leigh syndrome	Renal tubulopathy; proteinuria	ND***
ITGA3/17q21.33	AR	Integrin α3	Epidermolysis bullosa junctional; interstitial lung disease	JEB7	Proteinuria; renal failure; hypoplastic kidney; crossed fused renal ectopia; focal segmental glomerulosclerosis	Yes
ARHGDIA/17q25.3	AR	Rho GDP dissociation in inhibitor 2	Hearing loss; Cortical blindness; Intellectual disability	CNS	Progressive renal failure; Renal biopsy: diffuse mesangial sclerosis; immature podocytes	ND
SCARB2/4q21.1	AR	Scuvenger receptor class B, number 2	Epilepsy, progressive myoclonic, with or without renal failure	CNS; Action myoclonus-renal failure syndrome	Ranging from proteinuria to NS and ESRD	ND
WT1/11p13	AD; somatic mutation	Wilms tumor 1	Wilms tumor, aniridia, and impaired intellectual development	CNS; NSSR; WT1-related disorders (previously known as Denys-Drash syndrome, Frasier syndrome, Meacham syndrome and WAGR syndrome).	Nephroblastoma (Wilms tumor); renal failure; genitourinary abnormalities	Very rare

Table 2: *Cont.*

Gene/Locus	Inheritance	Protein Target	Associated Pathophysiological Pathway/Clinical Manifestations	Phenotype	Renal Involvement	Recurrence after KT
LMX1B/9q33.3	AD	Lim homeobox transcription factor 1-β	Abnormalities in skin, nails, skeletal in Nail-patella syndrome	Pure NS or Nail-patella syndrome	FSGS; hematuria, Proteinuria	Not
INF2/14q32.33	AD	Inverted formin-2	Neuropathy and myopathy in Charcot-Marie-Tooth disease	Pure NS or Dominant intermediate Charcot-Marie-Tooth disease	FSGS; proteinuria; progressive CKD	ND
CD2AP/6p12.3	AD	CD2-associated protein	N/A	NS	FSGS; proteinuria; progressive CKD	CD2AP influences the immune response and development of recurrent renal diseases
MYH9/22q12.3	AD	Human non-muscle myosin heavy chain-9	Macrothrombocytopenia and sensorineural hearing loss	May-Hegglin anomaly; Sebastian syndrome; Fechtner syndrome; Epstein syndrome	Proteinuria, NS; ESRD	Potential risk has been described
AVPR2/Xq28	X-linked	AVPR-2	N/A	Diabetes insipidus, nephrogenic	Polyuria; hypernatremia; decreased urine osmolality	ND
AQP2/12q13.12	AR; AD	Aquaporin 2	N/A	Diabetes insipidus, nephrogenic	Polyuria; hypernatremia; decreased urine osmolality	ND

Note: Abbreviations: AD: autosomal dominant; AR: autosomal recessive; AS: Alport syndrome; AVPR: Arginine vasopressin receptor-2; CKD: chronic kidney disease; CNS: congenital nephrotic syndrome; ESRD: end stage renal disease; FD: Fabry disease; GFB: glomerular filtration barrier; GMB: glomerular basement membrane; JEB7: junctional epidermolysis bullosa-7 with interstitial lung disease and nephrotic syndrome; KT: kidney transplantation; ND: not described; NS: nephrotic syndrome; NSSR: nephrotic syndrome steroid-resistant; *Afibrinogenemia congenital, Dysfibrinogenemia congenital and Hypodysfibrinogenemia congenital are non-renal affected phenotypes caused by FGA gene variants. **Only Transthyretin Amyloidosis result of amyloidogenic pathogenic variants (ATTRv) was considered. ***Potential risk of recurrence has been described.

3.3 Chronic Kidney Disease

Chronic kidney disease is a major global health burden with multifactorial causes. In its terminal stage, patients require renal function replacement therapy through dialysis or transplant [50].

Regarding protein misfolding, some causes of CDK are directly associated (they will be described in detail separately in the following sections); however, within the multiple mechanisms of CKD, misfolding has been reported to be associated with CKD [51–54].

In CKD heat shock gene Sirtuin 1 (Sirt1), which is linked to Hsp, mitophagy, and programmed cell death, has been described. Maintaining kidney health and kidney cell survival requires Sirt1 gene balance. Sirt1 is a stress-response and chromatin-silencing factor. It is an NAD(+)-dependent histone deacetylase involved in various nuclear events such as transcription, DNA replication, and DNA repair [55]. Two reported causes associated with disturbances in Sirt1 gene expression are: (i) core body temperature disturbances and (ii) gram negative bacterial lipopolysaccharides; both of these, inactivate the heat shock gene Sirt1, with acceleration of protein aggregation that involves the Hsp and amyloid beta [51,56] (Table 1).

There is growing evidence that UPR signaling is involved in renal disease progression, which is triggered by hypoxia, oxidative stress, inflammation, high glucose, and functional genetic deficiency of glomerular proteins [52]. Ischemia-reperfusion injury is a common cause of AKI that results in hypoxia, and ER-stress is well recognized as the initial response to ischemia-reperfusion injury [57].

In animal models of AKI andDN, the involvement of UPR in the development of renal fibrosis and progression to end stage renal disease (ESRD) has been reported [58]. In humans, UPR dysregulation was correlated to severity of progression from AKI to CKD, with upregulated expression of Bip, p-PERK, and CHOP and reduced expression of XBP1s [59].

3.4 Fabry Disease

Fabry disease (FD) is a multisystemic X-linked lysosomal storage disorder caused by mutations in the α-galactosidase A (α-Gal-A) enzyme, which normally catalyzes the removal of terminal α-galactose residues from glycosphingolipids. Deficiency of α-Gal-A leads to intracellular accumulation of these macromolecules within lysosomes [60–63]. The enzyme is encoded by the GLA gene (301500 OMIM®), and most FD patients carry single-point mutations [62].

Garman (2007) reported that mutations resulting in a complete loss of enzymatic activity typically affect residues buried within the protein core, whereas mutations associated with partial residual activity are more often located on surface-exposed residues. Some mutations do not alter the mature α-Gal-A structure directly but instead induce protein misfolding. Certain AAs are particularly critical for α-Gal-A folding, and mutations affecting these residues are strongly associated with misfolding. On the other hand, there is an implication of α-Gal-A folding and the frequency of GLA point mutations: (i) most of the missense genetic variants that cause FD produce changes in the α-Gal-A hydrophobic core protein and (ii) more than half of missense genetic variants code for buried AAs residues [64] (Table 2).

The clinical phenotype is directly correlated with residual enzymatic activity. The classic phenotype, seen mainly in males, presents with early-onset symptoms, minimal residual activity, and widespread manifestations including chronic neuropathic pain, angiokeratomas, cornea verticillata, and progressive renal, cardiac, and cerebrovascular disease. The late-onset phenotype is characterized by some residual activity and single-organ involvement, most often kidney or heart [60]. Due to X-linked inheritance and random X-chromosome inactivation (Lyonization), females present with highly variable clinical expression [60].

Nephropathy is a major complication in FD patients. It is characterized by proteinuria and a progressive GFR decrease [60,65]. Due to progression of FD nephropathy, “classic” males presented with ESRD requiring

renal replacement therapy at the mean age of 42 years [65]. In females, for the above reasons, renal involvement is more variable [60,65]. In renal damage due to FD, typically it is assumed that the initial event is produced by the abnormal deposit of non-metabolized α-Gal-A substrate, globotriaosylceramide, and its associated metabolites. This leads to a cascade of events that include the alteration of energy metabolism, the injury of small vessels, the dysfunction of ion channels in endothelial cells, the increase of oxidative stress, the alterations of autophagy, ischemia, and its final result, tissue fibrosis [65]. However, the role of misfolding and ER stress was underestimated and only recently highlighted by experts [66,67] based on the report that certain GLA genetic variants as c.376A>G and c.13 A/G, can produce α-Gal-A misfolding and activate the process of UPR and ER stress [68,69].

Lenders et al. (2025) proposed that in FD, the three canonical UPR branches—ATF6, IRE1, and PERK—are activated downstream of misfolding. More than 900 GLA variants have now been reported, with diverse effects on synthesis, processing, and stability of α-Gal-A [66]. Nonsense, splice-site, and frameshift mutations result in loss of function due to premature termination, typically associated with the classic phenotype in males. In contrast, missense mutations show heterogeneous biochemical effects, ranging from null activity (often involving catalytic site residues) to partially retained enzymatic activity. Importantly, ER stress is thought to contribute substantially to disease pathogenesis, although its direct impact cannot yet be clearly distinguished from secondary lysosomal dysfunction. Moreover, current clinical phenotype (classic vs. late-onset) does not reliably indicate whether substrate accumulation or ER stress predominates in pathogenesis [66].

Chronic induction of the UPR by continuous production of misfolded proteins may promote apoptosis or inflammation, thereby worsening renal pathology [70]. This mechanism has been experimentally demonstrated: ER retention and UPR activation were observed in a Drosophila model expressing two GLA variants (p.A156V and p.A285D) [71].

In FD, disease-causing mutations act primarily through protein misfolding, and several variants are known to be responsive to pharmacological chaperone therapy. Migalastat, for example, stabilizes α-Gal-A variants and restores enzymatic activity in eligible patients [72] (see: https://galafoldamenabilitytable.com/hcp/).

3.5 Von Hippel-Lindau Disease

Von Hippel–Lindau (VHL) syndrome is an autosomal dominant (AD) cancer predisposition disorder caused by germline mutations in the VHL tumor suppressor gene on chromosome 3p, affecting approximately 1 in 36,000–50,000 live births [73–76]. According to Knudson's "two-hit" hypothesis, carriers inherit one mutant allele, but tumorigenesis only occurs after somatic loss of the wild-type allele via loss of heterozygosity, point mutation, or promoter hypermethylation [73,77].

VHL protein (VHLp) functions as the substrate adaptor of a Cullin-2 (CUL2)–based E3 ubiquitin ligase complex binding elongin B/C through a conserved BC-box motif (amino acids 157–172—VHL-ElonginC-ElonginB Complex—VBC) and recruiting CUL2 to ubiquitinate hypoxia-inducible factor α (HIFα) under normoxic conditions, thus regulating proteostasis of key transcription factors [78]. Emerging evidence shows that nascent pVHLp initially associates with the T-complex protein-1 ring complex (TriC) chaperonin and Hsp70/Hsc70, which mediate ATP-dependent folding and trigger release into the VBC complex [79]. For example, the L158P mutation within the H1 helix disrupts elongin C binding, leading to accumulation of TRiC-bound, misfolded VHLp and failure of VBC assembly [79].

Impaired folding of VHLp prevents HIFα degradation, resulting in constitutive activation of angiogenic factors (VEGF, PDGF vascular endothelial growth factor, platelet derived growth factor) and metabolic reprogramming that drive the highly vascular tumors characteristic of VHL disease—clear-cell renal cell

carcinoma, pheochromocytoma, and hemangioblastomas. Moreover, misfolded VHLp may aberrantly interact with other client proteins, including p53 and NF-κB, exacerbating oncogenic and fibrotic signaling [73].

The interplay between chaperonin-mediated folding and VHLp function underscores a broader connection between VHL syndrome and disorders of protein quality control. Strategies to enhance VHLp folding—via small-molecule chaperones or TRiC modulators—are supported by *in vitro* studies demonstrating chaperonin-dependent VHLp maturation [79] and may help restore VBC complex assembly, promote HIFα turnover, and mitigate tumorigenesis in VHL syndrome.

Autosomal dominant pathogenic variants in VHL/3p25.3 gene affect VHLp folding and produce VHL phenotype (For more details, see Table 2).

3.6 Autosomal Dominant Tubulointerstitial Kidney Disease Uromodulin-Related

Autosomal dominant tubulointerstitial kidney disease (ADTKD) (also called medullary cystic kidney disease 2 and/or familial juvenile hyperuricemic nephropathy) is characterized by a family history with AD inheritance, urine sediment with minimal proteinuria, hyperuricemia, early-onset gout, and renal cysts, with slow progressing from CKD to ESRD at varying ages (range of 20 and 70) [80–83].

Uromodulin (UMOD), previously known as Tamm-Horsfall protein, is the most abundant glycoprotein present in normal urine [84,85]. UMOD encodes uromodulin and there are more than 100 UMOD mutations that have been identified, with the pathogenic variants mostly concentrated in exons 3 and 4, affecting cysteine residues with some frequency [80,84]. UMOD mutations have been thought to contribute to uromodulin improper folding, leading to UPR, ER stress, and apoptosis [80]. ADTKD-UMOD is then an underdiagnosed genetic cause of focal segmental glomerulosclerosis (FSGS) mediated by protein misfolding and its consequences [80,86,87].

3.7 Alport Syndrome

Type IV collagen is a major structural component of the glomerular basement membrane (GBM) [88]. It is composed of three self-assembling heterotrimers, which arise from a combination of six distinct subunits synthesized in the ER (COL4A1–COL4A5) [88,89]. During fetal development, the heterotrimers consist primarily of COL4A1 and COL4A2 chains, whereas in mature glomeruli the predominant isoforms include COL4A3, COL4A4, and COL4A5 [90].

COL4A5, COL4A3, and COL4A4 genes encode for three out of this six subunits and genetic variants in COL4A5 (Approximately 80% of cases, X-linked inheritance), COL4A3, and COL4A4 (approximately 20% of cases, with autosomal dominant or recessive inheritance) can produce ER stress and UPR [91].

In the kidneys, pathogenic variants in type-IV collagen cause disease through GBM abnormalities. Because type-IV collagen is also expressed in other tissues, affected patients frequently present with extrarenal manifestations such as hearing loss and ocular defects. The renal phenotype of Alport syndrome (AS) results from defective GBM, typically beginning with proteinuria and hematuria and progressing to CKD over 10–20 years [92–94].

Pathogenic variants associated with AS phenotype are COL4A3/2q36.3 (AD/AR—Type-IV collagen Alpha-3 chain); COL4A4/2q36.3 (AD/AR—Type-IV collagen Alpha-4 chain); COLA5/Xq22.3 (X-linked—Type-IV collagen Alpha-5 chain) and COLA6/Xq22.3 (X-linked—Type-IV collagen Alpha-6 chain) (For more details, see Table 2).

3.8 Congenital Nephrotic Syndrome and Hereditary Glomerulosclerosis

Congenital nephrotic syndrome (CNS) typically manifests within the first three months of life and is characterized by heavy proteinuria (>40 mg/m^2/hour), hypoalbuminemia (<25 g/L), edema, and hyperlipidemia [95]. CNS may arise from congenital infections such as syphilis, toxoplasmosis, or viral agents. However, the most frequent causes are autosomal inherited (dominant or recessive) genetic variants affecting proteins of the glomerular filtration barrier [96–100]. In this review, we focus on genetic variants that disrupt protein folding; other etiologies fall outside the scope of this work.

Other hereditary forms of glomerulosclerosis, leading to nephrotic syndrome (NS) or FSGS at later stages of life, may also result from genetic variants that impair protein folding and promote misfolding with pathological consequences.

Several pathogenic variants of genes encoding components of the blood-glomerular barrier can produce protein misfolding-UPR-ERAD and are associated with nephrotic syndrome. A more detailed description of the genotype-phenotype relationship is provided in Table 2.

3.9 Primary Glomerular Disease

ER stress, UPR, and autophagy have been demonstrated in three experimental rat models of primary glomerular disease [101–103]: (i) membranous nephropathy (passive Heymann nephritis), (ii) MPGN (anti-THY1 nephritis), and (iii) FSGS (puromycin aminonucleoside nephrosis) [104–106].

In primary human glomerulopathies, increased expression of ER stress markers (such as ER chaperones and CHOP) has been observed in kidney biopsies from patients with FSGS, membranous nephropathy, MCD, and MPGN [103]. Despite these findings, the precise mechanisms linking ER stress to human disease remain incompletely understood, underscoring the need for further research. Pathogenic variants associated with FSGS are described in Table 2.

3.10 Diabetic Nephropathy

The relationship between DN, ER stress, and the UPR has been extensively demonstrated in experimental models, including both animal studies and *in vitro* systems [103,107–110]. These investigations have generated hypotheses linking protein misfolding, ER stress, and UPR activation to the pathogenesis of DN. In 2017, Cibulsky wrote that *"loss of XBP1 and induction of ATF6 in podocytes are sufficient to activate a maladaptive UPR that is causally linked to diabetic nephropathy"* [103]. In his review, he also outlined several additional pathophysiological pathways through which ER stress and UPR contribute to the development and progression of DN in experimental models [103].

More recently, other pathways related to protein misfolding, ER-stress, and UPR have been described in DN:

Deletion of IRE1α in mice podocytes [111].

Stress oxidative activation [112].

Dysregulation of GRP78 molecular chaperone [113].

Tubulointerstitial injury mediated by ATF5 ana HSP60 [114].

Pyroptotic and apoptotic podocyte injury by inlammasome activation [115].

Maladaptive unfolded protein response induced by CD248 [116].

3.11 Nephrogenic Diabetes Insipidus

Diabetes insipidus (DI) is an acquired or inherited disorder characterized by polyuria (urine output > 4 L/24 h), extremely low urine osmolality, and polydipsia, resulting from impairment of the

arginine vasopressin (AVP) system [117–119]. This defect leads to an inability to concentrate urine, causing pathologically elevated extracellular fluid osmolality [120–122], and subsequent intracellular disturbances [121–123].

Four major forms of DI have been described:

(i) Gestational: occurs during pregnancy due to excessive production of vasopressinase (a cysteine aminopeptidase) by placental trophoblasts, which cleaves AVP [124].
(ii) Dipsogenic: results from primary polydipsia, where excessive fluid intake suppresses AVP activity [125].
(iii) Neurogenic (central): the most common type, caused by inadequate synthesis or release of AVP [126].
(iv) Nephrogenic: characterized by renal tubular resistance to AVP, usually due to genetic variants in AVP receptor type 2 gene (AVPR2) (X-linked recessive) or aquaporin 2 (AQP2) (AD or AR) [127].

We will develop this fourth group, caused by protein misfolding due to genetic variants, as this is the purpose of this work.

Congenital nephrogenic DI is more frequent than the acquired form (≈80% vs. 20%). Approximately 75% of congenital cases are caused by pathogenic variants in AVPR2, while mutations in AQP2 are less common [128] (Table 2). AVPR2 variants are typically classified into two broad groups: (i) loss-of-function mutations, which impair receptor expression, trafficking, or signaling, and (ii) gain-of-function mutations, which produce constitutively active receptors [1]. Loss-of-function variants can be further divided into five subcategories based on molecular defect and subcellular localization, although these details fall beyond the scope of this review.

Mutations in AQP2 also contribute to nephrogenic DI, with distinct inheritance patterns. Autosomal recessive variants often lead to protein misfolding, resulting in AQP2 retention within the ER and subsequent proteasomal degradation [129] (Table 2). In contrast, autosomal dominant variants typically affect the C-terminal region of AQP2, disrupting its trafficking to the apical plasma membrane [1]. These mechanisms underscore the pivotal role of protein misfolding in the pathogenesis of nephrogenic DI.

3.12 Kidney and Urinary Lithiasis

Urinary lithiasis affects approximately 10% of the general population, with calcium-containing stones representing the majority of cases. Among these, calcium oxalate is the most frequent crystalline component, accounting for nearly 80% of stones [130]. Lithogenesis occurs when urinary solutes reach supersaturation, favoring crystal nucleation and growth, or when inhibitory factors of crystallization are insufficient. Among the various lithogenic factors, hyperoxaluria has been identified as a major contributor to stone formation [130,131].

As previously noted, Tamm–Horsfall protein (THP), also known as uromodulin, is a glycoprotein synthesized and secreted by epithelial cells of the thick ascending limb of the loop of Henle, and represents the most abundant protein in normal human urine [132,133]. Under physiological conditions, THP inhibits calcium oxalate crystal aggregation [134]. However, its activity is strongly influenced by urinary concentration, pH, and ionic strength, allowing THP to exert a dual effect—either inhibitory or promotive—on lithogenesis depending on the prevailing environmental conditions [135].

Carvalho et al. and Hess et al. investigated carefully selected patients with urinary lithiasis who lacked the common predisposing lithogenic factors. Their studies showed that: (i) daily urinary excretion of THP did not differ significantly between stone formers and healthy controls; however, (ii) THP isolated from stone formers exhibited reduced carbohydrate content, particularly lower levels of sialic acid, compared with controls [132,136]. These findings led to the hypothesis that protein composition may influence lithogenesis. Beyond the previously recognized role of THP/uromodulin and its glycoprotein variability, subsequent

research has emphasized other mechanisms, including: (i) enzymatic activity, (ii) crystal nucleation, growth, aggregation, and adhesion mediated by proteins. Collectively, this evidence suggests that protein misfolding does not play a central role in the pathogenesis of urinary lithiasis [136].

3.13 Therapeutic Options for the Treatment of Human Kidney Diseases Involving Protein Misfolding

As highlighted in previous sections, protein misfolding in kidney diseases may act either as a primary pathogenic mechanism or as a secondary factor within a broader pathological context. Accordingly, therapeutic strategies must be tailored to the underlying role of misfolding in each condition.

In diseases where protein misfolding plays only a secondary (non-causal role) treatment should primarily target the initiating process rather than the misfolding itself. This group includes several forms of amyloidosis not driven by genetic variants. Examples are: Immunoglobulin light chain amyloidosis (treatment: Chemotherapy to treat the cellular morphological changes), AA amyloidosis (treatment targeting the underlying chronic inflammatory disease), β2 microglobulin amyloidosis associated to chronic dialysis (treatment: High flux dialyser membranes, haemodialysis, β2 microglobulin adsorption columns, renal transplantation) are examples of these pathologies [137].

On the other hand, in kidney diseases where protein misfolding represents a primary pathogenic mechanism, therapeutic approaches must be tailored to directly target this process.

Pharmacological therapies aimed at restoring proper protein folding can be broadly classified into three categories according to their mechanism of action: (i) protein stabilizers—small pharmacological chaperones that bind to unfolded proteins and direct them toward a lower free energy minimum, folding and stabilizing the unfolded proteins, (ii) aggregation inhibitors—prevent formation of amyloids by bind reversibly to misfolded proteins; can lead to completely folding the protein, and stabilizing this new completely or partially folded structure, and (iii) proteostasis enhancers act on the UPR pathway to upregulate chaperones and other protein quality control components [138].

In humans, several kidney diseases caused by genetic variants that promote protein misfolding have available therapeutic options. Among these, renal amyloidosis currently offers the widest range of targeted treatments.

Inotersen and patisiran are antisense oligonucleotides with target on transthyretin hepatic production for hereditary amyloidosis transthyretin-mediated treatment, while gene editing CRISPR-Cas9 RNA targeting transthyretin is a promising strategy. Tafimidis is a protein stabilizer with transthyretin misfolding target for wild-type amyloidosis transthyretin-mediated ATTRwt [45].

In FD, migalastat acts as a pharmacological chaperone that stabilizes α-Gal-A, enhancing its correct folding and lysosomal trafficking, and thereby addressing the underlying misfolding defect [71].

Proteostasis enhancers such as sodium 4-phenylbutyrate (4-PBA) have shown potential therapeutic effects in AS, nephrogenic DI, and CNS [138–141]. Similarly, taurodeoxycholic acid (TUDCA) has been proposed as a candidate therapy for CNS [1,136]. Among protein stabilizers, tolvaptan and mozavaptan represent potential pharmacological options for NDI [1,41].

For von VHL disease, proteostasis enhancers such as IDF-1174 and HIF-1 modulators have also been proposed [73,142,143].

In animal models, multiple compounds targeting protein misfolding, ER stress, and the UPR have been tested, including: 4-PBA (unfolded protein folding), GSK2606414 (PERK inhibitor), Guanabenz (eIF2α phosphatase inhibitor), KIRA6 (IRE1 RNase inhibitor), Salubrinal (eIF2α phosphatase inhibitor), TUDCA (unfolded protein folding), HLJ2 (XBP1s agonist), (±)-8-ADC (XBP1s agonist), and quercetin (IRE1 RNase activator) [58].

In the present work, however, the focus will remain on therapies for human renal diseases in which protein misfolding—primarily due to genetic variants—plays a significant role (Table 2).

4 Limitations of the Present Study and Future Perspectives

The narrative and non-systematic design of this work represents a limitation. On the other hand, the constant innovation in the field means that this work may summarize the current state of the topic and become outdated in the near future.

However, there is evidence that the axis protein misfolding-ER stress-UPR plays a significant role in the development of human kidney diseases and is a progressive factor in kidney injury [144]. For this reason, despite the aforementioned limitations, we reviewed the current and future prospects on the subject:

Currently, pharmacological chaperones are known that act by correcting protein misfolding; migalastat for "amenable" genetic variants in FD is the first example [145]. Chaperones 4-PBA (tested for clinical use in cystic fibrosis) and TUDCA (tested for clinical use in amyotrophic lateral sclerosis) are well-studied drugs that have been investigated in renal and non-renal human diseases [146,147]. Others chemical chaperones as lumacaftor, elexacaftor, tezacaftor and tafamidis have been approved for clinical use, although these have not yet been studied extensively in kidney disease [146,148] (for currently available therapies for human kidney disease, see Table 3).

Antisense oligonucleotides siRNA can directly reduce the misfolded proteins production and they are promising future therapeutic strategies [111]. Inhibition of APOL1 expression is being investigated in clinical trials [114] and siRNAsthat inhibit UMOD expression are available for research [111].

Table 3: Human kidney diseases caused by protein misfolding and specific therapeutic options.

Disease	Specific Molecule	Category	Protein/Gene Target
ATTRv	Inotersen and patisiran	Antisense oligo Nucleotides	Transthyretin hepatic production
ATTRv	CRISPR-Cas9	Gene editing	RNA targeting Transthyretin
ATTRwt	Tafimidis	Protein stabilizer	Transthyretin misfolding
Fabry disease	Migalastat	Protein stabilizer	α-Gal-A misfolding

Note: Abbreviations: ATTRv: Transthyretin Amyloidosis Result of Amyloidogenic Pathogenic Variants; ATTRwt: Transthyretin Amyloidosis Non-Genetic (Acquired); CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats.

5 Conclusions

Protein misfolding plays a central and increasingly recognized role in the pathogenesis of human kidney diseases, with accumulating evidence revealing new mechanisms since its initial description. Broadly, protein misfolding may: (i) damage renal tissue through pathological aggregation of misfolded proteins; (ii) impair physiological processes dependent on the correct structure and function of specific proteins; and (iii) induce secondary cellular alterations, including ER stress and activation of the UPR.

The first category encompasses disorders associated with the overproduction and deposition of misfolded proteins, such as renal amyloidosis. The second group includes genetic diseases in which mutations generate structurally unstable proteins incapable of performing their physiological roles, as seen in FD, VHL disease, ADTKD, AS, CNS and DI. In these conditions, protein misfolding exerts a direct causal effect. A third group comprises disorders in which protein misfolding has been demonstrated in experimental models and is likely to be relevant in humans, including primary glomerular diseases and DN.

Finally, the emergence of therapeutic strategies specifically designed to target protein misfolding underscores its significance as a pathogenic mechanism and highlights the potential for mechanism-based interventions in renal medicine (Table 3). The role of protein misfolding-UPR-ERAD-ER stress in the

pathophysiology of CKD progression is clearly growing and it is of greater importance in the hereditary genetic causes of CKD that were included in the present work.

The field of protein misfolding in human kidney diseases is of interest as translational medicine, for the discovery of new therapies for clinical use, even in combination.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

4-PBA	sodium 4-phenylbutyrate
α-Gal-A	α-galactosidase A
AA	amino-acid
AD	autosomal dominant
AR	autosomal recessive
ADTKD	autosomal dominant tubulointerstitial kidney disease
AKI	acute kidney injury
AL	light chain amyloidosis
ALECT2	leukocyte cell–derived chemotaxin-2 amyloidosis
AQP2	aquaporin 2
ASK1	activating apoptosis signal-regulating kinase 1
AS	alport syndrome
ATF4	activating transcription factor 4
ATF6	activating transcription factor 6
AVP	arginine vasopressin
AVPR2	AVP receptor type 2 gene
CHOP	C/EBP homologous protein
CKD	chronic kidney disease
CNS	congenital nephrotic syndrome
CUL2	cullin-2

DI	diabetes insipidus
DN	diabetic nephropathy
eIF2α	eukaryotic translation initiation factor 2 alpha
ER	endoplasmic reticulum
ERAD	endoplasmic reticulum associated degradation
ER-OR	endoplasmic reticulum-overload response
ESRD	end stage renal disease
FD	fabry disease
FSGS	focal segmental glomerulosclerosis
GADD34	DNA damage protein 34
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GM1	monosialotetrahexosylganglioside 1
GRP78	glucose-regulated protein 78
HIFα	hypoxia-inducible factor α
Hsp	heat shock proteins
IRE1	inositol-requiring enzyme 1
JNK	c-Jun N-terminal kinase
MCD	minimal change disease
MPGN	mesangioproliferative glomerulonephritis
NS	nephrotic syndrome
PERK	protein kinase R-like ER kinaseS1P: site-1 protease
S2P	site-2 protease
Sirt1	shock gene Sirtuin 1
THP	tamm–horsfall protein
TRAF2	tumor necrosis factor receptor-associated factor 2
Tric	T-complex protein-1 ring complex
TUDCA	taurodeoxycholic acid
UGGT	UDP-glucose/glycoprotein glucosyltransferase
UMOD	uromodulin
UPR	unfolded protein response
UPS	ubiquitin–proteasome system
VBC	Von Hippel-Lindau-ElonginC-ElonginB Complex
VHL	Von Hippel–Lindau
VHLp	Von Hippel–Lindau protein
XBP1	X-box binding protein 1

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