

Endoplasmic Reticulum stress in chronic kidney disease. New molecular targets from bench to the bedside

In depth review

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ABSTRACT

The identification of new biomarkers/pharmacological targets for chronic kidney disease (CKD) is required for the development of more effective therapies. Several studies *in vitro* and *in vivo* have shown the importance of the endoplasmic reticulum (ER) (cellular organelle devoted to protein biosynthesis and maturation, and cellular detoxification processes) in the pathophysiology of CKD. Hence, the synthesis and development of novel drugs against the different ER intracellular pathways is crucial in order to slow down the development and progression of renal diseases. This review aims to dissect the role of the different ER branches (PERK, IRE1 α , ATF6) and their function in CKD, providing potential insights for the development of new treatments.

KEYWORDS: endoplasmic reticulum, chronic kidney disease, unfolded protein response, reticulon

Endoplasmic reticulum

The endoplasmic reticulum (ER) is a continuum of tubules and vesicles morphologically divided in “rough” ER (containing ribosomes attached on the cytosolic border that serves as the site of biological protein synthesis)[1] and “smooth” ER, lacking ribosomes.

Lack or presence of ribosome reflects the multi-functional nature of the ER. In eukaryotic cells, the rough ER has a pivotal function in protein biosynthesis serving as point for the secretory pathway and in the folding and maturation of protein within the cell [2], while the smooth ER is involved in carbohydrates metabolism, drugs detoxification and calcium storage [3].

Protein folding is required to create a functional protein able to exert its function; the ER is a cellular organelle that rectifies abnormal protein folding/function by acting on protein that need to be physiologically replaced/restored or have been damaged by external insults; this process is defined as “unfolded protein response” (UPR). ER could be considered as a signalling platform that responds to stimuli from in and outside the cells with the aim of maintaining cellular functions.

External perturbations of the ER, such as nutrient excess, oxidative stress, iron imbalance, Ca^{2+} leakage from the ER, viral infections and hypoxia are considered the most important causes of ER stress and results in accumulation of unfolded proteins [4], an event that is considered, *per se*, as direct cause of ER stress/dysfunction [5].

Activation of the UPR is considered a double-edged sword as it can trigger either pro-survival pathways (early activation) or pro-apoptotic ones (sustained activation) [6, 7]. The sustained activation of the UPR has been involved, not only in the pathophysiology of CKD [8, 9], but also in alteration of innate immunity, dysregulation of metabolism and cell differentiation processes [10].

The ER interact with different cellular organelles: the specific interaction of the ER with mitochondria is mediated by contact points known as mitochondria-associated membranes (MAM) [11]. MAM are important in cellular homeostasis because they regulate lipids and Ca^{2+} movements between the ER and the mitochondria. Recent evidences suggest that ER-MAM alterations could participate to the pathophysiology of insulin resistance [11], a known determinant implicated in CKD in diabetes [12].

ER-mitochondria interaction plays a key role in regulating cell-death signalling through sequestration of intracellular calcium [13]. Non-sustained ER stress/UPR activation induces ER and mitochondria coupling and calcium transfer as increased Ca^{2+} uptake by the mitochondria stimulates bioenergetics and adenosine triphosphate (ATP) production as an adaptative response.

Severe ER stress (with sustained IRE1 and PERK activation/UPR response) results in activation of pro-apoptotic pathways that leads to mitochondrial Ca^{2+} overload, mitochondrial dysfunction and release of pro-apoptotic factors [14].

Alterations in the ability of the ER membrane-resident sarco-endoplasmic reticulum Ca^{2+} /ATPase pump and inositol 1,4,5-triphosphate receptors, essential processes for efficient mitochondrial respiration and maintenance of normal cell bioenergetics, have been proposed to cause ER stress and cell apoptosis [15].

Mitochondria dysfunction has been linked with oxidative stress and CKD in podocyte [16] and Szeto *et al.* have shown important changes in mitochondrial structure in glomerular cells and proximal tubular epithelial cells in an experimental mouse model of 28-weeks high-fat diet induced glomerulopathy [17]. Further, studies conducted on renal biopsies from patients with focal segmental glomerulosclerosis exhibited an increased mitochondrial damage [16].

The interplay between the ER and mitochondria is crucial to understand the pathophysiology of CKD.

Interestingly, it has been suggested that Nogo-B, an ER protein, regulates the distance between the ER and mitochondria [18]. Low levels of Nogo-B may increase the ER-mitochondria interaction and, secondarily, the susceptibility to apoptosis under sustained stress conditions. Conversely, the presence of Nogo-B during ER stress could reduce the mitochondria-ER interaction and protect cells from apoptosis [18].

The Unfolded protein response

RNA-like ER kinase (PERK), inositol-requiring protein1 (IRE1) and activating transcription factor 6 (ATF6) are ER transmembrane proteins that contain an ER luminal stress-sensing domain and a cytoplasmic enzymatic one. These proteins constitute the three UPR branches: they regulate the transcription factors eIF2 α /ATF4, XBP1 respectively and promote chaperones activation [10].

Activation of PERK through Bip (an ATP-dependent chaperone) promotes a pro-survival signal that represses protein synthesis and prevents further influx of client proteins (protein that need to be processed to reach complete maturation) in the ER [19].

Eif2 α /ATF4 is a regulator pathway controlling the transcription of essential genes for adaptative functions involved in amino acid metabolism, cell differentiation processes and angiogenesis [20].

ATF4 is also an important regulator of autophagy, a mechanism that removes unnecessary or dysfunctional cellular components [19]. As an example, ATF4 regulates autophagy-mediated gene transcriptional program in response to amino acid starvation and ER stress [21].

IRE1 is the most ancient of the UPR sensors, being conserved from yeast to humans. When ER demand and capacity of protein folding is balanced in non-disease conditions IRE1 is present in a non-phosphorylated non active oligomer while, in condition of ER stress, IRE1 autophosphorylates and oligomerizes into multimers. During the initial phase of ER stress (adaptive response) IRE1, in its phosphorylated oligomeric state, determines splicing of the transcript of XBP-1 transcription factor allowing the translation of an activated form of XBP-1 transcription factor, which, in turn, promotes the expression of chaperones favouring cell survival [22, 23]; this process is common in both mammals and plants [24]. Conditions of chronic ER stress and sustained IRE1 activation result in reduced XBP-1 splicing and IRE1 becomes an important executor of apoptosis [24, 25].

The third UPR response, driven by ATF6, results in the activation of the chaperone system that stimulates structural components of the ER including sarcoplasmic ER Ca²⁺-ATPase2, cellular processes that promote protein-folding capacity [26].

The “transient activation” of these transcription factors (UPR response) reestablishes the balance between misfolded and folded protein in favour of the former [27]; the activation of the UPR can therefore be considered a cellular protective response to an external insult causing ER stress. Conversely, the chronic presence of ER stress results in a “sustained activation” of the UPR response that in turn promotes the activation of pro-apoptotic signals and becomes noxious for the cell through the activation of the PERK-eIF2 α -CHOP-Caspase 3/7 pro-apoptotic cascade [28]. (Fig. 1)

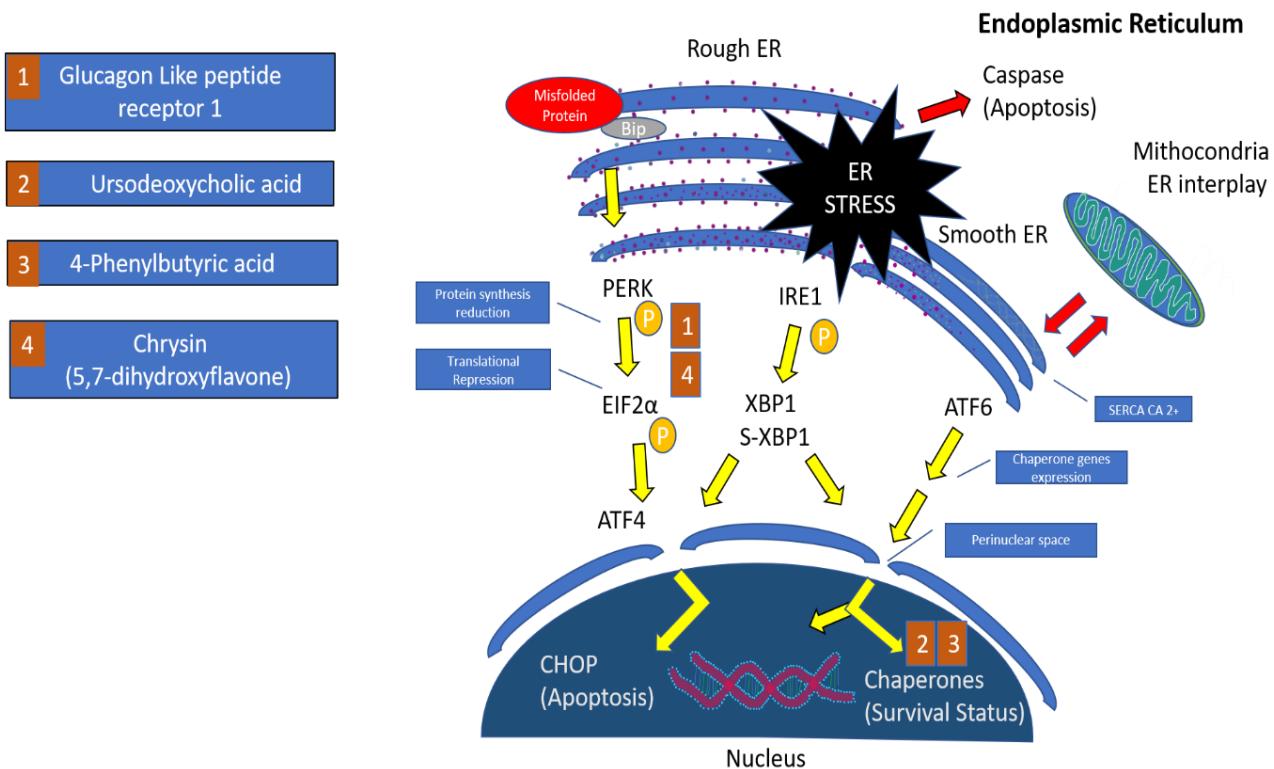


Fig. 1: Schematic representation of ER and UPR under stress condition and putative current therapeutic approaches
 Diagram representing the ER and UPR in condition of ER stress within the cell. ER stress-mediated accumulation of misfolded proteins triggers the activation of the PERK, IRE1 α and ATF6 stress sensor through the molecular chaperone Bip. Prolonged insults, secondary ER stress and the sustained UPR activation result in cellular apoptosis. Mitochondria-ER interaction modulates the Ca²⁺ content in the mitochondria and secondary activation of autophagy/apoptosis processes. Putative treatment strategies modulating ER/UPR pathways towards cell survival are mapped: compounds 1 and 2 interfere with the PERK-Eif2 α axis, while compounds 3 and 4 interfere with chaperones functions.

Chronic kidney disease and ER/UPR response

CKD, mainly represented by hypertensive and diabetic nephropathies, is a growing pathology that is reaching epidemic proportion in Europe and worldwide [29, 30]. The CARHES (Cardiovascular risk in renal patients of the health examination survey) study, led by the Italian Society of Nephrology in partnership with the Italian Society of Cardiologists, published a detailed analysis of the prevalence of CKD and associated cardiovascular risk in Italy. Among 9000 patients studied, 40-50% were affected by CKD, while its prevalence was found to increase with age and to be similar across genders [31, 32].

Diabetic nephropathy (DN) affects about one-third of patients with diabetes mellitus and is ranked as the first cause of end-stage renal disease in the world [33]. DN and other CKD are silent pathologies linked by a progressive decline in renal function and parallel increase in cardiovascular morbidity and mortality [34].

Furthermore, CKD has an important impact on the national health service, especially if we consider the health-related costs attached to renal replacement therapy and the costs to society (e.g. loss of working hours) [35]. CKD patients are characterized by a wide spectrum of kidney pathologic lesions such as glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Renal biopsy in CKD patients can be classified into three main groups: classical diabetic nephropathy (DN), non-diabetic renal disease (NDRD) and DN plus NDRD (mixed forms) [36].

In CKD, chronic perturbations such as hyperglycaemia, dyslipidaemias and haemodynamic insults (elevated systemic-hypertension and intraglomerular pressure) result in ER stress [37] and are important factors driving renal function decline and progression towards end stage renal failure [38].

The renal damage seen in CKD might be the result of direct injury (disease mediated fibrosis) or a manifestation of wound repair in response to injury, where the response against the disease exceeds the potential for restoration [39, 40].

The structural tissue-related damage is driven by perturbations (e.g. metabolic, haemodynamic) that lead to ER stress and sustained UPR-mediated cell death, chronic inflammation and fibrosis [41, 42]. Unresolved chronic sustained inflammation driven by ER stress, as seen in CKD, is a promoter for uncontrolled healing, fibrosis and tissue damage [43, 44].

Sustained activation of the UPR, such as IRE1 α , results in the activation of tumor necrosis factor receptor associated factor and of the proinflammatory transcription factor AP-1, which, in turn, have been shown to promote the activation of pro-inflammatory pathways such as NF- κ B, NOD1/2 and RIP-dependent cascades [10]. Similarly, PERK activation and eIF2 α phosphorylation increases NF- κ B stability. ER stress in macrophages supports polarization towards a proinflammatory phenotype driven by NF- κ B [45]. ER stress is also characterised by an increase in pro-inflammatory cytokines, such as IL1 β and IL18; deletion of IRE1 α in macrophages promotes their polarization towards a non-inflammatory phenotype [46–48].

Epithelial cells exposed to ER stress lose their characteristics and undergo an epithelial-to-mesenchymal transition which in turns participates to the fibrotic process (deposition of extracellular matrix, and secretion of profibrotic mediators) upon tissue injury [49–51]. Transforming growth factor- β (TGF- β)-1 is a prosclerotic cytokine that plays a crucial role in ER stress induced fibrosis, and the UPR activation has been shown to play a role in the wound repair and tissue remodelling process [42, 52]. In cultured renal tubular cells, TGF- β 1 induces the expression of ER stress markers and profibrotic factors, which can be reduced by inhibitors of UPR such as chemical chaperones [53, 54]; further, sXBP1 appears to be required for extracellular matrix production and secretion, through ER enlargement [55, 56].

Clinical and experimental studies have suggested that proteinuria is an active player in the progression of CKD and a cause of tubular interstitial fibrosis and inflammation [57]. Indeed, chronic proteinuria has a toxic effect on tubular cells and, by activating ER stress, results in the sustained activation of the UPR that in turn drives the tubulointerstitial disease [58–60].

Studies have shown UPR activation in tubular cells exposed to albumin [61, 62]; more specifically, albumin-mediated activation of PERK-ATF4 pathway, through the expression of lipocalin 2, appears to play a role in tubular apoptosis and renal lesions: the inhibition of this pathway by chemical chaperones slows renal deterioration in proteinuric mice [58].

It is very clear that the ER and UPR are important for cell and tissue homeostasis both in physiology and diseases; dissecting the mechanism of ER/UPR activation could provide important information for the development of new drugs.

Interventions modulating the ER/UPR response

Several molecules/putative drugs have been shown to modulate the function and the crosstalk among the different branches of the UPR in kidney disease.

Glucagon like peptide (GLP)-1 receptor agonists

Protein kinase-A signalling elicited by GLP-1 receptor agonists differentially modulates the UPR PERK/eIF2a arm, transcription factor ATF4, XBP1 splicing and CHOP, promoting β-cell survival [63, 64]. Similar mechanisms could be postulated for the renoprotective effect of GLP-1 analogues in diabetic kidney disease [65, 66] but more studies are warranted.

Chemical chaperones

Inhibition of ER stress/UPR activation using chaperones has been shown to improve the progression of CKD. Specifically, the chemical chaperone 4-phenylbutyric acid (4-PBA) [67] seems to have a direct protective effect on renal tubular cells *in vitro* through the modulation of aristolochic acid-induced ER stress/UPR response and related inflammatory cascade response [68]. It has also been demonstrated that 4-PBA protects human glomerular mesangial cells *in vitro* from lipid-mediated injury by modulating PERK-eIF2α pathway [69] and ameliorates renal function in models of focal segmental glomerulosclerosis [70].

Further, 4-PBA seems to be able to reduce resistant artery contractility and increase nitric oxide-mediated endothelial vasodilation through a chaperone/UPR-mediated mechanism, resulting in correction of haemodynamic perturbations and kidney protection [71]. *In vivo*, 4-PBA limits the progression of chronic kidney disease in Dahl salt-sensitive rats [72] and is renoprotective in the angiotensin II/deoxycorticosterone acetate/salt murine model of CKD [73].

Ursodeoxycholic acid (UDCA), another chemical chaperone that is known to inhibit ER stress and UPR response [74], has demonstrated a protective role on kidneys and eyes in experimental animal models of diabetes [75, 76].

Indeed, the two chemical chaperones UDCA and 4-PBA, in combination, have been proposed as potential novel therapeutic approach for the treatment of diabetic nephropathy [74].

Modulation of ER proteins

The ER protein, RTN1, correlates inversely with renal function in patients with diabetic nephropathy: RTN1 overexpression in renal cells induces an increase in ER stress and apoptosis, whereas RTN1 knockdown attenuates hyperglycaemia-induced ER stress and apoptosis [77].

RTN1A acts by interacting with PERK through its N-terminal and C-terminal domains. The sustained RTN1A-PERK interaction promotes PERK-mediated apoptosis; knockdown of RTN1A expression *in vivo* inhibits the interaction/sustained activation of PERK and attenuates ER stress and renal fibrosis in mice model of unilateral ureteral obstruction and diabetic nephropathy, suggesting that RTN1A contributes to the progression of kidney disease by inducing ER stress [77].

Similarly, downregulation of the ER protein Nogo-B has been implicated in sustained stimulation of the PERK/ATF4/ATF6 pathway in norepinephrine-mediated cardiomyocyte hypertrophy and TGF-β1-induced cardiac fibroblast activation [78].

We recently demonstrated that overexpression of sNogo-B (the N-terminus fragment of the ER protein Nogo-B) in the circulation, prevents diabetes mediated Nogo-B downregulation and ameliorates diabetic kidney disease by reducing albuminuria, hyperfiltration, abnormal angiogenesis and protecting glomerular capillary structure [79]. Systemic sNogo-B overexpression in diabetic mice is associated with inhibition of diabetes-mediated upregulation of VEGF-A signalling and eNOS, AKT and GSK3β phosphorylation [79]. Collectively, these studies provide the

first evidence that modulation of the ER protein Nogo-B could protect the vasculature in diabetes and may represent a novel therapeutic target for diabetic vascular complications [79]. Ongoing studies are exploring whether sNogo-B could inhibit/modulate sustained diabetes-mediated PERK/ATF4/ATF6 pathway activation.

Flavonoids

Chrysin (5,7-dihydroxyflavone) is a natural flavonoid found in propolis and mushrooms that has anti-inflammatory, antioxidant and anticancer properties. In *in vitro* and *in vivo* experimental model of diabetes, chrysin treatment blocked high glucose/diabetes-mediated ER stress/UPR responses and podocyte apoptosis via inhibition of PERK-eIF2 α -ATF4-CHOP activation [80].

Conclusions

Multi-target approaches are required to delay the progression of CKD. Discovery of new ER biomarkers/molecules implicated in the regulation of molecular mechanisms regulating ER stress mediated sustained UPR response in CKD may lead to the development of new therapies for this devastating disease.

BIBLIOGRAFIA

1. Schwarz DS, Blower MD. The endoplasmic reticulum: structure, function and response to cellular signaling. *Cell Mol Life Sci* 2016; 73(1):79-94.
2. Mandon EC, Trueman SF, Gilmore R. Protein translocation across the rough endoplasmic reticulum. *Cold Spring Harb Perspect Biol* 2013; 5(2): a013342.
3. Missiroli S, et al. Endoplasmic reticulum-mitochondria Ca(2+) crosstalk in the control of the tumor cell fate. *Biochim Biophys Acta Mol Cell Res* 2017; 1864(6):858-64.
4. Karna KK, et al. The Role of Endoplasmic Reticulum Stress Response in Male Reproductive Physiology and Pathology: A Review. *World J Mens Health* 2019; 37:e40.
5. Wang M, Kaufman RJ. Protein misfolding in the endoplasmic reticulum as a conduit to human disease. *Nature* 2016; 529(7586):326-35.
6. Malhotra JD, Kaufman RJ. Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? *Antioxid Redox Signal* 2007; 9(12):2277-93.
7. Walter F, et al. Imaging of single cell responses to ER stress indicates that the relative dynamics of IRE1/XBP1 and PERK/ATF4 signalling rather than a switch between signalling branches determine cell survival. *Cell Death Differ* 2015; 22(9):1502-16.
8. Maekawa H, Inagi R. Stress Signal Network between Hypoxia and ER Stress in Chronic Kidney Disease. *Front Physiol* 2017; 8:74.
9. Markan S, et al. Up regulation of the GRP-78 and GADD-153 and down regulation of Bcl-2 proteins in primary glomerular diseases: a possible involvement of the ER stress pathway in glomerulonephritis. *Mol Cell Biochem* 2009; 324(1-2):131-8.
10. Hetz C. The unfolded protein response: controlling cell fate decisions under ER stress and beyond. *Nat Rev Mol Cell Biol* 2012; 13(2):89-102.
11. Rieusset J. Role of Endoplasmic Reticulum-Mitochondria Communication in Type 2 Diabetes. *Adv Exp Med Biol* 2017; 997:171-86.
12. Karalliedde J, Gnudi L. Diabetes mellitus, a complex and heterogeneous disease, and the role of insulin resistance as a determinant of diabetic kidney disease. *Nephrol Dial Transplant* 2016; 31(2):206-13.
13. Marchi S, et al. Mitochondrial and endoplasmic reticulum calcium homeostasis and cell death. *Cell Calcium* 2018; 69:62-72.
14. Bravo-Sagua R, et al. Cell death and survival through the endoplasmic reticulum-mitochondrial axis. *Curr Mol Med* 2013; 13(2):317-29.
15. Cardenas C, et al. Essential regulation of cell bioenergetics by constitutive InsP3 receptor Ca2+ transfer to mitochondria. *Cell* 2010; 142(2):270-83.
16. Daehn I, et al. Endothelial mitochondrial oxidative stress determines podocyte depletion in segmental glomerulosclerosis. *J Clin Invest* 2014; 124(4):1608-21.
17. Szeto HH, et al. Protection of mitochondria prevents high-fat diet-induced glomerulopathy and proximal tubular injury. *Kidney Int* 2016; 90(5):997-1011.
18. Sutendra G, et al. The role of Nogo and the mitochondria-endoplasmic reticulum unit in pulmonary hypertension. *Sci Transl Med* 2011; 3(88):88ra55.
19. Teske BF, et al. The eIF2 kinase PERK and the integrated stress response facilitate activation of ATF6 during endoplasmic reticulum stress. *Mol Biol Cell* 2011; 22(22):4390-405.
20. Rzymski T, et al. Role of ATF4 in regulation of autophagy and resistance to drugs and hypoxia. *Cell Cycle* 2009; 8(23):3838-47.
21. B'Chir W, et al. The eIF2alpha/ATF4 pathway is essential for stress-induced autophagy gene expression. *Nucleic Acids Res* 2013; 41(16):7683-99.
22. Wu H, Ng BS, Thibault G. Endoplasmic reticulum stress response in yeast and humans. *Biosci Rep* 2014; 34(4): e00118.
23. Salzberg Y, et al. Reduced Insulin/Insulin-Like Growth Factor Receptor Signaling Mitigates Defective Dendrite Morphogenesis in Mutants of the ER Stress Sensor IRE-1. *PLoS Genet* 2017; 13(1):e1006579.
24. Chen Y, Brandizzi F. IRE1: ER stress sensor and cell fate executor. *Trends Cell Biol* 2013; 23(11):547-55.
25. Hetz C, Saxena S. ER stress and the unfolded protein response in neurodegeneration. *Nat Rev Neurol* 2017; 13(8):477-91.
26. Chemaly ER, Troncone L, Lebeche D. SERCA control of cell death and survival. *Cell Calcium* 2018; 69:46-61.

27. Zhang K, Kaufman RJ. From endoplasmic-reticulum stress to the inflammatory response. *Nature* 2008; 454(7203):455-62.
28. Fribley A, Zhang K, Kaufman RJ. Regulation of apoptosis by the unfolded protein response. *Methods Mol Biol* 2009; 559:191-204.
29. Orantes-Navarro CM, et al. The Chronic Kidney Disease Epidemic in El Salvador: A Cross-Sectional Study. *MEDICC Rev* 2019; 21(2-3):29-37.
30. Schiffi, H. and S.M. Lang. [Obesity and kidney disease – renal consequences of an “epidemic”]. *Dtsch Med Wochenschr* 2017; 142(19):1466-72.
31. De Nicola L, Dal Canton A, Gruppo di Ricerca CARHES. [Epidemiology of chronic kidney disease in Italy: the CARHES study]. *G Ital Cardiol* 2010; 11(5S3):106S-8S.
32. De Nicola L, et al. [Epidemiology of chronic kidney disease in Italy: current state and contribution of the CARHES study]. *G Ital Nefrol* 2011; 28(4):401-7.
33. Gembillo G, et al. Role of Vitamin D Status in Diabetic Patients with Renal Disease. *Medicina (Kaunas)* 2019; 55(6):273.
34. Go AS, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351(13):1296-305.
35. Klarenbach SW, et al. Economic evaluation of dialysis therapies. *Nat Rev Nephrol*, 2014. 10(11):644-52.
36. Bermejo S, Pascual J, Soler MJ. The current role of renal biopsy in diabetic patients. *Minerva Med* 2018; 109(2):116-25.
37. Bakker W, et al. Endothelial dysfunction and diabetes: roles of hyperglycemia, impaired insulin signaling and obesity. *Cell Tissue Res* 2009; 335(1):165-89.
38. Gnudi L, Gentile G, Ruggenenti P. Patients with diabetes mellitus. In Turner N, Lamiere N, Goldsmith DJ, Winearl CG, Himmelfarb J, Remuzzi G (eds), *Oxford textbook of clinical nephrology*. 2016: Oxford University Press (Oxford, UK), pp. 1199-247.
39. Rockey DC, Bell PD, Hill JA. Fibrosis—a common pathway to organ injury and failure. *N Engl J Med* 2015; 372(12):1138-49.
40. Venkatachalam MA, et al. Failed Tubule Recovery, AKI-CKD Transition, and Kidney Disease Progression. *J Am Soc Nephrol* 2015; 26(8):1765-76.
41. Cybulsky AV. Endoplasmic reticulum stress, the unfolded protein response and autophagy in kidney diseases. *Nat Rev Nephrol* 2017; 13(11):681-96.
42. Kropski JA, Blackwell TS. Endoplasmic reticulum stress in the pathogenesis of fibrotic disease. *J Clin Invest* 2018; 128(1):64-73.
43. Bettigole SE, Glimcher LH. Endoplasmic reticulum stress in immunity. *Annu Rev Immunol* 2015; 33:107-38.
44. Todd DJ, Lee AH, Glimcher LH. The endoplasmic reticulum stress response in immunity and autoimmunity. *Nat Rev Immunol* 2008; 8(9):663-74.
45. Blackwell TS, Christman JW. The role of nuclear factor-kappa B in cytokine gene regulation. *Am J Respir Cell Mol Biol* 1997; 17(1):3-9.
46. Lebeaupin C, et al. ER stress induces NLRP3 inflammasome activation and hepatocyte death. *Cell Death Dis* 2015; 6:e1879.
47. Oh J, et al. Endoplasmic reticulum stress controls M2 macrophage differentiation and foam cell formation. *J Biol Chem* 2012; 287(15):11629-41.
48. Shan B, et al. The metabolic ER stress sensor IRE1alpha suppresses alternative activation of macrophages and impairs energy expenditure in obesity. *Nat Immunol* 2017; 18(5):519-29.
49. Cuevas EP, et al. LOXL2 drives epithelial-mesenchymal transition via activation of IRE1-XBP1 signalling pathway. *Sci Rep* 2017; 7:44988.
50. Moon SY, et al. Endoplasmic reticulum stress induces epithelial-mesenchymal transition through autophagy via activation of c-Src kinase. *Nephron Exp Nephrol* 2014; 126(3):127-40.
51. Pang XX, et al. Urotensin II Induces ER Stress and EMT and Increase Extracellular Matrix Production in Renal Tubular Epithelial Cell in Early Diabetic Mice. *Kidney Blood Press Res* 2016; 41(4):434-49.
52. Chiang CK, et al. Endoplasmic reticulum stress implicated in the development of renal fibrosis. *Mol Med* 2011; 17(11-12):1295-305.
53. Dihazi H, et al. Secretion of ERP57 is important for extracellular matrix accumulation and progression of renal fibrosis, and is an early sign of disease onset. *J Cell Sci* 2013; 126(16):3649-63.
54. Liu SH, et al. Chemical chaperon 4-phenylbutyrate protects against the endoplasmic reticulum stress-mediated renal fibrosis in vivo and in vitro. *Oncotarget* 2016; 7(16):22116-27.
55. Baek HA, et al. Involvement of endoplasmic reticulum stress in myofibroblastic differentiation of lung fibroblasts. *Am J Respir Cell Mol Biol* 2012; 46(6):731-9.
56. Matsuzaki S, et al. Physiological ER Stress Mediates the Differentiation of Fibroblasts. *PLoS One* 2015; 10(4):e0123578.

57. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. *N Engl J Med* 1998; 339(20):1448-56.
58. El Karoui K, et al. Endoplasmic reticulum stress drives proteinuria-induced kidney lesions via Lipocalin 2. *Nat Commun* 2016; 7:10330.
59. Cravedi P, Ruggenenti P, Remuzzi G. Proteinuria should be used as a surrogate in CKD. *Nat Rev Nephrol* 2012; 8(5):301-6.
60. Ruggenenti P, Cravedi P, Remuzzi G. Mechanisms and treatment of CKD. *J Am Soc Nephrol* 2012; 23(12):1917-28.
61. Lindenmeyer MT, et al. Proteinuria and hyperglycemia induce endoplasmic reticulum stress. *J Am Soc Nephrol* 2008; 19(11):2225-36.
62. Ohse T, et al. Albumin induces endoplasmic reticulum stress and apoptosis in renal proximal tubular cells. *Kidney Int* 2006; 70(8):1447-55.
63. Gaballah HH, et al. Mechanistic insights into the effects of quercetin and/or GLP-1 analogue liraglutide on high-fat diet/streptozotocin-induced type 2 diabetes in rats. *Biomed Pharmacother* 2017; 92:331-9.
64. Yusta B, et al. GLP-1 receptor activation improves beta cell function and survival following induction of endoplasmic reticulum stress. *Cell Metab* 2006; 4(5):391-406.
65. Vikulova OK, et al. Renal effects of glucagon-like peptide receptor agonists in patients with type 1 diabetes mellitus. *Ter Arkh* 2018; 90(6):59-64.
66. Dieter BP, Alicic RZ, and Tuttle KR. GLP-1 receptor agonists in diabetic kidney disease: from the patient-side to the bench-side. *Am J Physiol Renal Physiol* 2018; 315(6):F1519-25.
67. Roy D, et al. Evidence that Chemical Chaperone 4-Phenylbutyric Acid Binds to Human Serum Albumin at Fatty Acid Binding Sites. *PLoS One* 2015; 10(7):e0133012.
68. Zhu S, et al. Endoplasmic reticulum stress mediates aristolochic acid I-induced apoptosis in human renal proximal tubular epithelial cells. *Toxicol In Vitro* 2012; 26(5):663-71.
69. Yang H, et al. Endoplasmic reticulum stress participates in inflammation-accelerated, lipid-mediated injury of human glomerular mesangial cells. *Nephrology (Carlton)* 2017; 22(3):234-42.
70. Yee A, et al. Proteostasis as a therapeutic target in glomerular injury associated with mutant alpha-actinin-4. *Am J Physiol Renal Physiol* 2018; 315(4):F954-66.
71. Naiel S, et al. Endoplasmic reticulum stress inhibition blunts the development of essential hypertension in the spontaneously hypertensive rat. *Am J Physiol Heart Circ Physiol* 2019; 316(5):H1214-23.
72. Yum V, et al. Endoplasmic reticulum stress inhibition limits the progression of chronic kidney disease in the Dahl salt-sensitive rat. *Am J Physiol Renal Physiol* 2017; 312(1):F230-44.
73. Mohammed-Ali Z, et al. Endoplasmic reticulum stress inhibition attenuates hypertensive chronic kidney disease through reduction in proteinuria. *Sci Rep* 2017; 7:41572.
74. Cao A, et al. Ursodeoxycholic acid and 4-phenylbutyrate prevent endoplasmic reticulum stress-induced podocyte apoptosis in diabetic nephropathy. *Lab Invest* 2016; 96(6):610-22.
75. Cao A, et al. Ursodeoxycholic Acid Ameliorated Diabetic Nephropathy by Attenuating Hyperglycemia-Mediated Oxidative Stress. *Biol Pharm Bull* 2016; 39(8):1300-8.
76. Chung YR, et al. Ursodeoxycholic Acid Attenuates Endoplasmic Reticulum Stress-Related Retinal Pericyte Loss in Streptozotocin-Induced Diabetic Mice. *J Diabetes Res* 2017; 2017:1763292.
77. Fan Y, et al. RTN1 mediates progression of kidney disease by inducing ER stress. *Nat Commun* 2015; 6:7841.
78. Li J, et al. Inhibition of Nogo-B promotes cardiac hypertrophy via endoplasmic reticulum stress. *Biomed Pharmacother* 2018; 104:193-203.
79. Hernandez-Diaz I, et al. Overexpression of Circulating Soluble Nogo-B Improves Diabetic Kidney Disease by Protecting the Vasculature. *Diabetes* 2019; 68(9):1841-52.
80. Kang MK, et al. Chrysin ameliorates podocyte injury and slit diaphragm protein loss via inhibition of the PERK-eIF2alpha-ATF-CHOP pathway in diabetic mice. *Acta Pharmacol Sin* 2017; 38(8):1129-40.