Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.07.045

Review on the neuron damage parameters in patients with end-stage renal disease

Basim Abd Al-Raheem Twaij[1], Hussein Kadhem Al-Hakeim[2]*, Mazin Fadhil Altufaili[3]
[1,2,3]Department of Chemistry, Faculty of Science, University of Kufa, Iraq.
***Corresponding author:** Hussein Kadhem Al-Hakeim, Department of Chemistry, Faculty of Science, University of Kufa, Iraq, Email:headm2010@yahoo.com

Submitted: 05 February 2023; Accepted: 15 March 2023; Published: 03 April 2023

ABSTRACT

Many studies have found toxic effects on the body and mental state at near and long-term parameters in end-stage renal disease (ESRD) patients of neuronal integrity. Consequently, studying chemical molecules that cause tissue damage to neurons is essential for understanding the mechanism of toxicity and available treatment prospects. Which includes some parameters of myelin basic protein (MBP), ionized calcium-binding adaptor molecule 1 IBA1, calcium-binding protein B (S100B), Glial fibrillary acidic protein (GFAP), neuroepithelial stem cell protein (Nestin), neurofilament light polypeptide (NFL), neuron-specific enolase, T-tau and claudin proteins.

The published papers on changes in neuronal damage final products in ESRD patients were reviewed, and the explanations obtained from previous research were collected. It is concluded from this review that causes an increase in parameters in patients with ESRD lead to neurodegeneration, which leads to severe damage to patients health that requires therapeutic intervention to reduce the harmful effects of parameters on the health of patients.

Keywords: *Damage, Parameters, Patients, Protien*

INTRODUCTION

End-stage renal disease (ESRD)

End-stage renal disease (ESRD) occurs when chronic kidney disease has advanced so far that the kidneys no longer work well enough to filter wastes and fluids from the blood, resulting in dangerous levels of buildup within the body [1]. ESRD is the loss of kidney function with this condition is irreversible. The two most common causes of ESRD are hypertension (high blood pressure) and diabetes [2]. There is also an increased risk for the condition if mother, father or sibling has kidney failure. There is a wide range of symptoms for ESRD, which can often be confused as indications of other medical conditions [3].

Patients may experience a wide variety of symptoms as kidney failure progresses. These include fatigue, drowsiness, decrease in urination or inability to urinate, dry skin, itchy skin, headache, weight loss, nausea, bone pain, skin and nail changes, and easy bruising [4]. Doctors can diagnose the disease with blood tests, urine tests, kidney ultrasound and kidney biopsy [5]. The prevalence rates and the impact of ESRD disease vary across the world and between different countries. There is evidence that the number of patients with ESRD worldwide is increasing [6]. Estimates have suggested that the prevalence in Japan is higher than 2,000 per million population

(pmp), while it is approximately 1,500 pmp in the United States and 800 pmp in the European Union [7]. The mean prevalence of ESRD in the Middle East was estimated (in 2009) to be lower, at 430 pmp [8]. However, a Saudi report estimated the prevalence of ESRD in the KSA in 2015 to be 1,100 pmp [9]. ESRD patients experience a multitude of mental and physio-somatic symptoms, including depression, anxiety, fatigue, fibromyalgia-like symptoms, muscular pain, insomnia, headache, and cognitive impairments[10]. Each nephron in a normal kidney contributes to the total GFR. The decline of kidney function is gradual and initially may present asymptomatically. The natural history of renal failure depends on the etiology of the disease but ultimately involves early homeostatic mechanisms involving hyperfiltration of the nephrons [11, 12]. The kidney maintains GFR, despite progressive destruction of nephrons, because the remaining normal nephrons develop hyperfiltration and compensatory hypertrophy. As a result, the patient with mild renal impairment can show normal creatinine values, and the disease can go undetected for some time [13].

Neuron damage parameters

Neurons A types of cell that receives and sends messages from the body to the brain and back to the body. The messages are sent by a weak electrical current. Also called nerve cell [14].

Although neurons are the longest-living cells in the body, large numbers of them die during migration and differentiation [15]. The lives of some neurons can take strange turns. Some diseases of the brain are the result of the unnatural deaths of neurons [16].

Physical damage to the brain and the spinal cord can also kill or disable neurons [17]. Damage to the brain caused by shaking or hitting the head, or because of a stroke, can kill neurons immediately or slowly, starving them of the oxygen and nutrients they need to survive [18].

During a multiple sclerosis attack, the immune system triggers inflammation along the nerves and at the glial cells. Oligodendrocytes are damaged, and myelin is damaged and stripped away from the axon. This process is called demyelination. Messages that pass along a demyelinated nerve become delayed or blocked [19].

METHODS

A literature search was performed using PubMed, Scopus, Medline, Embase, and the Cochrane database systematic reviews. Keywords used as search terms were End Stage Renal Diseases", "Dialysis", "Hemodialysis", "Depression", "Cytokines", "Neuron damage, "Chronic Kidney Diseases", "Myelin", " Ionized calcium-binding adaptor molecule 1", "Calcium-binding protein B", "Glial fibrillary acidic protein", "Neuroepithelial stem cell protein", "Neurofilament light polypeptide", "neuron-specific enolase","T-tau",and "claudin proteins". In our analysis, we did not place any restrictions on how long the evaluation may take. The database only includes articles written in English. To be included, research have to have examined the link between ESRD and one of the parameters.

Some parameters lead to neuron damage, which can be detailed in this research.

1. Myelin basic protein (MBP)

The classic isoforms of myelin basic protein (MBP) range in nominal molecular mass from 14 to 21.5 kDa, and are essential to maintaining the structural integrity of the myelin sheath of the central nervous system (CNS) [20]. In addition to forming compacted myelin internodes by membrane adhesion, the protein potentially participates in dynamic processes such as cytoskeletal turnover at leading edges of membrane ruffles and processes, and mediated signaling pathways during myelin formation. This MBP variant is structurally polymorphic, being an exemplary intrinsically-disordered protein [21].

The structure of MBP is best described as collections of dynamic conformational ensembles with only weak tertiary interactions the nature of which depend on the environment [22].

Increased degradation of myelin is believed to be an important step that leads to multiple sclerosis pathology [23]. Transmigration of leukocytes across the vasculature, and a compromised Blood Brain Barrier participate in the neuroinflammation of multiple sclerosis [24]. MBP is present in multiple sclerosis tissue and chemokines and cytokines are essential to inflammation and the developing lesion, the inflammatory role of MBP in mediating the pathogenesis of multiple sclerosis in ESRD [25]. ESRD is a major issue in healthcare and can also cause peripheral nerve damage. A hallmark of myelinated fibers is saltatory nerve conduction, which enables faster and more efficient propagation of signals as compared with unmyelinated axons of the same diameter [26]. As expected from its major role in mammalian nervous system physiology, myelination defects in humans usually have significant neurological manifestations [27]. Diseases of myelin represent a large, heterogeneous group with regard to clinical characteristics, pathophysiology, and etiology [28]. Hereditary and acquired pathologies can be distinguished, of which inflammatory, infectious, toxic, and metabolic are the most prevalent in the ESRD [27]. Increased MBP causes high myelin basic protein was MS is the most common cause for this, but other causes may bleeding of the central nervous system, central nervous system trauma and certain brain diseases [29].

MBP promotes myelin membrane stacking and the formation of the major dense line, which is disturbed in demyelinating conditions, including MS and demyelinating neuropathies [30].

Not have any research about decreased MBP in ESRD patients.

2. Ionized calcium binding adaptor molecule 1 (IBA1)

Ionized calcium-binding adapter molecule 1 (Iba1) is a 147-amino acid calcium-binding protein that is expressed in microglial macrophage. Also called allograft inflammatory factor 1 (AIF1), is a well-established marker for microglia/macrophages. It is a 17-kDa EF hand calcium binding protein and it is upregulated during the activation of microglia/macrophages. The protein is localized in the cytoplasm and nucleus of cells. Iba1 in the cytoplasm has actin-crosslinking activity [31] and is critically involved in certain aspects of motility-associated rearrangement of the actin cytoskeleton, such as in membrane ruffling and in the building of phagocytic cups, an early step of phagocytosis [32]. No reports are available on the role of Iba1 in the nucleus. Because studies of Iba1 have focused on its role in microglia, little has been published regarding the types of cell expressing Iba1 outside the CNS.

IBA1 was also detected as a potential factor which contribute to apoptosis and inflammation in kidney diseases leading to ESRD [33]. In kidney infiltrations of activated macrophage (Iba1) into tissues increased significantly with age [34].

It has been reported that the expression of Iba-1 is increased in activated microglia [35], suggesting that the increased expression of Iba-1 can be used as a marker for microglial activation. Organic osmolytes and brain water changes in acute kidney injury [36]. Increased plasma urea leads to increased astrocyte and neuronal urea concentrations, microglia have also been extensively studied for their harmful roles in neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, as well as cardiac diseases, glaucoma, and viral and bacterial infections [37, 38]. Other study found that increased microglia that one of the strongest genetic risk factors for Alzheimer's disease, cannot metabolize lipids normally [39]. Increased Iba-1 become activated following exposure to pathogen-associated molecular patterns and/or endogenous damage-associated molecular patterns and removal of the immune-suppressive signals [40]. Activated microglia can acquire different phenotypes depending on cues in its surrounding environment [41].

Not have any research about decreased MBP in ESRD patients.

3. Calcium-binding protein B (S100B)

Calcium binding protein B (S100B) is a protein present in high concentrations in astroglial and oligodendroglial cells in the CNS ; a release of

S100β by these cells may represent glial response to inflammation, ischemia, and metabolic stress [42]. The secretion of S100β could also be seen as a terminal event of the inflammatory pathway that underlies delirium development and propagation. An interruption of the blood–brain barrier secondary to inflammation may result in a communication between leukocytes and astrocytes, leading to subsequent activation of astrocytes, with release of S100β manifesting clinically as delirium [43, 44].

This pathway highlights the relationship between stress-induced cytokines and astrocytes [45]. S-100B level was found to be increased in patients undergoing hemodialysis. The kidneys normally metabolize S-100B ; therefore in renal failure, serum levels may be expected to be higher due to decreased renal clearance [46]. Considering the relationship between ESRD and cerebrovascular disorders in patients, increasing levels of serum S-100B may be associated with neurological tissue injury[47]. The also evaluated the hemodialysis effect and found that serum S-100B level was higher in post-hemodialysis compared to pre-hemodialysis [48]. As neurochemical markers, serum S-100B can be useful for early diagnosis of brain damage, the purpose of study was to determine serum S-100B level in patients undergoing hemodialysis to compare these values with the control group [49]. Serum S100B levels were associated with depressive symptoms in ESRD [50]. Another factor contributing to higher levels following hemodialysis could be the insufficient permeability of the synthetic hollow-fiber membrane to the S100B protein that could result in ineffective removal. investigating the effect of dialysis on serum S-100B level in the literature [51]. Some studies no effect sex was observed on serum concentrations of S100B [52]. Assuming cerebrospinal fluid S100B as a marker of development, glial activation or even brain damage, investigations regarding the sex dependence of its concentration may be useful in gaining an understanding of sex variations in the behaviour and the pathological course of, as well as susceptibility to, many brain disorders [53]. One of the study reinforce the sex effect on synaptic plasticity and suggest a sex dependence of neural communication mediated by extracellular S100B without restricting the influence of astrocytes on the developmental phase [54].

Not have any research about decreased MBP in ESRD patients.

4. Glial fibrillary acidic protein (GFAP)

Glial fibrillary acidic protein (GFAP) is a protein that is encoded by the GFAP gene in humans [55]. It is a type III intermediate filament (IF) protein that is expressed by numerous cell types of the CNS , including astrocytes and ependymal cells during development [56]. GFAP has also been found to be expressed in glomeruli and peritubular fibroblasts taken from kidneys [57]. GFAP is thought to help to maintain astrocyte mechanical strength [58] as well as the shape of cells, but its exact function remains poorly understood, despite the number of studies using it as a cell marker [59]. The initial GFAP dimers combine to make staggered tetramers, which are the basic subunits of an intermediate filament. Since rod domains alone do not form filaments, the non-helical head and tail domains are necessary for filament formation [60].

There are multiple disorders associated with improper GFAP regulation, and injury can cause glial cells to react in detrimental ways [61]. increase in brain soluble inflammatory mediators was accompanied by cellular signs of inflammation a marker for activated glial cells during brain inflammation [62]. Compared with ESRD had increased GFAP expression in astrocytes in both the cerebral cortex and the corpus callosum [63]. GFAP and showed no dependence on renal clearance. Further support was found for an association with others renal function [64]. GFAP levels could reflect neuronal damage in obese of ESRD [65]. GFAP circulating levels have been described in the context of traumatic brain injury [66]. Increased GFAP has been shown to alter with changing hormone levels [67]. Sex steroids were found particularly effective to elicit alterations in both the amount and immunoreactivity of GFAP [68]. some studies finding indicate a sexual dimorphism caused by different levels of GFAP in the intact male and female [69]. The biomarkers IL-6 and GFAP are well known in the

clinical setting for their usability in traumatic brain injury prediction [70]. Relationship between GFAP tension and albumin concentration, showed the parabolic correlation of the experimental concentrations and the linear correlation in the pathophysiologic ranges [71].

Albumin enters brain across blood-brain barrier by molecular diffusion, it is found at a low concentration. it is found at a low concentration albumin was demonstrated to be identical to GFAP [72], as GFAP is a specific CNS protein in particular of glial cells [73]. In the spinal cord, astrocytes are activated following peripheral inflammation or the nerve injury and may manifest as increased expression of astrocytic markers such as GFAP [74]. Not have any research about decreased GFAP in ESRD patients.

5. Neuroepithelial stem cell protein (Nestin)

Nestin is a type VI intermediate filament (IF) protein [75]. These intermediate filament proteins are expressed mostly in nerve cells where they are implicated in the radial growth of the axon. Seven genes encode for the heavy (NF-H), medium (NF-M) and light neurofilament (NF-L) proteins, nestin in nerve cells, synemin α and synemin β in muscle cells, and syncoilin (also in muscle cells) [76]. Nestin expression in embryonic and adult kidney has been reported [77]. In immature glomeruli, Nestin is expressed in the progenitors of glomerular endothelial cells. Nestin is also transiently expressed by epithelial cells of immature proximal tubules in the newborn kidney [77, 78]. Upon differentiation, nestin becomes downregulated and is replaced by tissue-specific intermediate filament proteins. During neuro- and gliogenesis, nestin is replaced by cell type-specific intermediate filaments, e.g. neurofilaments and GFAP [79].

Increased Nestin cells is also under research in preclinical models of disease, especially neurodegenerative diseases and bone marrow malignancies (Baez-Jurado, Hidalgo-Lanussa et al. 2019). Nestin was re-expressed in tubular cells in adult kidney. Some interstitial myofibroblasts also expressed Nestin. Nestin expression in tubulointerstitium is correlated with interstitial fibrosis. Also demonstrated that increased Nestin expression is associated with phenotypic changes of renal cells induced by hypoxia [80]. Nestin has recently received attention as a marker for detecting newly formed endothelial cells. Nestin is an angiogenesis marker of proliferating endothelial cells in colorectal cancer tissue [81].

A large body of evidence points to Nestin as a unique intermediate filament that accompanies self-renewal capacity in several subsets of stem cells and progenitors, particularly those of the neural and mesenchymal lineages [82]. The roles of Nestin in cancer cells have not been clarified fully, although Nestin correlates with growth, migration, invasion, and metastasis of some cancers. Nestin is also highly expressed in proliferating vascular endothelial cells in cancer tissues and metastatic [83]. Nestin of the neural tube give rise to two major classes of glial cells, astrocytes and oligodendrocytes, which structurally and functionally support the neurons and their axons in the CNS [21].

Not have any research about decreased Nestin in ESRD patients.

6. Neurofilament light polypeptide (NFL)

Neurofilament light polypeptide (NFL), also known as neurofilament light chain, is a neurofilament protein that in humans is encoded by the NEFL gene [84]. Neurofilament light chain is a biomarker that can be measured with immunoassays in cerebrospinal fluid and plasma and reflects axonal damage in a wide variety of neurological disorders. It is a useful marker for disease monitoring in amyotrophic lateral sclerosis, MS Alzheimer's disease [85], and more recently Huntington's disease. Higher numbers have been associated with increased mortality [86]. NF are constantly released from axons reflecting normal aging. However, during axonal damage, NF are released in larger quantities into the extracellular space, the cerebrospinal fluid (CSF), and eventually into the blood [87].

Neurofilament light protein is the smallest of three subunits that make up neurofilaments, which are major components of the neuronal cytoskeleton. NfL is released from damaged neurons [88].

Evidence of accelerated age-related increase in NFL levels in children with CKD to lead ESRD Some the study of two different populations showed a positive correlation between blood NFL, indicating that blood NFL level may be partially influenced by renal function [89]. Studies have shown that myelinated neuron damage is common among patients with ESRD because of altered blood perfusion [90]. Demonstrated that increased NFL levels are associated with relevant variables of kidney function and brain structure. That decreased kidney function may be linked to abnormal neuronal integrity in patients with pediatric CKD that lead to ESRD [91]. NFL, which is the main component of the cytoskeleton of myelinated neuron axons, is released from the damaged axons. NFL expression reflects subcortical neuronal damage and white matter damage [92]. Patients with ESRD who had cognitive impairment had marginally higher plasma NFL concentrations. NFL concentration was not correlated with the biochemical parameters ESRD impacts plasma NFL levels and their accuracy in reflecting neurodegeneration [93]. The NFL is sensitive to detect the neuroaxonal damage, but it is not highly specific as overlapping levels exist among different neurodegenerative diseases except lateral sclerosis [94]. The axons within white matter are vulnerable during ultrafiltration, and axon damage might explain the increase in plasma NFL. Additionally, sympathetic hyperactivity is a common phenomenon in patients with ESRD [95]. The hypothesized NFL to be positively correlated with pro-inflammatory markers (IL-6) and to be negatively correlated with the anti-inflammatory IL-10 [96]. The study tested the additional hypothesis NFL levels would be associated with symptom severity in psychopathological domains known to be related to structural brain alterations such as depressive and negative symptoms and cognitive dysfunction [97]. That NFL would be a better biomarker for spinal cord degeneration than GFAP, since axonal rather than glial degeneration is the pathological hallmark of myelopathy [98]. A positive correlation was evident between plasma NFL and fasting glucose. Plasma NFL levels were not correlated with fasting insulin and insulin resistance. Plasma NFL levels were significantly different across the diabetes groups [99].

Not have any research about decreased NFL in ESRD patients.

7. Neuron-specific enolase

Enolase is a crucial catabolic enzyme that converts 2-phosphoglycerate to phosphoenolpyruvate in the glycolytic pathway for ATP production [100]. NSE is a cytosolic protein that participates in axonal transport. Its expression levels can fluctuate depending on energy demand within a cell. Furthermore, when axons are injured, NSE is upregulated to maintain homeostasis; based on its cellular origin and function, NSE is believed to be a surrogate marker of neuronal damage. NSE selectively labels injured axons in the patients, while, NSE is nearly undetectable in non-injured axons from control subjects [101].

NSE is largely confined to neurons, however, baseline serum levels (10 ng/ml) originate from red blood cells[102]. Sudden increases in serum NSE have been reported after various types of neurological damage including ESRD [103], ischemic stroke [104], and cerebral hemorrhage [105]. Recent investigations have suggested that following TBI elevated serum levels of NSE may be influenced by the glymphatic system rather than BBB injury. Previous studies have shown that animals with intact glymphatic function exhibit significant increases in serum NSE after experimental traumatic brain injury (TBI), while those with glymphatic suppression failed to display a similar increase [106]. Interestingly, both control and glymphatic suppressed animals experienced equivalent BBB dysfunction TBI, supporting the hypothesis that NSE reaches the bloodstream via the glymphatic system [101].

Previous research has shown that long-term neurological impairment is more common in athletes who sustain repetitive TBI [107]. Interestingly, given that the half-life of serum NSE is 24–48 h with peak serum levels occurring within 6-h post-TBI, these findings also suggest sustained release of NSE into the peripheral

circulation after repetitive TBI, even in the absence of recent head trauma [108].

Not have any research about decreased NSE in ESRD patients.

8. T-tau

The microtubule binding protein Tau is predominantly expressed by neurons and preferentially localized within axons [100]. Tau facilitates axonal trafficking and neuronal signaling by binding tubulin subunits, stabilizing microtubular networks, and crosslinking microtubule bundles to establish neuronal viscoelastic properties [101]. Viscoelasticity in the brain enables stretching and retraction against mechanical forces due to the flexibility of microtubule bundles. Unlike focal brain injury, which is typically caused by a direct impact to the head resulting in cerebral contusions and hematomas [101], diffuse brain injury is caused by inertial forces (e.g., stretch, twist, and retraction) that occur during rapid head rotation [102].

Tau appears to mediate the viscoelastic response to these forces; however, inertial stress beyond threshold limits can disrupt microtubule networks, leading to diffuse axonal injury (DAI) [109]. A recent study by Ahmadzadeh et al. evaluated Tau viscoelasticity in the context of mechanical strain, by applying high and low strain rates to a micromechanical model of axonal microtubules cross-linked by Tau proteins. Interestingly, at lower strain rates, mechanical forces were mitigated by extension of the Tau proteins, which allowed microtubules to slide relative to one another without damaging axonal structure. Conversely, higher strain rates disrupted Tau and transferred the mechanical load directly to microtubule bundles, resulting in breakdown and dissociation of the axonal microtubule network [110]. These findings not only support the hypothesis that axonal injury depends on the magnitude and severity of TBI, but also that Tau serves as a cytoskeletal shock-absorber and a potential biomarker for DAI in response to mechanical loading in the brain [111].

Abnormally phosphorylated Tau is subject to proteolytic cleavage by at least six different proteases, some of which generate neurotrophic fragments beneficial to neurons, and others that produce neurotoxic species resistant to proteasomal/autophagosomal degradation [112]. Ca2+ activated calpains and thrombins can cleave Tau at multiple sites, generating a variety of fragments. However, whether these Tau cleavage products are neuro-protective or degenerative remains unclear [113]. Puromycin-sensitive aminopeptidase (PSA) and high temperature requirement serine protease A1 (HTRA1) are proteases that assist in clearing soluble Tau through proteolytic degradation. Cathepsins are lysosomal proteases that can be released into the cytoplasm under pathological conditions and produce Tau fragments highly susceptible to abnormal phosphorylation [114]. Neurotoxic Tau fragments can aggregate to form insoluble neurofibrillary tangles. Recent studies have demonstrated that these tangles do not necessarily activate apoptotic mechanisms [112], but rather induce cellular dysfunction by creating a chronic energy deficit at the mitochondrial level, where N-terminal fragments consisting of Tau amino acids 22–46 enter the mitochondria and interfere with the production of ATP [115].

Not have any research about decreased Tau in ESRD patients

9. Claudin proteins

Claudins are a family of proteins which, along with occludin, are the most important components of the tight junctions (zonulae occludentes) [116]. Tight junctions establish the paracellular barrier that controls the flow of molecules in the intercellular space between the cells of an epithelium . They have four transmembrane domains, with the N-terminus and the C-terminus in the cytoplasm [117].

Claudins are small (20–24/27 kilodalton (kDa)). Transmembrane proteins which are found in many organisms, ranging from nematodes to human beings. They all have a very similar structure. Claudins span the cellular membrane 4 times, with the N-terminal end and the C-terminal end both located in the cytoplasm, and

two extracellular loops which show the highest degree of conservation [118].

Claudins have both cis and trans interactions between cell membranes. Cis-interactions is when claudins on the same membrane interact, one way they interact is by interaction is when claudins of neighboring cells interact through their extracellular loops. Cis-interactions is also known as side-to-side interactions and trans-interactions is also known as head-to-head interactions [119].

Since their discovery, literature regarding the status of claudins in various cancers is constantly expanding, and in contrast to the general thought that claudins expression would decrease during tumorigenesis as tight junctions are lost during cellular transformation, claudins expression seems to change in a tissue specific manner. Tan et al. [120] have shown that the expression and distribution of claudin- 1 is associated with cell dissociation status in pancreatic cancer cells through mitogen-activated protein kinase 2 activation. By contrast, claudin-7 has been found to be decreased in invasive ductal carcinomas, head and neck cancer and metastatic breast cancer [121]. On the other hand, Claudin-3 and -4 are frequently elevated in various cancers including pancreatic ductal adenocarcinoma, prostate, uterine, ovarian cancer and breast cancer while hepatocellular and renal carcinomas expressed lower levels of claudins-4 and -5 [122]. While, lower expression of claudin-2 was also seen in breast and prostatic carcinomas, expressions of claudin-1 and claudin-7 that were undetectable in normal cervical squamous epithelium increased in the cervical neoplasia [123]. Intriguingly, recent studies have shown that expression of certain claudins especially claudin-1 and claudin-4 increases during metastasis and genetic inhibition of their expression has profound effect on the metastatic abilities of cancer cells though in a tissue specific fashion [124].

Irrespective of the diverse source of cancer growth and/or heterogeneity among cancer patients regarding the cancer originated from the same tissue source, it is well accepted that Epithelial to Mesenchymal Transition (EMT) is a cellular event central to the initiation and progression of tumorigenesis. Although their differentiated properties vary, they are composed principally of epithelial cells with similar basic features including polarity and barrier function. Cell adhesion weakens or is lost during the process of EMT or as dedifferentiation of epithelial cells [125]. A critical role of E-cadherin, principal constituent of adherens junction, in the regulation of EMT is known, however it does not help understand the diversity/heterogeneity among the cancers [126].

Most claudins are expressed in the renal tubule. Each segment and cell expresses multiple isoforms. It is widely believed that the specific set of claudins expressed by each nephron segment determines the unique paracellular permeability properties of that segment [127]. In addition, the glomerulus also expresses claudins. Parietal epithelial cells express claudin-1. Mature podocytes form slit diaphragms, which are a specialized form of intercellular junction, but tight junctions are also present during fetal development and reappear during podocyte injury . Claudin-5 and -6 have both been detected in podocytes [128].

The role of claudins in the genetic predisposition to other kidney diseases, as well as in the pathogenesis of acquired kidney diseases, remains largely unexplored [129]. Given the importance of claudins in the development and maintenance of polarized epithelia, renal tubule transport function, and potentially in glomerular epithelial cell function, they will probably be found to be involved in many different disease processes within the kidney [130].

CONCLUSION

Parameters on ESRD patients leads to an increase in toxic neurons in the end-products, which increases the risk of poor psychological state and cognitive difficulties. Therefore, therapeutic intervention is necessary to reduce the negative effects of damaged neurons, including hemodialysis and screening necessary to estimate the elevation of parameters.

REFERENCES

1. Guo, L., et al., Diuretic resistance in patients with kidney disease: Challenges and opportunities. 2023. 157: p. 114058.
2. Banerjee, D., et al., Management of hypertension and renin-angiotensin-aldosterone system blockade in adults with diabetic kidney disease: Association of British Clinical Diabetologists and the Renal Association UK guideline update 2021. 2022. 23(1): p. 1-31.
3. Aier, A., et al., Psychological aspects in children and parents of children with chronic kidney disease and their families. 2022. 65(5): p. 222.
4. Akhtar, M., et al., Diabetic kidney disease: past and present. 2020. 27(2): p. 87-97.
5. Luciano, R.L. and G.W. Moeckel, Update on the native kidney biopsy: core curriculum 2019. American Journal of Kidney Diseases, 2019. 73(3): p. 404-415.
6. Nesrallah, G.E., et al., Canadian Society of Nephrology 2014 clinical practice guideline for timing the initiation of chronic dialysis. Cmaj, 2014. 186(2): p. 112-117.
7. Barsoum, R.S., Chronic kidney disease in the developing world. New England Journal of Medicine, 2006. 354(10): p. 997-999.
8. Najafi, I., Peritoneal dialysis in Iran and the Middle East. Peritoneal dialysis international, 2009. 29(2_suppl): p. 217-221.
9. Izeidi, P.P., et al., Cost estimate of chronic hemodialysis in Kinshasa, the Democratic Republic of the Congo: A prospective study in two centers. Hemodialysis International, 2020. 24(1): p. 121-128.
10. Asad, H.N., et al., A causal-pathway phenotype of chronic fatigue syndrome due to hemodialysis in patients with end-stage renal disease. 2023. 22(2): p. 191-206.
11. Jwad, S.M. and H.Y.J.R.F. AL-Fatlawi, Diabetic Nephropathy and Its Effect on the Physiological Factors of The body. 2022. 8: p. 10.
12. Mikkelsen, H., et al., Glomerular proteomic profiling of kidney biopsies with hypertensive nephropathy reveals a signature of disease progression. 2023. 46(1): p. 144-156.
13. Lees, J.S., et al., Author Correction: Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. 2020. 26(8): p. 1308-1308.
14. Brash, J.L., Spinal cord pathology of ovine CLN5 and CLN6 neuronal ceroid lipofuscinoses (Batten disease): A thesis submitted in partial fulfilment of the requirements for the Degree of Master at Lincoln University. 2023, Lincoln University.
15. Pickett, L.A., et al., Microglia phagocytosis mediates the volume and function of the rat sexually dimorphic nucleus of the preoptic area. 2023. 120(10): p. e2212646120.
16. Decourt, B., et al., The cause of Alzheimer's disease: the theory of multipathology convergence to chronic neuronal stress. 2022. 13(1): p. 37.
17. Lei, F., et al., GSK-3 inhibitor promotes neuronal cell regeneration and functional recovery in a rat model of spinal cord injury. 2019. 2019.
18. Grader, E. and A.J.T.b.i.r.w. Bateman, Introduction to brain anatomy and mechanisms of injury. 2017: p. 15-35.
19. Rahman, M., et al., Emerging Role of Neuron-Glia in Neurological Disorders: At a Glance. 2022. 2022.
20. Vassall, K.A., V.V. Bamm, and G.J.B.J. Harauz, MyelStones: the executive roles of myelin basic protein in myelin assembly and destabilization in multiple sclerosis. 2015. 472(1): p. 17-32.
21. Bigbee, J.W.J.G.o.t.N.S., Cells of the Central Nervous System: An Overview of Their Structure and Function. 2023: p. 41-64.
22. Vassall, K.A., et al., Substitutions mimicking deimination and phosphorylation of 18.5-kDa myelin basic protein exert local structural effects that subtly influence its global folding. 2016. 1858(6): p. 1262-1277.
23. Bando, Y.J.C. and E. Neuroimmunology, Mechanism of demyelination and remyelination in multiple sclerosis. 2020. 11: p. 14-21.
24. Wimmer, I., et al., PECAM-1 stabilizes blood-brain barrier integrity and favors paracellular T-cell diapedesis across the blood-brain barrier during neuroinflammation. 2019. 10: p. 711.
25. Cui, L.-Y., S.-F. Chu, and N.-H.J.I.i. Chen, The role of chemokines and chemokine receptors in multiple sclerosis. 2020. 83: p. 106314.
26. Bromberg, M.B., Peripheral Neuropathies: A Practical Approach. 2018: Cambridge University Press.
27. Stadelmann, C., et al., Myelin in the central nervous system: structure, function, and pathology. 2019. 99(3): p. 1381-1431.
28. Eggermann, K., et al., Hereditary neuropathies: clinical presentation and genetic panel diagnosis. 2018. 115(6): p. 91.
29. Łowiec, P., P. Trzonkowski, and K. Chwojnicki, Multiple sclerosis–new therapeutic directions. 2019.
30. Raasakka, A. and P.J.C. Kursula, How does protein zero assemble compact myelin? 2020. 9(8): p. 1832.
31. Ziegler, V., et al., Mesangial cells regulate the single nephron GFR and preserve the integrity of

the glomerular filtration barrier: An intravital multiphoton microscopy study. 2021. 231(4): p. e13592.
32. McDermott, M., et al., Mammalian phospholipase D: Function, and therapeutics. 2020. 78: p. 101018.
33. Ho, Y.-S., et al., Impact of unilateral ureteral obstruction on cognition and neurodegeneration. 2021. 169: p. 112-127.
34. Kambhampati, S.P., et al., Systemic dendrimer nanotherapies for targeted suppression of choroidal inflammation and neovascularization in age-related macular degeneration. 2021. 335: p. 527-540.
35. Dello Russo, C., et al., Exploiting microglial functions for the treatment of glioblastoma. 2017. 17(3): p. 267-281.
36. Shi, F.-J., et al., Is Iba-1 protein expression a sensitive marker for microglia activation in experimental diabetic retinopathy? 2021. 14(2): p. 200.
37. Chib, S., S.J.N. Singh, and Teratology, Manganese and related neurotoxic pathways: A potential therapeutic target in neurodegenerative diseases. 2022: p. 107124.
38. Kadian, M., G. Sharma, and A. Kumar, Iron-Calcium Crosstalk in Neurodegenerative Diseases, in Brain-Iron Cross Talk. 2023, Springer. p. 109-137.
39. Williams, T., D.R. Borchelt, and P.J.M.n. Chakrabarty, Therapeutic approaches targeting Apolipoprotein E function in Alzheimer's disease. 2020. 15(1): p. 1-19.
40. Wolters, E.C., et al., Naïve BM-derived stem cells (Neuro-Cells) may modify acute and chronic neurodegenerative disorders by modulating macrophage behaviors. 2021. 1(1): p. 3.
41. Tamaru, T., et al., Glial scar survives until the chronic phase by recruiting scar-forming astrocytes after spinal cord injury. 2023. 359: p. 114264.
42. das Neves, S.P., et al., Altered astrocytic function in experimental neuroinflammation and multiple sclerosis. 2021. 69(6): p. 1341-1368.
43. Bonsack, B., et al., Brief overview: Protective roles of astrocyte-derived pentraxin-3 in blood-brain barrier integrity. 2019. 5(3): p. 145.
44. Zhang, W., et al., The blood brain barrier in cerebral ischemic injury–Disruption and repair. 2020. 1(1): p. 34-53.
45. Braun, M., et al., White matter damage after traumatic brain injury: a role for damage associated molecular patterns. 2017. 1863(10): p. 2614-2626.
46. Alpdemir, M., et al., Serum neuron specific enolase and S-100B levels in hemodialysis and peritoneal dialysis patients. 2019. 35(2): p. 83.
47. Liao, G., et al., Antidyslipidemia Pharmacotherapy in Chronic Kidney Disease: A Systematic Review and Bayesian Network Meta-Analysis. 2023. 15(1): p. 6.
48. Hernandez, L., et al., Blood–brain barrier and gut barrier dysfunction in chronic kidney disease with a focus on circulating biomarkers and tight junction proteins. 2022. 12(1): p. 1-14.
49. Kawata, K., R. Tierney, and D.J.H.o.c.n. Langford, Blood and cerebrospinal fluid biomarkers. 2018. 158: p. 217-233.
50. Maciak, K., A. Dziedzic, and J.J.T.F.J. Saluk, Possible role of the NLRP3 inflammasome and the gut–brain axis in multiple sclerosis-related depression. 2023. 37(1): p. e22687.
51. Zhao, Z., et al., Applying membrane technology in microalgae industry: A comprehensive review. 2023. 172: p. 113041.
52. Lu, T. and J.C.J.B.o.s.D. Mar, Investigating transcriptome-wide sex dimorphism by multi-level analysis of single-cell RNA sequencing data in ten mouse cell types. 2020. 11(1): p. 1-20.
53. Cattane, N., et al., Preclinical animal models of mental illnesses to translate findings from the bench to the bedside: Molecular brain mechanisms and peripheral biomarkers associated to early life stress or immune challenges. 2022. 58: p. 55-79.
54. MacDonald, A.J., et al., Astrocytes in neuroendocrine systems: An overview. 2019. 31(5): p. e12726.
55. Cansell, C., et al., Dietary fat exacerbates postprandial hypothalamic inflammation involving glial fibrillary acidic protein-positive cells and microglia in male mice. 2021. 69(1): p. 42-60.
56. Hol, E.M. and Y.J.C.S.H.p.i.b. Capetanaki, Type III intermediate filaments desmin, glial fibrillary acidic protein (GFAP), vimentin, and peripherin. 2017. 9(12): p. a021642.
57. Yadav, R., M. Batra, and R. Chauhan, Role of immunohistochemistry for diagnosis of non-infectious diseases. 2021.
58. Battaglia, R.A., Proteostasis of Glial Intermediate Filaments: Disease Models, Tools, and Mechanisms. 2021, The University of North Carolina at Chapel Hill.
59. Sethi, Y., et al., Broken Heart Syndrome: Evolving Molecular Mechanisms and Principles of Management. 2023. 12(1): p. 125.
60. Mónico, A.M.d.O., Lipoxidación de vimentina y su interacción con zinc. 2020.

61. Topaloğlu, U., H. Sağsöz, and M.E.J.T. Akbalik, Distribution of cytoskeletal proteins in the cat testis during the pre-pubertal and post-pubertal periods. 2023. 197: p. 1-9.
62. Tzioras, M., et al., Invited Review: APOE at the interface of inflammation, neurodegeneration and pathological protein spread in Alzheimer's disease. 2019. 45(4): p. 327-346.
63. Hénaut, L., et al., Cellular and molecular mechanisms associated with ischemic stroke severity in female mice with chronic kidney disease. 2019. 9(1): p. 1-11.
64. Berry, K., et al., Hepatic and renal function impact concentrations of plasma biomarkers of neuropathology. 2022. 14(1): p. e12321.
65. Iqbal, Z., et al., Astrocyte L-Lactate Signaling in the ACC Regulates Visceral Pain Aversive Memory in Rats. 2023. 12(1): p. 26.
66. Shahub, S., et al., A Proof-of-Concept Electrochemical Skin Sensor for Simultaneous Measurement of Glial Fibrillary Acidic Protein (GFAP) and Interleukin-6 (IL-6) for Management of Traumatic Brain Injuries. 2022. 12(12): p. 1095.
67. Kadry, H., et al., A blood–brain barrier overview on structure, function, impairment, and biomarkers of integrity. 2020. 17(1): p. 1-24.
68. Boorman, D.C. and K.A.J.J.o.N.R. Keay, Sex differences in morphine sensitivity are associated with differential glial expression in the brainstem of rats with neuropathic pain. 2022. 100(10): p. 1890-1907.
69. Daly, C.M., et al., Sex differences in response to a high fat, high sucrose diet in both the gut microbiome and hypothalamic astrocytes and microglia. 2022. 25(2): p. 321-335.
70. Trautz, F., et al., Survival-time dependent increase in neuronal IL-6 and astroglial GFAP expression in fatally injured human brain tissue. 2019. 9(1): p. 1-15.
71. Zheng, Z., et al., Albumins as Extracellular Protein Nanoparticles Collaborate with Plasma Ions to Control Biological Osmotic Pressure. 2022: p. 4743-4756.
72. Hladky, S.B., M.A.J.F. Barrand, and B.o.t. CNS, Elimination of substances from the brain parenchyma: efflux via perivascular pathways and via the blood–brain barrier. 2018. 15(1): p. 1-73.
73. Gaudet, A.D. and L.K.J.N. Fonken, Glial cells shape pathology and repair after spinal cord injury. 2018. 15(3): p. 554-577.
74. Zhang, C., et al., Spatiotemporal dynamics of the cellular components involved in glial scar formation following spinal cord injury. 2022. 153: p. 113500.
75. Abdelkareem, R.M., et al., Immunohistochemical expression of nestin as cancer stem cell marker in gliomas. 2019. 5(1): p. 047-051.
76. Bomont, P.J.C.O.i.C.B., The dazzling rise of neurofilaments: Physiological functions and roles as biomarkers. 2021. 68: p. 181-191.
77. Ogorevc, M., et al., Differences in Immunohistochemical and Ultrastructural Features between Podocytes and Parietal Epithelial Cells (PECs) Are Observed in Developing, Healthy Postnatal, and Pathologically Changed Human Kidneys. 2022. 23(14): p. 7501.
78. Agarwal, S., et al., Renal cell markers: lighthouses for managing renal diseases. 2021. 321(6): p. F715-F739.
79. Bornstein, S.R., I. Berger, and C.J.S. Steenblock, Are Nestin-positive cells responsive to stress? 2020. 23(6): p. 662-666.
80. Zoja, C., C. Xinaris, and D.J.F.i.P. Macconi, Diabetic nephropathy: novel molecular mechanisms and therapeutic targets. 2020. 11: p. 586892.
81. Fu, Z. and Y.J.C.M. Yuan, The role of tumor neogenesis pipelines in tumor progression and their therapeutic potential. 2023. 12(2): p. 1558-1571.
82. Mariniello, K., et al., Stem cells, self-renewal, and lineage commitment in the endocrine system. 2019. 10: p. 772.
83. Jaramillo-Rangel, G., et al., Nestin-expressing cells in the lung: the bad and the good parts. 2021. 10(12): p. 3413.
84. Alirezaei, Z., et al., Neurofilament light chain as a biomarker, and correlation with magnetic resonance imaging in diagnosis of CNS-related disorders. 2020. 57(1): p. 469-491.
85. Travica, N., M. Berk, and W.J.C.o.i.p. Marx, Neurofilament light protein as a biomarker in depression and cognitive function. 2022. 35(1): p. 30-37.
86. Garcia-Gancedo, L., et al., Objectively monitoring amyotrophic lateral sclerosis patient symptoms during clinical trials with sensors: observational study. 2019. 7(12): p. e13433.
87. Ferreira-Atuesta, C., et al., The evolution of neurofilament light chain in multiple sclerosis. 2021. 15.
88. Zhao, Y., et al., Neurofilament Light (NF-L) Chain Protein from a Highly Polymerized Structural Component of the Neuronal Cytoskeleton to a Neurodegenerative Disease Biomarker in the Periphery. 2021. 7(2).
89. Akamine, S., et al., Renal function is associated with blood neurofilament light chain level in older adults. 2020. 10(1): p. 1-7.

J Popul Ther Clin Pharmacol Vol 30(7):e408–e420; 03 April 2023.

90. Morgenstern, J., et al., Neuron-specific biomarkers predict hypo-and hyperalgesia in individuals with diabetic peripheral neuropathy. 2021. 64(12): p. 2843-2855.
91. van der Plas, E., et al., Associations between neurofilament light-chain protein, brain structure, and chronic kidney disease. 2022. 91(7): p. 1735-1740.
92. Hsu, Y.-K., et al., Evaluating brain white matter hyperintensity, IQ scores, and plasma neurofilament light chain concentration in early-treated patients with infantile-onset Pompe disease. 2022.
93. Hermann, P., et al., Plasma Lipocalin 2 in Alzheimer's disease: potential utility in the differential diagnosis and relationship with other biomarkers. 2022. 14: p. 1-12.
94. Marra, C.M., et al., Serum Neurofilament Light in Neurosyphilis: A Pilot Study. 2023. 50(1): p. 42-44.
95. Hou, Y.-C., et al., The role of plasma neurofilament light protein for assessing cognitive impairment in patients with end-stage renal disease. 2021: p. 267.
96. Hawn, S.E., et al., Methylation of the AIM2 gene: An epigenetic mediator of PTSD-related inflammation and neuropathology plasma biomarkers. 2022. 39(4): p. 323-333.
97. Bavato, F., et al., Altered neuroaxonal integrity in schizophrenia and major depressive disorder assessed with neurofilament light chain in serum. 2021. 140: p. 141-148.
98. de Natale, E.R., et al., How molecular imaging studies can disentangle disease mechanisms in age-related neurodegenerative disorders. 2023: p. 455-492.
99. Zhang, Y., et al., Calcium pyruvate attenuates fat deposition by augmenting fatty acid oxidation and inhibiting glucose oxidation in juvenile large yellow croaker (Larimichthys crocea) consuming a high-fat diet. 2023. 562: p. 738778.
100. Binder, L.I., A. Frankfurter, and L.I.J.T.J.o.c.b. Rebhun, The distribution of tau in the mammalian central nervous system. 1985. 101(4): p. 1371-1378.
101. Kawata, K., et al., Blood biomarkers for brain injury: What are we measuring? 2016. 68: p. 460-473.
102. Johnson, V.E., W. Stewart, and D.H.J.E.n. Smith, Axonal pathology in traumatic brain injury. 2013. 246: p. 35-43.
103. Lee, D.A., et al., Significance of serum neuron-specific enolase in transient global amnesia. 2021. 89: p. 15-19.
104. Roh, H.-T., W.-Y.J.J.o.s. So, and h. science, The effects of aerobic exercise training on oxidant–antioxidant balance, neurotrophic factor levels, and blood–brain barrier function in obese and non-obese men. 2017. 6(4): p. 447-453.
105. Nass, R.D., et al., The role of postictal laboratory blood analyses in the diagnosis and prognosis of seizures. 2017. 47: p. 51-65.
106. Lindblad, C., et al., Influence of blood–brain barrier integrity on brain protein biomarker clearance in severe traumatic brain injury: a longitudinal prospective study. 2020. 37(12): p. 1381-1391.
107. Bailes, J.E., et al., Role of subconcussion in repetitive mild traumatic brain injury: a review. 2013. 119(5): p. 1235-1245.
108. Ayubcha, C., et al., Radiotracers, Positron Emission Tomography Imaging and Traumatic Brain Injury, in Biomarkers in Trauma, Injury and Critical Care. 2022, Springer. p. 1-21.
109. Keating, C.E. and D.K.J.N.o.d. Cullen, Mechanosensation in traumatic brain injury. 2021. 148: p. 105210.
110. Ahmadzadeh, H., D.H. Smith, and V.B.J.B.j. Shenoy, Viscoelasticity of tau proteins leads to strain rate-dependent breaking of microtubules during axonal stretch injury: predictions from a mathematical model. 2014. 106(5): p. 1123-1133.
111. Nowak, M.K., Effects of Subconcussive Head Impacts on Neural Integrity and Function in Attention-Deficit/Hyperactivity Disorder. 2022: Indiana University.
112. Chesser, A.S., S.M. Pritchard, and G.V.J.F.i.n. Johnson, Tau clearance mechanisms and their possible role in the pathogenesis of Alzheimer disease. 2013. 4: p. 122.
113. Tompa, P., et al., On the sequential determinants of calpain cleavage. 2004. 279(20): p. 20775-20785.
114. Zhang, L., R. Sheng, and Z.J.A.b.e.b.S. Qin, The lysosome and neurodegenerative diseases. 2009. 41(6): p. 437-445.
115. Atlante, A., et al., A peptide containing residues 26–44 of tau protein impairs mitochondrial oxidative phosphorylation acting at the level of the adenine nucleotide translocator. 2008. 1777(10): p. 1289-1300.
116. Lynn, K.S., R.J. Peterson, and M.J.B.e.B.A.-B. Koval, Ruffles and spikes: Control of tight junction morphology and permeability by claudins. 2020. 1862(9): p. 183339.
117. Pan, Y.-Y., et al., Structure Composition and Intracellular Transport of Clathrin-Mediated Intestinal Transmembrane Tight Junction Protein. 2022: p. 1-17.
118. Kohlway, A.S., Cause and effect: Hepatitis C virus infection and host innate immune response. 2013: Yale University.

119. Fuladi, S., et al., Computational modeling of claudin structure and function. 2020. 21(3): p. 742.
120. Adil, M.S., S.P. Narayanan, and P.R.J.T.B. Somanath, Cell-cell junctions: structure and regulation in physiology and pathology. 2021. 9(1): p. 1848212.
121. Bhat, A.A., et al., Claudin-1, a double-edged sword in cancer. 2020. 21(2): p. 569.
122. HASELOFF, R.F. and I.E.J.N. BLASIG, HANNELORE BAUER, HANS CHRISTIAN BAUER. 2005: p. 325.
123. Wang, H., X.J.I.J.o.C. Yang, and E. Pathology, The expression patterns of tight junction protein claudin-1,-3, and-4 in human gastric neoplasms and adjacent non-neoplastic tissues. 2015. 8(1): p. 881.
124. Singh, A.B., A. Sharma, and P.J.J.o.o. Dhawan, Claudin family of proteins and cancer: an overview. 2010. 2010.
125. Heijink, I.H., et al., Epithelial cell dysfunction, a major driver of asthma development. 2020. 75(8): p. 1902-1917.
126. Shil, S., Master Of Veterinary Science. 2014, Anand Agricultural University.
127. Yu, A.J.J.o.t.A.S.o.N.J., Claudins and the kidney. 2014. 26(1): p. 11-19.
128. Günzel, D. and A.S.J.P.r. Yu, Claudins and the modulation of tight junction permeability. 2013. 93(2): p. 525-569.
129. Seeger-Nukpezah, T., et al., The hallmarks of cancer: relevance to the pathogenesis of polycystic kidney disease. 2015. 11(9): p. 515-534.
130. Gong, Y. and J.J.P.A.-E.J.o.P. Hou, Claudins in barrier and transport function—the kidney. 2017. 469: p. 105-113.