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REVIEW ARTICLE

Linking chronic kidney disease and Parkinson's disease: a literature review

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Abstract

Chronic kidney disease (CKD) has been typically implicated in cardiovascular risk, considering the function the kidney has related to blood pressure, vitamin D, red blood cell metabolism, and electrolyte and acid-base regulation. However, neurological consequences are also attributed to this disease. Among these, recent large epidemiological studies have demonstrated an increased risk for Parkinson's disease (PD) in patients with CKD. Multiple studies have evaluated individually the association of blood pressure, vitamin D, and red blood cell dysmetabolism with PD, however, no study has reviewed the potential mechanisms related to these components in context of CKD and PD. In this review, we explored the association of CKD and PD and linked the components of the former to propose potential pathways explaining a future increased risk for PD, where renin-angiotensin system, oxidative stress, and inflammation have a main role. Potential preventive and therapeutic interventions based on these associations are also explored. More preclinical studies are needed to confirm the potential link of CKD conditions and future PD risk, whereas more interventional studies targeting this association are warranted to confirm their potential benefit in PD.

Keywords Chronic kidney disease · Parkinson's disease · Renin-angiotensin system · Oxidative stress · Anemia

Introduction

As the life expectancy increases, and the prevalence of the elderly population increases, more focus is attributed to chronic degenerative diseases. Parkinson's disease (PD) is the second most common neurodegenerative disease, after Alzheimer's (de Lau and Breteler 2006; Lee and Gilbert 2016; Nussbaum and Ellis 2003). Its prevalence increases with age, affecting 1 to 2% of the population over 60 years (Tysnes and Storstein 2017; Wirdefeldt et al. 2011). The cardinal signs characteristic of PD include resting tremor, rigidity, bradykinesia, which can be exhibited as hypomimia, hypophonia and micrographia, and postural and gait impairment, characterized by decreased arm swing, and multiple small steps. These present with a unilateral onset, respond to levodopa therapy, and patients can develop dyskinesia (Williams and Litvan 2013). Besides these motor symptoms, PD patients experience a range of non-motor symptoms, including constipation, sleep disorders, orthostatic hypotension, depression, among others (Tolosa et al. 2006; Massano and Bhatia 2012). These cardinal signs have been typically attributed to the loss of dopaminergic neurons in the substantia nigra (Shulman et al. 2011). Although great efforts have been made to fully understand the pathophysiology and cause of this dopaminergic cell loss, no mechanism that explains the exact cause of this disease has been described. Several factors have been associated with an increased risk of developing PD such as diabetes, vitamin D deficiency, anemia, and hypertension, among others (Yue et al. 2016; Knekt et al. 2010; Rozani et al. 2019; Hou et al. 2018).

Chronic kidney disease (CKD) results from chronic kidney damage, which can be confirmed via renal markers and reduction of estimated glomerular filtration rate (eGFR) to less than 60 ml/ min/ 1.73m^2. The elderly population has an increased prevalence of CKD, owed primarily to an increase in risk factors such as diabetes, hypertension, and other

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cardiovascular risk factors (Mallappallil et al. 2014). Moreover, patients with CKD have an increased cardiovascular risk (Roderick et al. 2009). However, not only are CKD patients at risk for cardiovascular diseases, but evidence has shown that neurological complications such as cognitive dysfunction, peripheral and autonomic neuropathies, and encephalopathy are common in these patients (Arnold et al. 2016). Furthermore, dementia is more prevalent in this population (Etgen et al. 2012), and albuminuria, a marker of renal damage, is associated with cognitive impairment (Deckers et al. 2017), which might suggest a contribution of CKD conditions to neurodegenerative processes.

In addition to these complications, case reports have shown reversible parkinsonism, a clinical disorder characterized primarily by bradykinesia, resting tremor, rigidity and postural instability, in uremic patients, attributing the basal ganglia affection to uremic toxins, vascular changes, and metabolic acidosis (Wang et al. 1998; Lee et al. 2006; Sheu et al. 2007; Wang and Cheng 2003). This was supported by a retrospective cohort study that demonstrated increased risk for parkinsonism in uremic patients (Lin et al. 2012). However, these studies did not evaluate the presence of parkinsonism in the context of PD, as these two terms are not equally meaning, and shall not be used interchangeably. On the other side, few large epidemiological studies have assessed PD risk in patients with CKD (Nam et al. 2019; Wang et al. 2014; Wang et al. 2017), demonstrating an increased risk for PD in this population (characteristics of these studies are shown in Table 1). Nonetheless, the mechanisms behind this potential relation are not yet elucidated. In this review, we explore the association of CKD and PD based on the elements that compose CKD, such as oxidative stress and uremia, hypertension, vitamin D insufficiency, and anemia, and propose different pathways that may explain this increased future risk.

Oxidative stress in uremia and in PD: Common pathological pathways?

Accumulating evidence indicates a main role of oxidative stress in CKD pathophysiology (Duni et al. 2019; Vaziri 2004; Gyurászová et al. 2020; Sung et al. 2013; Liakopoulos et al. 2017; Kao et al. 2009; Ling and Kuo 2018). Studies have shown oxidative stress markers are present even in early stages of the disease (Kuchta et al. 2011; Annuk et al. 2001). The mechanism underlying oxidative stress in CKD involves greater presence of pro-oxidant substances producing reactive oxygen species (ROS), and a reduction in antioxidant processes. This greater presence of ROS is attributed to an impairment in mitochondria function, responsible for over-production of ROS, which is seen in CKD patients (Galvan et al. 2017; Granata et al. 2009). Moreover, a study evaluating rats with CKD demonstrated an up-regulation of NADPH oxidase, an

Table 1 Characteristics of studies evaluating PD risk in patients with CKD

Study	Place of study	Population of study	Years of follow up	Age of population (mean ± SD)	PD incidence (per 1000-person-years)	HR (95% CI) for PD
Nam et al. (2019)	South Korea	With CKD: 593,444 Control: 2,986,991	5.2 ± 1.3	CKD cohort: 72.5 ± 5.8 Control: 70.7 ± 5.0	Based on eGFR: ≥90: 1.73 60–90: 1.61 30–60: 2.18 < 30: 2.29 Control: 3.17	Adjusted HR[a] based on eGFR: 30–60: 1.36 (1.31–1.42) <30: 1.47 (1.32–1.63)
Wang et al. (2014)	Taiwan	With ESRD: 8325 Control: 33,382	ESRD cohort: 2.56 ± 3.24 Control: 5.51 ± 3.81	ESRD cohort: 64.5 ± 15.2 Control: 64.5 ± 15.2	ESRD: 4.88	Adjusted HR[b] in overall population with ESRD: 1.73 (1.39–2.15)
Wang et al. (2017)	South Korea	With CKD: 2998 Control: 503,091	7.92	CKD cohort: 67.78 ± 5.49 Control: 67.32 ± 5.59	Control: 2.83 CKD overall: 3.62 Based on eGFR: 30–60: 3.70 15–29: 8.26 <15: 7.92	Adjusted HR[c] based on eGFR: 30–60: 1.12 (0.63–1.97) 15–29: 2.38 (0.99–5.72) <15: 2.60 (1.17–5.80)

PD: Parkinson's disease, CKD = Chronic Kidney disease, ESRD = End-stage renal disease, eGFR = estimated glomerular filtration rate, ml/min/1.73m^2, SD = Standard deviation, HR = Hazard ratio, CI = confidence interval

[a]: Adjusted for: age, sex, body mass index, smoking status, alcohol consumption, physical activity, hypertension, dyslipidemia and diabetes mellitus

[b] = Adjusted for: age, sex, urbanization, and comorbidities

[c] = Adjusted for: age, sex, hypertension, diabetes mellitus, and dyslipidemia

enzyme responsible for the formation of ROS (Vaziri et al. 2003). Apart from mitochondrial dysfunction, another mechanism for elevation of ROS levels in CKD patients are uremic toxins. These promote inflammation via priming of polymorphonuclear leukocytes (Gyurászová et al. 2020; Tumur et al. 2010), which exacerbate oxidative stress as generation of myeloperoxidase by these cells promotes nitric oxide (NO) inactivation and ROS generation, the first necessary for its antioxidant function at kidney level (Modlinger et al. 2004; Kisic et al. 2016). Moreover, accumulation of homocysteine in CKD patients increases oxidative stress levels related to an inhibition of antioxidant activity of superoxide dismutase (SOD) (Massy et al. 2001). Regarding antioxidant processes, hemodialysis contributes greatly to this manner, as studies have observed that even a single session of hemodialysis increases lipid peroxides and decreases antioxidants (Peuchant et al. 1994; Jackson et al. 1995), which perpetuates damage and oxidative stress. In fact, this process increases as CKD progresses (Dounousi et al. 2006), which may derive from hemodialysis and its effect on ROS and antioxidants levels. Hemodialysis increase in oxidative stress levels are attributed to an activation of polymorphonuclear leukocytes which promote inflammation and ROS production (Cristol et al. 1994; Borazan et al. 2004). In this manner, over activation of immune response due to uremic toxins and hemodialysis promotes an inflammatory state, which added to the oxidative stress environment, contributes to CKD.

Similar to CKD, oxidative stress plays a major role in the pathophysiology of PD. Moreover, mitochondria dysfunction contributes primarily to ROS formation in PD (Schapira 2008), considering that the brain tissue is considerably vulnerable to oxidative stress, as most energy derives from oxidative phosphorylation and has high unsaturated lipid concentration, apart from the low density of antioxidant enzymes in this tissue (Floyd 1999; Hall et al. 2012). Complex I deficiencies in the respiratory chain origin most of the ROS in PD (Blesa et al. 2015). Furthermore, toxins used in animal models are based among other mechanisms on inhibition of this complex (Blesa and Przedborski 2014; Greenamyre et al. 2010), explaining the main role mitochondria has in PD genesis. On the other side, inflammation contributes to PD, as observed and discussed in CKD. Microglia activation and increase pro-inflammatory cytokines' levels have been observed in animal models of PD (Członkowska et al. 1996), and this activation enhances NADPH oxidase activity in microglia, which in turn form ROS and contribute to the neurotoxicity of this process (Surace and Block 2012). Interestingly, as angiotensin II has shown to have inflammatory properties, inducing ROS via NADPH oxidase when binding to AT1 receptors (Seshiah et al. 2002; Benigni et al. 2010), studies have analyzed its role in animal models of PD, demonstrating that inflammatory response to these PD inducing toxins could be mediated via angiotensin II (Joglar et al. 2009; Rodriguez-Pallares et al. 2008). In fact, several reviews have discussed the presence of a renin-angiotensin system (RAS) in brain (Wright and Harding 2011; Wright and Harding 2013), and AT1 receptors have been shown to be present in high density in human striatum and substantia nigra (Rey et al. 2007), suggesting a role in the disease.

When analyzing the link between PD and CKD regarding oxidative stress and inflammation, two suggestions for this appear: RAS and peripheral inflammation via a damaged blood brain barrier. A recent review analyzed Alzheimer's disease and CKD association, and postulated an overactivated RAS in CKD pathology, mediated by an overactivation of renin owed among other causes, to sympathetic activation (Zhang et al. 2020). This then may activate angiotensin II and, in conditions where blood brain barrier is disrupted as CKD (Mazumder et al. 2016), may reach brain tissue binding to AT1 receptors, causing ROS formation and oxidative stress, damaging neuronal tissue. This has been proposed in hypertension mechanisms, where the increased permeability of the blood brain barrier may allow access of angiotensin II to brain regulating pressure centers (Biancardi et al. 2014; Biancardi and Stern 2016). However, as AT1 receptors are also find in striatum and substantia nigra, this might be a pathway in which angiotensin II links CKD and PD. A study in an animal model of CKD showed disruption of SOD and catalase activities, as well as astrocytosis, in substantia nigra (Mazumder et al. 2019), indicating how oxidative stress conditions in CKD might reflect in neuronal damage. Moreover, as inflammation is present in CKD, and as blood brain barrier disruptions due to the disease may be found, systemic inflammation might contribute to neuroinflammation, a component essential in PD. A study evaluated the risk of PD in patients with serum elevated IL-6, a pro-inflammatory cytokine, and found a significantly increased risk compared to controls (Chen et al. 2008). In this manner, disruption of blood brain barrier and increase in RAS might contribute to link the inflammatory and oxidant conditions in CKD with PD brain damage.

Apart from the mechanism involving a disrupted brain blood barrier, a study in an animal model of CKD described a reno-cerebral reflex involving RAS when exposed to high-salt intake (Cao et al. 2015), where renal afferent sympathetic nerves activate brain RAS and this enhances renal RAS activity via efferent sympathetic activation, perpetuating kidney damage and fibrosis. As angiotensin II has inflammatory and ROS inducing properties, this brain RAS activation mediated by kidney damage might contribute to greater concentrations of angiotensin II in brain tissue, and activate AT1 receptors, inducing oxidative stress and inflammation in brain regions where these receptors are present, such as striatum and substantia nigra (Rey et al. 2007), thus eliciting a possible link between PD and CKD (shown in Fig. 1). However, more studies evaluating oxidative stress in brain regions in CKD

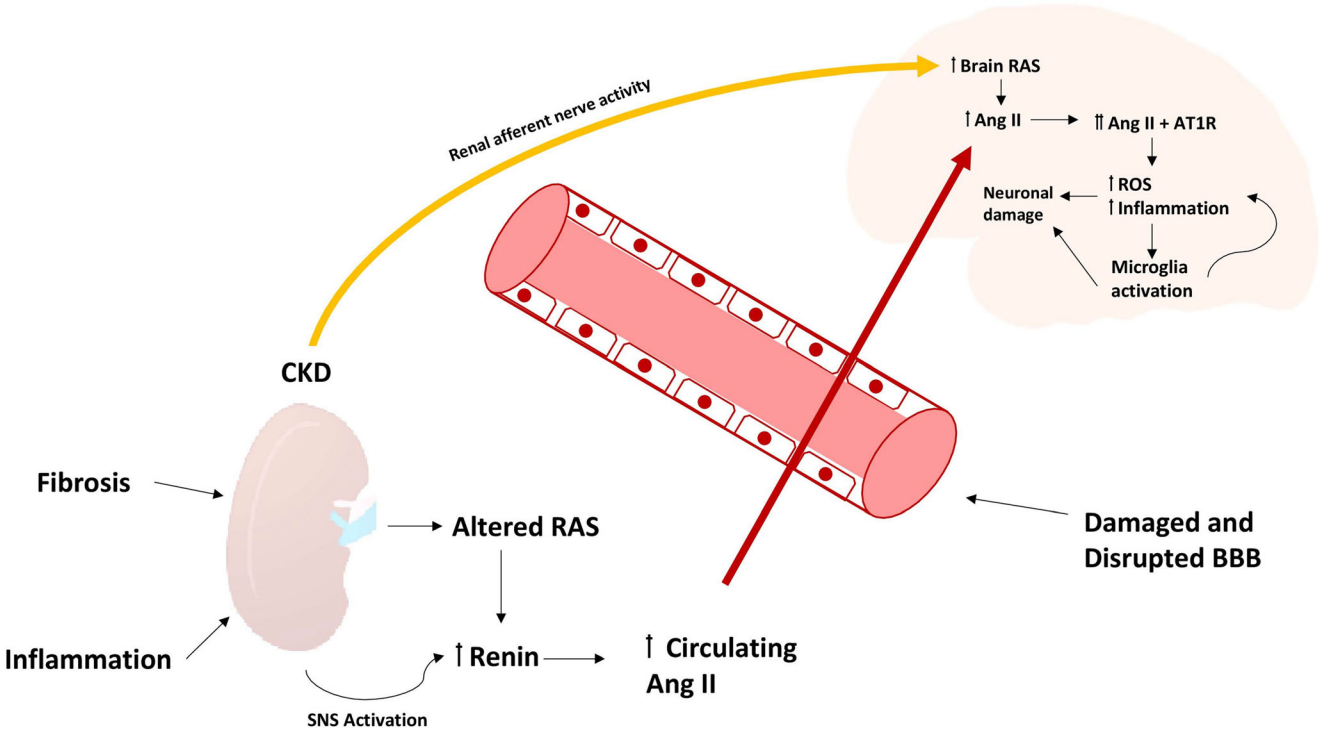

Fig. 1 Hypothesis of the link between CKD and PD based on the overactivation of circulating and brain RAS. CKD conditions involve an altered RAS due to increased renin which lead to increase circulating angiotensin II levels. This in conditions of altered BBB barrier reach brain regions and bind to AT1 receptors, inducing oxidative stress and microglia activation. Moreover, SNS activation in CKD leads to increased activity of brain RAS, and increased angiotensin II levels, which may bind AT1 receptors, inducing neuronal damage. CKD = chronic kidney disease, PD = Parkinson's disease, RAS = renin-angiotensin system, AT1R = angiotensin II receptor type 1, BBB = blood-brain-barrier, SNS = sympathetic nervous system, ROS= reactive oxygen species, Ang II= angiotensin II

conditions are needed, particularly to elicit if renal and brain RAS systems' activation originated due to CKD mediate any oxidative stress damage in substantia nigra.

Hypertension in CKD and PD risk

Patients with CKD experience a high prevalence of hypertension, especially as the disease progresses (Agarwal et al. 2003; United States Renal Data System 2019), considering that the kidney has a main role in regulating solute excretion and RAS activation. The pathophysiology involved in the high blood pressure is multifactorial, and several reviews have studied these mechanisms (Tedla et al. 2011; Huan et al. 2015). As the kidney's function deteriorates due to tissue damage, sodium excretion decreases (Hall 2003), leading to a higher extracellular volume prompting a volume-dependent pressure increase. Moreover, as mentioned earlier, an overactivated RAS system is present in patients with CKD (Zhang et al. 2020; Weidmann et al. 1971; Sim et al. 2011), which together with an overactivated sympathetic nerve activity (Klein et al. 2003) contribute to the pathophysiology of hypertension in CKD. The interrelated mechanisms of these systems are well explained by the reno-cerebral reflex described due to high salt intake in an animal model (Cao et al. 2015). Furthermore, oxidative stress present in CKD conditions contributes to this increase in blood pressure related to inactivation of NO, which lead to endothelial dysfunction (Vaziri et al. 1998). Other mechanisms related to endothelins and renal prostaglandins are described in other studies, as elevated levels of endothelins are present in CKD patients with high levels of blood pressure (Dhaun et al. 2006; Kohan 2010).

Patients with PD experience blood pressure disorders related to an autonomic dysfunction (Asahina et al. 2013), thus having an impaired regulation of blood pressure, showing fluctuations in this value (Tsukamoto et al. 2013). Considering hypertension as risk factor for PD, various meta-analysis have studied their association and have found an increased risk of presenting PD in hypertensive population (Hou et al. 2018; Chen et al. 2019). The pathophysiological mechanisms for this relation are however speculative. One idea relies on the ischemic damage generated by chronic hypertensive states on basal ganglia, thalamus, and brain stem (Qiu et al. 2011; Greenberg et al. 2009), which could affect dopaminergic neurons. On the other side, oxidative stress and RAS system are common mechanism shared between these diseases (Manrique et al. 2009). The latter combined with a disrupted blood brain barrier due to hypertensive state (Biancardi et al. 2014; Zhang et al. 2010) could lead to an increase in circulating angiotensin II in brain regions with

AT1 receptors, and circulating inflammatory cells, causing oxidative stress and inflammation, affecting neuronal tissue. Moreover, blockade of AT1 receptors in animal hypertensive models have shown to protect and improve blood brain barrier permeability (Kucuk et al. 2002; Pelisch et al. 2011), showing how RAS system contributes to this barrier disruption. Another mechanism that may link hypertension and PD is endothelin-mediated, as CKD patients with high endothelin levels experience endothelial dysfunction and high blood pressure levels which may be reduced with its antagonism (Dhaun et al. 2006; Kohan 2010; Goddard et al. 2004). Endothelin's role in PD has been related to induction of oxidative stress and inflammation (Jain et al. 2014), and the high levels of this peptide in hypertensive conditions may promote neuronal damage via these mechanisms. In this manner, hypertensive states seen in CKD could contribute to the future PD risk mainly by RAS system, disruption of blood brain barrier, and endothelin and ischemia-induced neuronal damage.

Vitamin D serum levels in CKD and association with PD

A great proportion of patients with CKD experience vitamin D deficiency (González et al. 2004; Bhan et al. 2010), and this proportion increases as the disease progresses (Pitts et al. 1998). Besides the classical idea that a reduced renal mass decreases 1-alpha-hydroxylase and thus decreases 1,25-dihydroxivitamin D, different mechanisms have been proposed for this deficiency. These involve a decrease in 25-hydroxivitamin D, substrate necessary for production of 1,25-dihydroxivitamin D in kidneys. This decrease in substrate has been associated to a reduction in its diet uptake (Krassilnikova et al. 2014), an impaired synthesis related to uremic toxins (Michaud et al. 2010), and loss of its serum binding protein due to proteinuria (Caravaca-Fontan et al. 2016). Moreover, a reduction in glomerular filtration and renal megalin expression in CKD impedes 25-hydroxivitamin to reach renal tubular cells and be converted to its active form (Takemoto et al. 2003; Dusso 2011). However, apart from the classical actions related to calcium and phosphorus metabolism attributed to vitamin D, increase evidence points for a non-classical pathway, where extra-renal 1-alpha hydroxylase is found to be involved and regulates inflammation, cellular differentiation and proliferation (Jones 2007; Townsend et al. 2005). The importance of this non-classical pathway relies on its effect on CKD progression. Among these pathways, vitamin D deficiency has been related to an overactivation of RAS system (Li 2010; Zhang et al. 2008), which as discussed previously, interacts, and contributes to progression of CKD via inflammation and oxidative stress. Furthermore, the supplementation of this vitamin is then related to a suppression of this system (Li 2010; Zhang et al. 2008; Li et al. 2002), supporting the inverse relation of these mechanism. Another important mechanism relies on vitamin D role in the immune system, as studies have shown that 1,25-dihydroxivitamin D3 suppresses activation of NF-kappa B protein (Zhang et al. 2007; Yu et al. 1995), which play a role in modulating immune response, demonstrating an anti-inflammatory mechanism, where its deficit as in CKD conditions could exacerbate and lead to its progression.

In PD patients, similar to CKD conditions, low vitamin D levels have been proven to prevail (Soliman et al. 2019; Sleeman et al. 2017) compared to controls. Moreover, systematic reviews have assessed the association between low vitamin D levels and PD and have found an increased future risk for PD and an inverse association with disease severity via Hoehn and Yahr (HY) and Unified Parkinson Disease Rating Scale (UPDRS) Part III measurements (Rimmelzwaan et al. 2016; Luo et al. 2018). Among possible explanations in these studies, the limited outdoor activity has been proposed, however, patients in early PD, where ambulation is not severely affected, also present with low vitamin D levels (Soliman et al. 2019; Evatt et al. 2011). The possible explanation for the increased risk for PD in these patients may lie on the neuroprotective effects that have been attributed to vitamin D, as animal models of PD have shown attenuation of inflammation and dopamine degeneration when treated with vitamin D (Calvello et al. 2017), and increase production of neurotrophic factors in glial cells (Sanchez et al. 2009). Moreover, high levels of vitamin D receptor and 1-alpha hydroxylase have been found in the substantia nigra (Eyles et al. 2005), supporting the idea of a neuroprotective effect in this brain region. In fact, considering that vitamin D is a liposoluble substance, this can travel through the blood brain barrier and bind to receptors in substantia nigra, exerting its neuroprotective effects. Taken these mechanisms into consideration, low levels of vitamin D commonly seen in CKD conditions could exacerbate inflammatory conditions and promote neuronal damage due to decrease neurotrophic factors. Moreover, an important link between low vitamin D levels in CKD and PD may rely on RAS system. As discussed previously, vitamin D deficiency contributes to an increase in renin and angiotensin II (Li 2010; Zhang et al. 2008), which promote oxidant and inflammatory conditions, and together with the presence of disrupted blood brain barrier like CKD could reach brain regions and bind AT1 receptors, leading to neuronal damage.

Anemia in CKD and PD risk

A high proportion of patients with CKD experience anemia and this proportion increases as CKD progresses (Stauffer and Fan 2014; Voormolen et al. 2010). The main mechanism involved in

its presence relies on a relative deficiency of erythropoietin (EPO) due to impaired kidney function (McGonigle et al. 1984; Babitt and Lin 2012), as EPO is produced via a hypoxia inducible manner mainly by renal cells (Suzuki and Yamamoto 2016). Moreover, other mechanisms play a role in anemia in CKD, one important being iron deficiency. In fact, a high percentage of patients with CKD have been found to be iron deficient (Ashby et al. 2009). Explanations to this deficiency have been attributed to an absolute and a functional deficiency (Babitt and Lin 2012). The latter is explained by increased levels of hepcidin in CKD patients (Zaritsky et al. 2009; Nemeth et al. 2004), which is in charge of regulating iron metabolism and in high levels inducing a reduction in its absorption and mobilization (Fishbane et al. 2009). Reduction of eGFR and inflammatory conditions in CKD contribute to this increase in hepcidin levels (Babitt and Lin 2012), leading to decreased iron levels, which are necessary for erythropoiesis.

In PD, discrepancy exists whether hemoglobin levels are low or normal in patients compared to controls (Kasten et al. 2010; Deng et al. 2017). Moreover, this discrepancy also persists when assessing iron serum levels in these patients, as some studies have found low serum iron, while other have found no differences compared to controls (Medeiros et al. 2016; Mariani et al. 2013). A retrospective cohort study assessing PD risk in iron deficiency anemic patients found an increased risk compared to controls (Hong et al. 2016). Considering that iron deposition in substantia nigra has been found in PD patients (Martin et al. 2008), and iron is responsible for oxidative stress processes (Núñez et al. 2012), the question arises as why low iron serum levels may predispose to an increased PD risk. The answer may rely on an iron maldistribution process (Cabantchik et al. 2013), as iron overload in brain tissue and abnormal low serum levels may coexist. This maldistribution may be linked to hepcidin, as this has been shown to be widely distributed in the murine brain (Zechel et al. 2006). Furthermore, studies assessing hepcidin in cell culture and animal models of PD have shown contradictory results (Liang et al. 2020; Xu et al. 2016). A review proposed a dual role model of hepcidin, as pre-treatment with hepcidin can ameliorate iron accumulation, but its increased due to inflammatory conditions may contribute to oxidative stress and neuronal damage (Vela 2018). Considering that CKD involves an inflammatory state, this may lead to hepcidin detrimental role in neuronal damage, inducing iron overload and oxidative stress conditions. On the other side, EPO has been shown to exert neuroprotective effects in animal models of PD (Erbaş et al. 2015), resulting from its effect as antioxidant, anti-apoptotic, and anti-inflammatory agent (Ehrenreich et al. 2004). Thus, iron dysmetabolism and hepcidin, and EPO levels in CKD may be a possible link between PD and this disease. The association of CKD components and its pathophysiology and PD are displayed in Fig. 2.

Therapeutic considerations of these associations

Considering the components that were discussed in the present review, different therapeutic modalities can be used for PD patients targeting the pathways previously mentioned, such as antioxidants for oxidative stress, anti-hypertensive medications, vitamin D supplementation, and iron chelators and erythropoietin. We reviewed any observational or interventional studies assessing these potential therapeutics. Considering antioxidant therapies and future PD risk, a meta-analysis showed patients with a dietary intake of vitamin E had a reduced risk for PD compared to controls (Etminan et al. 2005), but no association was found with other antioxidants such as vitamin C or beta-carotenes. However, more recent studies have shown inconsistent results (Hughes et al. 2016; Yang et al. 2017; Takeda et al. 2014). Two meta-analysis evaluating randomized clinical trials on the effect of antioxidant agents in PD showed no effect on disease progression (Negida et al. 2016; Attia et al. 2017).

On the other side, a meta-analysis evaluating anti-hypertensive medications and future PD risk observed an insignificant risk ratio for PD in overall anti-hypertensive agents use (Mullapudi et al. 2016), showing in subgroup analysis a significant risk reduction only in calcium channel blockers. Despite this reduction, a recent phase III randomized clinical trial assessing isradipine, a dihydropyridine calcium channel blocker, in PD patients showed isradipine failed to affect clinical progression of the disease (Parkinson Study Group STEADY-PD III Investigators 2020). Nonetheless, a pilot study evaluating an angiotensin converting enzyme (ACE) inhibitor in PD patients showed this may serve in management of motor fluctuations (Reardon et al. 2000), but a great limitation was its small sample size ($n = 7$ patients). Another study demonstrated ACE inhibitor use and a reduced number of falls in PD patients (Laudisio et al. 2017). These results exhibit the need of more clinical studies to elucidate the role of RAS modulating agents and other anti-hypertensive agents in PD.

A study evaluating EPO treatment in PD patients demonstrated its safety and tolerability in this population, showing in addition an improvement in motor function (Pedroso et al. 2012). However, its small sample size and the lack of a placebo control group limit the interpretation of these results regarding motor function. The same group of authors assessed EPO treatment in cognitive function in another sample of PD patients compared to placebo and observed a discrete improvement in this parameter, not different however, to the placebo group (Pedroso et al. 2018). Another study showed EPO treatment significantly improved non-motor, but not motor, symptoms compared to control (Jang et al. 2014). Considering iron depositions in substantia nigra, a study evaluated deferiprone, an iron chelator agent, in PD patients and observed a reduction in iron accumulation in substantia nigra

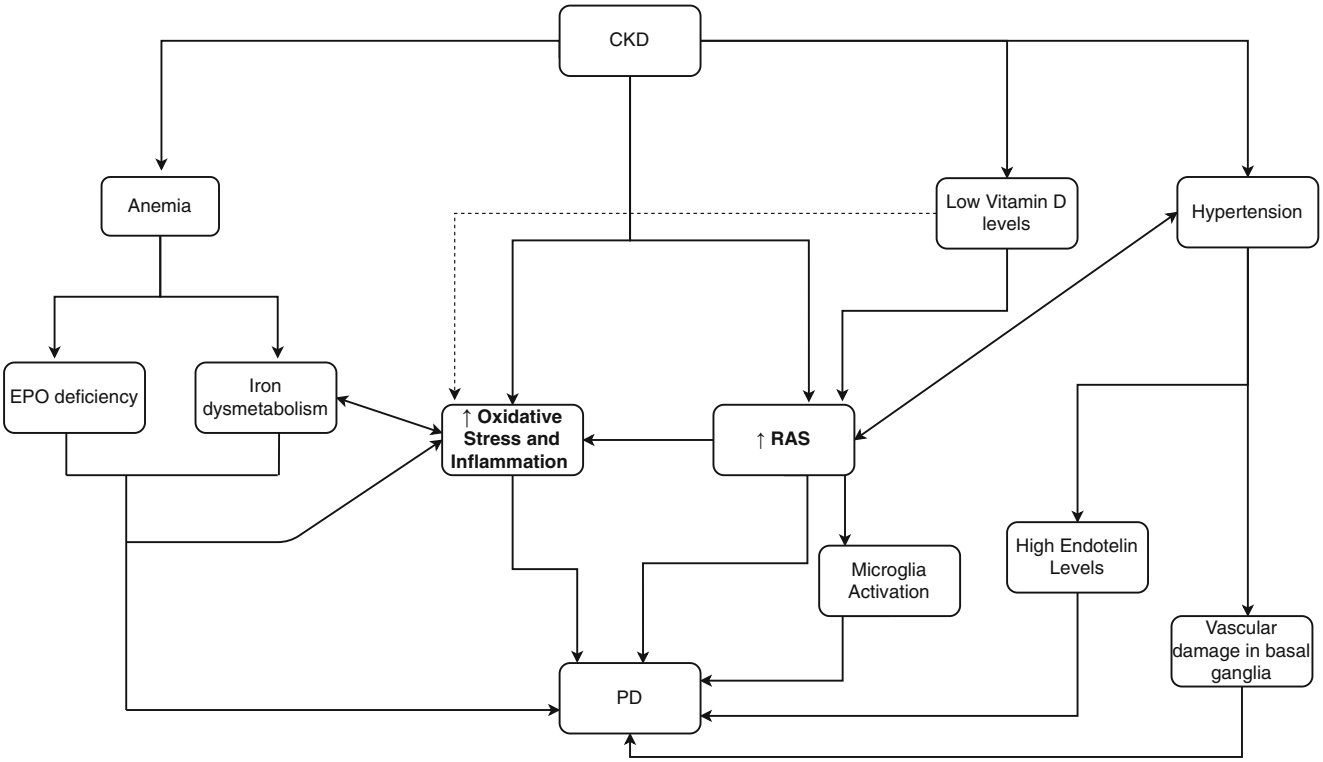

Fig. 2 Association of elements that compose CKD and PD. The main pathways in which most components of CKD may be indirectly linked to PD involve increased oxidative stress, inflammation, and RAS. However, anemic conditions due to EPO deficiency and iron dysmetabolism whereas vascular damage and high endothelin levels in hypertensive state may be directly linked to PD. CKD = chronic kidney disease, PD = Parkinson's disease, RAS = renin-angiotensin system, EPO = erythropoietin

and in UPDRS motor scores, relating this reduction to ceruloplasmin, an iron modulator, activity (Grolez et al. 2015). Another study assessing this agent showed a decrease in iron accumulation in dentate and caudate nucleus, but only few patients had a reduction in substantia nigra. Moreover, no significant improvement was observed in UPDRS motor scores compared to control (Martin-Bastida et al. 2017).

Lastly, vitamin D supplementation in PD patients has been evaluated in two studies. One showed that patients with Vitamin D supplementation had less worsening of HY and UPDRS part II compared to control (Suzuki et al. 2013), while the other showed no differences in PD severity, quality of life, balance or cognition compared to control, demonstrating however a difference in balance only when grouping patients based on age, having younger patients a greater benefit of vitamin D (Hiller et al. 2018).

Remarks on these associations: Correlations do not imply causation

It is important to consider that some mechanisms discussed in this review do not imply a direct causal effect on PD incidence. As described above, patients with CKD have high markers of oxidative stress, and reduction of antioxidant capacity, however, this mechanism is not unique for CKD, as these patients may have multiple comorbidities that may predispose to an oxidant environment, and the relation between these two conditions is to be viewed with caution. Nonetheless, in this review, we presented speculative pathways related to kidney function that may contribute to PD based on oxidant properties, as RAS and sympathetic mechanisms. Another mechanism that must be considered with caution is hypertension. On the one side, as hypertensive patients have been observed to have an increased risk for PD, the link between CKD related hypertension and PD might not be direct and specific. This is supported by hypertension contributing itself to future incidence of CKD. On the other side, the altered kidney's contribution in function of RAS and overactivation of sympathetic system to hypertensive state is not to be neglected and might indirectly contribute to this association.

Anemia and vitamin D deficiency seen in CKD might be directly related to PD, considering the role the kidney has in vitamin D and red blood metabolism. This is supported by the increased prevalence of these conditions as CKD progresses. As vitamin D and EPO have a neuroprotective function, and iron dysmetabolism is observed in PD patients, the abnormalities present in CKD related to these elements might have a direct association to the later onset of PD. Nonetheless, this review considers that, although the mechanisms of hypertension and oxidative stress might not be specific for CKD and directly relate to PD, the pathways proposed in this study are interconnected and based primarily on RAS and its oxidant

Table 2 Other mechanisms in the potential CKD-PD relation

Acid-base balance abnormalities	Electrolyte balance abnormalities
Acidotic state in severely impaired renal function: • Anti-inflammatory cytokines reduced and pro-inflammatory state increased in metabolic acidosis of CKD (Zahed and Chehrazi 2017; Ori et al. 2013). • Increased levels of angiotensin II, aldosterone, and endothelin 1, and their inflammatory properties (Wesson et al. 2020). • Induced ammoniagenesis and ammonia related neurotoxicity via astrocyte dysfunction (Wesson et al. 2020; Rama Rao et al. 2003).	• Disrupted kalium, sodium, magnesium (Mg), and calcium metabolism in CKD, tendency towards hyperkalemia, dysnatremia and dysmagnesemia (Dhondup and Qian 2017). • Mg necessary in brain regions for neurotransmission, and disrupted levels in PD (Jin et al. 2018). • Hyperkalemia diuretic treatment with potential interactions with levodopa treatment (Bitner et al. 2015). • Lower sodium levels inversely associated with dyskinesia in PD patients (Mao et al. 2017).

CKD = Chronic kidney disease; PD = Parkinson's disease

and inflammatory properties, thus, vitamin D deficiency and anemia, which are more specific for CKD, and hypertension, which is common but unspecific for CKD, might synergistically contribute to PD. It is important to mention, however, that the pathways proposed, linking CKD elements reviewed, are speculative and might lead to further research to confirm these potential associations.

Other mechanisms linking CKD and PD

In this review, we focused on analyzing the association of CKD and PD based on oxidative stress caused by CKD conditions, hypertension, vitamin D deficiency, and anemia. Furthermore, we integrated sympathetic nervous system role in RAS activity, oxidative stress, and inflammation in CKD (as shown in Fig. 1). However, there are other elements present in CKD that could be associated with PD, and these are shown in Table 2.

Conclusion

CKD and PD share common mechanisms regarding their pathophysiology. When breaking down CKD components and analyzing their association with PD, this review links evidence showing different potential pathways that may lead to an increased future risk for PD in patients with CKD, as retrospective cohort studies have shown. One potential pathway discussed is RAS system, as this is increased in CKD conditions, and this has been involved in preclinical studies of PD. Furthermore, studies evaluating therapies that target CKD components in PD have shown variable results. Further studies are needed to confirm the therapeutic potential of these interventions.

Authors' contributions All authors contributed to the elaboration of this manuscript. All authors have approved final article version.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to report.

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