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Review

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Review

Respiratory complications and sleep disorders in children with chronic kidney disease: a correlation often underestimated

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Keywords: lung function; sleep-disordered breathing; hypoventilation; central apnoea; chronic kidney disease; end-stage renal disease; quality of life.

Educational Aims

The reader will come to appreciate that:

- Respiratory aspects are often overlooked in children with CKD;
- The quality of sleep is often not investigated in children with CKD;
- hildren with CKD have respiratory complications and sleep disorders that further worsen their quality of life and cause increased morbidity and mortality; Paediatricians must be aware of these complications and act early.

Future research directions

The study of sleep and respiratory function must be included in the diagnostic-therapeutic protocols of children with CKD. Well-designed studies are needed in order to better describe the respiratory complications and sleep disorders in children with CKD. We need to define how to best investigate the respiratory and sleep breathing abnormalities in these children and the optimal timing of such investigations.

Abbreviations

CKD: chronic Kidney Disease;

ESKD: end-stage kidney disease;

SD: sleep disorder;

SDB: sleep-disordered breathing;

PLMD: periodic limb movement disorder;

RLS: restless leg syndrome;

HD: haemodialysis;

PD: peritoneal dialysis;

CO: carbon monoxide;

6MWT: 6-minutes walking test;

FVC: forced vital capacity;

FEV1: forced expiratory volume in the first second;

MIP: maximal inspiratory pressure;

OSA: obstructive sleep apnea;

ESADA: European Sleep Apnea Database;

CSA: central sleep apnea;

PSG: polysomnography;

PSQ: Pediatric Sleep Questionnaire;

CRP: C-reactive protein;

IL-6: interleukin-6;

PEF: peak expiratory flow;

DLCO: diffusing capacity for carbon monoxide;

eGFR: estimated glomerular filtration rate;

IL-10: interleukin-10.

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Abstract

Chronic Kidney Disease (CKD) is characterized by a progressive and irreversible loss of kidney function which gradu¬ally leads to end-stage kidney disease (ESKD). Virtually all the organs are damaged by the toxicity of uremic compounds. The lungs may be affected and the impaired pulmonary function may be the direct re¬sult of fluid retention and metabolic, endocrine and cardiovascular alterations, as well as systemic activation of the inflammation. An increased prevalence in sleep disorders (SD) is also reported in patients with CKD, leading to a further negative impact on overall health and quality of life. While these complex relationships are well

documented in the adult population, these aspects remain relatively little investigated in children. The aim of this review is to provide a brief overview of the pathophysiology between lung and kidney and to summarize how CKD may affect respiratory function and sleep in children.

1. Introduction

Chronic kidney disease (CKD) is a clinical syndrome caused by many disorders and characterized by a progressive and irreversible decrease of kidney function, which gradually progresses to end-stage kidney disease (ESKD). The incidence of CKD in Europe is around 11–12 per million of age-related children for CKD stages 3–5, and 8 per million for CKD stages 4–5 [1,2]. A wide range of complications result from the loss of kidney function and multiple organ systems may be affected. Consequently, as the life expectancy of these patients has increased with dialysis technology improvement, systemic complications of CKD are likely to become increasingly important [3]. Pulmonary involvement associated with CKD has gained increased attention and a variety of pulmonary manifestations have been described over time, especially in the adult populations [4]. Respiratory complications may be related to circulating uremic toxins or may indirectly result from fluid overload, electrolyte disorders, acid-base imbalances, anemia, immunosuppression, extraosseous tissue calcifications and malnutrition, which are common issues in ESKD patients [5]. Likewise, sleep-related disorders, such as sleep-disordered breathing (SDB), insomnia, periodic limb movement disorder (PLMD), restless leg syndrome (RLS) and poor sleep quality are more often described in CKD adult patients, compared to the general population. Although less investigated than adults, children who undergo dialysis appear to experience a higher prevalence of these disorders, mostly linked to changes in central chemoreceptor sensitivity and pharyngeal narrowing due to fluid overload, metabolic acidosis and accumulation of uremic toxins [6-8]. From the routine clinical viewpoint, it is possible that the respiratory and sleep changes in children with CKD remain often underestimated.

The aim of this review is to provide insights on the mechanisms underlying lung involvement, respiratory function impairment and sleep disturbances in children with CKD, in order to increase the awareness and optimize the management of these disturbances.

2. Lung involvement in CKD

Lung and kidney function are closely related. Either CKD itself, or the therapeutic options, including haemodialysis (HD) and peritoneal dialysis (PD), can severely affect the lungs. It is reasonable to think that the complex pathophysiology that supports pulmonary involvement in CKD could be similar in children compared to adults. Patients suffering from CKD or undergoing dialysis are exposed to frequent pulmonary injuries whose pathogenesis is complex and heterogeneous, involving alteration in volume and in plasma oncotic pressure, heart failure, anemia, malnutrition, altered calcium-phosphorous metabolism, chronic systemic inflammation and immune function (**Figure 1**). Fluid overload, in association with decreased plasma oncotic pressure secondary to hypoalbuminemia, can lead to pulmonary oedema, pleural effusions and lung congestion. Heart failure and other cardiac diseases, common findings in CKD, may also contribute to the development of congestive heart failure and may further complicate the aetiology of pulmonary oedema [9]. Furthermore, in patients with CKD the increase of pulmonary capillary permeability due to uremia and mediated by high plasma levels of endothelial cell-derived glycoproteins [von Willebrand Factor, tissue plasminogen activator, urokinase-type plasminogen activator, soluble thrombomodulin, endothelin-1, Intercellular Adhesion Molecule 1, Vascular cell adhesion protein 1, and Monocyte chemoattractant protein-1] and Vascular Endothelial Growth Factor further contributes to pulmonary congestion [10]. An increased venous return and uremic endothelial dysfunction of the vascular wall, in addition to hypoxia, due to high prevalence of sleep apnea in this population, are risk factors for pulmonary hypertension, which is ten times more prevalent in CKD and HD children than in the general pediatric population [11]. This condition must be suspected and investigated early, because pulmonary hypertension remains asymptomatic until right ventricular dysfunction becomes apparent with dyspnea, fatigue, chest pain and cyanosis [12,13].

Anemia resulting from impaired production of erythropoietin and hepcidin-mediated iron-restricted erythropoiesis is another important cardiovascular and pulmonary risk factor in children, which may contribute to dyspnea and may adversely impact the quality of life of the patients [14]. Also, malnutrition is another common condition in children with CKD; in association with hypercatabolic status and uremic respiratory muscle dysfunction, malnutrition can decrease muscle mass and can lead to the worsening of the respiratory muscles efficiency and to the deterioration of the respiratory function tests [15,16].

Pulmonary calcifications are a recognized complication of CKD, caused by the deposition of calcium in lung tissue, mostly seen in patients with advanced stages of CKD. This condition is quite rare in the pediatric age, even despite an autopsy study of 120 pediatric kidney transplant recipients and/or

HD children identified soft tissue calcifications in 60% of the subjects, with the lungs among the most involved organs [17]. The deposition of calcium salts occurs predominantly at the alveolar epithelial basement membranes and, in case of extensive injuries, alteration of pulmonary function could be severe [18,19]. Chest x-rays may be normal or show confluent or patchy opacities, especially in the upper lobe area and in the vessels of the chest wall, while high-resolution computed tomography [CT] scans remain the most sensitive imaging in detecting even small lesions. Pulmonary calcifications should be kept in mind when children on dialysis develop unexplained radiographic changes or pulmonary symptoms. At the same time radiologists must be able to identify the imaging patterns of this complication. [20].

Recent studies suggest that an increased expression of pro-inflammatory mediators, produced by injured kidney, could promote lung impairment. In a recent study in a murine model of alveolar involvement with leukocyte infiltration, an increase of Th17 cells in the lungs and in the systemic circulation, and an enhanced airway contractility were rapidly observed in response to kidney injury. It is noteworthy that all these effects on lung were long lasting despite the resolution of the kidney disease [21].

Finally, subjects with CKD also experience severe immune dysregulation of the innate and adaptive immunity, which seems to be independent from the underlying disease. The immune impairment is generally present from the early phase of the disease and predisposes to recurrent infections and poor vaccine responses, which are one of the most common causes of morbidity and mortality in chronic kidney dysfunctions [22,23]. Many underlying conditions are responsible for the impaired immunological response, including uremic toxins, endocrine abnormalities, especially vitamin D-parathyroid hormone axis alteration, and intestinal dysbiosis, which, in turn, promotes pathogen overgrowth and loss of intestinal barrier integrity [24]. In particular, the uremia-associated pro-inflammatory condition and the resulting oxidative stress can lead to the impaired T-cell system, causing premature immunological aging, which seems to be irreversible by renal replacement therapy, including kidney transplantation [25]

2.1 Lung function and exercise testing in children with CKD

As a consequence of lung involvement, in CKD adult patients pulmonary function is often impaired and many studies reported both obstructive and restrictive spirometry patterns, pointing out a close association with the severity of kidney damage [26,27]. Impaired diffusion capacity of carbon monoxide (CO), reflecting the interstitial involvement of the lungs, has also been described,

especially in those patients receiving long-term (more than 5 years) HD [28]. Unfortunately, lung function assessment is not a routine clinical practice in the management of adult and pediatric patients with CKD, and the prevalence, characteristics and clinical implications of pulmonary dysfunction in individuals with different degrees of kidney impairment, are poorly described [26,29]. There are few reports on links between pulmonary dysfunction and mortality in patients with CKD and even fewer studies involved children. *Mukai et al.* documented that, in adults, lung dysfunction, and in particular restrictive lung patterns, are associated with the degree of kidney function impairment and the presence of comorbidities; at the same time. These variables are an independent predictor of increased mortality in CKD patients [30]. In an observational cross-sectional study of 40 children (age range 8-17 years) with CKD, *Teixeira et al.* documented a significant reduction of the pulmonary functional capacity, measured at the 6-minutes walking test (6MWT). The mean walked distance at 6MWT was, in fact, around 64% of the mean distance predicted (396 ± 71 vs 620.2 ± 44 meters, $p < 0.001$) with a positive correlation between the result of the test, forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) [31]. Pulmonary edema, often described as '*uraemic lung*', resulting from fluid overload, anemia, hypoproteinemia and depressed myocardial function can also lead to the collection of fluid near the small airways, resulting in reversible airway obstruction and air trapping [32]. Dialysis treatment, removing the excess fluid from the body, decreases water content of the lungs and the pressure on airways, often resolving the obstruction [33]. In 1991, *Paul et al.* measured lung volumes in 45 children with CKD and in 10 healthy controls. They documented that lung volumes were frequently reduced in children with CKD, while, during a HD session, the mean FEV_1 increased significantly [34]. More recently, in a case-control study, *Youssef et al.* evaluating the pulmonary function and plasma Nitric Oxide (NO) level in 20 children with ESKD, documented significantly lower values of forced volumes (FVC, FEV_1) and forced expiratory flows (FEF 25-75) compared to controls. In addition, plasma NO levels were significantly higher in patients with ESKD, suggesting the possibility that NO could be involved in the deterioration of pulmonary function and that it could be used as a marker of clinical course. Finally, the authors documented the positive effect of dialysis on FVC and a negative, although not significant, correlation between the lung function and duration of treatment [35]. However, other studies reported that, in children with CKD, volume overload may be associated with a restrictive spirometry pattern (defined as FEV1/FVC ratio > 0.7 and an FVC < 80% of the predicted value) [32]. As a result of uremic myopathy, in association with chronic inflammation and decreased protein-calorie intake, children with CKD also show reduced respiratory muscle mass and strength, which, in turn, leads to a decrease in pulmonary functional capacity, exercise capacity, dyspnea and is an independent predictor of mortality in these patients [36,37]. Muscle weakness may also be related to the dialytic treatment

itself. In a cross-sectional study on 40 children with CKD, *Painter et al.*, using an isokinetic muscle function system, showed that HD patients achieved lower peak torque values and low exercise capacity, not completely rectified by transplantation [38]. Likewise, *Alayli et al*. found a positive correlation between muscle strength and physical performance, expressed as 6MWT test, suggesting that muscle weakness may be a contributing factor to reduced aerobic exercise capacity in children on peritoneal dialysis [39]. Recently, there was a growing awareness of the benefits of aerobic exercise for these patients and in a meta-analysis of four studies on 110 adults undergoing dialysis treatment, regular inspiratory muscle training significantly improved muscle strength, lung function, maximal respiratory pressures and the 6MWT distance [40]. These findings indicate the need of early implementation of physical function, regardless of modality, for children and adults with CKD and in patients on dialytic treatment.

3. CKD-related sleep disorders

Many studies reported that patients with CKD, in particular those with ESKD, show an increase in sleep-related disorders, compared to the general population. Sleep disturbances range from 30% to 80% and are associated with serious complications regarding general and mental health, body pain, fatigue, physical functioning, cardiovascular and metabolic disease [41,42]. As for lung function, most of the data pertain to the adult population. In many articles, kidney failure frequently co-exists with RLS/PLMD, a neurological sensory-motor disorder characterized by an uncontrollable need to move the limbs during sleep or resting time, which is associated with a worse quality of life [43,44]. While in the general population this condition is described in 5-15%, RLS is reported in up to 25% of patients with ESKD [45-48]. In a cross-sectional study of 788 adult kidney transplant patients and 161 dialyzed patients, the presence of RLS symptoms was strictly associated with depression and the relationship remained significant even after accounting for insomnia [49]. Several factors may explain the relatively high frequency of RLS/PLMD in children with CKD: iron deficiency, which is frequent in this population, has been implicated in the etiology of secondary RLS [50]. Even in healthy subjects, iron deficiency has long been recognized as a risk factor for RLS and, until now, the usual therapeutic approaches include iron supplementation [51].

There are also numerous studies in adult populations regarding SDB. It is well known that obstructive sleep apnea (OSA) contributes to the onset and progression of CKD through intermittent hypoxia, hypertension, sympathetic nervous system activity, oxidative stress and metabolic dysregulation [52]. *Marrone et al*. in the European Sleep Apnea Database (ESADA) cohort study from 7700 unselected adult patients with suspected obstructive sleep apnea, documented that severe nocturnal hypoxemia

may be a risk factor for kidney dysfunction, even if present for only a part of the night [53]. In turn, CKD, especially in the latter stages of the disease, could be a risk factor for OSA and central sleep apnea (CSA). Although the exact mechanisms are not well known, uremia-induced neuropathy and myopathy, in association with altered chemosensitivity of ventilatory drive, and hypervolemia leading to upper airway oedema and obstruction, are some of the variables that correlate CKD and nocturnal oxygen saturation [54-57] (**Figure 2**). OSA is the most frequent sleep disorder also in the general paediatric population and it is characterized by repeated upper airway obstruction during sleep, that leads to hypoxaemia and sleep fragmentation, while CSA and hypoventilation are less common, even if their real prevalence in childhood is unknown and probably underestimated [58].

So far, there are only few paediatric studies that demonstrate a greater prevalence of sleep disorders in children suffering from CKD and in that undergoing dialysis, compared to the healthy paediatric population. While paediatric OSA in healthy children is mostly related to tonsillar and adenoidal hypertrophy, in children with CKD many other mechanisms could play a role. Fluid accumulated in the legs during the day may shift rostrally into the neck during sleep, leading to distension of the great veins and swelling of the pharyngeal soft tissue and predisposing to upper airway obstruction [59]. In addition, uremic status decreases the upper airway muscle tone during sleep, because of neuronal depressive effects of uremic toxins, and seems to be reversible after dialysis [60-62]. Children with CKD may also experience CSA due to metabolic disturbances, acidosis and uremia. All these conditions can alter chemoreceptor sensitivity and can lead to an increased ventilatory drive and ventilatory over-shoot, lowering CO_2 below the apnea threshold and resulting in apnea. Furthermore, there are some reports highlighting that nocturnal hypoventilation could result because of bicarbonate-based dialysis fluid with metabolic alkalosis and compensatory nocturnal reduction in minute volume [62].

If untreated, sleep disturbances can cause significant adverse consequences such as cardiovascular, metabolic and neurodevelopmental disorders, increasing the risk of morbidity and mortality and reducing the quality of life of the affected children [63-65]. *Tsampalieros et al*, in 2019, studying 13 children in stage 2-5 of CKD with PSG and ambulatory blood pressure monitoring, showed that the obstructive apnoea/hypopnea index is strongly correlated with night time blood pressures of these patients [66]. In 2005 *Davis et al.* conducted a telephone or clinic-based interview in 21 children and adolescents on chronic dialysis, identifying a sleep disturbance in 18 cases (86%), in particular SDB (46%), RLS/periodic limb movement (29%) and excessive daytime sleepiness (60%) [7]. Few years later, the same authors conducted a survey of sleep habits and sleep disturbances in 159 school-aged

patients with CKD through a set of five questionnaires. Sleep disturbances were present in 93 patients (58.5%), with a prevalence ranging from 50% in children on conservative therapy to almost 77% in dialysis patients. The presence of a sleep disturbance correlated with a decrease in health-related quality of life scores and was independent of the CKD stage [67]. Unfortunately, most of these studies identified SDB on the basis of subjective sleep scales and not through objective tools such as polysomnography (PSG) or home sleep apnoea testing. In 2013, a case-control study evaluated 25 ESKD children on HD, using a sleep questionnaire and a full-night PSG. Data from the questionnaires revealed markedly affected sleep quality in HD children, as reflected by excessive day time sleepiness, night awakening, difficult morning arousal and limb pain, while PSG analysis showed in affected children differences in sleep architecture, less slow wave sleep, similar rapid eye movement and non-rapid eye movement sleep time, more SDB and more periodic limb movement disorders [68]. More recently, *Amin et al.* evaluated 19 children with CKD stages 3–5 (7 children on dialysis) and collected data from PSG, the Epworth Sleepiness Scale Score, the Pediatric Sleep Questionnaire (PSQ) and the Pediatric Quality of Life Inventory at the time of the PSG. Based on PSG results, the authors found a 37% prevalence of SDB, either central or obstructive sleep apnea, while the validated sleep questionnaires did not correlate with the obstructive apnea-hypopnea index, pointing out the limitations of sleep questionnaires in diagnosing SDB in the CKD population [60]. Finally, in 2017, *Gomes et al.* confirmed the results of the previous study, testing by PSG and questionnaire the quality of sleep in 8 children on PD; a sleep disorder was present in 5 children (62.5%), but the authors warned that data resulting from the sleep questionnaire underestimated PSG findings [69]. The possible role of different type of dialysis and of kidney transplantation on sleep disturbances remains unclear. Some authors documented that daytime HD patients had the worst sleep quality and that melatonin rhythm was present only in nocturnal HD, being suppressed in daytime HD and in automatic PD [70]. However, other authors did not find significant differences between patients on continuous cycling PD and on HD [7]. Similarly, in some studies conducted only on adults, kidney transplantation has been associated with a SDB improvement, while others showed only marginal or no improvement [71-73]. As SDB may have serious repercussions on life of patients with CKD, a systematic sleep assessment should be part of the management.

4. The role of systemic inflammation

A persistent activation of the inflammatory response has been recognized in patients with CKD. Markers of systemic inflammation, such as C-reactive protein (CRP) or interleukin-6 (IL-6) are independent predictors of increased mortality [74,75]. Although data suggest an upregulation of the pro-inflammatory cytokine production in patients with CKD, the etiology of systemic inflammation remains unknown. Some authors did not document major differences in serum cytokine levels

between long-term dialysis patients and those not yet dialyzed, suggesting that ESKD itself, rather than the dialysis procedure, may be an important cause of elevated cytokine concentration [76]. Interestingly, some spirometric parameters, such as VC, FVC, peak expiratory flow (PEF), seem to be significantly lower in patients with elevated serum CRP levels, which seem to be negatively correlated also with diffusing capacity for carbon monoxide (DLCO) [29,77-79]. Furthermore, the accumulation of proinflammatory cytokines could play a role in muscle wasting through the stimulation of protein catabolism via the ubiquitin–proteasome pathway. This process could therefore affect respiratory muscles, potentially resulting in lung damage [29]. Many studies in adults have demonstrated that increased levels of cytokines and chemokines in ESKD can promote kidney fibrosis and, at the same time, affect lung fibrosis and DLCO [80,81]. In 2013, *Taraz et al.* conducted a cross-sectional study evaluating the relationship between sleep quality and circulating levels of anti-inflammatory markers in 72 HD adult patients. Poor sleepers showed significantly lower levels of serum interleukin-10 (IL-10) in combination with higher serum triglyceride and parathyroid hormone concentrations, being at high risk for cardiovascular disease [82]. Because cardiovascular disease accounts for most deaths also in children with CKD [83], the detection and prevention of the underlying mechanisms may have important effects on clinical outcomes. Long-term studies of the role of chronic inflammatory status on both pulmonary involvement and sleep disorders in children with CKD are necessary.

5. Conclusions

As the life expectancy of children with CKD has significantly improved, systemic complications of kidney disease are likely to become increasingly important. Among the most common complications, lung function assessment and the evaluation of sleep quality are not part of the routine clinical practice, especially in younger subjects. Nonetheless lung function is an indicator of increased morbidity and mortality and SDB are associated with negative effects on behaviour, neuro-cognitive function and school performance, as well as metabolic and cardiovascular consequences. So, we emphasize the importance of early and regular evaluation of lung function and sleep disorders. At the same time, we hope that well-designed studies will be shortly conducted, in order to better characterize the respiratory complications and sleep disorders in these patients.

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Figure 1. Kidney and lung linkage.

Figure 2. Bidirectional relationship between SDB and CKD.