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Literature review on the cross-link between ocular and renal disease: renin angiotensin aldosterone system is a main actor

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Abstract. – OBJECTIVE: Chronic kidney disease (CKD) and ocular disease share several cardiovascular risk factors as well as pathogenetic mechanisms having Renin-Angiotensin-Aldosterone System (RAAS) as main actor. Moreover, kidney and eyes have common genetic and embryonic origin. In this literature review, we present main evidence supporting this association for early identifying diseases affecting both systems and evaluating potential multi-target therapeutic strategies.

MATERIALS AND METHODS: We performed a literature review of the current peer-reviewed English-language randomized controlled studies (RCTs), reference lists of nephrology or ophthalmology textbooks, review articles and relevant studies with ocular or eye and kidney or renal diseases as keywords until March 2020. Prospective and retrospective studies as well as meta-analyses and latest systematic reviews were included.

RESULTS: We evaluated a total of 683 records, finally selecting 119 articles related to ocular and renal diseases. Records were divided into two areas: chronic and acute kidney disease and ocular or eye diseases. Some of the examined studies were discarded for population biases/intervention or deemed unfit.

CONCLUSIONS: Based on our results, we conclude that there is evidence of a clear association between kidney and eye diseases, being this cross-link mainly based on RAAS dysregulation. Our review suggests that it may be useful to screen CKD patients for associated ocular diseases, such as cataract, glaucoma, diabetic retinopathy and age-related macular degeneration. A comprehensive study of CKD and proteinuric patients should include careful eye examination. Renal impairment in young patients should prompt a search for ocular disease, such as TUNA syndrome or oculo-renal syndrome, in particular if family history of concurrent ocular and renal disease is present. Anti-RAAS agents are mostly recommended in patients with renal and ocular impairment.

Key Words:
Eye, Chronic kidney disease, Ocular disease, Oculo-renal syndrome.

Introduction

Chronic kidney disease (CKD) represents a common disorder in the general population[1] with important extrarenal systemic consequences, including cardiovascular, neurologic, endocrine, skeletal, hematologic, cutaneous and metabolic abnormalities. Nevertheless, the direct negative effects of CKD on ocular system were not clearly identified[2,3]. CKD and eye diseases have several aspects in common, such as cardiovascular risk factors (diabetes, hypertension, smoking and obesity)[3]. Moreover, it is important to notice that these diseases share pathogenetic mechanisms, in particular renin angiotensin aldosterone system (RAAS) upregulation, determining endothelial dysfunction, inflammation and oxidative stress[4]. Kidney and eye functional units have similar anatomical and physiological features, as glomerulus and choroid are widely vascularized with peculiar vessel networks. In fact, inner retina and

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glomerulus share similar filtration barrier with the RAAS regulating both of them. Furthermore, eye and kidney have a common genetic and embryonic development and, consequently, are both affected by a number of genetic diseases, such as oculo-renal and TUNA syndromes[5].

Aim

In this review we present main evidence found in the literature supporting the association between ocular and renal disease considering RAAS as the main common pathogenetic mechanisms.

Materials and Methods

We conducted a literature review of the current knowledge on renal and ocular associated diseases. Records with ocular or eye and kidney or renal diseases as keywords published until March 2020 were considered for this review.

Types of Studies

We analysed all randomized controlled trials (RCTs) and quasi-RCTs evaluating the current knowledge about renal disease associated with ocular diseases and RAAS.

Electronic Searches

1. Cochrane Renal Group's specialised register.
2. ClinicalTrial.gov (http://www.clinicaltrials.gov).
3. WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/).
4. MEDLINE.

We checked the reference lists of nephrology or ophthalmology textbooks, review articles, and relevant studies.

Results

Results of the research are summarized in Figure 1. Records identified from databases (n =683). We evaluated 683 randomized controlled trials (RCTs), reference lists of nephrology or ophthalmology textbooks, review articles and relevant studies. Some records were removed before screening because they were duplicate (n =10), marked as ineligible by automation tools (n =22), or for other reasons (n =182). Finally selecting 119 studies included in review; studies included are about chronic and acute kidney disease, ocular diseases or both. However, some of the examined and reviewed studies were discarded because of population biases or intervention or deemed unfit.

Discussion

Renin-Angiotensin-Aldosterone System (RAAS)

RAAS is a systemic hormonal system implicated in arterial blood pressure regulation and electrolyte-fluid homeostasis. Remarkably, local RAAS were found in several organs and tissues, such as kidney and eye, with a potential role in ocular and kidney diseases, although the extent of their influence is yet to be determined. A pivotal role of RAAS in the progression of renal damage in proteinuric nephropathies has been widely described[6-9]. The RAAS inhibitors have reno-protective and antiproteinuric effects, due in part to improvement in renal hemodynamic, and in part to beneficial effects on endothelial function by oxidative stress, systemic inflammation, and fibrosis, as reported by another study[10] comparing RAAS inhibitors with other antihypertensive drugs. In fact, Angiotensin II (AngII) is able to stimulate intracellular signaling pathways, promoting enzymatic production of oxygen-derived free radicals (ROS), oxidation of LDL, endothelial impairment, matrix degradation and thrombosis. Recent evidence[7] has shown the existence of a "tissue" renin Angiotensin system in which local AngII biosynthesis may be activated by Renin and/or Angiotensinogen taken up from bloodstream. This tissue system is responsible for the vascular and cardiac remodeling action of RAAS and of the intrarenal dynamics. Local RAAS is involved in the maintenance of ocular fluid and electrolyte balance and in the angiogenesis process, which is fundamental for an adequate oxygenation of ocular cells. Indeed, RAAS system influences the blood flow in retina, iris and ciliary body, strictly regulating intraocular pressure (IOP) through changes in balance between aqueous humor (AqH) production and outflow. Angiotensin II (AngII) is a peptide hormone which increases systemic blood pressure by producing direct vasoconstriction. Moreover, it has prothrombotic potential, favouring platelets adhesion and aggregation, as well as through the stimulation of plasminogen activator inhibitors (PAI)-1 and PAI-2. Notably, AngII exerts an inflammatory effect, inducing endothelial dysfunction *via* reactive oxygen species production[11]. In addition,

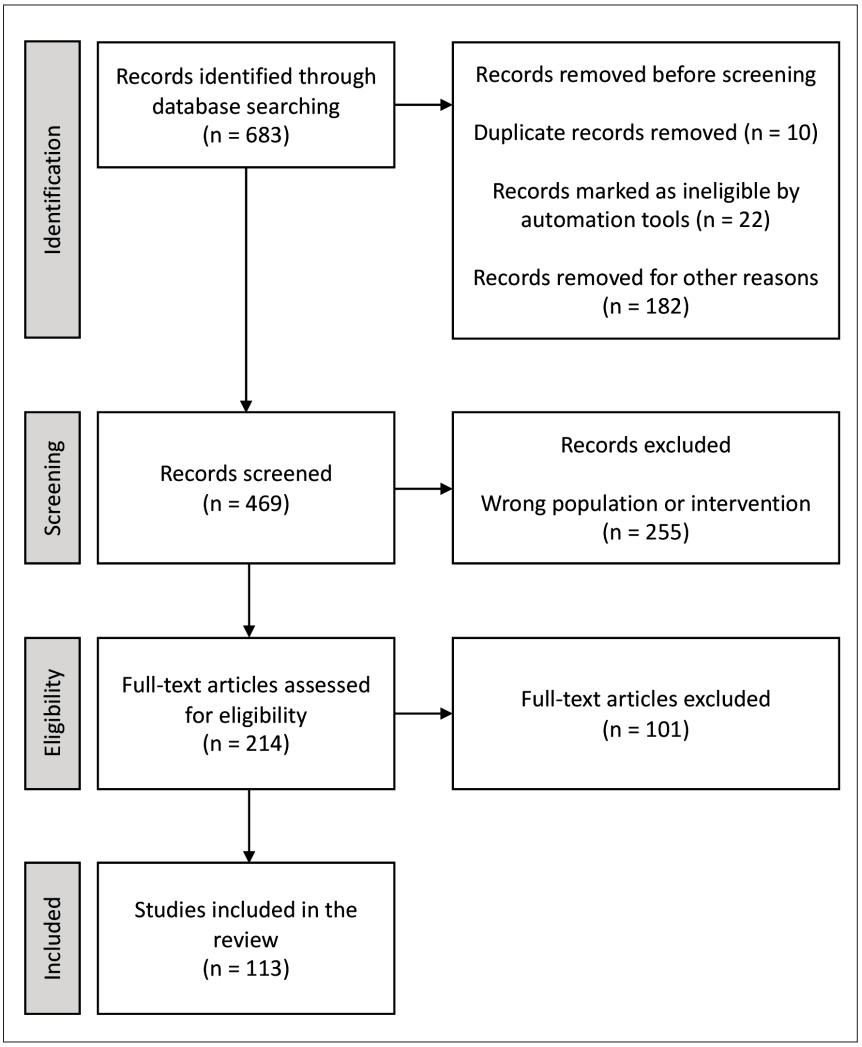

Figure 1. Results of the research.

RAAS stimulates the growth of cardiac cells and smooth muscle cells when hypertension, atherosclerosis, or endothelial damage are present, contributing not only to the development of renal and cardiovascular disease (CVD) but also to the pathogenesis of neural, adrenal, ocular and autoimmune diseases[12]. The AngII receptor Type 1 (AT1R)[13] is the primary RAAS receptor, and it is involved in retinal neovascularization with ischemia, in primary open angle glaucoma (POAG)[14] and in ocular sarcoidosis[15]. Furthermore, considering a local RAAS in mice lacrimal gland[16], we expected some benefits from the administration of Angiotensin-converting enzyme (ACE) inhibitors or ATR1 blocker (ARB) in patients suffering from dry eye. Nonetheless, in reviewing the three Diabetic REtinopathy Candesartan Trials (DIRECT), no protective effect was seen for dry eye syndrome[17]. Ramirez et al[13] showed that changes in regulation of ocular RAAS balance may exacerbate optic nerve damages with ocular hypertension in rabbits. Usui et al[14] demonstrated that AngII and AT1R were increased in experimental corneal neovascularization and the extent of neovascularization was reduced by ARB in this model. RAAS was shown to be involved in DR and glaucoma, which are responsible for the majority of irreversible vision losses in developed countries[17]. Glaucoma is a disease affecting 70 million people, glaucoma accounts for the second most common cause of blindness worldwide[1]. Elevated IOP is one of the major risk factors in glaucoma along with age, race, family history, thin cornea, oxidative stress and myopia. The pathophysiology of this disease is not completely clarified. Glaucoma is classified into primary and

secondary, according to aetiology and AqH dynamics. The presence of predisposing ocular or systemic diseases, such as uveitis, trauma, CKD and diabetes defines secondary glaucoma. Elevated IOP and decreased ocular perfusion pressure are risk factors for glaucoma development and progression[18]. Haemodialysis (HD) produces various effects on IOP, but exact mechanisms are not clear. In fact, the increased, decreased, as well as unchanged IOPs were described in course of HD in several case reports and studies[19]. It was hypothesized that impairments in osmotic pressure caused by increased urea concentration in the AqH may result in fluid overload in eye anterior chamber. Another plausible explanation to this condition could be the accumulation of toxic metabolites in the trabecular meshwork blocking AqH outflow, leading to eye pain, blurry vision and headaches, with significant morbidity for dialysis patients[20]. In addition, a greater risk for glaucoma in CKD patients may be due to a lower erythropoietin production with, consequently, reduced antiapoptotic, anti-inflammatory and neuroprotective activities[21]. RAAS may be implicated in glaucoma pathogenesis through its effects on AqH production and drainage[20]. For example, captopril and candesartan were shown to be neuroprotective against retinal ganglion cell loss in a rat chronic glaucoma model, suggesting a role of AngII in glaucomatous optic neuropathy pathogenesis. In the literature, results are conflicting as Singapore Malay Eye Study (SiMES)[22] reported that CKD is associated with higher IOP, while Wang et al[23] and Gao et al[24] found an association between CKD and glaucoma. It is well known that CKD is associated with traditional cardiovascular risk factors as dyslipidaemia, obesity, hypertension, smoke, diabetes, as well as non-traditional cardiovascular risk factors as inflammation, oxidative stress, anaemia and endothelial dysfunction (determining accelerated atherosclerosis)[6,25]. In recent years, many scholars[26] reported that same risk factors and pathogenic mechanisms lead to the most common eye diseases, including glaucoma, age-related macular degeneration (AMD), diabetic retinopathy (DR) and cataract. In addition, RAAS, playing a major role in kidney function regulation, was found to similarly influence retina components. Indeed, retina microvasculature, muller cells, ganglion cells, retinal pigment epithelium, lacrimal gland, conjunctiva and cornea are in close relation with RAAS modulation. Notably, elevated levels of pro-renin, renin, and AngII are present in eyes affected by non-proliferative and proliferative DR[27]. For this reason, RAAS is not only responsible for systemic fluid balance and blood pressure control through the kidney but it seems to contribute to the intraocular pressure (IOP) equilibrium as well as the maintenance of the vitreous humour in eyes[2,28]. Interestingly, mineral metabolism disorders, which are responsible for cardiovascular calcifications and increased cardiovascular mortality in CKD patients, contribute to the development of the most common age-related eye diseases, such as AMD and cataracts with metastatic calcification of both conjunctiva and cornea[29]. Retinal detachment is a rare manifestation of end stage renal disease (ESRD) patients undergoing HD, due to the increased permeability in choriocapillaris with consequent retinal fluid accumulation[30]. In addition, central cornea thickening is associated with CKD, likely caused by increased uraemia with toxic damage of corneal endothelium[28]. Abnormalities in mineral metabolism are frequently observed in CKD. The term Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) indicates a clinical syndrome which includes a variety of systemic bone disorders due to mineral, skeletal and vascular abnormalities. Changes in homeostatic mechanisms regulating serum calcium, phosphate, vitamin D and parathyroid hormone (PTH) concentrations lead to the development of CKD-MBD and renal osteodystrophy. Calcium balance is primarily mediated by PTH and calcitriol (1,25-dihydroxyvitamin D) through the regulation of intestinal absorption, bone formation and resorption as well as urinary excretion[31-34].

Phosphorous balance is also maintained by PTH with contributions from other factors, including Fibroblast Growth Factor 23 (FGF-23) and its cofactor Klotho, an aging-suppressor gene, which favours renal excretion of phosphorous. Klotho is a pathogenic factor in CKD progression *via* its influence on Vitamin D metabolism and phosphate as well as on vascular calcification and soft tissue[35]. Metastatic calcifications may additionally occur on the eyelid margins, conjunctiva and cornea, whereas conjunctival erythema, also known as "red eyes of uraemia", may be present when increased plasmatic phosphate levels induce corneal and conjunctival precipitation of calcium pyrophosphate or with Vitamin D deficiency[36]. Similarly, along with CKD progression, calcium and phosphorous may precipitate in the context of both intra-palpebral conjunctiva and Bowman's layer of the cornea, producing band keratopa-

thy[37]. Klotho family proteins include α-Klotho, β-Klotho, and γ-Klotho. Of these, α-Klotho is highly expressed in kidneys while γ-Klotho is expressed in both kidneys and eyes. In particular, Klotho was found in retina and plays an important role in retinal function, although mechanisms are not well known. Studies[38,39] on animal models showed that Klotho gene (KL) is a regulator of retinal pigment epithelium, therefore the decline in KL expression could favor the retinal pathology (AMD and cataract). Notably, other findings indicate that Klotho is deeply involved in myelination of the optic nerve and oligodendrocyte maturation[40].

Vitamin D is involved in the metabolism of several target tissues expressing vitamin D receptors, such as retina. Associations between low 25-hydroxyvitamin D (25OHD) concentrations and AMD[41] were documented. Indeed, recent evidence[42,43] suggests that vitamin D may be a protective factor in AMD pathogenesis through its anti-inflammatory, antiangiogenic and antifibrotic properties. Serum 25(OH)D suppresses the proliferation of immune cells and produces pro-inflammatory cytokines and inflammatory markers, including C-reactive protein, associated with AMD. The third National Health and Nutritional Examination Survey (NHANES III)[44] reported that high serum 25(OH)D levels are inversely associated with early AMD. Similarly, the Carotenoids in Age-related Eye Disease Study (CAREDS)[45], described that appropriate Vitamin D intake are associated with a lower risk for early AMD in women. Conversely, in Korean National Health and Nutrition Examination Survey[46], high blood levels of 25(OH)D were inversely associated with late AMD in men (but not in women). AMD is a degenerative disease and is characterized by extracellular lipofuscin deposition and retinal pigmentary changes in the macula, with the atrophy of retinal pigment epithelium and/or choroidal neovascularisation[47,48]. Many polymorphisms in complement factor H (CFH), located on chromosome 1q31, are associated with AMD and with kidney diseases, such as atypical haemolytic uremic syndrome, whereas C3 variants are associated with IgA nephropathy and the deficiency of both CFH and C3 is linked to type II membranoproliferative glomerulonephritis, which leads to kidney failure and early onset retinal drusen (structurally and compositionally identical to those occurring in AMD)[49]. CFH is a fluid-phase regulator of complement alternative pathway, suggesting that alternative pathway dysregulation is a common pathogenetic feature of these ocular and renal conditions as Blue Mountains Eye Study (BMES) confirmed[50]. AMD is the leading cause of blindness and visual loss in the world, frequently associated with CKD. Apolipoprotein E (APOE2) allele is linked to increased risk of both CKD and AMD *via* its effects on lipid metabolism which determines accelerated atherosclerosis that may aggravate the course of CKD contributing to the development of AMD[51]. Atherosclerosis of choroidal circulation with atheroma-like lipid deposits in Bruch's membrane were found in AMD and microvascular disease involving smaller vessels in both renal and retinal circulations may explain this association. Two large studies, NANHES III[52] and BMES[53], showed a three times increased risk of AMD in CKD patients. In the Beaver Dam Eye Study (BDES)[54], the elevated levels of serum cystatin C – known marker of renal disease – were associated with 15-year cumulative incidence of early AMD and exudative AMD. A possible explanation for the association between macular degeneration and renal damage is also based on secondary effects of RAAS upregulation. This pathogenetic axis relies on the triggering by pro(renin) receptor activation of the mitogen-activated protein kinase-extracellular signal-regulated protein kinases 1 and 2 (MAPK-ERK 1,2) cascade[55]. MAPK-ERK 1,2 is classically activated when pro-renin-renin axis is upregulated responding to extracellular stimuli as growth factors, cytokines, hormones, oxidative stress[56,57]. In fact, it has been described that MAPK-ERK 1,2 signalling is an important therapeutic target in macular degeneration, and it is also hyperactivated in proteinuric nephropathies as diabetic nephropathy. Also, diabetic retinopathy (DR) is the result of microvascular retinal changes and ischemia caused by diabetes, which may eventually lead patients to blindness. Hyperglycaemia causes intramural pericyte death and thickening of the basement membrane contributing to altered permeability of both the vascular walls and the blood-retinal barrier. At the first stage, named non-proliferative diabetic retinopathy, symptoms are not evident even if microaneurysms may be present with subsequent macular oedema, blurring, darkening or impaired vision[58]. Subsequently with progression to the stage of proliferative diabetic retinopathy, oxygen reduction in retina activates the generation of fragile blood neo-vessels, which grow along retina and produce alterations, including cotton wool spots, microvascu-

lar abnormalities, superficial retinal or vitreous haemorrhages and blurring, with significant visual loss. Fibrovascular proliferation may also result in tractional retinal detachment and, if the neovascularization process involves the angle of eye anterior chamber, neovascular glaucoma may occur. Strong epidemiological links between capillary abnormalities in retina and CKD likely suggest the involvement of long-lasting increased glucose concentrations and reduced capillary perfusion[59,60]. Main pathogenetic mechanisms of DR are oxidative stress and hyperglycaemia, followed by the production of AGEs, determining osteoblastic differentiation, retinal pericytes calcification and altered expression of proinflammatory cytokines. Interestingly, atherosclerosis, which is promoted by derangements in vasa vasorum of conductance vessels, has similarities with abnormalities in retina and kidney capillaries[61,62]. Associations between renal and ocular diseases in diabetes patients are well documented. The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR)[63] found a relation between microalbuminuria and/or proteinuria and DR, while other clinical studies[64,65] reported an association between CKD and DR. However, an association between CKD and retinopathy was also reported in general population and in non-diabetic individuals[64]. Indeed, retinal microvascular signs, such as retinal microaneurysms, haemorrhages, hard exudates and cotton wool spots were found to be related with CKD[65]. Other studies, such as the Atherosclerosis Risk in Communities Study (ARIC)[66] and the Cardiovascular Health Study (CHS)[67] showed that retinopathy is related to an increased risk for CKD and the NHANES[52] found that retinopathy is a strong predictor of mortality in CKD adult patients. Other authors[68] underline that cystatin C is an independent risk factor for DR, suggesting that retina and kidney likely share some risk factors for microvascular impairments secondary to diabetes mellitus, having RAAS as a major mediator[2]. Diabetes also predisposes to the onset of cataracts, in fact high levels of glucose react with proteins in the eye, producing by-products which deposit within the lens. Cataract is an opacity of the eye lens, causing partial or total blindness and treatment is conventionally represented by surgery. Cataract is classified into three main types: nuclear sclerotic, cortical and posterior subcapsular (PSC)[51]. Possible mechanisms explaining cataract formation in CKD patients are the oxidative stress and the chronic water accumulation with consequent development of osmotic cataract, due to the entrapment of urea in the lens. Advanced glycation end products (AGEs), a heterogenous group of structures produced by high oxidative stress or hyperglycaemia, cause cell apoptosis and proinflammatory cytokines generation, which contribute to cataract genesis leading to damages in kidney podocytes and endothelial cells. Once again, all described pathogenic mechanisms appear to be sustained by RAAS hyperactivation[53]. However, it is unclear whether cataract formation/progression is associated with CKD, as results from several studies are in contrast. Blue Mountains Eye Study (BMES) and Beaver Dam Eye Study (BDES)[50,52] did not find any association between CKD and cataracts although in the study BDES an association between these two diseases was found using cystatin C as a marker of renal damage[36]. Of note, cystatin C is currently considered the most reliable renal function parameter in general population[37,38]. Furthermore, increased risk of developing cataracts and recurrence after surgery were reported in kidney transplanted patients, associated with the use of highly-dose steroids and immunosuppressive drugs[39].

Congenital Oculo-Renal Syndromes

The kidneys and eyes share organogenesis and genetic pathways, including Pax2, Pax6, BMP7, LAMB2, TBMs, ALMS1 and WT1[2,4,69]. Mutations in these genes give rise to a wide variety of oculo-renal syndromes. Renal impairment in young patients should suggest a search for ocular abnormalities, in particular, if family history of concurrent ocular and renal diseases exists[70].

Alport syndrome, is a hereditary glomerulonephritis involving collagen α3α4α5 (IV). This condition results in sensorineural deafness, corneal erosions, anterior lenticonus and renal failure[71]. The collagen α3α4α5 (IV) is a major component of basement membrane kidney glomerular and cochlea[72].

Anderson-Fabry disease is a genetic lysosomal storage disease, recessive X-linked, with incomplete penetrance in heterozygous females. This genetic disorder causes a deficiency in the enzyme ***α-***galactosidase, with globotriaosylceramide accumulation (a-glycolipid) in vessels and various organs with relative insufficiency[73]. While males show severe symptoms, large range of phenotypes (from asymptomatic to severely symptomatic) are observed in women. Symptoms are diverse, including early cataract, strokes as well as hypertrophic left ventricle and renal failure[74].

At the ocular level, a verticillated cornea may be present (vortex keratopathy), clouding of corneas, conjunctival and retinal vascular abnormalities and anterior/posterior spoke-like cataract. Interestingly, this kind of clouding does not affect the vision. Kidney abnormalities include proteinuria, which is often the first sign of kidney involvement evolving to end-stage renal failure at the third-forth decade[75,76].

Papillorenal syndrome (or renalcoloboma) presents an autosomal dominant transmission, and it is characterized by renal hypo-dysplasia and optic nerve abnormalities with a Pax2 pathogenic variant. Renal failure is reported with ocular abnormalities, in particular optic nerve coloboma or dysplasia[77]. The diagnosis of renal coloboma syndrome is based on renal ultrasound examination and/or histologic examination, ophthalmologic findings, family history and molecular genetic testing. At present, Pax2 is the only gene whose pathogenic variants are known to cause renal coloboma syndrome[78-80].

Joubert Syndrome (JS) represents a group of congenital anomalies, including oculo-renal-cerebellar syndrome (ORC) or Hunter Jurenko syndrome, in which the molar tooth sign is pathognomonic. It consists in a midbrain-hindbrain malformation, with an incidence of 1/80,000 live births[81]. The neurological aspects associated with JS are ataxia, hypotonia, developmental delay, intellectual disability, neonatal breathing dysregulation and abnormal eye movements. This disease may present retinal dystrophy, hepatic fibrosis, nephronophthisis, and polydactyly[81]. JS may present with six different phenotypic: with ocular defect, with renal defect, with oculo-renal defects, with hepatic defect, with oro-facio-digital defects. JS presents an autosomal recessive inheritance, even if rare X-linked recessive cases have been reported. JS is a disease called "ciliopathies", caused by primary ciliary dysfunctions[82,83] and have been identified ten causative genes, all encoding for proteins of the primary cilium or the centrosome.

Oculo-renal-cerebellar syndrome (ORC syndrome or Hunter Jurenko syndrome) is an autosomal recessive pathology characterized by microcephaly, cerebellar agenesis, mental retardation, paraplegia, optic nerve atrophy and paresis of ocular muscles. Teeth malocclusion and sclerosing glomerulopathy with immune complex deposition were described in some cases[84].

Renal dysplasia-cataracts-blindness is an autosomal recessive disease presenting with microcornea, glaucoma, convulsions and polycystic kidneys (medullary cysts)[85,86].

Lowe syndrome or oculo-cerebro-renal-syndrome (OCRL) is an X-linked disease associated with multisystem impairments and characterized by congenital cataracts, hypotonia, cognitive developmental delay and renal complications. Muscle atrophy, hair loss, osteopenia, arthritis, cerebral atrophy with mental retardation and psychosis are also present, as well as renal tubular defect and ocular alterations, such as, glaucoma, megalocornea and buphthalmos. The diagnosis of OCRL is associated with a behavioural disturbance consisting of temper tantrums, stereotypy, stubbornness and obsessions/unusual preoccupations. This phenotype is not to be attributed to visual, motor and intellectual disabilities of OCRL because it may represent a specific effect of the OCRL gene dysfunction within the central nervous system[87-90].

WAGR(O) syndrome is a rare genetic syndrome in which affected children are predisposed to develop Wilms' tumour, Aniridia, Genitourinary anomalies or Gonadoblastoma, Retardation and/or Obesity, which give the acronym WAGR(O) syndrome[91]. The condition takes its origin from a deletion on chromosome 11 in the 11p13 region, resulting in different gene losses, including the PAX6 ocular development gene and the Wilms' tumour gene, which may also cause genitourinary anomalies. In addition, there is a deletion of the gene for brain-derived neurotrophic factor (BDNF), located on 11p14.1, probably associated with obesity and excessive eating in a subset of WAGR(O) patients. This pathology is characterized by congenital aniridia, cataracts and ptosis, while about 50% of patients develop Wilms' tumour. It can be transmitted in an autosomal dominant way.

Senior-Loken syndrome is a rare hereditary oculo-renal syndrome or "ciliopathy". It is an autosomal recessive disease, with a prevalence of 1/1.000.00[92]. This condition was reported for the first time in 1961, as a combination of nephronophthisis and retinal degeneration in children. In Senior-Loken syndrome, retinal lesions are variable, from amaurosis to retinitis pigmentosa. Leber's congenital amaurosis is a severe form of retinal dystrophy, leading to blindness in infancy, nystagmus and a diffuse atypical retinal pigmentation and pallor of the optic disc. Retinitis pigmentosa is characterized by bone spiculae pigmentation of the retina and initial manifestations are night blindness which slowly progresses

to daytime blindness[93,94]. Other ocular findings are cataract, Coat's disease, and keratoconus. Related renal disorders are identical to those seen in isolated nephronophthisis: polyuria, polydipsia and impaired concentrating ability are the earliest signs. It is usually insidious in onset, progressively leading to end-stage renal disease at a young age. The main histological findings are tubular atrophy, interstitial fibrosis, thickening and lamellation of the tubular basement membrane[95].

Pierson syndrome is a severe oculo-renal syndrome, autosomal recessive, with congenital nephrotic syndrome and complex ocular abnormalities. This condition is caused by mutations in the LAMB2 gene with loss of function of laminin β2, an essential component of the glomerular and other basement membranes. Different laminin isoforms are present in all basement membranes and play critical roles for adhesion, differentiation, migration and maintenance of functional integrity of adjacent cells. The ocular lesions are microcoria, abnormalities of the lens (lenticonus posterior), cornea and retina, while kidney disease may start prenatally with renal failure[96].

Congenital nephrotic syndrome (CNS) constitutes a heterogeneous group of conditions having in common the disruption of normal glomerular permeability and selectivity. At present, molecular causes of CNS are known to be mutations of genes encoding for nephrin in Finnish type CNS and podocin in autosomal recessive steroid-resistant nephrotic syndrome with these proteins playing essential roles in the formation of the slit diaphragm[97]. Moreover, autosomal dominant WT1 mutations are able to cause CNS and diffuse mesangial sclerosis in patients with Denys-Drash syndrome. Furthermore, Matejas et al[95] delineated a new autosomal recessive entity comprising severe CNS with diffuse mesangial sclerosis and distinct eye abnormalities clinically characterized by microcoria, hypoplasia of iris and ciliary body, lenticonus posterior and corneal and retinal anomalies, which are associated with human laminin β2 deficiency. Some authors[97] hypothesized that it could be a variant form of Pierson syndrome.

Alström syndrome is a rare (prevalence is 1/1.000.000) autosomal recessive ciliopathy caused by mutations in ALMS1, a ciliary protein characterized by cone-rod dystrophy in infancy, accompanied by hearing loss, obesity, insulin resistance, type 2 diabetes, hypertriglyceridemia, short stature, dilated cardiomyopathy as well as renal, pulmonary and hepatic dysfunction[98,99].

Sensenbrenner syndrome or cranio-ectodermal dysplasia is an extremely rare autosomal recessive oculo-renal syndrome (12 cases reported in the literature) and is characterized by ocular and renal involvement associated with cranio-ectodermal abnormalities[100].

Mutations in three Bardet-Biedl syndrome (BBS)-related genes (BBS2, BBS4, and BBS6) were identified in several cases of Meckel-Gruber syndrome[101]. Meckel-Gruber syndrome is usually lethal and typically presents occipital encephalocele, postaxial polydactyly and polycystic kidneys. Associated abnormalities include orofacial clefting, genital anomalies, CNS malformations and liver fibrosis. Pulmonary hypoplasia is the leading cause of death. Inheritance is autosomal recessive[102].

The Bardet-Biedl syndrome (BBS) is a ciliopathic human genetic disorder mainly characterized by rod-cone dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotropic hypogonadism, complex female genitourinary malformations, and renal abnormalities. The first case was reported in South London in 1866. BBS is a pleiotropic disorder with variable expressivity and a wide clinical spectrum observed both within and between families[103]. Renal manifestations include renal dysplasia with renal parenchyma malformations, lower and upper urinary tract malformations and cystic tubular disease (e.g., nephronophthisis), often presenting with polyuria, polydipsia and urinary concentrating defects. Less frequently, glomerular diseases are present, such as focal segmental glomerulosclerosis. Reported eye abnormalities are strabismus, cataracts and astigmatism among others[104]. There is significant phenotypic and molecular overlap between BBS and other ciliopathies and mutations in genes that cause this disease could also lead to other distinct ciliopathy syndromes.

McKusick-Kaufman syndrome (MKKS) with mutations in MKKS gene (BBS6) presents clinical and molecular overlap with BBS, hence, it has to be considered as a part of its spectrum. In fact, mutations in Meckel-Gruber syndrome-related genes MKS1, MKS3 and CEP290 could cause BBS, thereby demonstrating phenotypic overlap between the two disorders. Similarly, JS and Senior-Loken syndromes may share similar clinical features with BBS[105].

Gene mapping and mutation analysis allowed new evidence to be found in oculo-renal syndrome pathogenesis and more accurate classifi-

cations of genetically heterogeneous diseases are available. Several malformations were matched to single developmental genes which share complete DNA sequences, such as the homeobox. These disease/gene matches include the oculo-renal syndrome and PAX2; aniridia and PAX6; Rieger syndrome and RIEG1/PITX2; cyclopia and Sonic hedgehog; cone-rod dystrophy, Leber's congenital amaurosis and CRX; recessive septo-optic dysplasia and HESX1[69].

Tubulointerstitial Nephritis with Uveitis (Tinu Syndrome)

The entity of tubulointerstitial nephritis with uveitis (TINU syndrome), known as renal-ocular syndrome, is an unusual and underdiagnosed cause of acute interstitial nephritis, firstly described by Dobrin et al[106] in 1975. The interstitial nephritis may precede, follow, or develop together with uveitis. More than 250 cases have been reported worldwide, mostly in ophthalmology and paediatric literatures. The mean age of presentation is 15 years (range is 9 to 74 years) and there is a female preponderance[107]. Currently, pathogenesis of TINU syndrome is unclear. Abed et al[108] reported, for the first time, the presence of autoantibodies recognizing a common antigen in tubular and uveal cells in a patient suffering from TINU syndrome. Indeed, specific basement membrane antigens were described to be immunogenic in animal models of acute interstitial nephritis and patients with acute interstitial nephritis may express antibodies against tubular basement membranes[109,110]. Clinical presentation is variable and was comprehensively reviewed by Mandeville et al[111] and Mackensen et al[112]. The most common early symptoms are fever, weight loss, weakening, fatigue and malaise. Other systemic symptoms include anorexia, abdominal or flank pain, arthralgias, myalgias and headache[113].

TINU syndrome causes renal manifestations, such as nocturia and polyuria, sterile and asymptomatic pyuria, microhaematuria, sub-nephrotic proteinuria and multiple renal tubular defects, including renal glycosuria and impaired renal function. The proximal tubule is frequently affected by this syndrome, resulting in proteinuria and normoglycemic glycosuria and, occasionally, a full-blown Fanconi syndrome with renal loss of glucose, phosphorous, bicarbonate and aminoacids[114]. Ocular impairments include blurred vision, photophobia, foreign body sensation, floaters, itching dry eyes, superficial keratitis, posterior synechiae, cataract and high IOP, with bilateral anterior uveitis being present in 80% of patients. Nevertheless, posterior or panuveitis may occur in 20% of patients, with eye pain and redness as well as visual impairment. Rarely, TINU syndrome may be associated with retinit and distal tubular dysfunctions, including distal renal tubular acidosis and nephrogenic diabetes insipidus. Generally, ocular disease and renal disease are independent, presenting different courses. The diagnosis of TINU syndrome is *per exclusionem*, based on the presence of uveitis and findings of acute interstitial nephritis in the absence of other diseases which are able to explain such alterations. Sjogren's syndrome, sarcoidosis, tuberculosis and toxoplasmosis should be included in the differential diagnosis. β2-microglobulin (marker of interstitial nephritis) and Krebs von den Lunge-6 (KL-6) protein have been reported as two potential diagnostic markers in TINU syndrome. In fact, KL-6 is significantly elevated in TINU patients compared to patients with other causes of uveitis. In addition, distal tubules of TINU patients stained strongly with anti-KL-6 antibody on kidney biopsies, suggesting that elevated KL-6 levels reflect the underlying renal lesion[115]. For these reasons, serum KL-6 levels may be a valuable tool in the diagnosis and the follow-up of patients affected by this syndrome. Similarly, urinary β2-microglobulinanalysis and human leukocyte antigen (HLA) typing are helpful in diagnosing this condition. Moreover, an association between TINU syndrome and HLA-DRB1 was reported. With respect to renal impairments, acute interstitial nephritis in the context of TINU syndrome may resolve spontaneously whereas systemic corticosteroids are reserved for patients with persistent or progressive renal failure. On the other hand, uveitis is treated locally with steroids and cycloplegic agents. There is a lack of prospective, randomized trials comparing steroid therapy with placebo or addressing the optimum dose and duration of treatment. Glucocorticosteroids and immunosuppressive drugs are usually administered. Immunomodulatory chemotherapeutic agents include azathioprine, methotrexate, cyclosporine, cyclophosphamide and mycophenolate mofetil. Their use is recommended in steroid-resistant or steroid-dependent patients or in those with systemic toxicity from this class of drugs[116].

Vasculitis and Ocular Disease

Retinal vasculitis is an eye inflammatory condition involving retinal vessels. It is characterized by intraocular inflammation and active

vascular and perivascular phlogistic infiltrate. Its occurrence is variable as it may present as an isolated idiopathic condition or as a complication of infective or neoplastic disorders. Retinal vasculitis may be also associated with systemic inflammatory disease[117]. In fact, retinal vessels may be involved in secondary systemic vasculitis, including systemic lupus erythematosus (SLE), or in primary systemic vasculitis, such as granulomatosis with polyangiitis, microscopic polyangiitis, granulomatous polyangiitis with eosinophilia (Churg-Strauss), Behçet disease or cryoglobulinemia, the latter usually being characterized by obstructive vasculitis with micro-thrombosis[118,119].

Conclusions

In conclusion, there is significant evidence of the association between ocular and renal diseases with a central role played by the RAAS. The data present in literature indicate that it may be useful to screen CKD patients for associated ocular diseases, such as cataract, glaucoma, RD and AMD. A comprehensive clinical evaluation of patients with CKD or ESRD should include examination of the external eye and direct ophthalmoscopy. Regular eye exams are strongly recommended in patients with proteinuria.

Renal impairments in young individuals should suggest a search for ocular diseases such as TUNA syndrome or oculo-renal syndrome, in particular if concurrent ocular and renal diseases are present in the family history. Furthermore, eye functions and related vascularization are reliably evaluated through non-invasive and cost-effective tests. These recommendations may be useful in order to early identify both ocular and renal diseases and evaluate the need for a multidisciplinary approach and for potential multi-target therapeutic strategies.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Authors' Contribution

Conceptualization, S.L. and A.M.; methodology, R.C and A.M.P.; software, F.E. and D.B.; validation, S.L. and M.S.; formal analysis, S.M. and P.M.; investigation, A.P.M. and F.T.; resources, S.L. and M.S.; data curation, D.B.; writing—original draft preparation, S.L. and M.S.; writing—review and editing, S.L. and R.C.; visualization, F.T. and P.M.; supervision, S.M. and P.M.; project administration, D.B and F.E.; funding acquisition, S.M. All authors have read and agreed to the published version of the manuscript, please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

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