Kidney and eye are inextricably linked in many diseases, both common and esoteric. Furthermore, patients with renal disease may require specific ophthalmic management. The best example in the developed world of the frequent need for clinical input from both specialties is in the care of diabetic patients who may develop nephropathy and retinopathy. Both of these complications may be asymptomatic initially, yet could benefit from active intervention from the respective clinical departments to delay, and even halt, progressive disease and the potentially devastating situations of renal failure and blindness. Microalbuminuria is associated with an increased risk of proliferative retinopathy and blindness [1]. Similarly, the association between high blood pressure and renal and retinal dysfunction is well recognized [2].

Conditions such as systemic lupus erythematosus frequently have renal involvement and they may present to the ophthalmologist with retinal haemorrhages, cotton wool spots and disc swelling unrelated to hypertension [3]; Wegener’s granulomatosis may result in a necrotizing glomerulonephritis and ocular inflammation of varying degrees of severity from mild conjunctivitis or episcleritis to severe necrotizing scleritis [4]. Less well-known associations between the eye and the kidney [5] include such conditions as Alport’s syndrome with lenticonus and the recognized abnormalities of Senior–Loken syndrome and Bardet–Ménetrier–Biedl syndrome, both of which can be associated with retinitis pigmentosa and renal dysfunction. The CHARGE syndrome (eye Coloboma, Heart abnormalities, choral Atresia, Retarded growth, Genitourinary abnormalities and Ear anomalies) and the phacomatoses including Sturge-Weber syndrome (choroidal haemangiomas, facial port wine staining and renal haemangiomas) and von Hippel disease (cerebellar haemangioblastomas, choroidal angiomas, phaeochromocytomas and renal carcinomas) are also well described. The conditions mentioned above do not constitute an exhaustive list of even some relatively common diseases.

More recently, a previously unreported renal–retinal association has been observed and investigated. The renal part of this disorder has been recognized for decades. The finding of electron-dense deposits in a ribbon-like arrangement within the lamina densa of the glomerular basement membrane, along with characteristic light microscopy and immunofluorescent findings, equates to the nephropathy known as mesangiocapillary (or membranoproliferative) glomerulonephritis type II or dense-deposit disease (DDD). The characteristic association of partial lipodystrophy (PLD) with low serum C3 levels, often accompanied by a circulating C3 nephritic factor or abnormality of complement factor H, is clearly recognized [6].

However, until <20 years ago, despite the nephrologist’s ready access to the ophthalmoscope, the retinal changes associated with DDD were unrecorded. Duvall-Young et al. [7] initially described drusen-like deposits and changes in the retinal pigment epithelium (RPE) in the fundus of a patient with PLD and mesangiocapillary glomerulonephritis (MCGN) type II (Figure 1). These lesions are similar to those seen in age-related macular degeneration (AMD). Patients with AMD may present with drusen (extracellular deposits beneath the RPE) and/or changes in the RPE and can go on to develop geographic atrophy (dry AMD) or choroidal neovascularization (CNV) [8]. Drusen in AMD are typically seen in patients over the age of 50 [9], in DDD, drusen may be seen in patients much younger [10]. After the original histological description in an enucleated eye and retrospective fundoscopy in the patient’s remaining eye, a series of patients were reported with PLD and DDD; all patients with nephrological features had the characteristic findings on fundoscopy [11]. These changes were not seen in patients with other types of glomerulonephritis. Intriguingly, they were also absent from a patient with PLD but no overt renal disease. Similar findings have since been reported from other centres [12,13].

Mullins and his colleagues [14] compared drusen in AMD with similar lesions found in patients with post-streptococcal and membranous glomerulonephritis (PSGN). However, although the individuals with PSGN were younger (45 and 49 years) than those with AMD, at present there is no established link with drusen seen in DDD and any other type of glomerulonephritis.

Vitreous fluorophotometry is not commonly used in day-to-day clinical practice, but patients with DDD and drusen-like deposits had increased penetration ratios of fluorescence in the posterior vitreous [15]. This is also reported in diabetes and retinitis pigmentosa and suggests a breakdown of the blood–retinal barrier. In addition, electrophysiological studies, such as the electro-oculogram
that measures the difference in standing potential between the cornea and the retina, have been documented as abnormal in these patients, suggesting a widespread RPE dysfunction [16].

A recent review of the original cohort of patients with biopsy-proven DDD, over 10 years after the presence of drusen was first noted, found that visual acuity in the four surviving patients remained unchanged [17]. On clinical examination and fluorescein angiography, there had been no significant progression in the retinopathy and none of the patients had developed signs of choroidal neovascularization (CNV). This is in contrast to patients with age-related changes who are at a 50% risk of progression to CNV over 5 years if they have drusen and RPE changes, and a 25% risk if they have drusen alone [18]. This suggests that factors other than just drusen may contribute to the development of CNV. Furthermore, renal transplantation does not appear to have affected the progression of retinopathy in these patients; three patients had undergone renal transplantation [17]. Other reports have come to a different conclusion [19].

In a recently published study [20], using lectins as a tool, the saccharide composition of drusen has been compared in the ageing eye with an eye from a patient with presumed DDD. (She had presented with a nephrotic syndrome, had PLD with a low serum C3 and circulating C3 nephritic factor; she was therefore presumed to have DDD although a renal biopsy was never undertaken.) Lectins are glycoproteins with a high affinity for specific saccharide units [21]. As the lectin-binding specificities are known, the saccharide composition of drusen can be inferred. The glycosylation pattern was studied using a panel of 20 biotinylated lectins known to bind the saccharides commonly present in humans (Figure 2). The similar lectin-binding pattern of drusen in both the ageing eye and in the (presumed) DDD eye in this study suggests a common pathway in the pathogenesis of drusen.

The saccharide composition of drusen both in AMD and (presumed) DDD has also been compared with the glomerular-dense deposits from three patients with biopsy-proven DDD; striking similarities have been found [22]. Both conditions, AMD and DDD, are associated with complement factor H (CFH) abnormalities [23]. CFH is an important regulator of the alternate pathway of the complement system. It acts in the fluid phase and has regulatory properties on the cell surface. CFH is mainly synthesised by the liver but is also produced locally by the RPE where it protects the tissue from the effects of inflammation and complement activation [24]. It has been shown that a missense mutation in factor H gene confers a higher risk for soft drusen formation and both types of advanced AMD, neovascular [25] and geographic atrophy [26].

The GBM does not have membrane-bound regulators and is dependent on the absorption of fluid phase regulators such as CFH from plasma. Patients who lack factor H (FH) express a defective factor H protein or have an inhibitor of FH that may present with DDD [6]. As mentioned above, DDD is also associated with the presence of C3 nephritic factor, an antibody directed against C3 convertase of the alternate pathway that prolongs the half-life of C3 10-fold [27]. Therefore, in both AMD and DDD, the complement pathway may be ‘overactive’ which may interfere with the ability of the body to recognize foreign pathogens. It can be envisaged that the resulting inflammatory response leads to local tissue damage in susceptible areas such as the retina and the glomeruli. The anatomical similarities between the renal glomerulus and the RPE–Bruch’s membrane–choriocapillaris complex [7,22] may make both prone to respond in a similar manner to these pathological insults. Alternatively, the activation of complement, the presence of which has been demonstrated in drusen [28] and in dense deposits [29], can initiate cell lysis and breakdown of the blood–retinal barrier function.

As a result, serum glycoproteins such as amyloid P and immunoglobulins may be deposited, resulting in the formation of drusen in the eye and possibly the characteristic dense deposits in the kidney. Further studies to determine the specific nature of the glycoproteins may be necessary to elucidate this enigma.

The overt message of this editorial, then, is to remind the nephrological community of the association between DDD and retinal drusen and report on the advances in understanding the composition of the abnormally deposited material. So, what is the subliminal message? It is that even in the age of the human genome, metabolomics, genomics and proteomics, clinical nephrologists should
continue to take a good look at the retina, and perhaps other anatomical structures, of their patients—who knows what might be seen and where it may lead?

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