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REVIEW

The role of osteopontin in kidney diseases

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Abstract

Background Osteopontin (OPN) is a pleiotropic glycoprotein expressed in various cell types in animals and in humans, including bone, immune, smooth muscle, epithelial and endothelial cells. Moreover, OPN is found in kidneys (in the thick ascending limbs of the loop of Henle and in distal nephrons) and urine. The protein plays an important role in mineralization and bone resorption. In addition, OPN is involved in the regulation of immunity and inflammation, angiogenesis and apoptosis. It was demonstrated that OPN and some OPN gene polymorphic variants are associated with the pathogenesis and progression of multiple disorders, such as cancer, autoimmune, neurodegenerative and cardiovascular diseases. Moreover, recent studies suggested that OPN is associated with the pathogenesis of renal failure.

Methods In this review, I briefly discussed the role of OPN and its gene polymorphisms in kidney physiology, as well as in various kidney diseases.

Findings and Conclusion Most studies reported that OPN expression is elevated in urolithiasis, and also in acute and chronic kidney diseases, and in renal allograft dysfunction. Moreover, it was demonstrated that polymorphic variants of the OPN gene may be associated with renal failure. However, some reports suggested that OPN is essential for tubulogenesis, and that it inhibits calcium oxalate crystal formation and retention, nitric oxide synthesis, cell apoptosis and promotes cell regeneration. Thus, further studies are required to fully understand the role of OPN in kidney physiology and pathology. Eventually, these studies may result in the identification of OPN as a valuable marker for renal dysfunction prognosis and treatment.

Keywords Kidney · Kidney disease · Marker · Osteopontin

Introduction

Osteopontin (OPN) is a secreted phosphoprotein 1 (SPP-1), also known as early T lymphocyte activation-1 (Eta-1) or uroprotein [1–3]. OPN is a member of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family proteins, identified in 1985 as a major sialoprotein of bone where it is involved in biomineralization and remodeling [1–5]. OPN is also expressed in a variety of cells which are not related to bone metabolism, such as activated T cells, macrophages, natural killer (NK) cells, neutrophils, dendritic cells, smooth muscle, epithelial and endothelial cells, neurons, adipocytes, Kupffer cells and many others [6]. Moreover, OPN is present in kidneys and secreted into urine. OPN is a pleiotropic glycoprotein with diverse physiological and pathological functions. A number of studies demonstrated that this protein enhances the adhesion of osteoblasts and osteoclasts to bone matrix, and stimulates osteoclasts activity (via interactions with one of the OPN receptors—αvβ3integrin), which results in bone resorption [6, 7]. In addition, OPN secreted by osseous cells regulates functions of monocyte-derived cells, including phagocytic macrophages, which are involved in the processes of resorption. Moreover, it was revealed that OPN inhibits hydroxyapatite accumulation and crystal growth [8]. In line with these data, OPN is considered to be an inhibitor of biomineralization.

In recent years, multiple studies indicated that OPN is not only associated with bone metabolism, but also acts as an regulator of immune response. This protein is chemotactic for macrophages, dendritic cells and T cells, stimulates antibody production by B cells, regulates nitric oxide production and increases interleukin (IL)-17 production by T helper (Th) 17 cells. In addition, OPN enhances the

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Th1-mediated inflammatory proces [6, 9, 10] and plays a key role in apoptosis, angiogenesis and cancer progression [6, 11]. Numerous reports suggested that OPN is a valuable marker of autoimmune disorders, including systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, asthma and liver diseases [11–18]. Studies performed in recent years provided new insights into the role of OPN in the pathogenesis of various kidney diseases.

Osteopontin: gene, structure, signaling

The human OPN gene is mapped on the chromosome 4 (4q21–4q25) and contains seven exons and six introns [6, 19]. The 5′-untranslated (5′-UTR) region contains exon 1. The 3′-UTR region consists of the last part of exon 7 and includes three polyadenylation sequences. Exons 2–7 contain coding sequences. Exon 7 contains the arg-gly-asp (RGD) motif and the central thrombin cleavage site [19]. Structurally, OPN protein, contains two fragments: N-terminal (which includes integrin receptor binding zones) and C-terminal (which binds two heparin molecules and CD44 variants) [20]. OPN protein is composed of 314 amino acids. The molecular weight of OPN is between 41 and 75 kDa [19], which can be explained by multiple post-translational modifications, including serine and threonine phosphorylation, O-linked glycosylation, transglutamination, sialylation and tyrosine sulfation [21–24]. These modifications affect OPN size and its functions. To date, three forms of human OPN transcript were identified: OPN-a (the full-length), OPN-b (without exon 5) and OPN-c (without exon 4) [25]. OPN was first described as a secreted protein (sOPN), however, later studies demonstrated that the protein can be produced intracellularly (iOPN) in dendritic cells and macrophages [26]. iOPN is the result of alternative initiation of transcription, and interacts with myeloid differentiation primary response protein 88 (MyD88), thereby negatively regulating Toll-like-mediated immune response [26, 27].

OPN contains several domains which are responsible for interactions with multiple ligands (surface receptors, intracellular signaling particles, calcium and heparin). The aspartate domain binds hydroxyapatite [28]. The RGD sequence binds αvβ3, αvβ1, αvβ5 and α5β integrins. The SVVYGLR sequence binds α9β1 and α1β1 integrins [29]. Interactions with various cells via integrins are associated with rapid nuclear factor kappa B (NFκB) activation [30, 31]. Heparin binding domain mediates interactions with CD44v3 receptor. Signaling via CD44, in turn, modulates T cell chemotaxis, adhesion and IL-10 production by macrophages [32].

Osteopontin in kidney physiology

In humans, OPN is expressed in both fetal and mature renal tissue. In the fetal kidney, OPN can be found in renal tubular epithelium, as well as in the ureteric buds and in some interstitial cells. Its expression is upregulated after 75–80 days of gestation [33]. In the normal adult kidney, OPN is expressed by the thick ascending limb of the loops of Henle. Moreover, OPN expression is observed in collecting duct epithelium, where it correlates with the number of macrophages in the tissue [33, 34]. Multiple factors increase OPN production, including hormones (parathyroid hormone, PTH), calcitriol, calcium, phosphate, cytokines (tumor necrosis factor alpha, TNF-α), high-protein and high-fat diet. In contrast, estrogen, estradiol and progesteron are factors which inhibit OPN expression [34].

As described earlier, OPN interacts with multiple surface proteins, which are localized in various tissues and organs, including human kidneys [28–32]. The αvβ3 and αvβ5 integrins are found in Bowman's capsule and glomerular epithelial cells. β1 integrin is expressed in glomerular and tubular epithelial cells, Bowman's capsule, as well as vascular epithelium [34, 35]. The CD44 OPN receptor is expressed in a distal tubule [36].

The role of OPN in normal human kidney is not fully understood, but some studies suggested that the protein is essential for tubulogenesis [36–38]. However, it was also demonstrated that in OPN-deficient mice kidneys develop without any abnormalities [39]. Thus, further research in this field is needed.

Multiple studies provided new insights into the protective role of OPN in renal stone formation. It was found that OPN is able to inhibit the nucleation, growth, and aggregation of calcium oxalate crystals in vitro [40–45]. Moreover, it was demonstrated that patients with kidney stones have lower urinary excretion of OPN than healthy controls [45–49]. In addition, it was suggested that some functional polymorphisms in the OPN gene may predispose to urolithiasis formation [47, 50]. Therefore, it was proposed that single nucleotide polymorphism (SNiP) genotyping, together with determination of urinary OPN concentration, could be helpful in detection of kidney stones formation. However, in contrast to these reports, some studies revealed that urine OPN levels did not differ between healthy controls and patients with renal stones [51]. In addition, some in vitro studies suggested that OPN stimulates deposition and adhesion of renal stones [52–54]. Therefore, more research in this field is necessary for further elucidation of OPN role in the kidney stone formation.

Osteopontin in kidney diseases

Numerous studies showed that OPN mRNA and protein expression is increased in animal models of renal diseases, including stone formation, tubulointerstitial nephritis, glomerulonephritis, acute ischemic renal injury, interstitial inflammation and fibrosis, hydronephrosis, chronic cyclosporine-induced nephropathy, lupus nephritis and many others [54–71]. All these reports showed that high OPN expression correlates significantly with proteinuria, reduction of creatinine clearance, fibrosis and macrophage and T-cell infiltration.

Several studies performed in humans also reported that OPN could be a promising biomarker for various kidney diseases.

Kidney cancer

Kidney cancer is one of the most common types of cancer worldwide [72]. A number of studies suggested that OPN plays an important role in the growth and invasion of human renal cancer (reviewed by Funakoshi et al. [73]). Liu et al. [74] found that OPN is associated with increased proliferation and invasion of human renal cancer ACHN cells. In another study Matusan et al. [75] analyzed the expression of OPN in normal renal tissue and in clear cell renal cell carcinomas (CRCCs). The group demonstrated a strong correlation between protein overexpression and progression of CRCC. Furthermore, Rabjerg et al. [76] showed that high OPN expression is associated with poor progression-free survival in patients with CRCC.

It is likely that OPN promotes carcinogenesis and metastasis by induction of matrix metalloproteinase (MMP)—2, 3 and urokinase-type plasminogen activator (uPA) [11]. In addition, OPN inhibits apoptosis of cancer cells, promotes formation of new blood vessels and enhances macrophage infiltration [65, 71, 77]. Moreover, OPN can bind to transformed cells via RGD domain and thus can enhance their survival by inhibition of nitric oxide synthesis [78].

Immunoglobulin A nephropathy

Immunoglobulin A nephropathy (IgAN) is also known as synpharyngitic glomerulonephritis or Berger's disease. The most characteristic feature of this disorder is deposition of IgA in the glomerular mesangium [79]. The pathogenesis of IgAN is not fully explained. There are reports suggesting that OPN is involved in the development of this nephropathy, however, some studies yielded opposite results. A study of Sano et al. [80] revealed that OPN and CD44 receptor are highly expressed in tubular cells and interstitial infiltrating cells in areas of tubulointerstitial injury. Another study conducted in children with IgAN showed that the urine level of OPN was higher in patients than in healthy controls and was associated with high OPN/creatinine ratio [81]. Moreover, it was found that during IgAN development, increased OPN mRNA expression correlates with macrophage infiltration [82]. Gang et al. [83] reported that the N-half (trombin cleaved) OPN in urine of IgAN patients correlates with albuminuria. In another study, Kaimori et al. [84] analyzed urinary OPN excretion and OPN mRNA expression in proximal tubules in a group of IgAN patients. However, no association between OPN mRNA expression or OPN urine level and clinical data or pathological findings in glomeruli and tubulointerstitial regions was found. Furthermore, the concentration of two forms of OPN (full and N-half) in plasma and urine of IgAN patients and healthy controls was measured in a study of Kitagori et al. [85], but the authors found no significant difference in OPN levels between these two groups.

Data about the role of OPN in IgAN are contradictory. Therefore, further studies are necessary to elucidate OPN's role in this disease pathogenesis and clinical course.

Minimal change disease and focal and segmental glomerulosclerosis

Minimal change disease (MCD) is one of the most prevalent glomerular diseases in children [86]. It is characterized by selective proteinuria, hypoalbuminemia, hypercholesterolemia, and absence of glomerular immune deposits or cellular infiltrates in the biopsy. In MCD, the podocytes injury is observed [87]. The disease may evolve to focal and segmental glomerulosclerosis (FSGS). FSGS affects both children and adults and can be distinguished from MCD by steroid resistance, non-selective proteinuria, loss of podocytes number and progressive kidney damage [87]. Despite intensive research, the pathogenesis of MCD and FSGS is only partly understood. The association between OPN and these pathologies was investigated in several studies. Wasilewska et al. [81] demonstrated that urinary OPN/creatinine ratio in children with MCD and FSGS was higher than in the control group. Moreover, in FSGS patients, the ratio was higher than in MCD group and correlated with interstitial changes and mesangial expansion. In another study, a positive correlation of OPN mRNA expression in proximal tubules and urinary OPN excretion was shown in MCD patients [83]. In contrast, Kitagori et al. [85] demonstrated that there was no significant difference in urine OPN levels between MCD patients and healthy controls. However, the plasma OPN concentration was higher in the MCD group. Gang et al. [83] obtained opposite results and showed that urinary excretion of OPN in

patients with MCD did not differ significantly from healthy controls. Furthermore, the group analyzed the size of urine OPN fragments. A 34-kD fragment (N-half) was detected in MCD patients, but not in controls. The N-half OPN in urine correlated positively with albuminuria. In another study by Mezzano et al., no OPN expression in renal biopsy specimens from MCD patients was found [88].

Due to few studies, evidence for the role of OPN in the pathogenesis of MCD and FSGS is still inconclusive. Therefore, further analyses are necessary.

Membranous glomerulonephritis

Membranous glomerulonephritis (MGN) is the second most common (after FSGS) cause of nephrotic syndrome in adults. It is a slowly progressive disease of the kidneys [89]. In the MGN course, proteinuria and edema (with or without renal failure) are observed, however, some patients may be asymptomatic. The primary MGN is a disorder of autoimmune orgin, but the disease can be also secondary, associated with tumors, infectious or autoimmune diseases and drugs [90]. The pathogenesis of MGN is associated with formation of immune complexes in subepithelial sites, which initiates complement activation and glomerular damage [91]. In most cases, deposits develop as a result of binding of circulating antibodies to endogenous antigens expressed on podocytes, or circulating pathogenic antigens planted in the subepithelial sites. Moreover, it is possible that autoantibodies bind to podocyte membrane antigens and lead to subepithelial deposition of immune complexes [92]. However, the autoimmune basis of MGN is not fully understood. A wide spectrum of immune mediators is currently investigated in the context of MGN. One of them is OPN. Two recent studies demonstrated that patients with progressive and nonprogressive MGN had an overexpression of OPN in the proximal tubules [88, 93]. Moreover, a strong correlation between the mRNA and the protein was found. High expression of OPN in kidneys was associated with increased infiltration of macrophages, as well as $CD4^+$ and $CD8^+$ T cells. In addition, OPN activates NFκB, which results in increased expression of proinflammatory cytokines (including transforming growth factor β, TGF-β), which can contribute to glomerular damage [93]. Thus, it was suggested that OPN could be a potential predictor of primary MGN progression. However, only these few studies were conducted to investigate the role of OPN in MGN, therefore further investigation in this field is indispensable.

Lupus nephritis

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, caused by endogenous and egzogenous factors. Deregulation of the immune system leads to production of autoantibodies, which form complexes with antigens and are deposited in various organs [94–97]. Lupus nephritis (LN) is one of the most serious manifestations of SLE [98]. Many studies demonstrated that OPN level is increased in the plasma and urine of SLE patients and may correlate with disease pathogenesis and clinical manifestations (reviewed in Kaleta [99]). In a study of Wong et al. [100], it was found that plasma OPN concentration is significantly higher in SLE patients with renal impairment than in patients without LN and in healthy controls. Moreover, increased OPN correlated positively with SLE Disease Activity Index (SLEDAI), as well as with IL-18 level. Similar findings were reported in children with SLE [12]. In another study conducted in LN patients, Kitagori et al. [85] measured the urine and plasma concentration of the full and N-half OPN but found no difference in urine full OPN concentration between patients and healthy controls. However, the levels of plasma full and N-half OPN were significantly higher in LN patients. Moreover, urine N-half OPN correlated positively with urine thrombin activity. In addition, the study revealed that plasma and urine full and N-half OPN concentrations were not associated with SLEDAI and estimated glomerular filtration rate (eGFR). The authors suggested that urine N-half OPN is associated with renal inflammation and may be a good prognostic marker for LN. Another study showed that OPN expression in LN patients was higher than in healthy controls, and correlated positively with intrarenal macrophage infiltration [101]. Moreover, the level of OPN was higher in active LN than in the inactive LN. Increased serum OPN level in LN patients was also demonstrated by Salimi et al. [102]. In addition, a few studies demonstrated that some OPN SNiP may be associated with LN. A study of Forton et al. [103], showed that the T allele of the rs1126616 polymorphism is associated with renal insufficiency in SLE patients. Similarly, Salimi et al. [102] genotyped the rs1126616 SNP in SLE patients and showed that the frequency of CT and TT genotypes was higher in SLE patients with LN compared to those without LN. This suggests that the T allele of this polymorphism is a risk factor for renal damage in SLE patients. In another study, Xu et al. [104] demonstrated that 9250 C>T OPN gene polymorphism is associated with the susceptibility to LN (the TT genotype was lower in SLE patients with LN).

In conclusion, a large body of data indicates that OPN and some of OPN gene polymorphisms have an impact on LN development in SLE patients.

Diabetic nephropathy

Diabetic nephropathy (DN) or diabetic kidney is a serious complication of diabetes. It is characterized by the presence of albuminuria, diabetic glomerular lesions, and loss of glomerular filtration rate (GFR) [105]. There is growing interest

in finding specific serum and urinary markers of DN, and determining their roles in the early detection of renal damage. Some authors reported that elevated OPN level is a predictor of nephropathy in diabetic patients. Kitagori et al. [85] measured the urine and plasma concentration of the full and N-half OPN in patients with DN. The study demonstrated that the level of the full OPN in plasma was significantly higher in patients than in healthy controls. However, there was no difference in urine OPN levels. Yamaguchi et al. [106] evaluated whether plasma and urine OPN concentrations in patients with type 2 diabetes (T2D) are associated with DN. They found that plasma OPN level is increased during DN progression, especially in the stage of renal failure, but in contrast, urinary OPN was not associated with renal disease in diabetic patients. The aim of another study was to assess possible associations between OPN (full and N-half) and nephropathy in patients with T2D [107]. Similar to study of Yamaguchi et al., plasma levels of the full OPN were significantly higher in diabetic patients compared with controls. In addition, there was a higher frequency of moderate renal insufficiency and lower eGFR in patients with T2D. Furthermore, an inverse correlation of OPN level and eGFR was observed. Morover, the group found a significant association of the full OPN, but not N-half, and the severity of DN. Serum OPN concentrations were also measured in adult patients with type 1 diabetes (T1D) by Gordin et al. [108]. It was showed that OPN was independently associated with the development of microalbuminuria and was a strong predictor of incipient DN. The aim of another study, conducted in pediatric patients with T1D was to evaluate serum OPN concentrations and its role in renal failure [109]. Diabetic patients had higher OPN levels than healthy controls. Moreover, OPN concentrations were higher in patients with microalbuminuria compared to those with normal albumin excretion. In addition, OPN levels correlated positively with higher systolic and diastolic blood pressure, body mass index (BMI) and lower high density lipoprotein (HDL) concentration.

Most of the results indicate that plasma full length OPN, but not urine or N-half OPN, might be a good marker for the susceptibility to DN. In addition, recent studies demonstrated that some OPN gene polymorphisms might be associated with a higher risk of kidney failure in diabetic patients. Cheema et al. [110] examined the association of OPN gene promoter polymorphism C-443T (rs11730582) with DN in Asian Indians. The group found a higher risk of DN among carriers of T allele and TT genotype. Moreover, the T allele correlated with higher proteinuria and lower eGFR. These results are in agreement with the study of Nicholas et al. [111] in which increased OPN levels were associated with proteinuria as well as DN. It was showed that rs11730582 polymorphism affects OPN expression [111, 112]. Elevated OPN expression is associated with higher TGF-β and matrix deposition in mesangial cells, which could contribute to the pathophysiology of DN. The association of three functional promoter gene polymorphisms: C-443T (rs117305820), delG-156G (rs17524488) and G-66T (rs28357094) with the predisposition to DN was analyzed in another case–control study [113]. It was demonstrated that the GG genotype of delG-156G polymorphism is associated with lower risk of DN. Moreover, patients with the GG genotype showed highest eGFR. In addition, the frequency of haplotypes G-T-delG and T-T-delG (allele of G-66T, T-443C, and delG-156G) was significantly higher in DN group and was associated with lower eGFR. All these three polymorphisms, located in a promotor region of OPN gene, affect its transcriptional activity. rs28357094 modifies the binding of specificity protein transcription factor 1 and 3 (Sp1/Sp3). rs17524488 and rs117305820 are associated with different bindings of still uncharacterized transcriptional factors [112].

These results indicate that OPN gene polymorphisms and their haplotypes might be a good marker of the susceptibility to DN. However, further studies are needed to increase our understanding of the OPN gene's role in disease pathogenesis.

Renal allograft rejection

While kidney transplantation is the most effective treatment for end-stage renal disease [114], the graft rejection still affects kidney viability and patient survival. Therefore, there is growing interest in finding non-invasive and early biomarkers for monitoring immune status of transplant recipients. One of the analyzed markers is OPN. OPN mRNA and protein were found to be elevated in renal transplant biopsies from patients with acute allograft rejection [115]. Moreover, it was demonstrated that OPN CD44 receptor was upregulated during rejection episodes [116]. In addition, higher levels of serum OPN were associated with the lower probability of rejection-free survival of patients after kidney transplantation [117]. All these studies showed that OPN may be a promising marker for the prediction of early acute kidney allograft rejection, but future studies in this field are required.

Conclusion

This review summarizes the advances in understanding the role of OPN in pathogenesis and outcome of various kidney diseases. Most of the results (summarized in Table 1) suggest that OPN can be associated with the pathogenesis of renal failure. However, some studies reported conflicting or inconclusive results. Reasons for such divergences

Table 1 Main studies of association between OPN and kidney diseases

Kidney disease	Possible role	Comments	References
Cancer	Yes	OPN is associated with increased proliferation and invasion of human renal cancer ACHN cells	[74]
		OPN is a prognostic marker for progression-free survival for RCC and ccRCC patients	[75, 76]
Immunoglobulin A nephropathy	Yes	OPN and CD44 are highly expressed in tubular cells and interstitial infiltrating cells in areas of tubulointerstitial injury	[80]
		Urine OPN level is elevated in IgAN and associated with high OPN/creatinine ratio	[81]
		During IgAN development, increased OPN mRNA correlates with macrophage infiltration	[82]
		N-half (thrombin cleaved) OPN in urine correlates with albuminuria	[83]
	No	No association of OPN mRNA and protein with clinical data and pathological findings in glomeruli and tubulointerstitial regions	[84]
		No difference in the full and N-half plasma and urine OPN between IgAN patients and controls	[85]
Minimal change disease, focal and segmental glomerulosclerosis	Yes	Urinary OPN/creatinine ratio in children with MCD and FSGS is higher than in the control group. In FSGS patients, the ratio was higher than in MCD group and correlated with interstitial changes and mesangial expansion	[81]
		A positive correlation of OPN mRNA expression in proximal tubules and urinary OPN excretion	[84]
	Yes/no	Plasma OPN levels higher in MCD patients than in the control group. No difference in urine OPN levels	[85]
	No	No difference in urine OPN between MCD patients and controls. Urine N-half OPN present in MCD patients but not in controls. The N-half OPN in urine correlated with urine protein level	[83]
		No OPN expression in renal biopsy specimens from MCD patients	[88]
Membranous glomerulonephritis	Yes	Overexpression of OPN in proximal tubules of patients with progressive and nonprogressive MGN OPN expression associated with interstitial monocytes/macrophages and $CD4^+$ and $CD8^+$ T cells infiltration and increased myofibroblastic activity	[88, 93]
Lupus nephritis	Yes	Plasma OPN level elevated in SLE patients with LN compared to patients without LN and healthy controls. Increased OPN correlates with SLEDAI and IL-18	[12, 100]
		OPN expression in LN patients higher than in healthy controls, and correlates with intrarenal macrophage infiltration. OPN concentration in active LN higher than in inactive LN	[101, 102]
	Yes/no	Plasma full and N-half OPN is higher in LN patients than in controls. No difference in urine full OPN between the two groups. Urine N-half OPN correlates with urine thrombin activity. Plasma and urine full and N-half OPN concentrations are not associated with SLEDAI and GFR	[85]
	Yes	OPN gene 707 C>T and 9250 C>T polymorphisms associated with LN susceptibility in SLE patients	[102–104]
Diabetic nephropathy	Yes	Plasma levels of full OPN are higher in diabetic patients compared with controls and correlate with higher frequency of moderate renal insufficiency, lower GFR and DN severity	[95]
		Serum OPN level is independently associated with development of microalbuminuria and is a strong predictor of incipient DN	[96]
		Higher OPN level in pediatric T1D patients than in healthy controls. OPN concentrations correlate positively with microalbuminuria	[97]
	Yes/no Yes	Plasma OPN level increased in diabetic patients and associated with DN. No difference in urine OPN levels OPN gene C-443T polymorphism associated with proteinuria, lower GFR and DN risk OPN gene delG-156G polymorphism associated with DN susceptibility and GFR. Haplotypes G-T-delG and T-T-delG (allele of G-66T, T-443C, and delG-156G) associated with higher DN risk and lower GFR	[73, 94] [110, 111] [112]
Allograft rejection	Yes	OPN is elevated in renal transplant biopsies in patients with acute allograft rejection. CD44 is upregulated during rejection episodes. High serum OPN is associated with the lower probability of rejection-free survival of patients after kidney transplantation	[115–117]

ccRCC clear cell renal carcinoma, *DN* diabetic nephropathy, *FSGS* focal and segmental glomerulosclerosis, *GFR* glomerular filtration rate, *IgAN* immunoglobulin A nephropathy, *IL* interleukin, *LN* lupus nephritis, *MCD* minimal change disease, *MGN* membranous glomerulonephritis, *OPN* osteopontin, *RCC* renal cell carcinoma, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *T1D* type 1 diabetes

may be clinical variety or low statistical power. In addition, only few studies were conducted to investigate the molecular mechanisms of OPN action. Therefore, future investigation is needed to verify if urine or plasma OPN (full length and N-half) concentration may serve as valuable predictive and prognostic marker of renal damage. Moreover, the role of OPN gene polymorphisms needs to be better explored. It will be helpful to prepare genetic profiles for predisposition to kidney diseases.

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Compliance with ethical standards

Conflict of interest The author declares that has no conflicts of interests.

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