Received: 6 May 2024 | Accepted: 5 August 2024

DOI: 10.1111/dme.15427

DIABETIC Medicine

REVIEW

Special Issue: From Bench to Bedside

Complement anaphylatoxins: Potential therapeutic target for diabetic kidney disease

Jingyuan Ma | **Wai Han Yiu** | **Sydney C. W. Tang**

Division of Nephrology, Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China

Correspondence
Sydney C. W. Tang, Division of Nephrology, Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China.
Email: scwtang@hku.hk

Funding information
Research Grants Council of Hong Kong (General Research Fund 17108222); Endowment Fund established at the University of Hong Kong for the Yu Professorship in Nephrology awarded to SCWT; philanthropic donations from Mr. Winston Leung, Mr. K.K. Chan, and Dr. Rita T Liu SBS of L & T Charitable Foundation Ltd. & Bingei Family of Indo Café

Abstract

Diabetic kidney disease (DKD) is the most common cause of kidney failure, characterized by chronic inflammation and fibrosis. The complement system is increasingly implicated in the development and progression of diabetic nephropathy. The important complement anaphylatoxins C3a and C5a are key mediators of the innate immune system, which regulates cellular inflammation, oxidative stress, mitochondrial homeostasis and tissue fibrosis. This review summarizes the involvement of anaphylatoxins in the pathogenesis of diabetic kidney disease, highlights their important roles in the pathophysiologic changes of glomerulopathy, tubulointerstitial damage and immune cell infiltration, and discusses the modulatory effects of new anti-diabetic drugs acting on the complement system. Based on available clinical data and findings from the preclinical studies of complement blockade, anaphylatoxin-targeted therapeutics may become a promising approach for patients with DKD in the future.

KEYWORDS

anaphylatoxins, complement, diabetic kidney disease

1 | INFLAMMATION IN DIABETIC KIDNEY DISEASE

Diabetic kidney disease (DKD) is the most common cause of chronic kidney disease (CKD) and one of the most prevalent complications of diabetes, characterized by increased urinary albumin excretion, decreased estimated glomerular filtration rate (eGFR) and hypertension, ultimately leading to kidney failure and replacement therapy. According to International Diabetes Federation (IDF) report, the global diabetes prevalence in people aged 20–79 is estimated to be 12.2% by 2045, with the highest prevalence (24%) in those aged 75–79 years, living in urban areas and high-income countries, affecting 783.2 million people.[1] Patients with type 1 (T1DM) or type 2 diabetes mellitus (T2DM) are all at risk for kidney disease, and about 40% of patients with diabetes will eventually develop DKD.[2] More importantly, accumulating evidence shows that patients with DKD are at a high risk of cardiovascular disease, hypertension, dyslipidaemia, gastroparesis and neuropathy that are associated with increased mortality and morbidity rate,[3] imposing a substantial economic and social burden. Clinically, DKD is diagnosed by the presence of albuminuria and/or reduced eGFR, along with typical kidney pathological changes of mesangial expansion, thickening of basement membrane, followed by

glomerulosclerosis, tubular atrophy, as well as interstitial collagen and fibronectin deposition,[4] eventually resulting in the progressive loss of kidney function.

The pathogenesis of DKD is a complex process driven by multiple pathophysiological factors including haemodynamic and metabolic changes (glucose and lipid metabolism), intestinal homeostasis and inflammation.[5] Chronic hyperglycaemia leads to accumulation of advanced glycation end products (AGEs), production of reactive oxygen species (ROS), pro-inflammatory cytokines and chemokines, which aggravate cellular damage via activation of the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signalling, protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signalling, protein kinase C, toll-like receptors (TLRs) signalling, C-C motif chemokine ligand 2 (CCL2)/C-C chemokine receptor type 2 (CCR2) signalling, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain containing (NLRP) inflammasome, transforming growth factor-beta (TGFβ) and nuclear factor kappa B (NF-κB) pathway.[6] In particular, chronic low-grade inflammation has emerged as an important factor for the progression of DKD.[7] Single-nucleus RNA sequencing demonstrated an increase in various types of leucocytes, namely T cells, B cells, monocytes and plasma cells in human diabetic kidney biopsy.[8] Metabolic alterations and glomerular hyperfiltration in diabetes activated these innate immune cells, resulting in the aberrant production of inflammatory cytokines (interleukin (IL)-1, IL-18, IL-6 and tumour necrosis factor alpha (TNFα)) and chemokines (CCL2, CCL5, CCL11 and chemokine (C-X3-C motif) ligand 1 (CX3CL1)).[7] In addition, the number of infiltrating macrophages and other immune cells in the diabetic kidney is correlated with histological damage and decline of kidney function in these patients.[9]

Preclinical studies proved that targeting TLR signaling,[10] CCL2 signaling[11] or NLRP inflammasome[12] could reduce the accumulation and activation of immune cells, especially macrophage infiltration and ameliorate diabetes-associated kidney damage in experimental mouse models of diabetic nephropathy (DN), suggesting a therapeutic potential of targeting inflammation in DKD. At present, several clinically used anti-diabetic drugs have been shown to exert secondary kidney-protective and anti-inflammatory properties. Findings from clinical trials such as Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) trials confirmed the kidney-protective effect of sodium-glucose cotransporter-2 inhibitor (SGLT2i) in patients with CKD with or without T2DM.[13] Incretin therapies including glucagon-like peptide-1 receptor agonists (GLP-1-RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4i) have been reported with immunomodulatory and anti-inflammatory effects. The cardiovascular outcome trials (CVOTs), Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) trial and Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial infarction 53 (SAVOR-TIMI 53) trials showed promising results for reducing albuminuria.[14] A recent meta-analysis of eight large randomized controlled trials further confirmed the additional beneficial effects of GLP-1RAs on kidney outcomes in patients with DKD.[15] However, other trials targeting inflammation in DKD including IL-1β antibodies, inhibitors of CCL2, CCR2 and NF-κB pathways have been stopped at phase 2 due to the lack of clinical efficacy or adverse drug reaction,[7] implying an inadequate knowledge on specific kidney inflammatory pathways that lead to the progression of DKD. Therefore, developing an effective anti-inflammatory therapy for DKD, especially for patients with advanced disease, remains a challenge.

As one of the major modulators of innate immunity, although the mechanisms of complement activation and downstream pathological effects vary among different kidney diseases, evidence suggests that the complement system contributes to kidney injury in various diseases including membranous nephropathy,[16] lupus nephritis,[17] IgA nephropathy,[18] anti-glomerular basement (GBM) membrane disease and acute kidney injury.[19] More important, the complement activation is also associated with traditionally non-immune-mediated kidney diseases such as focal segmental glomerulosclerosis (FSGS) and DKD,[20,21] indicating the additional role of complement activity beyond its immune-related function such as regulation of

What's new?

- Complement anaphylatoxins C3a and C5a have emerged as key mediators of diabetic kidney disease (DKD) which contribute to the pathophysiologic changes of immune cell infiltration, glomerulopathy and tubulointerstitial damage during disease progression.
- New class of anti-diabetic drugs (SGLT2 inhibitors, GLP-1 receptor agonists and DDP-4 inhibitors) exert kidney protective effects in DKD by inhibiting complement cascade.
- Combination therapy with an anaphylatoxin-targeting approach may hold a potential promise in combating DKD.

tissue homeostasis and mitochondrial activity.[22] In recent years, a growing body of evidence from experimental studies has suggested that the complement system, especially the anaphylatoxins C3a and C5a, plays a pivotal role in the progression of DKD.[23] This review aims to summarize existing knowledge of the complement anaphylatoxins in the development of DKD, highlighting their roles in different pathophysiological processes during disease progression and discussing the therapeutic potential of complement-targeted drugs.

2 | COMPLEMENT SYSTEM AND ANAPHYLATOXINS

The complement system is an important component of the innate immune system, which plays a crucial role in antibody-mediated immunity. It encompasses three main physiological activities: protecting against bacterial infections, connecting the innate and adaptive immune responses, and eliminating immune complexes and inflammatory by-products.[24] The complement system consists of more than 40 soluble proteins and membrane-bound receptors in the bloodstream of the human body. Complement proteins are primarily produced and secreted by the liver in an inactive form and become activated in an enzyme cascade once triggered by bacteria, viruses, immune complexes or injured tissues.[25] There are three activation pathways in the complement system, namely the classical, lectin and the alternative pathways. In classical and lectin pathways, C4 is cleaved by C1q or mannan-associated serine protease-2 (MASP-2), respectively, into C4a (anaphylatoxin) and C4b, which leads to the activation of C2, generating C3 convertase (also called C4b2a) that activates C3. All three pathways converge at the cleavage of C3 by C3 convertase into C3a (anaphylatoxin) and C3b, which is the main effector molecule of opsonization and phagocytosis. Furthermore, excess C3b binds to C3 convertase to form C5 convertase, resulting in the generation of C5a (anaphylatoxin) and C5b, which eventually leads to the formation of the membrane attack complex (MAC) for targeted cell lysis (Figure 1).[26,27]

The small fragment (74–77 amino acids) of anaphylatoxins C3a, C4a and C5a derived from the α-chain cleavage of C3, C4 or C5 are glycoproteins with complex helical structures.[28] Besides the fundamental role in regulating innate immune responses, increasing evidence has suggested that C3a and C5a are involved in diverse biological

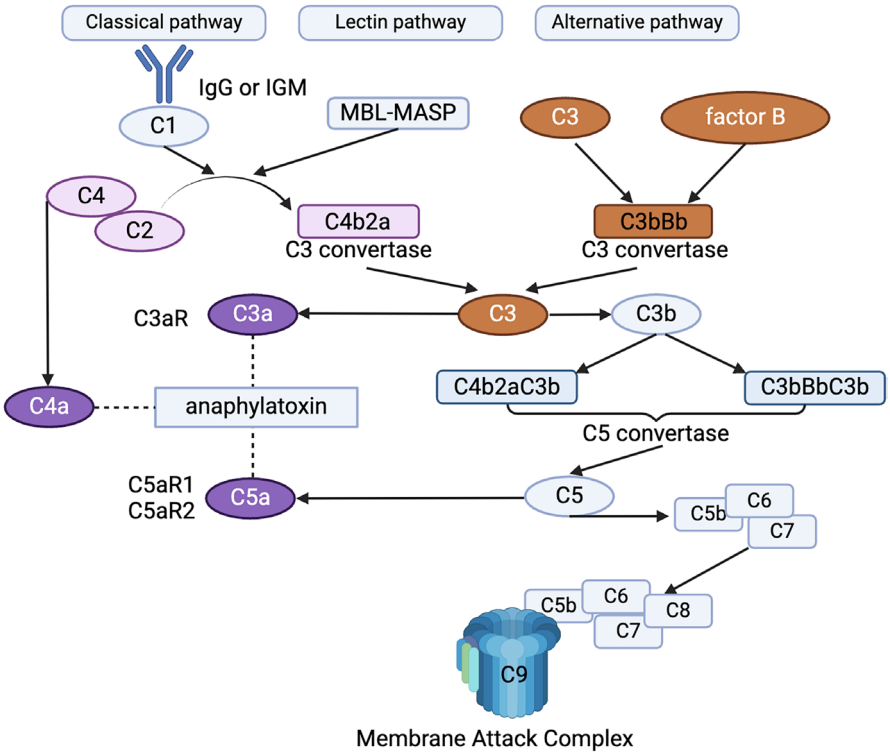

FIGURE 1 The complement cascade and anaphylatoxin formation. The complement cascade consists of a series of enzymatic reactions that respond to infection and danger signal in the immune system. The complement cascade is activated through three different pathways, namely classical, lectin and alternative pathways. These pathways converge at the cleavage of C3 to produce C3a (anaphylatoxin) and C3b. Excess C3b binds with C4b2a (C3 convertase) to form C4b2aC3b (C5 convertase), which cleavages C5 into C5a (anaphylatoxin) and C5b. Finally, C5b mediates the formation of membrane attack complex (MAC) that forms pores on the cellular membrane, resulting in cell death. This figure was created using BioRender.

processes such as tissue regeneration, fibrosis and vascular permeability by binding to their respective membrane-bound receptors, C3a receptor (C3aR) and C5a receptor 1 and 2 (C5aR1/C5L2).[29] These receptors share similar structures, but different signal transduction and functions. C3aR (55 kDa) and C5aR1 (39 kDa) are G-protein-coupled receptors that are widely expressed in human kidney such as proximal tubular epithelial,[30] endothelial cells,[31] podocyte[32] and various immune cells.[33] Activation of C3aR and C5aR1 leads to calcium influx and the initiation of downstream signalling pathways including mitogen-activated protein kinase (MAPK), phosphatidyl inositol 3 kinase gamma (PI3Kγ) and Akt pathway.[29] While they are initially considered to drive pro-inflammatory responses, C3aR has been found to exert a strong anti-inflammatory effect[34] and can counteract C5aR1-driven inflammatory responses and regulation of immune cell function in endotoxin-shock[35] and systemic lupus erythematosus.[36] Apart from pro-inflammatory function, accumulating evidence demonstrates that C5aR1 also impacts tissue homeostasis, cell metabolism and differentiation.[37] Unlike C5aR1, C5L2 does not couple to G protein and is initially thought to be an inactive decoy receptor which is now known to mediate pro-inflammatory responses.[38]

Recent evidence reported the expression of intracellular complement system, also called the complosome. Intracellular C5a/C5aR1 signalling in lysosomes and endosomes is involved in the regulation of β-catenin stability for preventing colorectal cancer.[39] Increased intracellular C3a production induced pro-inflammatory cytokine production and survival in T cells upon stimulation.[40] Thus, the existence of complosomes suggests an additional role of complement system in the control of cellular homeostasis such as glycolysis, mitochondrial respiration and autophagy worthy of further investigation.

Although C4a is structurally similar to C3a and C5a, experimental data obtained so far do not fully support its functional classification as an anaphylatoxin and no specific receptor has been discovered for C4a yet. In contrast, C4a exhibited significant inhibitory effects on chemotaxis of immune cells and generation of ROS.[41,42] It also caused skin reactions and muscle contractions,[43] reduced cell activities and prevented lung injury.[44]

3 | ACTIVATION OF COMPLEMENT SYSTEM IN DKD

Apart from host defence, both systemic and local complement activations play an important role in the inflammatory responses of various diseases such as autoimmunity, neurodegenerative diseases, cancer and infections. The activation of complement system in DKD has been previously reported in kidney biopsy,[45–48] plasma,[49] serum[47] and urine[50–52] clinical samples and are summarized in Table 1. Based on preclinical and clinical evidence of complement activation during the development and progression of DKD, recent studies have been focused on how the two anaphylatoxins C3a and C5a contribute to the development of different pathophysiological changes including glomerulosclerosis, endothelial damage, tubulointerstitial inflammation and fibrosis in DKD.

4 | GLOMERULOPATHY IN DKD

Glomerulopathic changes are common in the early stages of DKD. Metabolic alterations such as hyperglycaemia activate the influx of macrophages and other immune cells to secrete the pro-inflammatory molecules and activate NF-κB and JAK/STAT pathways, leading to chronic inflammation.[54] Plasma and urinary levels of C3a and C5a were significantly higher in patients with DKD than in diabetic patients without kidney damage. Notably, increased urinary C3a and C5a levels were significantly correlated with serum creatinine, urinary protein and eGFR in patients with DKD, indicating the importance of locally produced complement anaphylatoxins in DKD.[49,55] Aberrant expression of C3a and C5a has been well documented in the glomeruli of patients with DKD. Glomerular C3aR1 expression was much higher in these patients than in healthy control.[53] In line with these clinical observations, experimental studies have shown significant upregulation of glomerular C3a and C5a as well as their corresponding receptors in different animal models of diabetes such as HFD-/STZ-induced and leptin-deficient obese (*ob/ob*) mouse models.[56–59]

Podocyte injury contributes to proteinuria and plays a key role in DKD progression. Podocytes are critical for maintaining the integrity and function of the glomerular filtration barrier. However, diabetes causes loss of foot processes, reduces podocyte density and even leads to cell death. Experimental studies have proven that podocyte injury in DKD is associated with inflammation, fibrosis, mitochondrial dysfunction and oxidative stress.[60] Treatment with complement antagonist C3aRA and C5aRA significantly reduced the expression levels of TNFα and IL-6 in the glomeruli of STZ-induced diabetic rats.[61] In another study, C3aR antagonist (SB290157)-treated diabetic mice exhibited increased podocyte density and less proteinuria via restoration of downregulated antioxidant superoxide dismutase 2 (SOD2) and reduction of protein oxidation. Exposure to C3a also caused a decrease in cyclic adenosine monophosphate (cAMP) levels, mitochondrial fragmentation and depolarization, accompanied by reduction in adenosine triphosphate (ATP) content in podocytes,

TABLE 1 Clinical evidence of complement system activation in DKD.

Sample type	Complement protein	Results	Reference
Kidney biopsy	C1q, C4d and C5b-9	Glomerular C1q, C4d and C5b-9 expressions were correlated with the severity of DKD	[48]
Kidney biopsy	C3, CD55, C1QA, CD46, C1QB, CFB, C4A/C4B, C7, CFH, C3AR1, CR1 and C2	The expression of glomerular and tubular complement proteins is related to the development of fibrosis in DKD	[53]
Kidney biopsy	C3c and C1q	C3c or C1q deposition in patients with DKD had significantly worse kidney outcomes than those without complement activation	[45]
Kidney biopsy	C1q, C3 and C4d	DKD patients with high C1q, C3 or C4d expression in glomeruli were more likely to progress to kidney failure	[46]
Plasma	C1q, MBL, Bb, C4d, C3a, C5a and sC5b-9	Patients with DKD had significantly higher plasma level of complement proteins than in patients with diabetes only	[49]
Serum and kidney biopsy	C7	The level of C7 in serum and proximal tubules was increased in early diabetic nephropathy (EDN) patients compared to healthy control	[47]
Urine	C3, C5, CD59, C9 and complement factor H (CFAH)	Urinary abundance of complement proteins was significantly associated with kidney failure in patients with T2DM and DKD	[50]
Urine	MBL	High MBL expression genotypes and high MBL concentrations are both associated with increased mortality rates in T1DM compared with low MBL expression genotypes and low MBL concentrations	[52]
Urine	C3, C4 and factor B (CFB)	Complement-derived peptides in urine may be associated with specific kidney disease aetiologies including DKD	[51]

indicating a direct pathogenic effect of C3a on mitochondrial integrity.[57]

Glomerular endothelium acts as a key player in the maintenance of the filtration barrier. Diabetes-associated inflammation causes endothelial dysfunction, increased sympathetic activity and altered kidney function.[62] A recent study showed that hyperactivation of C5a contributed to the acceleration of DKD by stimulating STAT3 signalling in glomerular endothelial cells (GECs) and disrupting the gut–kidney axis.[63] Exposure to high glucose with concomitant C3a treatment increased the levels of p-inhibitor of nuclear factor kappa B (IKBα) and TGFβ and p-Smad3 in human GECs, suggesting that C3a induced glomerular fibrosis and inflammation by regulating NF-κB and TGFβ/Smad3 signalling pathways.[64] Besides, both C3aR and C5aR1 were detected in the glomeruli of DKD patients, and blockade of C3a/C3aR and C5a/C5aR1 signalling alleviated fibrosis by regulating Wnt/β-catenin pathway and reducing upregulation of α-SMA in both diabetic rats and GECs treated with high glucose and C3a/C5a, suggesting the involvement of complement system in endothelial–myofibroblast transition (EndMT).[61]

5 | TUBULOINTERSTITIAL DAMAGE IN DKD

Kidney tubules and interstitium are crucial for regulating kidney function including reabsorption of water and nutrients, secretion of hormones and excretion of waste products. Tubular injury and tubulointerstitial fibrosis are closely correlated with kidney dysfunction during DKD.[65] Deposition of C3a, C5a, C3aR and C5aR1 was significantly higher in the tubulointerstitium of patients with DKD than in healthy controls.[58,66] With prolonged hyperglycaemia, oxidative stress, inflammation and haemodynamic changes, kidney tubular epithelial cells (TECs) undergo epithelial–mesenchymal transition (EMT) which leads tubulointerstitial inflammation and fibrosis, resulting in cell death and tubular atrophy.[67] High glucose triggers infiltration of inflammatory cells and secretion of various cytokines and chemokines in TECs to accelerate the progression of DKD.[6] STZ-induced diabetic mice treated with C5aR1 antagonist PMX53 showed significant reduction in urinary albumin and 8-isoprostane, and attenuated inflammation,

oxidative stress and tubulointerstitial fibrosis.[22] Also, blockade of C5a with NOX-D21 resulted in an improvement of kidney function and reduction in extracellular matrix (ECM) accumulation in *db/db* mice. In HK-2 cells, C5a stimulated the production of TGF-β by activating the PI3K/Akt signalling pathway, which is associated with cell proliferation, fibroblast activation and matrix formation.[66]

More recently, it has been shown that complement C5a/C5aR1 activation disrupts tubular mitochondrial homeostasis during the development of DKD. Transcriptome analysis revealed that treatment with PMX53 in mice reversed diabetes-induced alterations in kidney mitochondrial fatty acid profile and improved mitochondrial architecture and bioenergetics by normalizing cardiolipin remodelling. In addition, C5a increased mitochondrial respiratory and ROS production in human proximal TECs.[22] Apart from mitochondrial reprogramming, C5a/C5aR1 is involved in diabetes-induced cell cycle arrest and tubular senescence. Mice with C5aR1 knockout or PMX53 treatment showed attenuated diabetes-induced cyclin-dependent kinase inhibitor p21 expression in kidney tubular and tubulointerstitial cells. RNA sequencing of whole kidney cortical tissues revealed that PMX53 modified TP53-regulated transcription of cell cycle and senescence-associated genes in diabetes.[68]

6 | IMMUNE CELL INFILTRATION IN DKD

Persistent kidney damage and maladaptive repair result in chronic low-grade inflammation that contributes to kidney disease progression, which is now considered one of the hallmarks of DKD.[69] Immune cells including macrophages, T- and B-lymphocytes are recruited into the injured kidney, leading to an excessive production of cytokines and growth factors, which further activate cellular and molecular processes and eventually result in kidney dysfunction.[69] As an integral part of innate immunity, the complement system orchestrates and regulates various steps of the inflammatory response.

Macrophages are the key effector cells with multiple functions in the innate immune system including elimination of dead cells and ECM remodelling by switching phenotypes via macrophage M1/M2 polarization.[70] Accumulation of infiltrated macrophages in the kidney is correlated with the severity of kidney damage and decline in kidney function in patients with DKD.[71] Complement anaphylatoxins trigger macrophage activation. C3a enhanced the expression of inflammatory cytokines such as IL-1β, IL-6, IL-18 and TNFα in macrophages under a diabetic milieu. More importantly, macrophage accumulation was remarkably diminished in the kidney of C3aR knockout mice compared with wild-type control in HFD-/STZ-induced diabetic mice.[56] Treatment with C3aR antagonist SB290157 reduced the glomerular monocyte/macrophage infiltration and protected mice from kidney injury in STZ-induced DN model.[57] Given that C5a is a potent mediator of inflammation, C5aR1 deficiency abrogated the increase in F4/80-positive cells in STZ-induced diabetic mice. In contrast, pharmaceutical blockade of the C5a/C5aR1 axis with PMX53 and NOX-D21 did not affect kidney inflammation in diabetic mice, showing no difference in F4/80-positive macrophage infiltration in the tubulointerstitium.[22,66] The contradictory results from these studies may be due to the complexity with C5L2 which has been demonstrated to play both pro- and anti-inflammatory roles in the immune system.[72]

Growing evidence indicates a critical role of T cells in the development of DKD. Infiltrated T cells, particularly $CD4^+$ T cell subsets including Th1, Th2, Th17 and regulatory T cells (Tregs) are responsible for local production of pro-inflammatory cytokines such as interferon-gamma (IFNγ) and TNFα that cause tissue damage of the kidney.[73] Increased proportion of $CD8^+$ T cells promoted podocyte injury and glomerulosclerosis in DKD.[74] Despite its role in innate immunity, the complement system also modulates adaptive immunity. In the HFD-/STZ-induced diabetic model, deletion of C3aR exerted kidney protection and reduced the number of $CD4^+$ and $CD8^+$ T cells in the kidney of diabetic knockout mice compared with diabetic wild-type mice. Moreover, microarray analysis revealed that knockout of C3aR altered adaptive immune responses of T cells and kidney inflammation in DN.[56] Complement receptors contribute to the modulation of Tregs. A decreased number of anti-inflammatory Tregs was found in patients with DKD, whereas adoptive transfer of $CD4^+$ $FoxP3^+$ Tregs significantly improved insulin sensitivity and reduced urinary protein and pro-inflammatory markers expression in *db/db* mice.[75] Interestingly, both C5aR1 deletion and PMX53 treatment protected against reduction of $FoxP3^+$ Tregs in STZ-induced diabetic mice.[22] All these findings suggest that complements regulate T-cell immunity and support a promising potential for complement inhibition as a future therapeutics for DKD.

7 | EFFECTS OF NEW ANTI-DIABETIC DRUGS ON THE COMPLEMENT SYSTEM

In recent years, several clinical trials have shown that the new classes of anti-diabetic drugs including

SGLT-2i, DPP-4i and GLP-1-RAs exert renoprotective benefits,[76–78] and those effects might be associated with modulation of the complement system. A comprehensive transcriptome analysis has shown a positive correlation between renal SGLT-2 expression and tubulointerstitial complement C5 synthesis in patients with DKD.[79] Proteomics analysis has revealed significant Kyoto encyclopaedia of genes and genomes (KEGG) pathway enrichment of complement cascade and downregulation of complement C3 in serum from newly diagnosed T2DM patients before and after dapagliflozin treatment.[80] However, contradictory findings have been reported in another cohort study of DapKid (Effects of Dapagliflozin Treatment on Urinary Proteomic Patterns in Patients With Type 2 Diabetes) in which serum levels of complement C3a were increased in T2DM patients with albuminuria after dapagliflozin treatment.[81] The discrepancy between these two studies indicates that SGLT2i might exert different effects on the complement system at different stages of diabetes and further study of SGLT2i on the local complement system is needed. In vivo, dapagliflozin significantly upregulated the expression of complement receptor type 1-related protein y (Crry), the key regulator of the complement system, and attenuated C3b and MAC deposition in kidneys of *db/db* mice.[82] Further studies have shown that the beneficial effect of SGLT2i on renal outcomes can be independent of glucose-lowering effect. For example, in non-diabetic CKD model of 5/6 nephrectomy, empagliflozin treatment decreased the upregulation of complement component 1Q subcomponent A chain (C1QA) and complement component 1Q subcomponent C chain (C1QC) gene expression, the first component of the complement system, in the nephrectomized rats.[83] GLP-1-RAs prevented the incidence of myocardial infarction in patients with T2DM by interfering with complement cascade as revealed by gene ontology (GO) and KEGG enrichment analyses.[84] Treatment of GLP-1-RA also reduced C1q and C3 production and protected against retinal ganglion cell death in the mouse model of glaucoma.[85] Although treatment of DPP-4i has shown the least renal benefits in patients with diabetes compared with SGLT2i and GLP-1-RAs,[86] DPP-4i could inhibit the lectin pathway of complement activation in vitro.[87] Together, these findings provide evidence that new classes of anti-diabetic drugs, to a certain extent, protect against organ dysfunction by modulating the complement system; however, whether they exert similar renoprotective mechanism in DKD requires further investigation. Therefore, the therapeutic use of complement-specific drugs may provide an effective treatment option for DKD.

8 | COMPLEMENT THERAPEUTICS FOR DKD

The complement system has long been studied for its pro-inflammatory properties in innate immune responses. Anaphylatoxin-targeted drugs have been approved for clinical use by the U.S. Food and Drug Administration (FDA), which have achieved therapeutic effects against many inflammatory diseases. For example, eculizumab and ravulizumab are C5 inhibitors that are currently used for treating atypical haemolytic uremic syndrome (aHUS) to improve haematological and kidney parameters.[88,89] Another C5aR inhibitor avacopan (CCX168) also improved kidney inflammation and function in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis patients.[90,91] Based on the clinical and preclinical findings, the complement system, particularly the anaphylatoxins C3a and C5a, is mostly linked with kidney damage in DKD. Although the clinical use of complement inhibitors for DKD remains uncertain, preclinical studies demonstrated that inhibition of anaphylatoxins or their receptors such as C3aR antagonist (SB290157),[57] C5a inhibitor (NOX-D21)[66] and C5aR1 antagonist (PMX53)[22] could modulate inflammatory and fibrotic pathways, mitigate kidney damage and improve kidney function in DKD, rendering complement inhibition an attractive therapeutic target in the future.

9 | CONCLUSION

With an increasing prevalence of diabetes worldwide and limited effective treatment, DKD imposes a huge burden on global healthcare expenditures. Therefore, it is crucial to find new therapeutic targets that slow down progression to kidney failure. While the aetiology of diabetes and its progression to DKD involves multiple factors and a complex interplay of cellular pathways, a new trend of combination therapy has emerged as an effective treatment approach over the conventional glycaemic and blood pressure control. Over the past decade, several new anti-diabetic drugs such as SLGT2i and GLP-1-RAs have been shown to exert therapeutic efficacy to reduce the risk of kidney disease progression in patients with diabetes. However, the underlying mechanism for renoprotective effects of these drugs remains unclear. Activation of the complement system is increasingly implicated in the development of DKD. Both clinical and basic research studies strongly implicated the anaphylatoxins C3a and C5a in different pathophysiological changes during disease progression including glomerulopathy, tubulointerstitial damage and immune cell infiltration, modulating both innate and adaptive

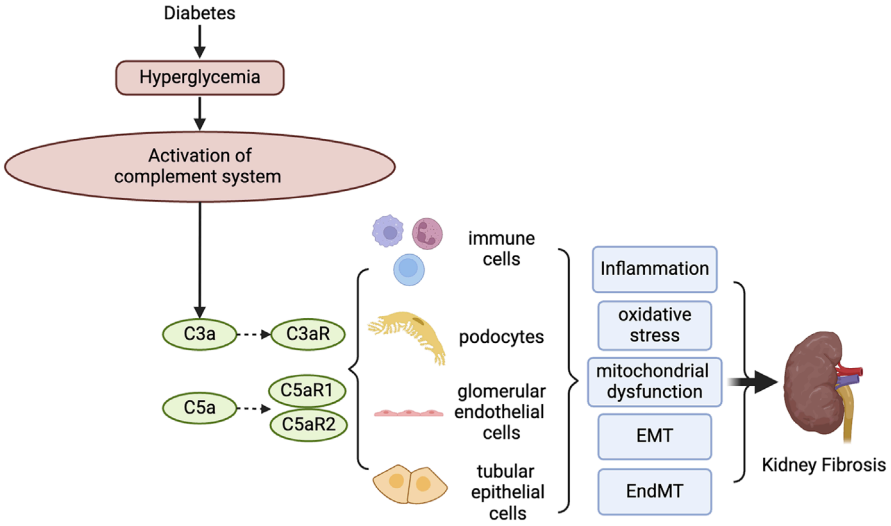

FIGURE 2 The role of anaphylatoxins in DKD. Hyperglycaemia activates the complement system in patients with diabetes that generates anaphylatoxins C3a and C5a, which bind to the corresponding receptors (C3aR, C5aR1 and C5aR2) on various kidney resident cells (podocytes, glomerular endothelial cells and tubular epithelial cells) and recruited immune cells that orchestrate cellular responses to diabetes-induced damage including inflammation, oxidative stress, mitochondrial dysfunction, epithelial–mesenchymal transition (EMT) and endothelial–myofibroblast transition (EndMT). Prolonged kidney injury and maladaptive repair result in DKD with kidney fibrosis and progressive loss of kidney function. This figure was created using BioRender.

immunity (Figure 2). Furthermore, blockade of the complement system has been shown to confer beneficial effects on experimental models of DKD in both T1DM and T2DM. Intriguingly, both clinical and animal studies have shown that new classes of anti-diabetic drugs could modulate the complement activation along with treatment of diabetes. These observations together with the kidney-protective effects of clinically used complement inhibitors in other diseases provide support for the potential clinical application of anaphylatoxin-targeted therapeutics as combination therapy of DKD. This may increase the kidney-protective efficacy and reduce the risk of other complications in patients with DKD. To this end, the exact molecular mechanisms by which the complement system is activated and how anaphylatoxins contribute to the development and progression of DKD deserve further investigation.

ACKNOWLEDGEMENTS

The research work related to the complement study and this review is supported by the Research Grants Council of Hong Kong (General Research Fund 17108222), an Endowment Fund established at the University of Hong Kong for the Yu Professorship in Nephrology awarded to SCWT, and philanthropic donations from Mr. Winston Leung, Mr. K.K. Chan and Dr. Rita T Liu SBS of L & T Charitable Foundation Ltd. & Bingei Family of Indo Café.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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How to cite this article: Ma J, Yiu WH, Tang SCW. Complement anaphylatoxins: Potential therapeutic target for diabetic kidney disease. *Diabet Med*. 2025;42:e15427. doi:10.1111/dme.15427