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Review article

The Role of Complement Cascade in Diabetic Kidney Disease: New Paradigms and Therapeutic Targets

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Abstract

Diabetic kidney disease (DKD) is a chronic complication of diabetes mellitus. DKD is a frequent entity, which occurs in approximately 30-40% of diabetic patients. Traditionally, DKD has been considered a non-inflammatory glomerular disease, being perceived as a condition induced primarily by metabolic and hemodynamic changes. Inflammation has been classified as a main phenomenon for the onset and progression of DKD. Today, the inclusion of the inflammatory component is fundamental for the comprehension of the onset and development of this disease. The inflammatory component has multiple pathways, within which the activation and regulation of the complement system is of particular interest. The mechanisms by which complement is part of the multiple inflammatory pathways in DKD are being increasingly understood, which will guide the development of strategies and therapeutic targets.

Keywords: ***Inflammatory, innovation, complement system, pathway, innate, dipeptidyl peptidase 4***

Introduction

Diabetic kidney disease (DKD) is a chronic complication of diabetes mellitus that can lead to end-stage renal disease (ESRD) and increased morbidity and mortality in patients with diabetes mellitus worldwide [1,2]. DKD is a frequent entity, which occurs in approximately 30-40% of diabetic patients and its appearance carries with it an increase in the direct and indirect costs of interventions in the diabetic patient [3,4,5]. Over the years, basic and applied research studies have been developed to describe the pathophysiological pathways involved in the onset and development of this disease. We focus this review on the role of the complement system in this particular scenario.

The classic and global vision of DKD has placed it as a non-inflammatory glomerular disease, directing its pathogenesis towards the classic pathways of hemodynamic and metabolic alterations as the cornerstone of its clinical course. However, this vision is limited by the recent discoveries and advances in the understanding of the immune response and especially inflammation as a central phenomenon in the development and evolution of the disease [6].

Such studies have demonstrated the interaction of multiple additional pathogenic pathways and inflammatory processes that are present during the course of DKD [7]. Within these, we must distinguish the participation of the complement system, a functional system of soluble plasma proteins and a small proportion of membrane proteins that interact with each other in a regulated manner and that participate in many of the effector functions of natural and acquired immunity [8,9]. We plan to review these basic pathways and their potential role in the pathogenesis of DKD and possible therapeutic options.

Overview of the Complement System

The complement system was first described at the end of the 19th century as a system that mediates the downstream effects of antibodies, complementing their function [9]. Currently, it is promulgated as a network made up of soluble and membrane proteins that respond to signaling pathways, leading to the activation of a proteolytic cascade and effector pathways of the immune response [7]. This can be activated through three different pathways [10]. First, there is the classical pathway mediated by immune complexes; second, the alternative pathway which is activated by cell surface constituents that are foreign to the organism; and finally, the lectin pathway, which is a kind of variant of the classical pathway, however, is activated without the need for the presence of antibodies [11,12].

The C1 factor is composed of 3 protein subunits, C1q, C1r and C1s.The binding of C1q to the Fc domains of IgM and IgG is the initial step in the activation of the classical complement pathway. Once this pathway is activated, plasma C4 is cleaved into C4a and C4b. C4b, will be part of the C3-convertase, which will go to the final activation of the complement [10]. C1q has been found in different pathophysiological models of kidney disease, both in kidney biopsies from patients with immune complex glomerulonephritis and in those with lupus nephritis [10].

On the other hand, the lectin pathway is activated by a group of sugar-binding proteins expressed on the bacterial surface. Among the proteins that can activate this pathway are: mannose binding lectin (MBL), ficolins A, B, or C, and collectins 10 and 11 [10]. When they interact with sugar residues, they activate serine proteases that can cleave C4, generating the same C3-convertase generated by the classical pathway (C4b2a) [10]. There is evidence that this pathway can be activated in the glomeruli, and could be involved in diseases such as IgA nephropathy or those measured by immunocomplexes [9,10].

The third pathway for the activation of the complement system corresponds to the alternative pathway, which, unlike the previous ones, does not require specific activators. The first factor in this pathway is C3, which is permanently at moderate plasma levels. C3 is cleaved into a small C3a fragment and a larger inactive C3b. However, C3b can change fate, that is, instead of entering a catabolism pathway, it forms a covalent bond with the germ surface that amplifies the alternative pathway. This fact and the intervention of factor B, D and certain complexes that act as convertase of C3b cause the germ to end up being opsonized by molecules of C3b; that is, recognized and phagocyted by macrophages. In parallel with the release of C3b, fragments of C3a of great functional importance are produced [10].

Finally, the three described pathways converge at the level of C3, creating an area of C3b binding on the surface of the targets. This C3b can react with any of the C3-convertase as trimolecular complexes: C4b2a3b or (C3b)2Bb. These complexes gradually lose the ability to cleave C3, gaining the ability to cleave C5, cleaving it into C5a and C5b fragments. The latter, C5b, can bind to C6 and C7 forming an amphophilic trimer, which contains a lipid-binding site, facilitating the binding of this complex to nearby cell membranes and mediating binding to C8 molecules [10]. This C5b-C8 complex will interact with the C9 protein, which polymerizes on the cell surface, constituting a pore through the lipid membrane [10]. The pore formed by the union on the cell surface of C5b-C9 allows the free flow of ions inside and outside the cell, favoring osmotic lysis [10]. Consequently, this is the final pathway of cell injury, it has been described in pathological models of membranous nephropathy and podocytopathies [9]. An overview of the complement system is shown in **Figure 1**.

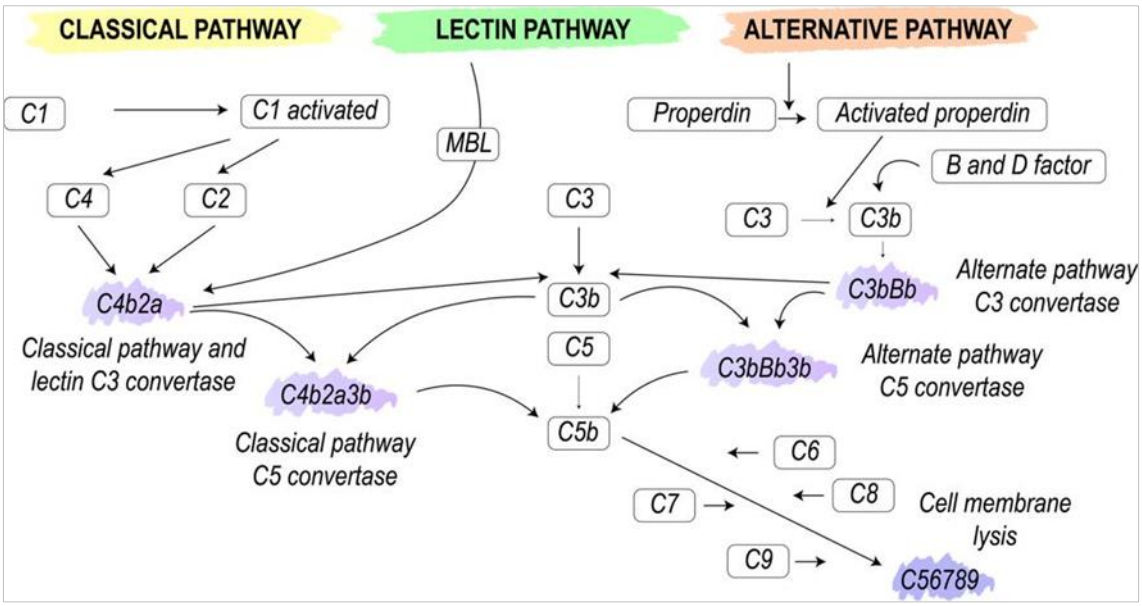

Figure 1. Overview of the complement system. The classical, lectin and alternative pathways are the three main components of the system; they converge on C3, eventually leading to the cleavage of C5, resulting in more reactions that result in cell membrane lysis.

Inflammation and Diabetic Kidney Disease

Traditionally, DKD has been considered a non-inflammatory glomerular disease, being perceived as a condition induced primarily by metabolic and hemodynamic changes, facts that have been modified in light of the new available evidence [14]; Inflammation has been classified as a main phenomenon for the onset and progression of DKD and with implications for its pathogenesis and treatment. In this sense, the inflammatory response and the immune system play an important role in the central axis of this pathology [13,14]. Within the different pathways involved in the inflammatory response, the activation of the complement system has aroused recent interest.

The pathophysiological processes that lead to the stimulation of inflammation and fibrosis are the product of the intervention of metabolic alterations, glomerular hyperfiltration, oxidative stress and production of reactive oxygen species (ROS), as well as the activation of innate immunity with the secondary development of inflammation and fibrosis [15]. So, with the recent accumulated evidence, inflammation has been established as the third pillar in the course of the disease [14].

RNA sequencing studies of the nucleus of kidney cells taken from biopsies of patients with type 2 diabetes mellitus support the activation of signaling pathways involved in inflammation [15,16]. On the other hand, the study of the diabetic kidney shows an increase in the presence of inflammatory cells, leukocytes in an order of 7 to 8 times in relation to the kidney of healthy subjects. Predominating some subpopulations of interest such as monocytes, B cells and plasma cells [15]. Advances in the knowledge of the pathogenesis of DKD make it increasingly clear that diabetes is a systemic inflammatory disease in which one of the organs that is most compromised is the kidneys.

The Role of Complement in Diabetic Kidney Disease

The fundamental role of the complement system is the innate immune defense, assuming a protective function against viruses and bacteria that it recognizes as pathogens, in turn promoting inflammation, due to its participation in the elimination of atypical cells that the body identifies as targets to be eliminated. Two main mechanisms are believed to explain the involvement of complement in the development of DKD, some of these are summarized in the Table 1 [6,8,17].

First, there is the activation of lectin in response to the glycation of proteins that are present on the surface of cells in hyperglycemia. The second mechanism involved is the dysfunction of complement regulatory mechanisms, mediated by the glycation of complement regulatory proteins in response to hyperglycemia [17-19]. Complement regulatory proteins, eg: CD59, prevent membrane attack complex (MAC) formation in the tissue itself. Increased blood glucose in diabetic patients could induce glycation of complement regulatory proteins and thus inactivate the proteins [17-19]. This connection between the complement system and DKD is supported by different experimental and clinical studies [18,20,21].

A factorial clinical trial in mice with streptozotocin-induced diabetes evaluated the possible role of mannose-binding lectin (MBL) in the development of DKD. They were able to establish that wild-type mice with streptozotocin-induced diabetes (a model of Type 1 diabetes mellitus) compared with diabetic MBL knock-out mice had less kidney damage, and showed increased levels of endogenous MBL after induction of diabetes. An increase in the half-life of recombinant human MBL associated with an increase in kidney weight, urinary albumin excretion, and expression of collagen IVα1 (Col4a1) mRNA was observed. This indicates that the appearance of diabetes could be due to a greater production of MBL and therefore to greater renal compromise [18].

Complement activation is implicated in most immune-mediated kidney diseases [9]. For example, complement C1q and C4 are strongly associated with lupus nephritis, C3 deposition is usually detected in renal biopsies from patients with immunoglobulin A (IgA) nephropathy, increased tubular expression of C5b-9 has been correlated with tubulointerstitial expression of transforming growth factor beta 1 (TGF-β1) and renal fibrosis in rapidly progressive idiopathic glomerulonephritis [9,20,21].

Complement C5a is the most effective mediator of inflammation by inducing the secretion of interleukin 6 (IL-6), IL-8, tumor necrosis factor alpha (TNF-α) [22]. C5a signaling is activated by interacting with two different receptors, C5aR and C5L2. In the kidney, C5aR is strongly expressed on tubular epithelial cells [4,23]. Proteomic analyzes in patients with type 2 diabetes mellitus and biopsy-proven DKD found that the abundance of C5, breakdown accelerating factor (DAF), and CD59 were positively correlated with the annual rate of decline in glomerular filtration rate. [24].

In a recently published experimental study, the levels of C5a and C5aR in kidney biopsies from DKD patients were examined and the contribution of C5a in the pathogenesis of DKD in db/db mice was investigated with the use of a new C5a inhibitor (NOX -D21), which binds and inhibits C5a in mice and human [25,26]. In this study, an increase in C5 complement deposition at the tubular level was demonstrated in patients with DKD, which was strongly associated with the progression of kidney disease. In addition, the therapeutic potential of C5a inhibition for renal fibrosis by means of NOX-D21 was evaluated in groups of diabetic mice, where the group administered NOX-D21 had a reduction in the level of serum triglycerides, the expression of sterol regulatory element-binding protein-1 and lipid accumulation in the diabetic kidney [25,26]. The rats. Furthermore, they also had reduced blood urea nitrogen and creatinine levels with less glomerular and tubulointerstitial damage, thus it was concluded that blockade of C5a signaling by NOX-D21 moderates altered lipid metabolism in diabetes and improves tubulointerstitial fibrosis by reducing TGF-β-driven lipid accumulation and fibrosis in the diabetic kidney [4]. This indicates that therapeutically targeting to the complement pathway can alleviate the progression of DKD. In addition, a large-scale cohort study found that diabetic patients with elevated plasma levels of C3 and C7 are more prone to kidney damage than the general population [25,26].

Another retrospective study with a total of 241 patients with DM2 with kidney diseases, diagnosed between January 2011 and August 2019 in the renal department of the First Affiliated Hospital of Nanjing Medical University, found that patients with glomerular deposition of C4c had worse course in developing kidney failure than those without C4c deposits, along with 24-hour urinary protein, higher triglycerides, but lower serum albumin, and higher interstitial inflammation score. Furthermore, serum C4 levels were positively correlated with urinary protein and serum C3 levels [27].

On the other hand, in patients with DKD an increase in the urinary excretion of C3b, Bb and MAC has been observed; the presence of these elements has been associated with progression to end-stage kidney disease and death [7,28]. However, without specifying the moment within the course of the disease where this activation occurs [7]. Genomic analyzes in DKD models have identified an increased expression of complement system proteins such as C3, CD55, C1QA, CD46, C1QB, CFB, C4A/C4B, C7, CFH, C3AR1, CR1, and C2 [16]. Additionally, advanced stages of DKD are associated with glomerulosclerosis which could indicate nonspecific complement activation, but differential transcriptomics of early stage DKD, before proteinuria or changes in eGFR, have also indicated that dysregulated expression of complement is the alteration. most significant [29].

The Complement System as a Therapeutic Target in Diabetic Kidney Disease

Activation of the complement system is a central element in the development of multiple inflammatory kidney diseases [9]. For this reason, efforts have been increased to develop drugs aimed at this system. Therapeutic resources aimed at the complement system are limited; eculizumab is one of the approved agents in the specific case of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS) [7].

Morigi, et al. demonstrated that C3aR antagonists favor preservation in the number of podocytes and prevent the development of proteinuria and worsening of renal function in DKD models [30]. These works have suggested that an increase in complement activity potentiates the inflammatory response and the progression of DKD [31]. At the moment, drugs aimed at inhibiting complement activity in the setting of inflammatory glomerular diseases measured by complement activation (other than DKD) are under development, with the possibility of future work that could reveal the role of these drugs in diabetic population [32,33].

The activation process of the complement system, as a component of the innate immune response, has been related to the development of microvascular complications of diabetes mellitus [34]. Dipeptidyl peptidase-4 (DPP-4) is a cell surface serine protease that is expressed in a wide variety of tissues. DPP-4 inhibitors are widely used in the treatment of type 2 diabetes and seem to produce beneficial pleiotropic effects beyond their hypoglycaemic action, for example, renoprotective and anti-inflammatory properties, without being able to establish the exact mechanisms [34,35]. A recent publication by Hoffmann et al. showed that DPP-4 inhibitors have in vitro activity on the lectin pathway involved in complement activation. This modulation of the complement system is still unclear as to its usefulness or clinical relevance in the management of the patient with DKD [34]. Currently, there are no effective therapeutic interventions that target the complement system. The effect of DPP-4 inhibitors on the complement system is shown in **Figure 2**.

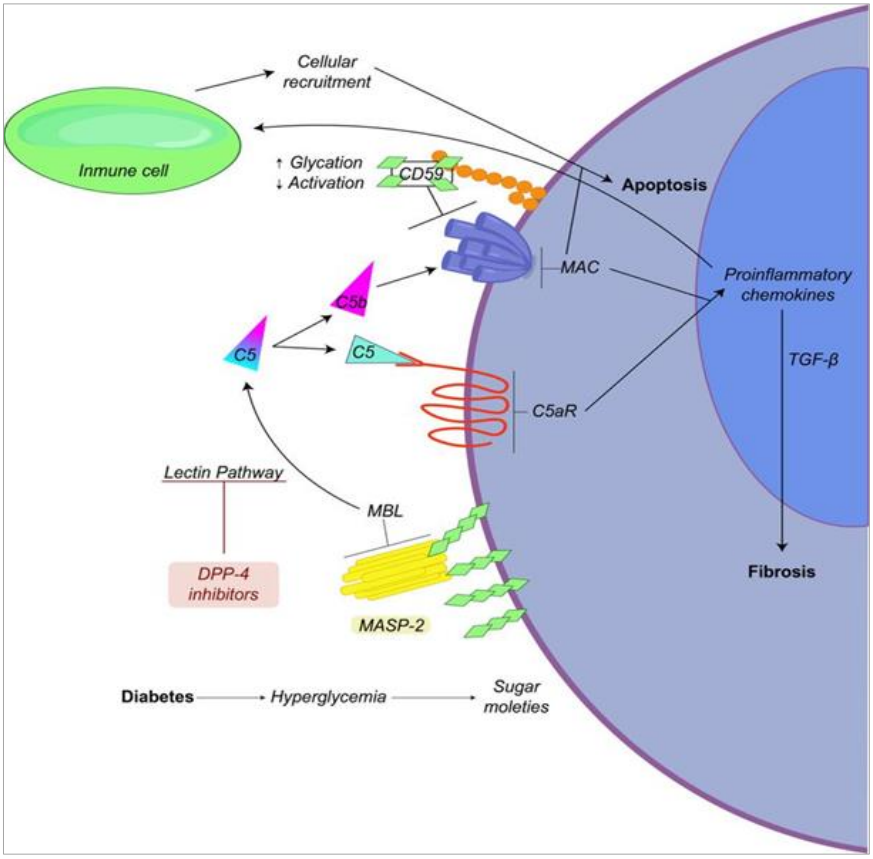

Figure 2. DPP-4 inhibitors and their action in the complement system, acting via the lectin pathway.

Table 1. Overview of the studies involving the different complement system components and their potential clinical relevance.

Complement	Primary author and year of publication	Population	Type of Study	Clinical Potential	Reference
C3a	Morgini et.2022	16 mice with Kidney damage and albuminuria 8mice received C3aR antagonist 8 control mice	Retrospective	C3a inhibition reduce mitochondrial dysfunction and oxidative stress in podocytes from diabetic mice	(30)
C7	Sircar et al. 2018	Post-mortem biological sample (blood and kidney tissue) 18 non-diabetic subjects 17 diabetic subjects	Retrospective	High concentrations of C7 are associated with early detection of DKD	(29)
C3	Rasmussen et al. 2018	95202 individuals from the general population	Prospective	High baseline concentrations of complement C3 were associated with an increased risk of retinopathy, nephropathy, and neuropathy diabetic in individuals from the general population	(36)
C5	Li et al. 2021	Kidney biopsies from patients with type 2 diabetes and DKD kidney biopsies from healthy patients 24 mice 8 mice control group 8mice with DKD 8 mice with DKD + C5aR antagonist	Retrospective	Inpatients with DM2, the positive regulation of C5a activated the transcriptional activator – 3, promoting the inflammatory response and greater renal fibrosis C5 complement blockade attenuated inflammation and renal dysfunction in db/db mice by suppressing the activator of transcription - 3	(37)
C5a	Jiang et al. 2022	217 diabetic patients who underwent kidney biopsy between 2010 and 2021	Retrospective	Complement deposition helps predict faster kidney function decline in DKD patients	(38)
MLB	Ostergaard et al. 2007	7 non-diabetic wild-type mice 8 non-diabetic MBL knockout mice 11 diabetic wild-type mice 11 MBL diabetic knockout mice	Retrospective	Increased MBL is associated with increased kidney weight, urinary albumin excretion and mRNA expression of IVα1 collagen	(39)

C5a	Tan 2020	Subjects with DM1 or DM2	Retrospective	Markedly elevated levels of C5a, C3a and C5b-9 in plasma were found in normoalbuminuric patients with DM1 or DM2, suggesting that the C5aR1 axis is active in human diabetes before the development of DKD	(40)
		18mice 6 mice were administered C5aR1 peptide inhibitor 12 mice control group		In mice, an increase in the excretion of C5a/C5aR1 was observed before the appearance of albuminuria (detectable renal damage) PMX53 significantly decreased the extent of renal structural injury, decreased renal fibrosis in diabetic mice	
C5a	Yiu et al. 2018	Biopsies of diabetic patients	Retrospective	An increase in C5a was found in renal tubule biopsies from patients with DKD suggesting an increase in the local inflammatory response in the kidney, and this was increased in direct proportion to renal injury	(41)
		10 diabetic mice 5 non-diabetic control mice		In mice that were treated with the C5a inhibitor NOX-D21, a decrease in the appearance of glomerulosclerosis was observed	
C7	Gou et al. 2021	31 patients (16 men and 15 women) with DKD who were hospitalized at Chu Hsien-I Memorial Hospital (Tianjin, China) from January 2020 to December 2022 and 30 healthy donors	Retrospective	miRNA are non-coding RNAs that can inhibit RNA expression through translation inhibition, in this study it was shown that miR-494-3p and miR-5p can down-regulate C7 expression, in conclusion reveals that the high level of expression of the C7 gene is regulated by miR-494-3p and miR-574-5p in early DKD	(42)
C3a	Li et al 2019	Renal biopsy of patients with DKD	Retrospective	A significant increase in C3aR expression was reported in kidney biopsies from patients with DKD compared to biopsies from patients without DKD. This was positively correlated with the percentage of glomerulosclerosis, serum creatinine, and interstitial fibrosis and tubular atrophy scores	(43)
		Mice with induced diabetics Diabetics-induced mice with C3aR deficiency		C3aR-deficient diabetic mice were found to exhibit significant lower levels of albuminuria compared to non-deficient diabetic mice	
Complement	Huang et al. 2019	24 mice; 8 mice control group 8 mice group with DM2 8 mice with DKD	Retrospective	Complement components C1q, MBL, MASP-2, factor B, C3 and C5b-9, were highly expressed in the kidneys of type 2 diabetic rats with DKD compared to the others groups	(44)
MLB	Zheng et al. 2018	72 biopsy-proven DKD patients	Retrospective	C5b-9, MBL, and MBL-associated serine protease 1 MASP1 were found to increase with DKD progression	(45)

Conclusion

Understanding the pathophysiology of DKD has made significant progress in recent years, moving away from the traditional approach of hemodynamic and metabolic alterations. Today the inclusion of the inflammatory component is fundamental for the compression of the onset and development of this disease. Said inflammatory component has multiple pathways, within which the activation and regulation of the complement system is of particular interest. The mechanisms by which complement is part of the multiple inflammatory pathways in DKD are increasingly understood, which will guide the development of strategies and therapeutic targets.

Ethics approval and consent to participate

Not applicable

List of abbreviations

DKD: Diabetic Kidney Disease
ESRD: Ends Stage Renal Disease
ROS: Reactive Oxygen Species
MBL: Mannose-binding lectin
DDP-4: Dipeptidyl peptidase 4
aHUS: atypical hemolytic uremic syndrome
GFR: Glomerular filtration rate

Data Availability

Not applicable

Conflicts of Interest

The authors declare there are no conflict of interests.

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Authors' contributions

Jorge Rico-Fontalvo, Gustavo Aroca-Martinez, Rodrig Daza-Arnedo, Juan Montejo-Hernández: general coordination, literature search

Jose Cabrales, Isabella Uparella, Tomas Rodriguez-Yanez: Main text writing and translation, corrections, general grammar, image creation

Carlos Narvaez, Jose Bohorquez, Beatriz Suarez: main text editing, literature search and reference organization, structure organization

References

[1] Sugahara M, Pak WLW, Tanaka T, Tang SCW, Nangaku M. Update on diagnosis, pathophysiology, and management of diabetic kidney disease. Nephrology (Carlton). junio de 2021;26(6):491-500.

[2] Rico Fontalvo JE, Rico Fontalvo JE. Enfermedad renal diabética: de cara a la prevención, diagnóstico e intervención temprana. Revista Colombiana de Nefrología. 2020;7(2):15-6.

[3] Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017;12(12):2032-45.

[4] Yiu WH, Li RX, Wong DWL, Wu HJ, Chan KW, Chan LYY, et al. Complement C5a inhibition moderates lipid metabolism and reduces tubulointerstitial fibrosis in diabetic nephropathy. Nephrology Dialysis Transplantation. 2018;33(8):1323-32.

[5] Fontalvo JER. Guía de práctica clínica para la enfermedad renal diabética. Revista Colombiana de Nefrología. 2021;8(2).

[6] Rico-Fontalvo J, Aroca G, Cabrales J, Daza-Arnedo R, Yánez-Rodríguez T, Martínez-Ávila MC, et al. Molecular Mechanisms of Diabetic Kidney Disease. IJMS. 2022;23(15):8668.

[7] Budge K, Dellepiane S, Yu SMW, Cravedi P. Complement, a Therapeutic Target in Diabetic Kidney Disease. Front Med (Lausanne). 2020;7:599236.

[8] Tang SCW, Yiu WH. Innate immunity in diabetic kidney disease. Nat Rev Nephrol. 2020;16(4):206-22.

[9] Poppelaars F, Thurman JM. Complement-mediated kidney diseases. Mol Immunol. 2020;128:175-87.

[10] Thurman JM. Complement and the Kidney: An Overview. Adv Chronic Kidney Dis. 2020;27(2):86-94.

[11] Ling M, Murali M. Analysis of the Complement System in the Clinical Immunology Laboratory. Clin Lab Med. 2019;39(4):579-90.

[12] Conigliaro P, Triggianese P, Ballanti E, Perricone C, Perricone R, Chimenti MS. Complement, infection, and autoimmunity. Curr Opin Rheumatol. 2019;31(5):532-41.

[13] Samsu N. Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment. Biomed Res Int. 2021;2021:1497449.

[14] Tang SCW, Yiu WH. Innate immunity in diabetic kidney disease. Nat Rev Nephrol. 2020;16(4):206-22.

[15] Jung SW, Moon JY. The role of inflammation in diabetic kidney disease. Korean J Intern Med. 2021;36(4):753-66.

[16] Woroniecka KI, Park ASD, Mohtat D, Thomas DB, Pullman JM, Susztak K. Transcriptome analysis of human diabetic kidney disease. Diabetes. septiembre de 2011;60(9):2354-69.

[17] Flyvbjerg A. The role of the complement system in diabetic nephropathy. Nat Rev Nephrol. mayo de 2017;13(5):311-8.

[18] Østergaard J, Thiel S, Gadjeva M, Hansen TK, Rasch R, Flyvbjerg A. Mannose-binding lectin deficiency attenuates renal changes in a streptozotocin-induced model of type 1 diabetes in mice. Diabetologia. 1 de julio de 2007;50(7):1541-9.

[19] Nakano D, Nishiyama A. A novel role of renin inhibitor in the complement cascade. Kidney International. 1 de octubre de 2018;94(4):650-2.

[20] Thurman JM, Le Quintrec M. Targeting the complement cascade: novel treatments coming down the pike. Kidney Int. 2016;90(4):746-52.

[21] Väkevä A, Meri S, Lehto T, Laurila P. Activation of the terminal complement cascade in renal infarction. Kidney International. 1995;47(3):918-26.

[22] Guo RF, Ward PA. Role of C5a in inflammatory responses. Annu Rev Immunol. 2005;23:821-52.

[23] Bamberg CE, Mackay CR, Lee H, Zahra D, Jackson J, Lim YS, et al. The C5a receptor (C5aR) C5L2 is a modulator of C5aR-mediated signal transduction. J Biol Chem. 2010;285(10):7633-44.

[24] Zhao L, Zhang Y, Liu F, Yang H, Zhong Y, Wang Y, et al. Urinary complement proteins and risk of end-stage renal disease: quantitative urinary proteomics in patients with type 2 diabetes and biopsy-proven diabetic nephropathy. J Endocrinol Invest. 2021;44(12):2709-23.

[25] Tang S, Wang X, Deng T, Ge H, Xiao X. Identification of C3 as a therapeutic target for diabetic nephropathy by bioinformatics analysis. Sci Rep. 2020; 10:13468.

[26] Guo H, Yan Z, Hu Y, Huang X, Pan C. Complement C7 is Specifically Expressed in Mesangial Cells and is a Potential Diagnostic Biomarker for Diabetic Nephropathy and is Regulated by miR-494-3p and miR-574-5p. Diabetes Metab Syndr Obes. 2021;14:3077-88.

[27] Duan S, Sun L, Nie G, Chen J, Zhang C, Zhu H, et al. Association of Glomerular Complement C4c Deposition with the Progression of Diabetic Kidney Disease in Patients with Type 2 Diabetes. Frontiers in Immunology 2020;11.

[28] Morita Y, Ikeguchi H, Nakamura J, Hotta N, Yuzawa Y, Matsuo S. Complement activation products in the urine from proteinuric patients. J Am Soc Nephrol. 2000;11(4):700-7.

[29] Sircar M, Rosales IA, Selig MK, Xu D, Zsengeller ZK, Stillman IE, et al. Complement 7 Is Up-Regulated in Human Early Diabetic Kidney Disease. Am J Pathol. 2018;188(10):2147-54.

[30] Morigi M, Perico L, Corna D, Locatelli M, Cassis P, Carminati CE, et al. C3a receptor blockade protects podocytes from injury in diabetic nephropathy. JCI Insight. 2020;5(5):131849.

[31] Fujita T, Ohi H, Komatsu K, Endo M, Ohsawa I, Kanmatsuse K. Complement activation accelerates glomerular injury in diabetic rats. Nephron. 1999;81(2):208-14.

[32] Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, et al. Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. J Am Soc Nephrol. 2017;28(9):2756-67.

[33] Selvaskandan H, Cheung CK, Muto M, Barratt J. New strategies and perspectives on managing IgA nephropathy. Clin Exp Nephrol. 2019;23(5):577-88.
[34] Hoffmann-Petersen IT, Holt CB, Jensen L, Hage C, Mellbin LG, Thiel S, et al. Effect of dipeptidyl peptidase-4 inhibitors on complement activation. Diabetes Metab Res Rev. 2021;37(3):e3385.
[35] Daza-Arnedo R, Rico-Fontalvo JE, Pájaro-Galvis N, Leal-Martínez V, Abuabara-Franco E, Raad-Sarabia M, Montejo-Hernández J, Cardona-Blanco M, Cabrales-Juan J, Uparella-Gulfo I, Montiel LS. Dipeptidyl Peptidase-4 Inhibitors and Diabetic Kidney Disease: A Narrative Review. Kidney Med. 2021;3(6):1065-1073
[36] Rasmussen KL, Nordestgaard BG, Nielsen SF. Complement C3 and Risk of Diabetic Microvascular Disease: A Cohort Study of 95202 Individuals from the General Population. Clin Chem. j018;64(7):1113-24.
[37] Li L, Wei T, Liu S, Wang C, Zhao M, Feng Y, et al. Complement C5 activation promotes type 2 diabetic kidney disease via activating STAT3 pathway and disrupting the gut-kidney axis. J Cell Mol Med. 2021;25(2):960-74.
[38] Jiang S, Di D, Jiao Y, Zou G, Gao H, Li W. Complement Deposition Predicts Worsening Kidney Function and Underlines the Clinical Significance of the 2010 Renal Pathology Society Classification of Diabetic Nephropathy. Front Immunol. 2022;13:868127.
[39] Østergaard J, Thiel S, Gadjeva M, Hansen TK, Rasch R, Flyvbjerg A. Mannose-binding lectin deficiency attenuates renal changes in a streptozotocin-induced model of type 1 diabetes in mice. Diabetologia. 2007;50(7):1541-9.
[40] Tan SM, Ziemann M, Thallas-Bonke V, Snelson M, Kumar V, Laskowski A, et al. Complement C5a Induces Renal Injury in Diabetic Kidney Disease by Disrupting Mitochondrial Metabolic Agility. Diabetes. 2020;69(1):83-98.
[41] Yiu WH, Li RX, Wong DWL, Wu HJ, Chan KW, Chan LYY, et al. Complement C5a inhibition moderates lipid metabolism and reduces tubulointerstitial fibrosis in diabetic nephropathy. Nephrol Dial Transplant. 2018;33(8):1323-32.
[42] Guo H, Yan Z, Hu Y, Huang X, Pan C. Complement C7 is Specifically Expressed in Mesangial Cells and is a Potential Diagnostic Biomarker for Diabetic Nephropathy and is Regulated by miR-494-3p and miR-574-5p. Diabetes Metab Syndr Obes. 2021;14:3077-88.
[43] Li XQ, Chang DY, Chen M, Zhao MH. Deficiency of C3a receptor attenuates the development of diabetic nephropathy. BMJ Open Diabetes Res Care. 2019;7(1):e000817.
[44] Huang Y, Xu J, Wu X, Chen X, Bai X, Zhuang Y, et al. High Expression of Complement Components in the Kidneys of Type 2 Diabetic Rats With Diabetic Nephropathy. Front Endocrinol (Lausanne). 2019;10:459.
[45] Zheng JM, Ren XG, Jiang ZH, Chen DJ, Zhao WJ, Li LJ. Lectin-induced renal local complement activation is involved in tubular interstitial injury in diabetic nephropathy. Clin Chim Acta. 2018;482:65-73.