OA Nephrology
Open Access

Critical review

Biomedicine

Extra-immunological role of complement activation in diabetic nephropathy

T Fujita*

Abstract

Introduction

Activation of complement cascades has been implicated in the crosstalk between the immune system and metabolism. Membrane attack complex, which is formed by activation of the complement system, plays a role in the formation of atherosclerotic plaque. Acylation stimulating protein, a C3 breakdown product (C3a desArg), is associated with insulin resistance and is implicated in tissue inflammation. Obesity and dyslipidemia-induced ASP-C5L2 (C5a receptor-like 2) axis stimulation induce diabetic microvascular endothelial dysfunction. Moreover, intracellular reactive oxygen species in the microvascular endothelium and the coagulation system also induce complement activation, resulting in acceleration of atherosclerosis and tissue injury in the kidney. A substantial amount of evidence has elucidated the association between complement activation and the progression of kidney injury. These insights into the pathological mechanisms associated with several complement pathways will aid in the development of novel therapeutic approaches. The aim of this review was to discuss the extra immunological role of complement activation in diabetic nephropathy.

Conclusion

The complement system is a versatile player not only in host defence but also in complex metabolic and regenerative functions. Further studies are warranted to identify in more detail components of the complement system as possible targets for prevention of diabetic nephropathy.

*Corresponding author
Email: fujita.takayuki@nihon-u.ac.jp

Department of Nephrology, Hypertension and Endocrinology, Nihon University School of Medicine, Tokyo, Japan

Introduction

The complement system carries out various tasks as part of innate immunity by recognizing and eliminating pathogens. However, the inappropriate activation of the system has been implicated in kidney disease. Recently, its extra-immunological role in metabolic disease has come to the foreground and has received increasing scientific attention. Complement components are overproduced by adipocytes and are activated in association with obesity and dyslipidaemia. In this review, we discuss recent advances in identifying the extra-immunological role of the complement system in the development and progression of diabetic kidney disease.

Discussion

The author has referenced some of his own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Activation of complement pathways in physiology and pathology

The complement cascade can be activated through three different pathways: the classical, alternative and lectin pathways. The three pathways are activated in a sequential manner, with activation of one component leading to activation of the next. The classical pathway is initiated by recognition of the antigen-antibody complex on binding with C1q. This leads to conformational changes resulting in the activation of C1r and C1s, and the formation of C1 complex. Then, C1 complex activates C4 and C2 leading to the formation of C3 convertase, C4b2a. Activation of the alternative pathway depends on spontaneous hydrolysis of C3 in plasma leading to the formation of C3(H_2O), which can bind to Factor B. Subsequent activation by Factor D results in the formation of C3(H_2O)Bb. This complex constantly cleaves another C3 molecule in plasma to C3a and C3b very slowly. In the physiological condition, C3b is protected by regulatory proteins such as Factor H and Factor I. However, C3bBb is formed and stabilized by Properdin under pathological conditions. Activation of the lectin pathway occurs in response to recognition of mannose-binding lectin (MBL) in various carbohydrate ligands. This induces activation of MBL-associated serin protease (MASP)-1 and MASP-2. MASP-2 cleaves C4 and subsequently C2, which leads to the formation of C3 convertase, C4b2a. These three pathways converge in the activation of C3 at the membrane of the target organ. Sufficient activation of C3 leads to the activation of C5 and a subsequent terminal complement pathway, resulting in the formation of membrane attack complex (MAC) and tissue injury[1,2]. A simplified diagram of the complement activation system is shown in Figure 1. In patients with type 2 diabetes (T2DM), the plasma levels of complement components are elevated, and the alternative pathway is activated in association with obesity and dyslipidaemia[3,4].

FOR CITATION PURPOSES: *Fujita T.* Extra-immunological role of complement activation in diabetic nephropathy. OA Nephrology 2013 Oct 25;1(2):19.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the concept on, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Nephrology
Open Access

Critical review

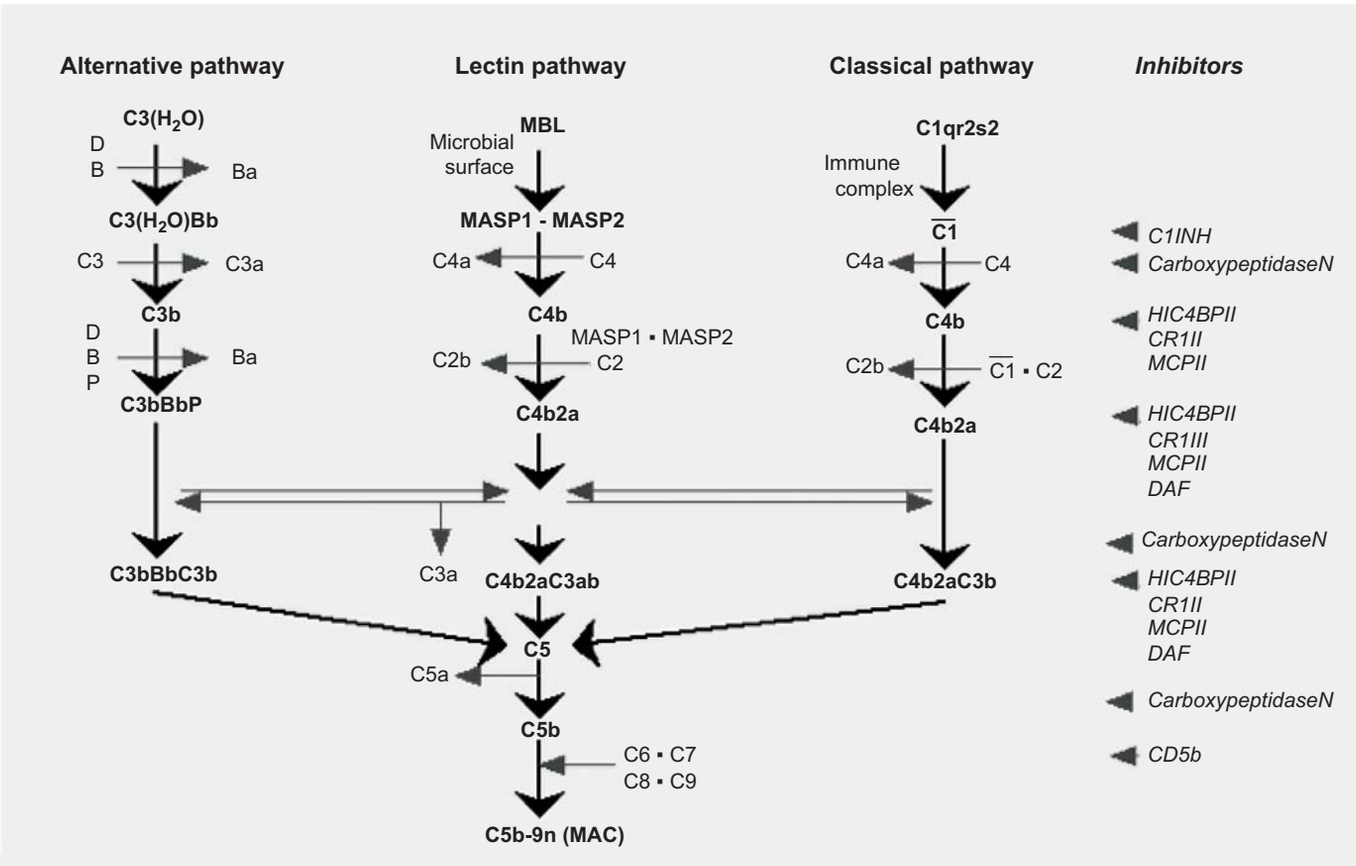

Figure 1: Schematic depiction of the complement system. The complement cascade is activated by one of the three pathways. Activation leads to the formation of C3 convertase, resulting in the formation of C5 convertase and membrane attack complex (MAC).

The traditional role of complement activation in kidney injury

The major function of the complement system has been thought to be recognition and elimination of exogenous antigens or abnormally produced auto-antibodies. Streptococcal antigen in acute proliferative glomerulonephritis, C3 nephritic factor in membrano-proliferative glomerulonephritis, and antigen-antibody complex in lupus nephritis and membranous nephropathy are well-known complement-implicated mechanisms in the establishment of glomerular injury[5,6]. IgA and C3 are deposited in the glomerular mesangium in patients with IgA nephropathy, suggesting IgA-initiated activation of the alternative complement pathway[7]. These abnormalities in the pathogenesis of various primary glomerular diseases and autoimmune diseases with renal involvement have been discussed. In metabolic diseases such as diabetes mellitus, the implication of complement activation has been poorly appreciated in the development of kidney involvement. Recently, the complement system has been shown to be causally involved in tissue injury in patients with diabetic nephropathy including obesity, dyslipidaemia and hypertension as well as in patients with autoimmune or infective diseases[8,9].

Crosstalk between the immune system and metabolism in tissue

Several factors in the immune response such as the complement system have been implicated in the crosstalk between the immune system and metabolism[10,11]. Recent data suggest that C3 plays a role in metabolic disorders[12,13]. The plasma C3 level is associated with the development of T2DM and several risk factors such as obesity, dyslipidaemia, and insulin resistance[14,15]. The link between complement activation and metabolic syndrome is substantiated by the observations that adipose tissue secretes complement components. Several adipocyte-derived cytokines activate proinflammatory cytokines and act on macrophages, which results in tissue injury in the diabetic kidney[16,17].

Role of complement activation in diabetic vascular complications

During the course of T2DM, the following pathophysiological states are

FOR CITATION PURPOSES: *Fujita T.* Extra-immunological role of complement activation in diabetic nephropathy. OA Nephrology 2013 Oct 25;1(2):19.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the concept on, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Nephrology
Open Access

often recognized in association with complement activation and renal involvement.

Atherosclerosis and Hypertension

The C5b-9n assembly is deposited in atherosclerotic lesions, and sublytic C5b-9n assembly induces smooth muscle cell and endothelial cell activation and proliferation[18,19]. These data suggest that activation of the complement system plays an important role in the formation and the rupture of atherosclerotic plaque and arteriosclerotic hypertension due to smooth muscle hypertrophy. Since smooth muscle cells do not express the complement inhibitory molecule (CD59), they represent a possible important target for complement activation[20]. Experimental studies using atherosclerotic rabbits have shown that C5b-9n deposition in the arterial wall preceded monocyte infiltration and foam cell formation[21].

Dyslipidaemia and Inflammation

Cholesterol accumulation regulates genes implicated in complement activation. Loading sterol into macrophages regulates levels of complement proteins[22]. In the postprandial hyperchylomicronemic condition, the alternative complement pathway is activated near adipose tissue[3]. Complement activation can promote systemic inflammation. A simplified diagram of the complement activation induced by chylomicron is shown in Figure 2. vanGreevenbroek et al.[15] reported that complement gene expression was up-regulated in patients with obesity and dyslipidaemia. Such up-regulation may subsequently influence downstream processes, including macrophage infiltration into adipose tissue and adipocyte insulin resistance. Adipocytokines crosstalk with pro-inflammatory cytokines and act to promote macrophage accumulation, which results in inflammation of the kidney[23].

Obesity and Insulin resistance

Active adipocytes overproduce complement components in patients with obesity. Serum C3 correlated with insulin resistance and homeostasis model assessment of insulin resistance[16]. The chylomicron-activated alternative pathway overproduces C3a[3]. C3a receptor (C3aR) expressed in adipose tissue is upregulated after ingesting ahigh-fat diet[13]. Interruption of the C3a-C3aR axis in a C3aR-/- mouse prevented diet-induced insulin resistance. Insulin is directly involved in nitric oxide production, and insulin resistance is associated with endothelial dysfunction[24]. Both obesity and the postprandial hyperchylomicronemic condition induce complement activation and acylation stimulating protein (ASP) production. Signalling of ASP via

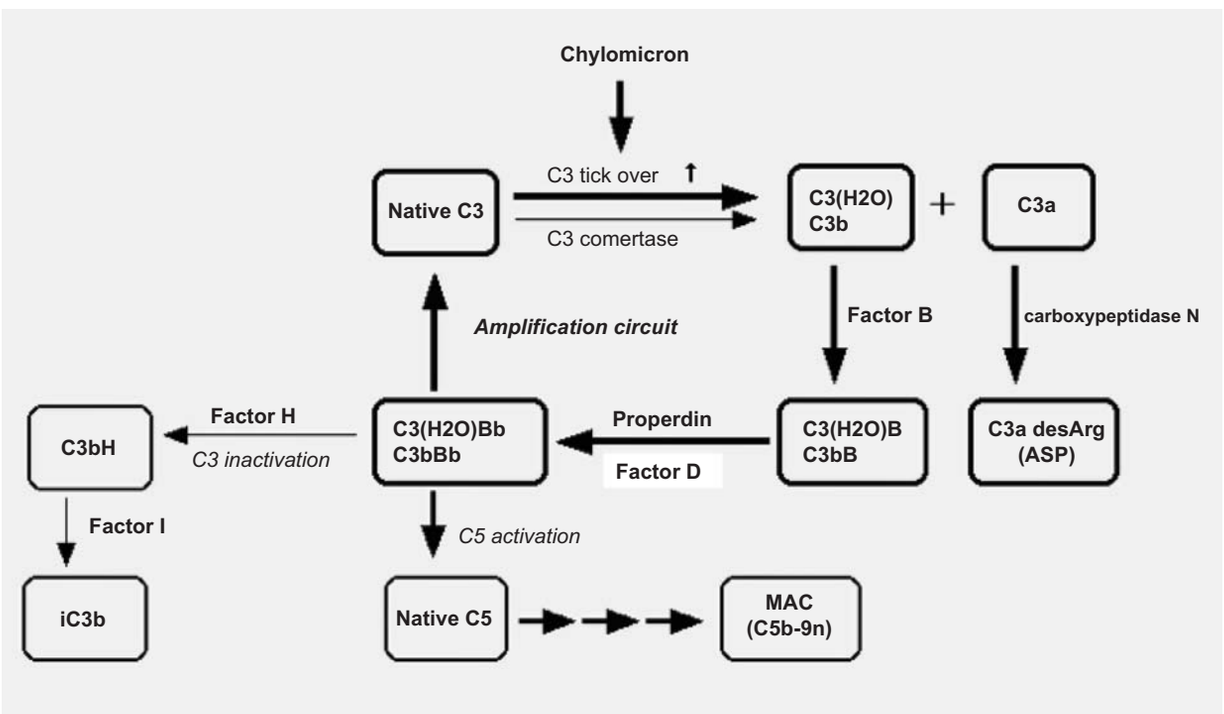

Figure 2: Acceleration of C3 tick over induced by obesity and dyslipidemia. Obesity-induced overproduction of C3 and the postprandial hyperchylomicronemic condition cause complement activation by accelerating the C3 amplification circuit. This leads to the formation of membrane attack complex and atherosclerotic plaque as well as the production of C3a and acylation stimulating protein (ASP). This leads to inflammation and insulin resistance in the tissues.

FOR CITATION PURPOSES: *Fujita T.* Extra-immunological role of complement activation in diabetic nephropathy. OA Nephrology 2013 Oct 25;1(2):19..

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the concept on, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Nephrology
Open Access

Critical review

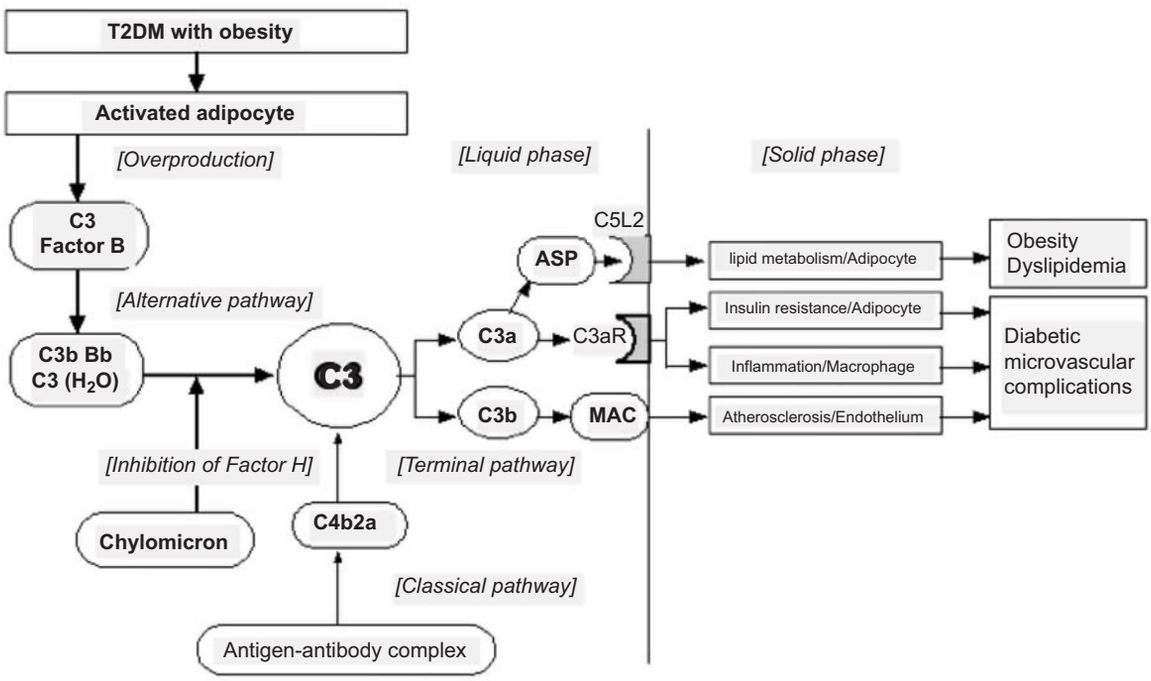

Figure 3: Possible role of complement activation in the development of atherosclerosis or tissue inflammation and insulin resistance. In patients with T2DM with obesity, activated adipocytes overproduce complement components such as C3 and Factor B. Chylomicron activates the alternative complement pathway by regulating the effect of Factor H. During this process, C3 is spontaneously and continuously converted to C3a and C3b. C3b excites the terminal complement pathway and forms membrane attack complexes (MACs), which contribute to the formation of atherosclerotic plaque. C3a contributes to the induction of insulin resistance in adipocytes and macrophages, and inflammation in vascular endothelial cells. C3a is immediately converted to acylation stimulating protein (ASP), which leads to the induction of triacylglycerol production and obesity.

C5a receptor-like 2 may contribute to adipose tissue inflammation and metabolism[25]. A simplified diagram of the complement system and insulin resistance is shown in Figure 3.

Ischemia/reperfusion injury and Reactive oxygen species (ROS)

Atherosclerotic persistent ischemia and reperfusion of peripheral micro vessels in organs induce inflammation that can lead to tissue injury. Complement activation has been known to play a role in the inflammation and tissue injury associated with ischemia/reperfusion injury in the kidney[26]. Intra-cellular production of reactive oxygen species in endothelial cells during ischemia/reperfusion may initiate nuclear factor-kappa B activation resulting in complement activation[27]. ROS generation is also a candidate major factor leading to diabetic nephropathy.

Coagulation and Endothelial injury

The coagulation cascade is able to activate the complement pathway. On the other hand, the coagulation cascade is activated by the complement system. MASP-2 plays a role in the activation of thrombin and subsequent generation of the fibrin mesh[28]. C5a can trigger the release of the endothelial surface proteoglycan heparansulphate, independent of the formation of MAC[29]. Wang et al.[30] reported that the lectin-like domain of thrombomodulin ameliorates diabetic nephropathy via complement inhibition. Even though coagulation and the complement system are two distinct systems, these networks have several common functional attributes in the progression of renal injury.

Conclusion

Complement activation plays a role in the progression of diabetic renal injury by an extra-immunological mechanism besides the traditional immunological mechanism. Especially, metabolic implications in renal endothelial injury have been appreciated and have received increasing attention in T2DM patients with obesity and dyslipidaemia. MAC contributes to the formation of atherosclerotic plaque, and ASP contributes to the expression of insulin resistance and tissue inflammation, resulting in renal microvascular complication.

FOR CITATION PURPOSES: *Fujita T.* Extra-immunological role of complement activation in diabetic nephropathy. OA Nephrology 2013 Oct 25;1(2):19.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the concept on, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Nephrology
Open Access

The complement system is a versatile player. Further studies are warranted to identify in more detail components of the complement system as possible targets for the prevention of diabetic nephropathy.

References

1. Walport MJ. Complement. First of two parts. N Engl J Med. 2001 Apr 5;344(14):1058-66.
2. Walport MJ. Complement. Second of two parts. N Engl J Med. 2001 Apr 12;344(15):1140-4.
3. Fujita T, Fujioka T, Murakami T, Satomura A, Fuke Y, Matsumoto K. Chylomicron accelerates C3 tick-over by regulating the role of Factor H, leading to overproduction of acylation stimulating protein. J Clin Lab Anal 2007; 21: 14-23.
4. Fujita T, Hemmi S, Kajiwara M, Yabuki M, Fuke Y, Satomura A, et al. Complement-mediated chronic inflammation is associated with diabetic microvascular complication. Diabetes Metab Res Rev. 2013 Mar;29(3):220-6.
5. Fujita T, Ohi H, Seki M, Miyaji H, Hatano M. Clinical Evaluation and Characterization of A Unique C3 Breakdown Factor Detected in A Patient with Acute Glomerulonephritis. Nephron 1987; 47: 56-61.
6. Ohi H, Watanabe S, Fujita T, Seki M, Hatano M. Detection of C3bBb-stabilizing activity (C3 nephritic factor) in the serum from patients with membranoproliferative glomerulonephritis. Journal of Immunological Methods 1990; 31: 71-6.
7. Endo M, Ohi H, Ohsawa I, Fujita T, Matsushita M, Fujita T. Glomerular deposition of mannnose-binding lectin (MBL) indicates a novel mechanism of complement activation in IgA nephropathy. Nephrology Dialysis Transplantation. 1998;13:1984-90.
8. Qin X, Goldfine A, Krumrei N, Grubissich L, Acosta J, Chorev M, et al. Glycation inactivation of the complement regulatory protein CD59: a possible role in the pathogenesis of the vascular complications of human diabetes. Diabetes. 2004 Oct;53(10):2653-61.
9. Uesugi N, Sakata N, Nangaku M, Abe M, Horiuchi S, Hisano S, et al. Possible mechanism for medial smooth muscle cell injury in diabetic nephropathy: glycoxidation-mediated local complement activation. Am J Kidney Dis. 2004 Aug;44(2):224-38.
10. Fantuzzi G.Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol. 2005 May;115(5):911-9.
11. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006 Oct;6(10):772-83.
12. Munkonda MN, Lapointe M, Miegueu P, Roy C, Gauvreau D, Richard D, et al. Recombinant acylation stimulating protein administration to C3-/- mice increases insulin resistance via adipocyte inflammatory mechanisms. PLoS One. 2012;7(10):e46883.
13. Mamane Y, Chan CC, Lavallee G, Morin N, Xu LJ, Huang J, et al. The C3a anaphylatoxin receptor is a key mediator of insulin resistance and functions by modulating adipose tissue macrophage infiltration and activation. Diabetes. 2009 Sep;58(9):2006-17.
14. Bjerre M, Kistorp C, Hansen TK, Faber J, Lip GY, Hildebrandt P, et al. Complement activation, endothelial dysfunction, insulin resistance and chronic heart failure. Scand Cardiovasc J. 2010 Oct;44(5):260-6.
15. vanGreevenbroek MM, Ghosh S, van der Kallen CJ, Brouwers MC, Schalkwijk CG, Stehouwer CD. Up-regulation of the complement system in subcutaneous adipocytes from nonobese, hypertriglyceridemic subjects is associated with adipocyte insulin resistance. J Clin Endocrinol Metab. 2012 Dec;97(12):4742-52.
16. Oh DY, Morinaga H, Talukdar S, Bae EJ, Olefsky JM. Increased macrophage migration into adipose tissue in obese mice. Diabetes. 2012 Feb;61(2):346-54.
17. Phieler J, Garcia-Martin R, Lambris JD, Chavakis T. The role of the complement system in metabolic organs and metabolic diseases. Semin Immunol. 2013 Feb;25(1):47-53.
18. Vlaicu R, Niculescu F, Rus HG, Cristea A. Immunohistochemical localization of the terminal C5b-9 complement complex in human aortic fibrous plaque. Atherosclerosis. 1985 Nov;57(2-3):163-77.
19. Niculescu F, Rus H. The role of complement activation in atherosclerosis. Immunol Res. 2004;30(1):73-80.
20. Seifert PS, Roth I, Schmiedt W, Oelert H, Okada N, Okada H, et al. CD59 (homologous restriction factor 20), a plasma membrane protein that protects against complement C5b-9 attack, in human atherosclerotic lesions. Atherosclerosis. 1992 Oct;96(2-3):135-45.
21. Schmiedt W, Kinscherf R, Deigner HP, Kamencic H, Nauen O, Kilo J, et al. Complement C6 deficiency protects against diet-induced atherosclerosis in rabbits. Arterioscler Thromb Vasc Biol. 1998 Nov;18(11):1790-5.
22. Suzuki M, Becker L, Pritchard DK, Gharib SA, Wijsman EM, Bammler TK, et al. Cholesterol accumulation regulates expression of macrophage proteins implicated in proteolysis and complement activation. Arterioscler Thromb Vasc Biol. 2012 Dec;32(12):2910-8.
23. Phieler J, Chung KJ, Chatzigeorgiou A, Klotzsche-von Ameln A, Garcia-Martin R, Sprott D, et al. The Complement Anaphylatoxin C5a Receptor Contributes to Obese Adipose Tissue Inflammation and Insulin Resistance. J Immunol. 2013 Sep 16. [Epub ahead of print]
24. Muniyappa R, Sowers JR. Role of insulin resistance in endothelial dysfunction. Rev Endocr Metab Disord. 2013 Mar;14(1):5-12.
25. Paglialunga S, Schrauwen P, Roy C, Moonen-Kornips E, Lu H, Hesselink MK, et al. Reduced adipose tissue triglyceride synthesis and increased muscle fatty acid oxidation in C5L2 knockout mice. J Endocrinol. 2007 Aug;194(2):293-304.
26. Zhou W, Farrar CA, Abe K, Pratt JR, Marsh JE, Wang Y, et al. Predominant role for C5b-9 in renal ischemia/reperfusion injury. J Clin Invest. 2000 May;105(10):1363-71.
27. Collard CD, Agah A, Stahl GL. Complement activation following reoxygenation of hypoxic human endothelial cells: role of intracellular reactive oxygen species, NF-kappa B and new protein synthesis. Immunopharmacology. 1998 Mar;39(1):39-50.
28. Gulla KC, Gupta K, Krarup A, Gal P, Schwaeble WJ, Sim RB, et al. Activation of mannan-binding lectin-associated serine proteases leads to generation of a fibrin clot. Immunology. 2010 Apr;129(4):482-95.
29. Zaferani A, Vivès RR, van der Pol P, Hakvoort JJ, Navis GJ, van Goor H, et al. Identification of tubular heparansulfate as a docking platform for the alternative complement component properdin in proteinuric renal disease. J Biol Chem. 2011 Feb 18;286(7):5359-67.
30. Wang H, Vinnikov I, Shahzad K, Bock F, Ranjan S, Wolter J, et al. The lectin-like domain of thrombomodulin ameliorates diabetic glomerulopathy via complement inhibition. Thromb Haemost. 2012;108(6):1141-53.

FOR CITATION PURPOSES: *Fujita T.* Extra-immunological role of complement activation in diabetic nephropathy. OA Nephrology 2013 Oct 25;1(2):19..

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to the concept on, design, and preparation of the manuscript, as well as read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.