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.

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(H2O), which can bind to Factor B. Subsequent activation by Factor D results in the formation of C3(H2O)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 serine 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. 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.

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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).

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. Recent data suggest that C3 plays a role in metabolic disorders. The plasma C3 level is associated with the development of T2DM and several risk factors such as obesity, dyslipidaemia, and insulin resistance. 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.

Role of complement activation in diabetic vascular complications
During the course of T2DM, the following pathophysiological states are
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\(^\text{18,19}\). 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\(^\text{20}\). Experimental studies using atherosclerotic rabbits have shown that C5b-9n deposition in the arterial wall preceded monocyte infiltration and foam cell formation\(^\text{21}\).

**Dyslipidaemia and Inflammation**
Cholesterol accumulation regulates genes implicated in complement activation. Loading sterol into macrophages regulates levels of complement proteins\(^\text{22}\). In the postprandial hypercholesteremic condition, the alternative complement pathway is activated near adipose tissue\(^\text{3}\). Complement activation can promote systemic inflammation. A simplified diagram of the complement activation induced by chylomicron is shown in Figure 2. vanGreevenbroek et al.\(^\text{15}\) 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\(^\text{21}\).

**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\(^\text{16}\). The chylomicron-activated alternative pathway overproduces C3a\(^\text{3}\), C3a receptor (C3aR) expressed in adipose tissue is up-regulated after ingesting a high-fat diet\(^\text{13}\). 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\(^\text{24}\). Both obesity and the postprandial hypercholesteremic condition induce complement activation and acylation stimulating protein (ASP) production. Signalling of ASP via

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**Figure 2:** Acceleration of C3 tick over induced by obesity and dyslipidemia. Obesity-induced overproduction of C3 and the postprandial hypercholesteremic 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.

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Critical review

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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