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Review Article

Role of Complement in Diabetes

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Abstract

Accumulating evidence suggests a role for the complement system in the pathogenesis of diabetes and the vascular complications that characterise this condition. Complement proteins contribute to the development of type 1 diabetes (T1D) by enhancing the underlying organ-specific autoimmune processes. Complement upregulation and activation is also an important feature of insulin resistance and the development of type 2 diabetes (T2D). Moreover, animal and human studies indicate that complement proteins are involved in the pathogenic mechanisms leading to diabetic microvascular and macrovascular complications. The adverse vascular effects of complement appear to be related to enhancement of the inflammatory process and the predisposition to a thrombotic environment, eventually leading to vascular occlusion. Complement proteins have been considered as therapeutic targets to prevent or treat vascular disease but studies have been mainly conducted in animal models, while human work has been both limited and inconclusive so far. Further studies are needed to understand the potential role of complement proteins as therapeutic targets for reversal of the pathological processes leading to T1D and T2D and for the prevention/treatment of diabetic vascular complications.

Keywords

Complement system, diabetes, diabetic vascular complications

1. Introduction

Diabetes is now a world-wide epidemic with increasing numbers of individuals with this condition, mainly related to increased incidence of type 2 diabetes mellitus (T2D), placing considerable burden on healthcare systems. According to the WHO Global Report on Diabetes (World Health Organization, 2016), the number of adults living with diabetes has almost quadrupled since 1980 to 422 million adults, and in 2012 alone diabetes caused 1.5 million deaths. Insulin resistance is a key pathogenic mechanism in T2D, which is initially compensated for by pancreatic β-cells insulin secretion. Subsequently, these cells are no longer able to keep up with the increased demand and relative insulin deficiency ensues leading to elevated glucose levels. In contrast, type 1 diabetes (T1D) is due to autoimmune destruction of the β-cells of the pancreas usually leading to complete insulin deficiency and elevated glucose levels (Zaccardi et al., 2016). Diabetic complications include heart disease, stroke, blindness, kidney failure and lower limb amputation (extensively reviewed by Forbes and Cooper, 2013). Therefore, there is a need to intensify preventive and therapeutic efforts, including exploration of novel approaches.

One such approach may be to target the inflammatory processes, which are acknowledged to play a major role in the pathogenesis of diabetes and its vascular complications (Donath, 2014). Over the past decades, increasing evidence suggests a role of the complement system as a mediator of inflammation in diabetes and its vascular complications (Phieler et al., 2013; Østergaard et al., 2005). However, the “hen or egg question” remains: is complement upregulation and activation a symptom of the underlying inflammatory process in diabetes thus representing an epiphenomenon, or is complement activation an important player that drives the progression of diabetes and/or the development of vascular complications?

The aim of this review article is to provide an up-to-date overview over the role of complement in diabetes and shed light on the open questions raised above.

2. Role of complement in beta cell destruction in type 1 diabetes

Similarly to other autoimmune conditions, type 1 diabetes (T1D) is characterised by activation of the immune system, in genetically susceptible individuals, which ultimately leads to insulin deficiency. The highly selective destruction of insulin-producing β-cells of the pancreas is primarily mediated by an attack of activated CD4+ and CD8+ T cells, with a number of islet-derived autoantigens involved in the autoimmune process (Boldison and Wong, 2016). The cellular destruction in T1D occurs at varying rates and clinical disease is not evident until over 90% of the cells are eliminated (Eisenbarth, 1986). B cells also play a role in disease pathogenesis given that animal work has shown that genetic or acquired B cell deficiency protects from autoimmune diabetes (Serreze et al., 1996; Xiu et al., 2008). The antibody response in T1D is frequently used to confirm the diagnosis, particularly in difficult cases when the clinical presentation is atypical. In addition to activation of the cellular and humoral immune responses, the innate immunity also contributes to the pathogenesis of T1D. A role for the complement system in the development of T1D is supported by: i) genetic studies showing association of allelic variants of complement proteins with autoimmune diabetes, ii) ability of islet cell antibodies to fix complement, and iii) animal and human studies confirming activation of the complement system early in disease pathogenesis (Torn et al., 2016; Gao et al., 2013; Axelgaard et al., 2017; Abdel-Latif et al., 2017). The enhancement of the organ-specific autoimmune process by complement proteins occurs through interaction with both the cellular and humoral immune systems (Lin et al., 2010; Noorchashm et al., 1999).

Earlier small scale, cross-sectional observational studies have shown associations between T1D and the rare C4 B allele (C4 B2.9) as well as C4 null allele C4AQ0 (McCluskey et al., 1983; Lhotta et al., 1996). A more robust longitudinal study analysing 15 complement polymorphisms, in the well-characterised individuals of The Environmental Determinants of Diabetes in the Young (TEDDY) study, has shown that only rs2230199 variant of C3 showed a significant

association with clinical T1D (Torn et al., 2016). Other complement polymorphisms have shown weak associations with islet cell autoimmunity but failed to demonstrate convincing links with clinical disease. An inherent difficulty in dissecting out the role of complement variants in T1D is related to these genes residing in an area close to human major histocompatibility complex (MHC), containing HLA genes with known T1D associations. MHC is characterised by widespread linkage disequilibrium and therefore complement genes are inherited as a block of "complotype" that includes HLA variants (Alper et al., 1989). Taken together, while there is evidence for a link between complement protein variants and T1D, the observed associations are generally weak and their role in identifying individuals at risk remains unclear.

Animal studies have shown that complement C3, a central complement protein, plays a direct role in streptozotocin-induced autoimmune diabetes. Mice deficient in C3 fail to develop experimental diabetes, thought to be due to upregulation of transforming growth factor-β producing Treg cells, which in turn modulate myeloid-derived suppressor cell function and control inflammation (Lin et al., 2010; Gao et al., 2013).

A study analysed C4d, a marker of antibody-mediated complement activation, in pancreatic tissue from 11 cadaveric organ donors with T1D, 7 from T2D, 11 controls and 16 who had diabetes-related antibodies but no clinical disease. Largely similar levels of C4d were detected in tissue samples from T1D and antibody-positive individuals, while it was hardly seen in controls or in those who had T2D. The similar levels of C4d in T1D and antibody-positive samples cast doubts on the importance of this complement protein in the development of clinical disease. However, two individuals in the antibody-positive group who showed elevated C4d tissue protein, also had evidence of tissue destruction suggesting that C4d may be play a role in the early stages of disease pathogenesis (Rowe et al., 2013).

Interestingly, not all complement proteins increase the autoimmune reaction as some appear to have a protective role. It has been documented before that individuals with complete deficiency

of C4A and C4B develop generalised multi-organ autoimmune disease but this does not necessarily hold true for the organ-specific autoimmune condition T1D. A study has suggested that C4A is protective by demonstrating an association between residual β-cell function and increased C4A copy number (or higher plasma protein levels), one month following the clinical diagnosis of T1D (Kingery et al., 2012). In contrast, C4B seems to have an adverse effect as lower C4B copy numbers (or decreased plasma protein levels) correlate with disease remission at 9 months of diagnosis. While the protective effects of C4A are interesting, it should be noted that copy numbers of C4A display a strong inverse correlation with number of HLADR3 alleles; therefore the observed protective effects may simply be due to less efficient immune response secondary to low DR3 alleles. The counter-argument, however, is that logistic regression analysis still showed a role for C4A in disease remission independently of HLADR3. While these data may prove to be clinically important, we should be cautious in our interpretations as only 34 patients with T1D were investigated and a larger scale study is required before exploiting the potential role of C4A and C4B as prognostic markers or therapeutic targets in T1D. The roles of different complement proteins in the pathogenesis of T1D are summarised in Table 1.

3. Role of complement in the development of type 2 diabetes

In addition to autoimmune diabetes, the complement system may also play a role in the development of type 2 diabetes (T2D) (Li et al., 2008; King and Blom, 2017). Insulin resistance (IR), associated with obesity, is key in the pathogenesis of T2D. Pancreatic β-cells initially compensate for the presence of IR by increasing insulin secretion in order maintain glucose levels in the normal range. However, a point is reached when insulin-secreting cells are unable to keep up with the high demands of IR and glucose levels become elevated leading to the development of T2D.

The central complement protein C3, produced by liver and fat cells, received special interest as plasma levels of this protein are associated with IR and predict the development of T2D (Engstrom et al., 2005; Wlazlo et al., 2014; Nishimura et al., 2017). In vitro work has shown that cultured fat cells produce C3 and protein synthesis is upregulated in the presence of inflammatory cytokines, which can also activate the complement pathway to generate C3a (Choy et al., 1992). However, some argue against a causal relationship between C3 and T2D, citing C3 association with glucose kinase regulatory protein (GKRP) locus as a potential explanation for the link between C3 plasma levels and hyperglycaemia (Borne et al., 2017). GKRP has shown a direct effect on glucose hemostasis through regulation of glucose storage and disposal by the liver as well as insulin secretion by pancreatic β-cells (Raimondo et al., 2015). Nevertheless, C3a, as well as C5a, have been shown to increase glucose uptake by adipocytes, which was reduced using C3aR and C5aR receptor blockers, ameliorating the weight gain following high carbohydrate and high fat feeding in rats (Lim et al., 2013). The role of C3 in IR is further highlighted by demonstrating that C3 knockout (KO) mice, under high fat diet conditions, have decreased adipose tissue and are lighter compared with wild type counterpart (Murray et al., 2000).

Activation of complement proteins contributes to the inflammatory response and worsening of IR, a concept supported by animal studies demonstrating that C3aR KO mice fed high fat diet display reduced inflammatory responses in adipose tissue coupled with improved insulin sensitivity (Lim et al., 2013). This suggests that C3a has a detrimental effect on IR and the development of diabetes. Paradoxically, C3a appears to be important for healthy insulin secretion as animal work has shown that complement factor D (also known as adipsin), primarily produced by adipose tissue, is critical for adequate insulin secretion, mediated by the downstream protein C3a (Lo et al., 2014). Furthermore, reduced plasma levels of factor D have been documented in T2D individuals with impaired insulin secretion, although the number of individuals studied is relatively small to make concrete conclusions and additional larger studies

are warranted (Lo et al., 2014). Furthermore, while factor D levels do not increase in obesity, reduced plasma levels of factor D have been documented in T2D individuals with impaired insulin secretion, although the number of individuals studied is relatively small to make concrete conclusions and additional larger studies are warranted (Pomeroy et al., 1997; Lo et al., 2014). In contrast, members of the alternative pathway, including complement factor B and complement system regulators H and I show increased levels in overweight individuals with a reduction observed after weight loss (Pomeroy et al., 1997; Moreno-Navarrette et al., 2010). While C3 levels showed a relationship with weight, C3a levels showed no such association suggesting that the alterations in alternative complement protein levels represent a compensatory mechanism to keep C3a levels stable.

To further complicate matters, even non-active complement proteins may play a role in IR as reduced generation of $C3a_{des\text{-}arg}$ (acetylation stimulation protein) has been implicated in improved insulin sensitivity (Murray et al., 2000; Koistinen et al., 2001), although this remains controversial as the independent role of $C3a_{des\text{-}arg}$ in KO animal studies can be difficult to establish.

Similarly to the observation in T1D, some complement proteins may play a protective role in T2D. Islet amyloid polypetide (IAP) has been implicated in the pathophysiology of T2D and reduced insulin secretion (Jurgens et al., 2011). C4b-binding protein appears to have a protective role by inhibiting IAP aggregation into protofibrils (Sjolander et al., 2012; Sjolander et al., 2016), therefore preserving β-cell function. Another protective molecule that received interest is CD59, which protects against membrane attack complex (MAC)-induced tissue destruction. CD59 appears to maintain glucose-stimulated insulin secretion by β-cells and CD59 KO animals display deranged glucose metabolism (Krus et al., 2014; Nagaraj et al., 2015). Interestingly, CD59 glycation compromises protein function, potentially creating a vicious cycle of worsening glycaemia and which may represent one mechanism for restoration of insulin secretion after a short period of aggressive glucose lowering therapies in newly diagnosed individuals with T2D

(Ghosh et al., 2014; Ghosh et al., 2015). Another direct link between glycaemia and complement proteins is related to the interaction between mannose-binding lectin (MBL) and fructoselysine, resulting in activation of the complement lectin pathway (Fortpied et al., 2010), consequently propagating the inflammatory response in T2D. MBL-associated serine protease 1 (MASP)-1 levels have been found to be elevated in T2D but whether this contributes to IR and development of diabetes or whether elevated protein levels are merely a marker of inflammation remains unclear (Krogh et al., 2017). Complement proteins may also be used for the prediction of future diabetes. It has been shown that increased properdin and complement activation products (soluble C5b-9 MAC) are associated with a family history of T2D, at least in the South Asian population (Somani et al., 2012). Table 2 provides a summary of the role of complement in T2D.

For further details on the link between insulin resistance/metabolic disease and the complement system, the reader may wish to refer to the recent comprehensive review (Moreno-Navarrete and Fernandez-Real, 2019).

4. Microvascular complications

Microvascular complications of diabetes include diabetic nephropathy, retinopathy, and neuropathy. In these conditions, mainly small vessels, i.e. capillaries and arterioles, in the kidneys, retina, and nervous system are affected. There is clear evidence for an involvement of complement in diabetic nephropathy and retinopathy. The role of the complement system in diabetic nephropathy and diabetic retinopathy, have been elegantly reviewed recently by Flyvbjerg (2017) and by Xu and Chen (2017), respectively. Complement factors that may be involved in diabetic microvascular complications are summarised in Figure 1.

Both animal and clinical studies have confirmed a prominent role of the complement lectin pathway in the development of diabetic nephropathy. Streptozotocin-induced diabetes in mice

resulted in elevated plasma levels of MBL (Østergaard et al., 2013) and glomerular deposition of MBL (Østergaard et al., 2016), while MBL-knockout mice developed less renal damage than wild-type mice (Østergaard et al., 2007). In T1D patients, MBL levels were higher in patients with albuminuria compared with patients with normoalbuminuria and correlated with levels of urinary albumin excretion (Saraheimo et al., 2005). In prospective studies, increased MBL levels predicted microalbuminuria (Hovind et al., 2005) and progression from macroalbuminuria to end-stage renal disease (Hansen et al., 2010). Similarly, MBL levels were elevated in T2D patients with nephropathy compared with patients with normoalbuminuria (Guan et al., 2015) and predicted the development of diabetic nephropathy in T2D (Hansen et al., 2006). Among the ficolins, H-ficolin may be associated with progression of renal disease as shown in a prospective study in T1D patients (Østergaard et al., 2014), while no human studies are available yet on L-ficolin or M-ficolin. In diabetic mice, however, the deletion of B-ficolin (the orthologue to human M-ficolin) had no influence on development of diabetic nephropathy (Holt et al., 2015). Renal tubular interstitial damage by local complement activation via the lectin pathway has been suggested based on co-localisation of MBL, MASP-1 and C5b-9 in kidney biopsy samples from patients with diabetic nephropathy (Zheng et al., 2018). Evidence for classical pathway activation in patients with diabetic nephropathy comes from observations of co-localisation of glomerular deposits of IgM, C1q and C4d (Bus et al., 2018), and increased renal expression of C1q, C1s, and C1r (at the mRNA level) (Woroniecka et al., 2011). Furthermore, increased plasma and urinary levels of Bb were detected in patients with diabetic nephropathy, suggesting also a role for the alternative complement pathway (Li et al., 2019). Increased C3 concentrations in renal tissue seem to be associated with diabetic nephropathy. Glomerular deposition of C3 was observed in several animal studies (Flyvbjerg 2017), and increased glomerular C3 expression was found in kidney biopsy samples from patients with diabetic nephropathy (Woroniecka et al., 2011). C3 plasma levels showed conflicting results. In a small study of 32 T2D patients including patients with normo-, micro- and macroalbuminuria,

increased plasma C3 levels were observed, and the C3 activation product C3a desArg (or acylation stimulating protein ASP) was significantly increased in patients with macroalbuminuria (Fujita et al., 2013). In a large study of 171 biopsy-proven patients with diabetic nephropathy, patients with C3 levels lower than 90 mg/dl had more severe diabetic nephropathy with a worse outcome, albeit not as independent risk factor (Zhang et al., 2018). These conflicting findings suggest that plasma C3 levels may not reflect local C3 concentrations in renal tissue of patients with diabetic nephropathy. In addition to increased complement activation, impaired complement regulation by glycation and inactivation of CD59 has also been associated with diabetic microvascular complications (Qin et al., 2004).

In diabetic retinopathy, increased systemic and local complement activation with deposition of complement components and activation products in the eye have been described. MBL serum levels were higher in diabetes patients with diabetic retinopathy than in diabetes patients without retinopathy (Geng et al., 2015). Deposition of C3d and C5b-9 but not MBL, C1q or C4 was detected in the choriocapillaries of patients with diabetic retinopathy suggesting complement activation via the alternative pathway (Gerl et al., 2002). Yet, classical pathway activation by retinal pericyte-reactive autoantibodies in patients with diabetic retinopathy (Zhang et al., 2016) or by plasma exosomes in diabetic mice (Huang et al., 2018) has also been described to contribute to retinal damage. Furthermore, reduced levels of complement regulators CD55 and CD59 were found in the retina of patients with diabetic retinopathy (Zhang et al., 2002).

Complement activation may also play a role in diabetic neuropathy, but the evidence is rather limited and further studies are required. Epineurial vascular C3 deposition was detected in patients with diabetic radiculoplexus neuropathy (Collins et al., 2010). Complement activation products C3d and C5b-9 were detected in endoneurial microvessels following sural nerve biopsies in patients with diabetic neuropathy (Rosoklija et al., 2000). In streptozotocin-induced

diabetic mice, a decrease in CD55 expression in the spinal cord preceded an increase of C3 expression, suggesting impaired complement regulation (Nie et al., 2015).

5. Macrovascular complications

Macrovascular diabetic complications are caused by stenosis or occlusion of coronary arteries, cerebral or peripheral blood vessels and can ultimately manifest as coronary heart disease (CHD) with/without myocardial infarction (MI), stroke, or peripheral arterial disease (PAD). These complications typically develop over years, secondary to clustering of multiple risk factors (including hyperglycaemia, obesity, dyslipidaemia, hypertension and renal involvement). The earliest abnormality in vascular pathology is endothelial dysfunction, progressing to the formation of atherosclerotic plaques, and culminating in plaque rupture and formation of an obstructive vascular thrombus, leading to organ damage. Proinflammatory and procoagulant changes accompany and drive these processes, and the complement system is thought to be crucially involved at every stage, as described in a number of recent review articles (Carter, 2012, Hertle et al., 2014, Lappegard et al., 2014, Vlaicu et al., 2016). In the atheromatous vessel wall and plaque, complement activation can be triggered by cholesterol crystals and modified lipoproteins, apoptotic/necrotic cells, while complement regulatory mechanisms are reduced by decreased expression of CD55 and CD59 (Hertle et al. 2014). In the early stage, complement activation may be even beneficial to remove cell debris, but unbalanced activation and regulation will further promote inflammatory processes. Complement activation products C5a and C5b-9 can activate endothelial cells leading to increased expression of adhesion molecules and subsequent invasion of inflammatory cells (Carter, 2012). So far, the majority of evidence for complement involvement in cardiovascular disease in general is focused on complement C3, components of the lectin pathway, and complement activation products including C5a or the terminal complex C5b-9. However, only a few animal and clinical studies, which are summarised

below, have focused on the diabetes setting and specifically investigated the role of complement in macrovascular diabetic complications. Complement factors that may contribute to macrovascular diabetic complications are depicted in Figure 1.

In diabetic rats, complement C6 knock-out significantly reduced signs of early vascular inflammation and morphologic alterations in mesenteric arteries including deposition of C3 and C9, suggesting that complement activation could be involved in the development of early diabetic vascular damage (Fischetti et al., 2011). Although the mechanism(s) of complement activation in ischaemia/reperfusion injury are still under debate, an important role has been attributed to lectin pathway activation by binding of MBL to natural antibodies (IgM) bound to neo-epitopes expressed on damaged cells (Gorsuch et al., 2012). MBL KO diabetic mice and MBL inhibition in diabetic rats resulted in reduced myocardial ischaemia/reperfusion injury and decreased myocardial infarct size (Busche et al., 2008, La Bonte et al., 2009). In diabetic mice, complement C3 promoted cerebral ischaemia/reperfusion injury, whereas C3 KO mice were protected, suggesting a role for C3 in diabetic stroke (Lin et al., 2018).

An early case-control study in patients with T2D showed elevated levels of C3d in diabetes patients with ischaemic heart disease (Figueredo et al., 1993). In a prospective study in patients with T2D, elevated levels of soluble C5b-9 predicted future cardiovascular events including cardiovascular mortality and nonfatal MI or stroke in patients with T2D who had already suffered MI (Mellbin et al., 2012). In patients PAD, among which 38% had diabetes, C3 serum levels were significantly elevated compared with healthy controls, and C3 and C4 levels correlated with the severity of atherosclerosis (Fehérvári et al., 2014).

The complement regulator CD59 is of special interest in the context of macrovascular complications of diabetes (Ghosh et al., 2015). Since hyperglycaemia and other risk factors directly and indirectly increase complement activation, complement regulation is particularly important to prevent damage by further upregulation of proinflammatory and prothrombotic

pathways. However, CD59 becomes inactivated by non-enzymatic glycation in diabetes (Acosta et al., 2000), and this has been suggested to contribute to the development of macrovascular complications. Indeed, in a diabetes mouse model, deficiency in CD59 accelerated the development of atherosclerosis with larger atherosclerotic lesions and increased MAC deposition (Liu et al., 2017). In humans, red blood cells from individuals with diabetes showed significantly reduced CD59 activity and were more sensitive to MAC-mediated lysis (Qin et al., 2004).

The complement system is also believed to contribute to atherothrombosis via its multiple links to the coagulation system (Conway, 2015). In the context of diabetes, we have shown that C3 is incorporated into plasma clots, affects clot structure and impairs fibrinolysis, particularly in diabetes patients, suggesting a novel mechanism for hypofibrinolysis in diabetes (Schroeder et al., 2010, Howes et al., 2012, Hess et al., 2012a, Hess et al., 2014). We and others have also reported elevated plasma levels of MASP-1 in patients with T1D (Jenny et al., 2015a) and in patients with T2D (Krogh et al., 2017). Since MASP-1 can promote clot formation by directly activating coagulation factors (Hess et al., 2012b, Jenny et al., 2015b, Jenny et al., 2018), this may represent another mechanism of complement-mediated atherothrombotic complications in diabetes.

Taken together, based on numerous animal and human studies on the role of complement in atherosclerosis and cardiovascular diseases, it is highly plausible that increased complement activation is also critically involved in the development of macrovascular complications of diabetes, but further and larger human studies in the diabetes setting are needed to prove it.

6. Complement as a therapeutic target to reduce complications in diabetes

Never before have so many complement proteins been considered as therapeutic targets (recently reviewed by Ricklin et al., 2018, and Harris et al., 2018). Up to date, however, there are

only few examples for complement-targeting therapies that have successfully entered routine clinical practice. The crucial question: Is there any evidence that patients with diabetes might benefit from anti-complement therapy to prevent diabetic vascular complications?

Complement as therapeutic target to reduce diabetic microvascular complications has so far been mainly evaluated in animal studies. Attempts to ameliorate diabetic nephropathy were undertaken with a C5 inhibitor (K-76 COONa) and C3a and C5a receptor antagonists, respectively, in diabetic rat models (Fujita et al., 1999; Li et al., 2014; Li et al., 2015). K-76 COONa decreased proteinuria and reduced mesangial expansion and C3 deposition in glomeruli (Fujita et al., 1999). Diabetic rats treated with a C3a receptor antagonist showed improved renal function and morphology with less cytokine release and extracellular matrix deposition (Li et al., 2014). The combined administration of C3a and C5a receptor antagonists improved renal function in diabetic rats and reduced fibrosis in diabetic rats and in vitro in human renal glomerular endothelial cells (Li et al., 2015). A different target may be thrombomodulin, a regulator of both complement and coagulation activation. Diabetic mice lacking the thrombomodulin lectin-like domain had aggravated diabetic nephropathy, and in vitro thrombomodulin lectin-like domain prevented glucose-induced complement activation on endothelial cells (Wang et al., 2012). In mice with diabetic retinopathy, local delivery of a soluble form of CD59 using an adeno-associated virus vector improved blood flow in retinal blood vessels and reduced local cell apoptosis and MAC deposition (Adhi et al., 2013).

In the field of cardiovascular diseases, complement inhibition to reduce complications of acute myocardial infarction (AMI) has been explored in numerous animal and clinical studies (recently reviewed by Emmens et al., 2017), however, usually without a special focus on diabetes. One study in diabetic rats showed that treatment with FUT-175, a strong inhibitor of C1r and C1s that possibly also exhibited inhibitory effects on other complement and further serine proteases, significantly decreased infarct size, complement deposition and neutrophil accumulation in the

diabetic heart when administered before reperfusion (La Bonte et al., 2008). Although many promising findings of anti-complement treatment in AMI were made, the high expectations of the C5 inhibitor pexelizumab in clinical studies were not quite fulfilled (Emmens et al., 2017). Still, there may be therapeutic options in certain subgroups of patients. In high-risk patients undergoing coronary artery bypass grafting, who had at least two or more risk factors including diabetes, pexelizumab did reduce morbidity and mortality (Haverich et al., 2006).

Taken together, despite of promising basic research clearly showing a role of complement in diabetes and development of diabetic complications, more efforts must be undertaken to evaluate whether complement inhibition may be a novel and additional therapeutic approach. Based on successful anti-complement therapy in certain human kidney and eye diseases, and results from animal studies in diabetic microvascular complications, there is a reason to suggest that targeting the complement system may reduce diabetic vascular complications in humans. So far there is no evidence that complement inhibition might prevent the development of T1D or T2D. Due to its important role in immune defense, complement inhibition always confers a risk of infection and hence the risk/benefit ratio of anti-complement therapies must be carefully considered. Whether it may be possible in the future to separate the damaging effects of complement in diabetes (and other diseases) from its important protective function against infection by specifically targeting a certain complement pathway and/or targeting complement activation exclusively at a specific location in the body, remains to be explored.

7. Conclusions and future directions

With its role in inflammatory processes and links to other systems in the body, such as the coagulation cascade, the complement system is involved in numerous clinical conditions, including the development of the two main types of diabetes. As summarised in Figure 2 in a schematic overview, complement proteins contribute to the pathogenesis of T1D by enhancing

the underlying autoimmune process, while complement upregulation appears to be is an important feature of insulin resistance and T2D. There is clear evidence from animal and human studies for an involvement of complement proteins in microvascular complications, such as diabetic nephropathy and retinopathy, and also macrovascular disease that results in myocardial infarction and stroke. Complement proteins do not only enhance the inflammatory milieu that predisposes to vascular disease but also increases the prothrombotic and hypofibrinolytic environment, thus directly contributing to vascular occlusion.

All this evidence would make complement proteins potential therapeutic targets to reduce the vascular complications in diabetes, which remain the main cause of morbidity and mortality in this condition. A particular challenge with the complement system is the presence of a large number of proteins and different pathways for activation, and the tight interactions with other cellular and humoral systems in the body. This makes it difficult to identify the best target that provides a benefit without increasing the risk of unwanted side effects. And while there is a substantial body of descriptive evidence that complement upregulation and activation occurs in diabetes and its complications, there is a general lack in interventional studies assessing the role of complement inhibitors. Further studies are clearly needed before concluding whether complement inhibition can prevent diabetes progression and/or development of vascular complications.

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Tables

Table 1. Role of complement proteins in the pathogenesis of type 1 diabetes (T1D).

Complement protein	Observed abnormality	Role in T1D pathogenesis
C3	Activated (association with protein polymorphism)	Reduction in Treg cells, enhancing the autoimmune response
C4d	Pancreatic deposition	Increased inflammatory reaction and tissue destruction
C4A	Altered copy number or protein plasma levels	High copy/levels associated with residual β-cell function (protective)
C4B	Altered copy number or protein plasma levels	Low copy/levels associated with remission (protective)

Table 2. Role of complement proteins in the pathogenesis of type 2 diabetes (T2D).

Complement protein	Observed abnormality	Role in T2D pathogenesis
C3	High plasma levels	Increase adipose tissue inflammation and IR; possible role in increased adiposity
C3a and C5a	Increased production	Increased adipose tissue inflammation and adiposity Paradoxically, C3a may increase insulin secretion
Factors I and H	Elevated plasma levels	Possible compensatory mechanism to keep C3a levels stable
C4b binding protein	Presence in islet cells	↓ IAP aggregation, thus preserving β-cell function (protective)
CD59	Increased glycation	Increased MAC, resulting in β-cell destruction
MBL	Interaction with fructoselysine	Activation of the complement system and ↑ inflammation
$C3a_{des\text{-}arg}$	Increased production	Possible role in IR

IR: insulin resistance, IAP: islet amyloid polypetide, MAC: membrane attack complex, MBL: mannan-binding lectin.

Figure captions

Fig. 1. Complement in micro- and macrovascular diabetic complications. Animal and/or human studies have provided evidence that the complement factors shown are involved in microvascular diabetic complications such as diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy, and in macrovasular diabetic complications such as cardiovascular disease, cerebrovascular disease, and peripheral arterial disease. Evidence from animal studies is highlighted in yellow, evidence from human studies is highlighted in green. Increased plasma (or serum) levels: p↑; decreased plasma (or serum) levels: p↓; tissue deposition: td; increased expression and/or activity in tissue: t↑; decreased expression and/or activity in tissue: t↓. ([1]) MBL knock-out and inhibition were protective. ([2]) C3 knock-out was protective.

Fig. 2. Role of complement in diabetes. This schematic overview summarises the complement proteins and putative mechanisms involved in the development of T1D, T2D, and diabetic vascular complications. F: factor; IR: insulin resistance; MAC: membrane attack complex; MASP-1: mannan-binding lectin-associated serine protease 1; MBL: mannan-binding lectin.