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Circulating C1q levels in health and disease, more than just a biomarker

Fleur S. van de Bovenkamp [a], Douwe J. Dijkstra [a], Cees van Kooten [b], Kyra A. Gelderman [c], Leendert A. Trouw [a,*]

[a] Department of Immunology, Leiden University Medical Center, Leiden, the Netherlands
[b] Department of Nephrology, Leiden University Medical Center, Leiden, the Netherlands
[c] Sanquin Diagnostic Services, Amsterdam, the Netherlands

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ABSTRACT

C1q is the recognition molecule of the classical pathway of the complement system. By binding to its targets, such as antigen-bound immunoglobulins or C-reactive protein, C1q contributes to the innate defense against infections. However, C1q also plays several other roles beyond its traditional role in complement activation. Circulating levels of C1q are determined in routine diagnostics as biomarker in several diseases.

Decreased C1q levels are present in several autoimmune conditions. The decreased levels reflect the consumption of C1q by complement activation and serves as a biomarker for disease activity. In contrast, increased C1q levels are present in infectious and inflammatory diseases and may serve as a diagnostic biomarker. The increased levels of C1q are still incompletely understood but are suggested to modulate the adaptive immune response as C1q is known to impact on the maturation status of antigen-presenting cells and C1q impacts directly on T cells leading to decreased T-cell activity in high C1q conditions.

In this review, we provide a comprehensive overview of the current literature on circulating levels of C1q in health and disease, and discuss how C1q can both protect against infections as well as maintain tolerance by regulating adaptive immunity.

1. Introduction

The complement system is a critical part of our immune defense against infections. It consists of a cascade of serum proteins which can be activated via three different pathways that each use pathway-specific recognition molecules. In this review, we will focus on C1q, the recognition molecule of the classical pathway of complement activation. When C1q binds to its ligands, such as antibodies on invading pathogens, activation of the classical pathway of the complement system commences. Besides C1q, the C1 complex comprises the enzymes C1r and C1s. Upon binding of C1 to its ligands, the enzymes become active, resulting in the cleavage of C4 and C2 and the formation of a classical pathway C3 convertase. This convertase can in turn cleave and thereby activate C3, which results in the release of the anaphylatoxin C3a, the opsonization of pathogens with C3b, and the formation of C5 convertases. The latter can lead to direct killing of pathogens through the formation of a membrane attack complex (C5b-9), whereas C3 fragments induce attraction of cells of the adaptive immune system expressing the appropriate complement receptors.

Remarkably, in addition to its role in the defense against infections, complement also protects against autoimmunity. For example, C1q deficiency is strongly associated with systemic lupus erythematosus (SLE) (van Schaarenburg et al., 2015). One of the proposed mechanisms, described as the waste disposal theory (Walport, 2001), is that C1q is required for the removal of dead cells, and that in the absence of C1q, dead cells are not removed efficiently (Nauta et al., 2002). This would result in exposure of intracellular molecules, eliciting an immune response against these (self) molecules (Botto et al., 1998). However, C1q is just one of many molecules opsonizing dead cells for uptake. In addition, while genetic deficiencies of other classical pathway components like C4 and C2 are also associated with SLE, they have a much lower penetrance of disease (Bowness et al., 1994; Lubbers et al., 2019; Pickering et al., 2008). Collectively, this indicates that the association between C1q deficiency and SLE cannot only be explained by classical pathway activity. Therefore, C1q is expected to have functions that are outside its role in the activation of the classical pathway.

In contrast to decreased C1q levels observed in several autoimmune diseases, increased C1q levels have been reported for multiple infectious

* Corresponding author at: Department of Immunology, L3-33A, Leiden University Medical Center, Postbus 9600, 2300 RC Leiden, the Netherlands.
E-mail address: L.A.Trouw@LUMC.nl (L.A. Trouw).

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and inflammatory diseases, including tuberculosis and sarcoidosis. In these conditions, the increased levels of C1q have been suggested to impact not only on the activity of the complement system but rather on the activity of the adaptive immune response.

In this review, we provide a comprehensive overview of the current literature on circulating levels of C1q in health and disease, and discuss how C1q can both protect against infections as well as maintain tolerance by regulating adaptive immunity.

2. Sources of C1q and regulation of production

It is now well accepted that extrahepatic complement production can take place for many components of the complement system (Lubbers et al., 2017). This is especially true for C1q, for which it is known that hepatocytes are not the source of production. This is best exemplified by the original observations that transplantation of wild-type bone marrow to C1q-deficient mice results in a complete restoration of circulating serum levels of C1q (Petry et al., 2001). Inversely, when bone marrow of C1q-deficient mice is transplanted into wild-type animals, this results in a gradual loss of circulating C1q. This pinpoints the hematopoietic system as the origin of C1q. More recently, also hematopoietic stem cell transplantation in human C1q-deficient patients revealed the same restoration of C1q levels with impressive impact on the clinical conditions of the patients (Arkwright et al., 2014; Olsson et al., 2016). Unfortunately, hematopoietic stem cell transplantation is still not without risk, which impacted also on the C1q-deficient patients (Olsson et al., 2016).

Within the hematopoietic cells, most studies have identified the myeloid lineage as the major source of C1q production. Both in humans and mice, strong C1q mRNA expression and protein production have been demonstrated for diverse populations of monocytes/macrophages and dendritic cells (Castellano et al., 2010, 2004; Faust and Loos, 2002; Loos et al., 1989). Interestingly, most studies have shown that monocytes, the blood-circulating precursor of various subsets of macrophages and dendritic cells, lack C1q expression, and that this capacity is obtained when cultured in vitro (Cao et al., 2003; Kaul and Loos, 1995; Lu et al., 1996). It is likely that the ability to express C1q is also obtained in vivo, when cells migrate into tissues and differentiate into macrophages or dendritic cells.

Over the past decades, the plasticity of the myeloid lineage and its functional diversity have been increasingly recognized (Sica and Mantovani, 2012; Varol et al., 2015). Within tissues, there is a clear distinction between blood monocyte-derived cells and resident cells with fetal origin (Guilliams et al., 2014). Moreover, these cells can have very diverse functions, including phagocytosis and waste disposal, antigen presentation, activation of adaptive immunity, immune modulation and repair. The local delivery and production of C1q by these cells must be seen in the context of these different functions. This is additional to the well-known role of C1q as a systemically circulating molecule, essential for classical pathway activation.

Since monocytes do not express C1q, the capacity to start expressing this molecule will likely be obtained upon migration and depend on the local conditions in the tissue, contributing to the differentiation of these cells. In vitro experiments indicate that the mode of activation of these cells results in differential effects on C1q production. For instance, activation of macrophages with LPS results in an increased production, whereas the same trigger downregulates expression in monocyte-derived dendritic cells (Castellano et al., 2004). Intriguingly, also anti-inflammatory agents like corticosteroids have been described to increase C1q production (Zimmer et al., 2012). The regulation of C1q production at the molecular level is still incompletely understood, but the transcription factors IRF8 and PU.1, regulators of myelopoiesis, have been reported to control the synchronized expression of the three chains of C1q (Chen et al., 2011). In addition, MafB was identified as a critical regulator of C1q production (Tran et al., 2017), and although interactions between MafB and IRF8 or PU.1 have been suggested, further analyses are required.

In the new era of single cell sequencing, important new insights have been obtained in cellular heterogeneity, including myeloid cell subsets, both in lymphoid organs as well as in non-lymphoid tissues. Interestingly, in unbiased analyses, C1q genes have been identified as gene products that can distinguish different myeloid subsets in for instance brain (Van Hove et al., 2019), gut (De Schepper et al., 2018), liver (Zhao et al., 2020) and kidney (Wu et al., 2018; Zimmerman et al., 2019). C1q expression has also been identified as a marker of tumor-associated macrophages (Roumenina et al., 2019a). This adds a novel level of complexity to the commonly used, but simplistic, division into pro- and anti-inflammatory myeloid cells, since C1q can both activate the complement system and regulate adaptive immunity (see Section 7).

Theoretically, there are at least three mechanisms how local C1q production can have functional consequences. First, C1q can activate the classical pathway locally, generating additional downstream products, like C3 fragments. The prerequisites for this activity are that the other components of the classical pathway are also present, either through local production or derived from the systemic compartment, and that C1q associates with the serine proteases C1r and C1s. Second, these proteases associated with C1q could cleave alternative targets, thereby activating non-canonical pathways. An example of this would be the reported activation of Wnt signaling (Naito et al., 2012). Third, C1q could interact with receptors for C1q, and in such a way activate diverse cellular processes (Ghebrehiwet et al., 2017). Although the expression of C1r and C1s by myeloid cells has been described, the exact composition of locally produced C1 is less well established and should be studied in more detail.

3. C1q testing in clinical diagnostics

C1q levels can be determined by different kinds of techniques such as nephelometry, ELISA or rocket immune electrophoresis, as has recently been reviewed by Sandholm and colleagues (Sandholm et al., 2019). In most routine diagnostic laboratories, nephelometry or turbidimetry is the technique of choice, since these techniques are used for many other serum proteins and are high-throughput methods. However, results on C1q levels obtained with these techniques may be affected by C1q-containing immune complexes and/or anti-C1q antibodies present in the sample (Sandholm et al., 2019). ELISA is a good alternative technique to determine C1q concentrations (Dillon et al., 2009). However, the upcoming European IVDR (In Vitro Diagnostics Regulation) legislation, where CE (Conformité Européenne) marked laboratory tests should be used when available, may confine the range of tests that can be used.

Low C1q levels can be the result of defective production or increased consumption. In the case of consumption, in general not only C1q levels but also levels of other complement components are low. For example, during a flare in SLE, C1q levels as well as C4 and C3 levels are decreased. High C1q levels are primarily the result of increased production.

In the case of a primary C1q deficiency observed with one of the immunochemical methods, genetic testing may be used as confirmation, although nowadays, genetics (mostly next generation sequencing/whole exome sequencing) is also used as first line of testing. Although several variations in the C1q genes have been associated with SLE severity (Guo et al., 2018), such information is often difficult to translate to the individual patient and newly found variants are not simply linkable to pathogenicity without protein-based confirmation studies (Brodszki et al., 2020).

C1q serum concentrations are determined for diagnostic or prognostic purposes in several clinical conditions. However, it is important to realize that, in general, the specificity and sensitivity of C1q levels (or other complement components) for specific diseases or clinical presentations are not very high (Ekdahl et al., 2018). Of course, in cases of primary or secondary deficiencies, measurements of the complement

protein will help to pinpoint which factor is absent in case of a type I deficiency (Brodszki et al., 2020). C1q deficiency is strongly associated with the development of SLE (80 % of C1q-deficient patients suffer from SLE (van Schaarenburg et al., 2015)) and other autoimmune diseases (see section 6.1), but interestingly about one tenth do not show signs of autoimmunity but suffer from infections only (Stegert et al., 2015; van Schaarenburg et al., 2015). Measuring C1q protein concentrations in patients with a suspected deficiency based on absent classical pathway activity is helpful to distinguish between C1q, C1r, C1s, C2, and C4 deficiency. In this context, it may be interesting to realize that not every functional assay is equally sensitive for low levels of C1q. The traditional hemolytic CH50 for instance may still result in significant hemolytic activity with very low levels of C1q in the serum, whereas in other plate-bound classical pathway activation assays the same low levels of C1q would frequently result in complete lack of activity. The determination of C1q concentration can also aid in the diagnostic trajectory and follow-up of SLE patients, since a decreased serum level of C1q is more specific for SLE than decreased levels of C3 and C4, although the sensitivity is low (Gunnarsson et al., 2002). Relative changes in complement protein levels in SLE are in general more important predictors of current or impending flares than the absolute levels (Birmingham et al., 2010). Furthermore, it has been shown that measuring complement protein levels, including C1q, is especially helpful in the context of lupus nephritis, where a flare often goes together with a decrease in C1q levels. In spite of this, C1q is currently not part of the diagnostic package as described in the SLE SLICC criteria (2012) that are often used to assess patients with a clinical picture fitting SLE.

The serum levels of C1q are of greater diagnostic significance in the context of angioedema, a clinical condition primarily manifested by sudden swelling of tissues (see Section 6.1.4). Decreased C4 levels and C1-esterase inhibitor (C1-INH) activity are mostly used to confirm aberrant C1-INH function leading to angioedema (Farkas et al., 2016). C1q comes into this picture to distinguish between the hereditary form of angioedema with normal C1q levels and the acquired form of angioedema, where decreased C1q concentrations are observed (Farkas et al., 2016; Patel and Pongracic, 2019). C1q levels are not (yet) measured in the routine diagnostic setting for the clinical conditions described in this review that are characterized by increased levels of C1q, e.g., tuberculosis (see Section 6.2.1.1) or kala azar (see Section 6.2.1.4).

It is important to mention that currently there is no formal international standard for C1q and that several techniques are used around the world to detect C1q. The calculation of the concentration is for each test based on different standards, which makes it difficult to directly compare C1q protein levels from one study to the other. However, different groups can be compared within studies, and differences based on those comparisons are described in this review.

As highlighted in Fig. 1, the levels of circulating C1q as measured in routine diagnostic labs for the (expected) low C1q indications often reveal C1q levels to be in the normal range, but importantly also frequently reveal the levels to be increased. With this review, we provide support for the notion that aberrant C1q levels may not only be relevant as a biomarker, but importantly may also impact on disease.

4. Traditional functions of C1q

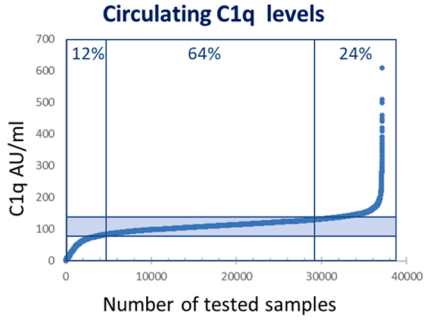
C1q is the recognition molecule of the classical pathway of the complement system and thereby protects against infections. Its targets include antigen-bound immunoglobulins, C-reactive protein and apoptotic cells. Upon binding of C1q to its targets, the enzymes C1r and C1s (which are together with C1q called the C1 complex) become active, resulting in the cleavage of C4 and C2 and the formation of a classical pathway C3 convertase. The resulting complement activation can lead to activation of the complement effector mechanisms; opsonization, anaphylatoxin release and formation of the membrane attack complex. Next to these traditional roles for C1q in activation of the classical pathway, also non-traditional roles have been described that we will discuss in Section 7.

5. Circulating C1q levels in health

5.1. C1q levels increase with age

There is a wealth of papers describing steady state circulating C1q levels in healthy individuals. Serum C1q levels are low in umbilical cord blood (Davis et al., 1979; Johnson et al., 1983; Yonemasu et al., 1978) and slightly increase in children (Davis et al., 1979; Prellner et al., 1987; Roach et al., 1981; Yonemasu et al., 1978), reaching adult levels after 2 years of age (Willems et al., 2019). During aging in adulthood, the C1q levels keep increasing (Prellner et al., 1987; Roach et al., 1981), with several reports describing an almost twofold increase in serum C1q levels (Watanabe et al., 2015; Yonemasu et al., 1978).

In line with the increase in serum C1q levels with age, also an increase in C1q levels in the cerebrospinal fluid (CSF) is reported (Smyth et al., 1994). Substantial differences in the C1q protein content of mouse and human brain tissue was observed with immunohistochemistry



Circulating C1q levels of samples sent in for routine diagnostics display both reduced and increased levels.

Circulating C1q levels, measured in routine diagnostic samples over a period of several years at Sanquin Diagnostics, Amsterdam, The Netherlands, plotted ranked from low to high. The C1q levels were determined using nephelometry and are presented as arbitrary units per ml. The normal range is established as 81-128 AU/ml which roughly corresponds with 127-201 µg/ml. The total of 37122 samples were sent in for analyses for diagnostic or prognostic purposes or to follow therapy outcome. The data set does include follow up samples. Importantly the plot shows that even though all current diagnostic analyses for C1q are done in the context of (expected) reduced C1q levels, here 12% of the samples, there are even more patients that display an increased C1q level, here 24%.

Fig. 1. Circulating C1q levels of samples sent in for routine diagnostics display both reduced and increased levels.
Circulating C1q levels, measured in routine diagnostic samples over a period of several years at Sanquin Diagnostics, Amsterdam, The Netherlands, plotted ranked from low to high. The C1q levels were determined using nephelometry and are presented as arbitrary units per ml. The normal range is established as 81−128 AU/mL (this roughly corresponds with 127−201 mg/L). The total of 37,122 samples were sent in for analyses for diagnostic or prognostic purposes or to follow therapy outcome.
The data set does include follow up samples. Importantly the plot shows that even though all current diagnostic analyses for C1q are done in the context of (expected) reduced C1q levels, here 12 % of the samples, there are even more patients that display an increased C1q level, here 24 %.

comparing very young to very old brain specimens (Stephan et al., 2013). Also under well-controlled conditions in mice, an increase in C1q levels in the brain (and other tissues) as well as an increase in serum C1q levels with age have been observed (Naito et al., 2012).

Importantly, not all studies observed a clear relationship between C1q levels and age (Gaya da Costa et al., 2018). This discrepancy might be explained by the different techniques used to determine C1q levels, study group size and extremes in the ages of the participants of the studies.

5.2. C1q levels are similar between men and women

Similar serum C1q levels between boys and girls from 1 to 19 years old were reported (Roach et al., 1981), which was later confirmed for another group of children from 1 to 5 years old (Prellner et al., 1987). Also in adults (20–69 years old), no differences in serum C1q levels between men and women were found (Gaya da Costa et al., 2018; Willems et al., 2019).

Although complement activity in female mice is lower than that in male mice, this is mainly due to limiting levels of terminal pathway components (C6 and C9), and serum C1q levels are not significantly different between female and male mice (Kotimaa et al., 2016).

6. Circulating C1q levels in disease

6.1. Clinical conditions associated with low levels of C1q

6.1.1. Decreased C1q levels during pregnancy are associated with complications

A role for C1q in pregnancy can be concluded from the observation that C1q-deficient mice get fewer and smaller pups than wild-type mice (Agostinis et al., 2010; Singh et al., 2011). In line with this, Singh and colleagues showed that C1q-deficient mice develop clinical symptoms of human preeclampsia, including hypertension and proteinuria (Singh et al., 2011). Together with the previously reported contribution of C1q to vascular and tissue remodeling (Agostinis et al., 2010), these studies suggest that defective C1q production may be involved in pregnancy disorders. There are still only few studies on the role of complement, and particular C1q, in human pregnancy complications. One study describes that serum C1q levels are not significantly different between pregnant and non-pregnant women, and remain similar throughout the pregnancy trimesters (Agostinis et al., 2016). However, serum C1q levels are reported to be decreased in preeclampsia patients compared to healthy pregnant women, despite similar placental C1q levels (Agostinis et al., 2016).

6.1.2. Systemic lupus erythematosus

In the prototypic systemic autoimmune disease SLE, in which many organs can be affected including the skin, kidneys and brain, complement - and especially C1q - plays an interesting and seemingly paradoxical role (Carroll, 2000; Walport et al., 1998). In a very small proportion of SLE patients, the disease is triggered by a genetic deficiency in C1q, while in the majority of SLE patients, that are C1q sufficient, C1q may actually contribute to disease activity as evidenced by decreased levels of C1q due to consumption. In fact, the circulating C1q levels are negatively correlated with the SLE disease activity index (SLEDAI) (Bengtsson et al., 1999; Jonsson et al., 1995; Lewis et al., 1971; Sandholm et al., 2019; Swaak et al., 1979; Tan et al., 2013). A related aspect of C1q biology in SLE is the presence of anti-C1q autoantibodies, which is associated with renal pathology. These antibodies will be discussed in Section 8 (anti-C1q antibodies in health and disease).

As discussed in the introduction, the strong association between genetic C1q deficiency and SLE was originally explained by the waste disposal theory (Walport, 2001), in which the absence of C1q would result in inefficient removal of dead cells (Nauta et al., 2002), exposure of intracellular molecules, and development of autoantibodies (Botto et al., 1998). C1q is just one of many molecules that contribute to the removal of dead cells, and genetic deficiencies of other classical pathway components have a much lower penetrance of disease (Bowness et al., 1994; Lubbers et al., 2019; Pickering et al., 2008). Therefore, it appears that C1q has functions outside its role in the activation of the classical pathway, influencing adaptive immunity, which will be discussed in Section 7.

6.1.3. Hypocomplementemic urticarial vasculitis syndrome

Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare autoimmune disease characterized by recurrent urticarial (skin) lesions appearing as vasculitis (McDuffie et al., 1973). Complement protein measurements revealed low serum levels of C1q and C4 and variable levels of C3 (Abdallah et al., 2010; Salim et al., 2018), hence the name of this syndrome. Like in SLE patients, anti-C1q antibodies can be found in HUVS patients, but now in 100 % of the patients (see Section 8 on anti-C1q antibodies) (Abdallah et al., 2010; Salim et al., 2018). Consequently, HUVS is also referred to as an immune complex disease, with increased serum levels of immune complexes (containing anti-C1q antibodies and C1q) (Tanaka et al., 2017). Deposition of immune complexes in the kidney has also been described (Pasini et al., 2014; Tanaka et al., 2017) and can cause nephritis in these patients. Low serum C1q levels are probably the result of C1q consumption and/or depletion, and like in SLE (see Section 6.1.2) may predispose to disease.

6.1.4. Angioedema

Another clinical condition associated with low levels of C1q is angioedema, bradykinin-mediated swelling of subcutaneous and mucous tissues. Hereditary angioedema (HAE) is usually caused by decreased C1-INH synthesis due to (heterozygous/homozygous) C1-INH deficiency (type I), or decreased C1-INH function due to synthesis of non-functional C1-INH (type II). Acquired angioedema (AAE) is usually caused by decreased C1-INH function due to C1-INH consumption (type I) or anti-C1-INH antibodies (type II) (Farkas et al., 2016).

Decreased C1q levels were reported in AAE patients (Breitbart and Bielory, 2010; Farkas et al., 2016; Patel and Pongracic, 2019) and result from C1q consumption, possibly not contributing to disease but being of diagnostic significance (see Section 3). In contrast, HAE patients generally have serum C1q levels in the low-normal range (Farkas et al., 2016; Patel and Pongracic, 2019), with some patients displaying reduced levels (Brasher, 1977; Brasher et al., 1975; Pickering et al., 1968). HAE patients with homozygous C1-INH deficiency were reported with undetectable C1q levels (due to C1q consumption), whereas their heterozygous family members with HAE had normal C1q levels (Blanch et al., 2006).

6.1.5. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease of the joints. Genetic variants of C1q associated with decreased levels of C1q predispose to RA (Trouw et al., 2013), which suggests that low serum C1q levels may predispose to autoimmunity. In line with this, it has been reported that serum C1q levels are lower in RA patients with a longer disease duration (more than 5/10 years) than in RA patients with a shorter disease duration (Ochi et al., 1988; Olsen et al., 1991). On the other hand, serum C1q levels are reported to be higher in RA patients with more than 20 affected joints (Ochi et al., 1988, 1984; Olsen et al., 1991), while Möttönen and colleagues reported that serum C1q levels do not correlate with the number of involved joints (Mottonen et al., 1989). Several studies described overall serum C1q levels to be higher in RA patients than in healthy controls (Mottonen et al., 1989; Ochi et al., 1988, 1984; Olsen et al., 1991). Original studies in the eighties, using radial immunodiffusion, reported increased C1q levels in serum and synovial fluid of a large cohort of RA patients (Ochi et al., 1980), while a more recent but small study did not reveal significant differences in plasma C1q levels measured by Luminex (Bemis et al., 2019). Altogether, conflicting data on C1q levels in RA patients have been

published.

6.2. Clinical conditions associated with high levels of C1q

6.2.1. Infectious diseases

6.2.1.1. Tuberculosis. In contrast to decreased C1q levels observed in pregnancy complications, several autoimmune diseases, and angioedema, increased C1q levels have been reported for several infectious and inflammatory diseases. Tuberculosis is caused by infection with *Mycobacterium tuberculosis* bacteria and generally affects the lungs. C1q mRNA levels measured in whole blood or PBMCs (Cai et al., 2014; Cliff et al., 2013; Esmail et al., 2018; Lubbers et al., 2018; Maertzdorf et al., 2011) as well as serum/plasma C1q levels (Bjorvatn et al., 1976; Cai et al., 2014; Lubbers et al., 2018) and pleural fluid C1q levels (Cai et al., 2014) are increased in tuberculosis patients and treatment decreases these levels back to normal (Cai et al., 2014; Cliff et al., 2013; Lubbers et al., 2018). Interestingly, serum C1q levels do not change upon BCG (Bacillus Calmette-Guérin) vaccination, indicating that an active infection is required for the induction of increased C1q levels (Lubbers et al., 2018). In experiments using non-human primates with tuberculosis, serum and bronchoalveolar lavage fluid C1q levels are increased, precede clinical onset and associate with disease severity (Dijkman et al., 2020; Lubbers et al., 2018).

The increased levels of C1q, induced by an active tuberculosis infection, appear to be in contrast with an evasion of the pathogen from complement attack, as now a more potent classical pathway is in place to kill the pathogen. Interestingly, the active tuberculosis infection also results in a massive increase in the levels of C1-INH, the natural inhibitor of the classical pathway (Lubbers et al., 2020). As discussed in more detail in Section 7, it appears that the pathogen induces increased C1q levels, possibly to inhibit adaptive immune responses, while limiting the impact of a potentiated classical pathway by the simultaneous upregulation of C1-INH.

6.2.1.2. Leprosy. Leprosy, an infectious disease caused by infection with *Mycobacterium leprae* or *Mycobacterium lepromatosis* bacteria, is characterized by damage of the nerves, respiratory tract, skin, and eyes. Whereas conflicting results obtained with different techniques (ELISA or radial immunodiffusion) have been published regarding plasma/serum C1q levels being decreased (Negera et al., 2018), unaffected (Lubbers et al., 2018), or increased (Bjorvatn et al., 1976) in leprosy patients, blood and skin C1q mRNA levels are increased in leprosy patients (Negera et al., 2018). Dupnik and colleagues confirmed increased C1q mRNA levels and additionally showed increased C1q deposition in the skin of leprosy patients (Dupnik et al., 2015).

6.2.1.3. Malaria. Malaria is caused by infection with *Plasmodium* parasites, of which five species regularly infect humans and *Plasmodium falciparum* is the most lethal in humans. Conflicting data on C1q levels in malaria patients have been published. Although decreased classical pathway activity has been reported for patients with *Plasmodium falciparum* infection and serum C1q levels were abnormally low in certain patients, mean serum C1q levels were actually slightly increased in the total group of patients (Adam et al., 1981; Phanuphak et al., 1985), possibly reflecting an acute phase response to infection. In line with this, increased C1q protein and mRNA levels were reported for malaria-infected placentas (Galbraith et al., 1980; Muehlenbachs et al., 2007). Whereas serum C1q levels are slightly decreased in mice with (cerebral) malaria, brain C1q levels were increased (Lackner et al., 2008), possibly due to systemic leakage of C1q into the brain.

6.2.1.4. Other infectious diseases. For several other infectious diseases, predominantly involving intracellular pathogens, increased serum C1q levels have been reported. A pronounced example is hepatitis C (Dumestre-Perard et al., 2002; Talaat et al., 2007), which is caused by infection with hepatitis C virus. Also kala azar (Kager et al., 1982), which is caused by infection with *Leishmania* parasites, displays substantial increased serum C1q levels.

For two other infectious diseases, namely neuroborreliosis, which is caused by infection with *Borrelia* bacteria, and meningitis, caused by a variety of microorganisms, plasma C1q levels are unaffected, but CSF C1q levels are increased (Henningsson et al., 2007; Mook-Kanamori et al., 2014; Shen et al., 2017). Possibly, the increased CSF C1q levels are more a reflection of increased leakage from the serum rather than increased systemic C1q production, although local C1q production may also contribute to increased CSF C1q levels (Morgan and Gasque, 1996).

6.2.2. Inflammatory diseases

6.2.2.1. Lungs. Besides increased C1q levels found in patients with the infectious disease tuberculosis (discussed in Section 6.2.1.1), also other pulmonary diseases have been associated with aberrant C1q levels. Sarcoidosis of the lung is characterized by granuloma formation and while the cause of this disease is unknown, modestly increased serum C1q levels have been reported for sarcoidosis patients (Lubbers et al., 2018). However, normal or slightly decreased serum C1q levels have been reported for patients suffering from bacterial and/or viral pneumonia, with normal C1q levels upon recovery (Lubbers et al., 2018). In line with this, patients with severe emphysema present decreased C1q levels, which has been shown to be induced by cigarette smoke and promote disease (Yuan et al., 2019). The authors report that (the lack of) C1q impacts on adaptive immunity by inducing an increased frequency of T helper 17 (Th17) cells, which results in increased pathology (Yuan et al., 2019) (see Section 7).

6.2.2.2. Liver. Decreased classical pathway activity (CH50) is reported for patients with chronic liver diseases (Inai et al., 1976; Kitamura et al., 1977; Yoshida et al., 1980). Since initially also decreased classical pathway component (C1, C4, and C2) levels were reported for these patients (Inai et al., 1976; Kitamura et al., 1977), it was suggested that classical pathway activation results in consumption of those components and thereby results in lower CH50 titers (as also described for SLE patients, see Section 6.1.2).

However, later studies reported increased C1q levels in patients with chronic liver diseases (Yoshida et al., 1980, 1983). Whereas serum C1q levels were normal in nonspecific reactive hepatitis and chronic inactive hepatitis, they were increased in chronic active hepatitis, acute viral hepatitis (see Section 6.2.1.4), and liver cirrhosis (Yoshida et al., 1983). In line with this, increased catabolic rates of C1q were reported in patients with chronic liver diseases (Potter et al., 1980).

Decreased CH50 titers despite increased C1q levels in patients with chronic liver diseases might seem contradictory, but can be explained by decreased levels of other complement components. These decreased levels can be the result of consumption through lectin/alternative pathway activation, or defective synthesis of those components as a consequence of liver damage, or a combination thereof.

6.2.3. Other diseases

6.2.3.1. Heart. Since C1q induces proliferation of vascular smooth muscle cells (Sumida et al., 2015), increased C1q levels may be a risk factor of cardiovascular disease. In line with this, serum C1q levels were reported to correlate with arterial stiffness (Hasegawa et al., 2019), suggesting that C1q levels are increased in patients with cardiovascular disease. Indeed, in patients with myocardial infarction, C1q mRNA levels as well as serum CH50 titers were significantly increased compared to controls (Yan et al., 2016).

Serum C1q levels are higher in acute coronary syndrome patients than in controls (Kishida et al., 2014). Adiponectin, which has

anti-atherogenic and anti-inflammatory properties, can form complexes with C1q, and these complexes are also increased in acute coronary syndrome patients (Kishida et al., 2014), but the role of C1q and these complexes is still unknown.

Overall, in different diseases involving the heart (e.g., cardiovascular disease, myocardial infarction, and coronary syndrome), increased C1q levels are reported.

6.2.3.2. Brain. C1q is not only present in the circulation, it can also be found in the central nervous system, in both the CSF and brain tissue. As discussed above, C1q levels in the brain increase with age. Several mental disorders and other brain disorders have been associated with increased C1q levels.

CSF C1q levels have been reported to be decreased in Alzheimer's disease patients (Smyth et al., 1994). C1q is produced locally in the brain, mainly by microglia. While serum C1q levels are similar between Alzheimer's disease patients and controls (Brachova et al., 1993), brain C1q mRNA and protein levels are increased in Alzheimer's disease patients (Brachova et al., 1993; Johnson et al., 1992; Terai et al., 1997; Tooyama et al., 2001; Yasojima et al., 1999), likely as a consequence of increased C1q production by microglia from Alzheimer's disease patients compared to controls (Lue et al., 2001). In line with these human data, C1q levels in the brain are increased in mouse models of Alzheimer's disease (Hong et al., 2016). Interestingly, a mouse model of Alzheimer's disease lacking C1q showed reduced pathology (Fonseca et al., 2004), suggesting a role for C1q in the pathogenesis of Alzheimer's disease.

Bipolar disorder, a chronic mood disorder, displays profound immunological alterations next to changes in the central nervous system. Chronic bipolar disorder patients were reported to have increased PBMC C1q mRNA levels compared to healthy controls, possibly as a compensatory mechanism for consumption (Akcan et al., 2018). In schizophrenia, serum C1q levels were reported to be increased in mothers whose offspring developed psychoses compared to mothers whose offspring were free from psychiatric disease. It has been suggested that increased exposure to maternal C1q during pregnancy may be a risk factor for the development of schizophrenia and other psychotic disorders in offspring (Severance et al., 2014).

Serum and CSF C1q levels were reported to be increased in patients with multiple sclerosis and patients with other neurological disorders (Schuller and Helary, 1983). Also acute ischemic stroke patients were reported to have increased serum C1q levels compared to healthy controls (Zhao et al., 2017). In line with this, serum C1q levels associate with the clinical severity of acute ischemic stroke (Wang et al., 2020).

In Rett syndrome, a neurodevelopmental disorder, decreased C1q expression has been described in human and mouse brain tissue, possibly as a consequence of loss of microglia in these patients (Lin et al., 2016).

6.2.4. Tumors

Several reports indicate that C1q impacts on tumor biology including vascularization and metastatic spread and acts as a cancer-promoting factor (Bulla et al., 2016). In glioblastoma multiforme, a common type of brain tumors, serum C1q levels are increased compared to healthy controls, and C1q deposition is observed in tumor tissue (Bouwens et al., 2015). In line with this, C1q mRNA levels are increased in gliomas compared to healthy brain tissue, and these levels are negatively associated with survival of glioma patients (Mangogna et al., 2019b). Also in renal cell carcinoma C1q mRNA levels are increased compared to control tissue, also negatively associating with survival (Mangogna et al., 2019a).

It has been shown that in renal cell carcinoma, macrophage-produced C1q hijacked by tumor cells results in C5a production and thereby inflammation, favoring cancer progression (Roumenina et al., 2019a). In line with these negative associations between C1q levels and survival, C1q has been described to promote tumor growth (Bulla et al., 2016). As expected, C1q-deficient mice display decreased tumor growth and prolonged survival (Bulla et al., 2016; Roumenina et al., 2019a), indicating a pronounced role for C1q in promoting tumor growth, explaining the aforementioned associations between high C1q levels and increased tumor growth.

While C1q mRNA levels are also increased in breast cancer tissue compared to control tissue, in this case these levels are positively associated with survival of breast cancer patients (Mangogna et al., 2019a). In line with this, C1q was found to induce apoptosis of several types of cancer cells including breast cancer (Bandini et al., 2016; Hong et al., 2009; Kaur et al., 2016), supporting a potentially protective role of C1q in cancer. Also in multiple myeloma, the patients with the highest C1q levels displayed an increased survival, even though overall multiple myeloma patients had decreased C1q levels (Xu et al., 2020).

For prostate cancer and lung adenocarcinoma the C1q mRNA levels are actually decreased (Hong et al., 2009; Mangogna et al., 2019a) compared to healthy tissues and negatively associate with survival (Mangogna et al., 2019a).

Overall, local and/or systemic C1q levels are generally increased in cancer, but appear to have a dual role, either promoting or inhibiting tumor growth.

7. C1q in adaptive immunity and other non-traditional functions

Besides its traditional complement-activating effect, C1q exhibits a variety of complement-independent activities, playing a role in pregnancy (reviewed by (Bulla et al., 2012)), autoimmunity (reviewed by (Son et al., 2015)), and tumors (reviewed by (Roumenina et al., 2019b)) (all also reviewed by (Ghebrehiwet et al., 2012; Kouser et al., 2015; Nayak et al., 2010, 2012; Thielens et al., 2017)). C1q is for example critical for tissue and vascular remodeling during pregnancy (Agostinis et al., 2010), explaining the association between decreased C1q levels and pregnancy complications. In addition, C1q regulates adaptive immunity in multiple ways.

Human T cells express C1q receptors (Chen et al., 1994), allowing C1q to steer T-cell responses. Recent mouse studies indicate that C1q may indeed impact on T-cell immunity. In mouse models of SLE, C1q inhibits $CD8^+$ T-cell responses (Ling et al., 2018). The authors propose a mechanism in which C1q is internalized and impacts on mitochondrial function via C1q receptors. In emphysema, absence of C1q leads to a shift from suppressive regulatory T-cell (Treg) responses to pro-inflammatory Th17 responses (Yuan et al., 2019). Human observational studies and mouse models indicate that in the tumor microenvironment, C1q exerts a T-cell inhibitory role (Roumenina et al., 2019a). From these studies a picture emerges that C1q is regulating the magnitude and quality of the T-cell response, but while one study highlights a role for $CD8^+$ T cells, other studies focus on the balance between Treg and Th17.

Besides its direct effect on T cells, C1q can influence other immune cells. Specific C1q/C1q receptor interactions may control the transition from the monocyte state (innate immunity) towards the professional antigen-presenting cell state (adaptive immunity) (Hosszu et al., 2010). In addition, macrophages and dendritic cells exposed to C1q exhibit a reduced capacity to produce pro-inflammatory cytokines, a diminished ability to promote inflammatory type Th1 and Th17 responses as well as a tendency toward sustaining regulatory T cells (Castellano et al., 2007; Clarke et al., 2015; Fraser et al., 2006). Thereby, C1q regulates immune-cell differentiation, cytokine secretion and macrophage polarization toward a tolerogenic phenotype (Benoit et al., 2012).

On the other hand, the association between increased C1q levels and multiple tumors is due to a cancer-promoting activity of C1q (increasing vascularization and metastasis) independent of complement activation (Bulla et al., 2016). Finally, in mice, C1q was shown to activate canonical Wnt signaling and promote aging-related phenotypes (Naito

et al., 2012). In line with that, C1q regulates cellular functions by autocrine and paracrine signaling, indicating the involvement of C1q receptors in the non-traditional functions of C1q, as reviewed elsewhere (Ghebrehiwet et al., 2017).

8. Anti-C1q antibodies in health and disease

Autoantibodies against many complement components have been described, including antibodies against C1q (reviewed in (Beurskens et al., 2015; Dragon-Durey et al., 2013; Norsworthy and Davies, 2003; Trouw et al., 2001). Detection of anti-C1q autoantibodies has to be performed using high salt buffers to prevent false positive signals from immune complexes binding to C1q (reviewed in (Beurskens et al., 2015)). Anti-C1q autoantibodies, like many other autoantibodies, are also present in a small part of the healthy population, with a reported prevalence between 2%–13% (Coremans et al., 1995; Horvath et al., 2001; Magro-Checa et al., 2016; Potlukova et al., 2008; Saadoun et al., 2006; Sinico et al., 2005).

Autoantibodies against C1q were first identified in patients with SLE (Uwatoko et al., 1987), where the prevalence of anti-C1q autoantibodies was later established to be around 30–40 % (Beurskens et al., 2015; Seelen et al., 2003). In later studies, the presence of anti-C1q autoantibodies was also detected in HUVS (100 % of patients) (Wisnieski and Jones, 1992) and in some other rheumatic and infectious conditions (Beurskens et al., 2015). Furthermore, anti-C1q autoantibodies were found in elevated numbers of women with recurrent pregnancy loss (Ohmura et al., 2019), miscarriages (Menzhinskaya et al., 2015) and pregnancy-associated autoimmune thyroid disorders (Vitkova et al., 2016).

Among SLE patients, anti-C1q antibodies are especially prevalent in individuals with lupus nephritis, where a frequency of up to 95 % is reported (Marto et al., 2005; Sinico et al., 2005; Trendelenburg et al., 2006). Moreover, the presence of anti-C1q antibodies correlates with disease activity in lupus nephritis patients (Cai et al., 2010; Tan et al., 2013). In these patients, anti-C1q antibodies were found to specifically accumulate in the kidney (Mannik and Wener, 1997). Murine models showed that anti-C1q antibodies contribute to renal damage only in the presence of renal immune complexes (Trouw et al., 2004).

In view of the reported effect of C1q on cells of the adaptive immune response, it would be interesting to know if the presence of anti-C1q autoantibodies may impact on the signaling of C1q through C1q receptors.

Besides naturally occurring anti-C1q autoantibodies, also therapeutic monoclonal antibodies targeting C1q exist and are being tested for the treatment of neurological diseases such as Guillain-Barré syndrome. In different mouse models, monoclonal anti-C1q antibodies reduced neuronal damage (McGonigal 2016 Acta Neuropathol Commun, Phuan 2013 Acta Neuropathol). The side effects of prolonged C1q inhibition are currently unknown, but may conceivably be similar as those observed in C1q deficiency (infections and SLE-like disease). Whether prolonged C1q inhibition will result in autoimmune or other complications should be monitored carefully.

9. Summarizing discussion

As summarized in Table 1, C1q levels can be either decreased or increased in disease. Decreased C1q levels have been reported for preeclampsia, autoimmune diseases, some inflammatory diseases (e.g., pneumonia and emphysema), acquired (but not hereditary) angioedema, and several tumors (e.g., multiple myeloma, prostate cancer, and lung adenocarcinoma). These decreased C1q levels can be caused by defective production (preeclampsia, minority of SLE patients, RA, emphysema), increased consumption (majority of SLE patients, some HUVS patients, acquired angioedema), and/or depletion by immune complexes or anti-C1q autoantibodies (HUVS).

Increased C1q levels were found for aging, infectious diseases, several inflammatory diseases, heart and brain diseases, and multiple tumors (glioblastoma multiforme, renal cell carcinoma, and breast cancer). The increase in circulating C1q levels in infectious diseases is probably caused by increased C1q production in response to pathogens (due to expansion of myeloid cells and/or increased expression by these cells), but the observed local increases in for example neuroborreliosis and meningitis can be a reflection of increased leakage from the circulation. Also in other diseases (e.g., chronic liver diseases and Alzheimer's disease), increased C1q levels are a consequence of increased (local) C1q production.

Table 1
C1q levels in disease. Overview of diseases in which C1q levels are reported to be decreased or increased.

Decreased C1q levels	Increased C1q levels
Preeclampsia	Aging
Autoimmune diseases	Infectious diseases
• Systemic lupus erythematosus	• Tuberculosis
• Hypocomplementemic urticarial vasculitis syndrome	• Leprosy (?)
	• Malaria (?)
• Rheumatoid arthritis (?)	• Hepatitis C
	• Kala azar
	• Neuroborreliosis
	• Meningitis
Inflammatory diseases	Inflammatory diseases
• Pneumonia	• Rheumatoid arthritis (?)
• Emphysema	• Sarcoidosis
	• Chronic liver diseases (?)
Acquired angioedema	Other diseases
	• Heart (cardiovascular disease, myocardial infarction, acute coronary syndrome)
	• Brain (Alzheimer's disease, bipolar disorder, schizophrenia, multiple sclerosis, acute ischemic stroke)
Tumors	Tumors
• Multiple myeloma	• Glioblastoma multiforme
• Prostate cancer	• Renal cell carcinoma
• Lung adenocarcinoma	• Breast cancer

(?) indicates that conflicting data on C1q levels in that disease have been published.

Besides its traditional complement-activating effect, C1q is also critical for tissue and vascular remodeling during pregnancy (Agostinis et al., 2010; Bulla et al., 2012), explaining the association between decreased C1q levels and pregnancy complications. In addition, C1q regulates adaptive immunity by dampening T-cell responses to self-antigens (Ling et al., 2018), predisposing for autoimmunity when decreased C1q levels are present. On the other hand, the association between increased C1q levels and multiple tumors is due to a cancer-promoting activity of C1q independent of complement activation (Bulla et al., 2016).

In conclusion, C1q can activate the classical pathway of the complement system allowing protection against infections, but it also actively regulates adaptive immunity maintaining tolerance. Therefore, circulating C1q levels are more than just a biomarker for disease.

Author statement

Fleur S. van de Bovenkamp: conceptualization, writing, **Douwe J. Dijkstra:** writing, **Cees van Kooten:** writing, **Kyra A. Gelderman:** writing, **Leendert A. Trouw:** conceptualization, writing.

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