THE BURDEN ASSOCIATED WITH COMPLEMENT 3 GLOMERULOPATHY (C3G)

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BACKGROUND

- C3G is a complex and chronic rare renal condition resulting from excessive activation of the complement alternate pathway (AP) due to autoantibodies or genetic mutations of AP regulatory proteins.(1)
- From the available evidence, the incidence of C3G is approximately 0.01 to 0.02 per 10,000 population per year.(2)
- C3G encompasses 2 major sub-types: dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), and the ratio of DDD to C3GN is approximately 1:3.(1-3)
- Currently, renal biopsy is considered as the gold standard for the diagnosis of C3G.(3)
- Clinical course of C3G varies from person to person. It can exist undiagnosed in many individuals. Diagnosed patients might have asymptomatic proteinuria or haematuria or deteriorating renal functions.(4)
- This highlights the need to consolidate existing evidence to better understand the clinical, economic and humanistic burden associated with the condition through a targeted literature review.

OBJECTIVE

- To gather and narratively synthesize evidence on the clinical, economic and humanistic burden associated with C3G (DDD and C3GN).

METHODS

- EMBASE and MEDLINE databases were searched for relevant English-language studies, which were selected based on pre-defined inclusion criteria (**Table 1**) using a 2-step screening process: (i) abstract screening and (ii) full-text screening (**Figure 1**).

Table 1. Criteria for including studies in the review

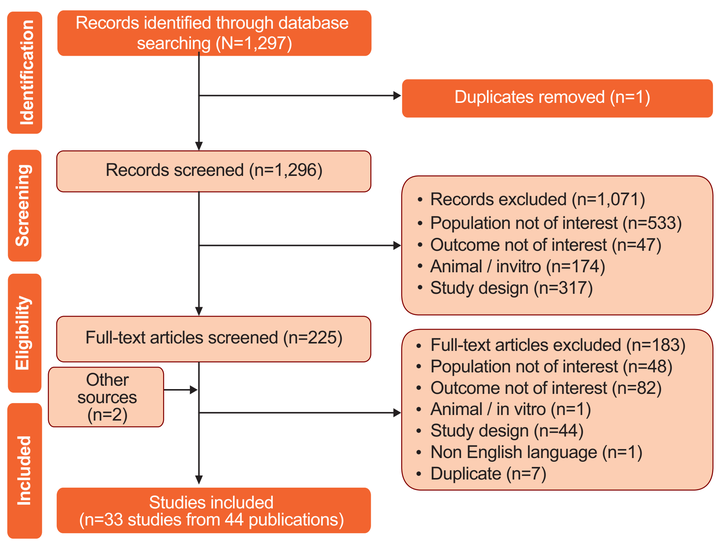
Population	Patients diagnosed with C3G (DDD/C3GN)
Interventions/comparators	NA
Outcomes	**Clinical burden**: comorbidities, proteinuria, eGFR, haematuria, serum creatinine, ESRD, dialysis, kidney transplant and post-transplant scenario
	Economic burden: all direct/indirect costs, productivity loss, absenteeism, presentism, out-of-pocket costs, co-payment information, resource utilisation, hospitalisation, length of stay and re-admission
	Humanistic burden: PROs, QoL/HRQoL, patient preferences, impact on daily living, QALY, DALY and caregiver burden
Study designs	Observational studies (retrospective, prospective, longitudinal, cross-sectional, real-world, registry etc.) Editorials, letters, RCTs, narrative reviews and case reports were excluded
Analysis	Descriptive statistics; data presented as numbers and/or percentages

Abbreviations: C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; DALY, disability-adjusted life years; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HRQoL, health-related quality of life; NA, not applicable; PRO, patient-reported outcome; QALY, quality-adjusted life years; QoL, quality of life; RCTs, randomised controlled trials

RESULTS

- Of the 1,297 records obtained, a total of 33 unique studies from 44 publications were included for the current review (**Figure 1**).

Figure 1. Study selection flowchart



The included studies were highly heterogeneous with respect to the patient and study characteristics.

Study characteristics

- Sample size and setting: The number of C3G patients in the included studies varied from 5 to 168.(5,6) The majority of the studies were conducted at single-centre (22 studies) vs multicentre setting (10 studies) vs database (1 study).
- Geographical distribution: More than a third of the studies were conducted in North America (12 studies), followed by Europe and Asia (9 studies each) and other regions (3 studies).
- Target indications: 16 studies were targeted to DDD, 4 to C3GN and the remaining included both types.

Patient characteristics

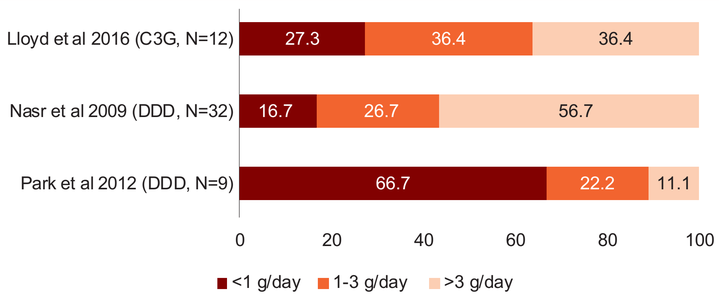
- Age and gender: The mean age of the patients included in the studies ranged from 6.8(7) to 42.5 years,(8) with gender balanced between DDD and C3GN.
- Race: Whites were predominantly affected: 62.5%(9) to 97.1%.(6)
- Comorbid conditions: The most frequently reported comorbid condition in C3G patients was hypertension, up to 93%.(10)

Clinical burden

C3G patients presented with varying symptoms

- Proteinuria: The mean proteinuria levels ranged from 1.25(11) to 5.1 g/day (12) in DDD patients and from 3(2) to 5 g/day(8) in C3GN patients.
  - The proportions of patients presenting with different proteinuria ranges (<1 g/day, 1-3 g/day and >3 g/day) are shown in **Figure 2**.(11,13,14)

Figure 2. Proportion of patients presenting with different proteinuria ranges at diagnosis

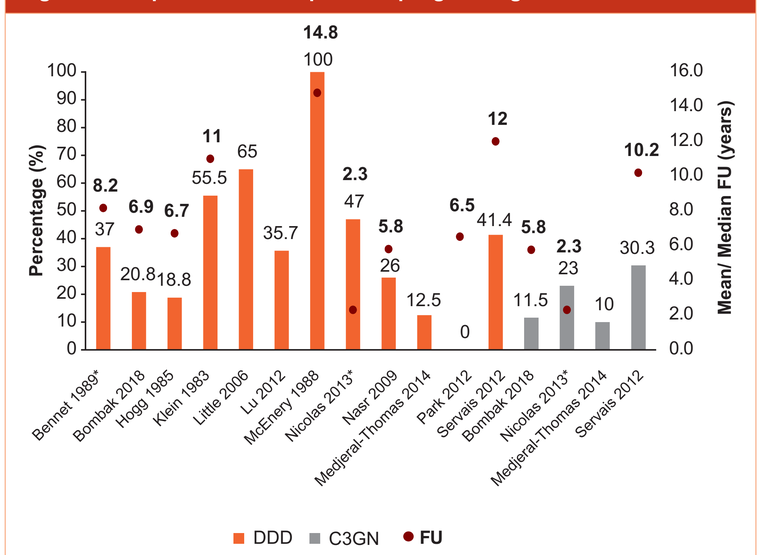


Studies on C3G includes both DDD and C3GN patients

Abbreviations: C3G, complement 3 glomerulopathy; DDD, dense deposit disease; g/day, grams per day

- Haematuria: Haematuria was a highly prevalent symptom that affected up to 100% of both DDD and C3GN patients.(8,11,14,15)
- Nephrotic syndrome: The proportion of patients presenting with nephrotic syndrome varied from 11.1%(10) to 80%(16) in DDD patients and from 20%(17) to 50%(18) in C3GN patients.
- Nephritic syndrome: Nephritic syndrome was reported in few studies and was more prevalent in C3GN patients. While the symptom was present in 5.6%(7) of DDD patients, it was observed in 37.5%(19) to 50%(17) of C3GN patients.
- Serum creatinine: The mean/median serum creatinine levels at presentation varied from 0.7 mg/dL(11) to 4.7 mg/dL(20) for DDD patients and from 1.4 mg/dL(2) to 4.2 mg/dL(20) for C3GN patients.
- Estimated glomerular filtration rates (eGFR): The mean/median eGFR levels at presentation ranged from 58.8(12) to 75.5 mL/min per 1.73 m^2(4) for DDD patients and from 30.7(17) to 128 mL/min per 1.73 m^2(19) for C3GN patients.
- End-stage renal disease (ESRD): As the condition progressed, a substantial proportion of patients in the included studies advanced to ESRD.
  - Approximately up to 30% of C3GN (follow-up ~10 years)(12) and 100% of DDD patients (follow-up ~15 years)(15) progressed to ESRD (**Figure 3**).

Figure 3. Proportion of C3G patients progressing to ESRD



*Median FU

Abbreviations: C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; DDD, dense deposit disease; ESRD, end-stage renal disease; FU, follow-up

- Various demographic, histological and clinical factors significantly associated with the progression to ESRD are shown in **Table 2**.

Table 2. Factors associated with progression to ESRD

Study name	Analysis type	Variable	HR (95% CI)	p value
Nasr et al 2009 (DDD)(14)	Cox regression analysis	Older age	1.052 (1.013 to 1.091)	0.008
Caliskan et al 2015 (C3G)(21)	Cox regression analysis	Lower haemoglobin at biopsy	2.526 (NR)	0.028
		eGFR at biopsy	0.838 (NR)	0.017
		Intensity of the C3 staining	4.60 (NR)	0.04
		Percentage of crescents	1.06 (NR)	0.001
		Glomerulosclerosis	1.08 (NR)	0.005
		Severity of interstitial fibrosis	2.61 (NR)	0.015
Medjeral-Thomas et al 2014 (C3G)(2)	Multivariate analysis	Crescentic GN	2.87 (1.34 to 6.12)	0.01
		DDD by EM	4.7 (1.22 to 18.1)	0.03
		Serum creatinine >1.5 mg/dL*	29.3 (1.18 to 727)	0.04

Studies on C3G includes both DDD and C3GN patients

Abbreviations: C3G, complement 3 glomerulopathy; CI, confidence interval; DDD, dense deposit disease; eGFR, estimated glomerular filtration rates; EM, electron microscopy; ESRD, end-stage renal disease; GN, glomerulonephritis; HR, hazard ratio; NR, not reported

- Composite endpoints: two composite endpoints were reported
  - Kidney failure and ≥50% eGFR decline from the baseline(22)
    - At a median follow-up of 2.3 years, 25.8% of C3G patients met the composite endpoint (22)
    - Younger age, lower eGFR, presence of crescentic and sclerotic glomerulai, severity of interstitial fibrosis and no remission of proteinuria contributed significantly to meeting the end point ($p<0.05$ for all).(22)
  - Doubling of serum creatinine from baseline and/or progression to chronic kidney disease (CKD) stage 5 and/or ESRD requiring dialysis or transplantation, or death(4)
    - At a mean follow-up of ~6 years, 41.7% of DDD patients and 39.1% of C3GN patients reached the composite endpoint(4)
    - Lower eGFR at diagnosis, an increase in the degree of tubular atrophy and/or interstitial fibrosis contributed significantly to meeting the end point ($p<0.001$ for all).(4)
- Dialysis: Approximately 65.2%(23) of DDD patients and 30.4%(12) of C3GN patients underwent dialysis.
- Transplantation: Transplantation rates were as high as 55.6%(7) (at a mean of 2.9 years since symptom onset) in DDD patients and 17.8%(12) in C3GN patients (10.2 years mean follow up).
- Post-transplantation complication: Disease recurrence was the most common post-transplantation complication in up to 100% of DDD and C3GN patients(24,2,13) resulting in up to 50% graft loss in DDD and 75% graft loss in C3GN patients.(2)

Economic and humanistic burden

- None of the included studies had information on the economic or humanistic burden associated with C3G.

LIMITATIONS

- Heterogeneity in the patient characteristics, sample size, study design, study objectives and the definitions used to report the study endpoints limits the ability to compare data.

CONCLUSIONS

- Patients diagnosed with both sub-types of C3G (DDD and C3GN) presented with similar symptoms with a sizable proportion progressing to ESRD irrespective of the treatments they were receiving.
- Existing evidence suggests that there is a high clinical burden associated with C3G in the diagnosed population and as their condition deteriorates a substantial proportion of these patients progress to ESRD, requiring them to undergo dialysis/transplantation.
- The inability of the current interventions to delay or arrest the progression of this condition and prevent ESRD highlights an unmet need in this population.
- There is a need to undertake research on the humanistic and economic burden to address this identified evidence gap and quantify the impact of the high clinical burden of C3G on patient and caregivers' quality of life and costs to healthcare systems.

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Conflict of Interest

Aneesh Thomas George, Nancy Zaour and Eimear Nic Lochlainn are permanent employees of Novartis.

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