Diagnostic value of serum anti-C1q antibodies in patients with lupus nephritis: a meta-analysis
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CRD summary
This review concluded that presence of autoantibodies against C1q may be a valuable adjunct for predicting lupus nephritis and assessing renal activity. The design of the included studies, lack of blinding of index test interpreters and analytical methods used in the review were all likely to overestimate accuracy (which was low). The conclusions are unlikely to be reliable.

Authors' objectives
To evaluate the diagnostic accuracy of autoantibodies against C1q (anti-C1q) in patients with lupus nephritis and provide evidence of a correlation between anti-C1q antibodies and lupus nephritis activity.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched for studies published in English to October 2011; search terms were reported. Bibliographies of included studies and reviews were searched. Conference abstracts without an associated full paper were excluded.

Study selection
Studies that assessed the accuracy of serum anti-C1q antibodies were eligible for inclusion. Eligible studies used enzyme immunoassay or a standard enzyme-linked immunosorbent assay (ELISA) for diagnosing lupus nephritis by comparing either patients with systemic lupus erythematosus (SLE) with and without lupus nephritis or patients with active and inactive lupus nephritis. Patients had to be diagnosed with SLE according to the 1982 revised or 1997 updated American College of Rheumatology criteria. Studies had to include at least 10 samples and provide sufficient data for the construction of 2x2 tables of test performance.

Most studies of the included studies were conducted in European countries. Most of the participants were women. Mean age at study entry ranged from 9.8 to 43 years. Mean disease duration was from 2.1 to 11.0 years. Most studies used ELISA. Twenty-four out of 25 studies confirmed lupus nephritis using biopsy.

Studies were selected by two independent reviewers.

Assessment of study quality
Study quality was assessed using the 14-point QUADAS tool.

The authors did not state how many reviewers assessed quality.

Data extraction
Two independent reviewers extracted data to construct 2x2 tables of test performance; disagreements were resolved by consensus or a third reviewer. Authors were contacted for missing data. Sensitivity, specificity, positive and negative likelihood ratios (LR+/-) and the diagnostic odds ratio (DOR) were calculated.

Methods of synthesis
Pooled estimates of sensitivity, specificity, positive and negative likelihood ratios and DOR along with 95% confidence intervals (CI) were calculated using a DerSimonian-Laird random-effects model (where heterogeneity was observed) or a Mantel-Haenszel fixed-effect model (no heterogeneity). Heterogeneity was assessed using the Cochran’s Q and I² statistics (>75% high heterogeneity, >50% moderate and <25% low). Summary receiver operating characteristic (SROC) curves were constructed using the Moses-Littenberg model; the area under the curve (AUC) was calculated. Threshold effect was tested using Spearman's rank correlation. Meta-regression was used to assess the impact of study quality, detection methods and ethnicity. Publication bias was investigated using funnel plots and the Egger test.
Results of the review

Twenty-five studies met the inclusion criteria (2,502 patients with SLE of which 1,317 had lupus nephritis; range 12 to 245). Twenty-two studies compared patients with SLE with and without lupus nephritis and nine compared active and inactive lupus nephritis.

All 25 studies avoided incorporation bias and clinical review bias, 22 studies reported appropriate patient selection, 18 had a representative patient spectrum, 23 studies each used an appropriate reference standard, avoided partial and differential verification bias, reported blinding of interpreters of the reference standard and reported on withdrawals, 10 studies avoided progression bias, five studies reported blinding of interpreters of index test and 19 reported interpretable and/or intermediate test results.

Overall, when comparing SLE patients with and without lupus nephritis anti-C1q antibodies had a pooled sensitivity of 0.58 (95% CI 0.56 to 0.61), specificity of 0.75 (95% CI 0.72 to 0.77), LR+ of 2.60 (95% CI 2.06 to 3.28), LR- of 0.51 (95% CI 0.41 to 0.63) and DOR of 6.08 (95% CI 3.91 to 9.47).

When comparing patients with active and inactive lupus nephritis, anti-C1q antibodies had a pooled sensitivity of 0.74 (95% CI 0.68 to 0.79), specificity of 0.77 (95% CI 0.71 to 0.82), LR+ of 2.91 (95% CI 1.83 to 4.65), LR- of 0.33 (95% CI 0.19 to 0.56) and DOR of 10.56 (95% CI 4.56 to 24.46).

Significant heterogeneity was observed for all analyses. Results for the multiple regression analysis were reported. There was no indication of threshold effect. Significant publication bias was detected.

Authors' conclusions

Anti-C1q antibodies had relatively fair sensitivity and specificity in the diagnosis of lupus nephritis, which suggested that presence of anti-C1q antibodies may be a valuable adjunct for predicting lupus nephritis and assessing renal activity.

CRD commentary

The review addressed a clear research question supported by reproducible inclusion criteria. Several relevant sources were searched, but non-English and unpublished studies were excluded so relevant data may have been missed. Study selection and data extraction were conducted in duplicate; it was unclear whether similar methods to reduce error and bias were used during the quality assessment.

Estimates of sensitivity and specificity were derived separately from heterogeneous studies; more robust models that maintain the within-study relationship between these studies are available. The graphs showing the SROC curve demonstrated substantial heterogeneity across the studies and the inappropriateness of the use of the Moses-Littenberg model to summarise these data. Not only were the estimates of accuracy reported quite low, the apparent case-control design of the studies, lack of blinding of interpreters of the index test and derivation of summary estimates of sensitivity and specificity separately using heterogeneous studies were all likely to over-estimate accuracy.

The authors overall conclusions are unlikely to be reliable.

Implications of the review for practice and research

Practice: The authors did not state implications for practice.

Research: The authors stated a need for studies to confirm the role of anti-C1q in evaluating the diagnosis and activity of lupus nephritis, especially when in combination with other clinical indices that were also useful in assessing active lupus nephritis.

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