Usefulness of serum IgG4 in the diagnosis and follow-up of autoimmune pancreatitis: a systematic literature review and meta-analysis

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CRD summary
This review found that serum immunoglobulin G4 serum levels were good markers for autoimmune pancreatitis and should be incorporated in its diagnostic workup. These conclusions should be interpreted with extreme caution given the possibility of missing studies, failure to assess study quality and heterogeneity between studies.

Authors’ objectives
To determine the usefulness of serum immunoglobulin G4 (IgG4) levels in the diagnosis and follow-up of patients with autoimmune pancreatitis.

Searching
MEDLINE, Web of Science, Scirus and Scopus were searched in September 2007 for full text studies published in English. Search terms were reported.

Study selection
Studies that evaluated serum immunoglobulin G4 (IgG4) concentrations in patients with autoimmune pancreatitis compared with one or more control groups were eligible for inclusion. Studies that assessed serum IgG4 levels in the follow-up of patients with autoimmune pancreatitis were also eligible. Studies were excluded if they lacked individual data, although it was unclear exactly what this constituted.

Reference standards used in the included studies were the Japanese, Spanish, Korean and Mayo Clinic criteria for autoimmune pancreatitis. The proportion of patients with autoimmune pancreatitis reported to be positive based on histology ranged from 56 to 100%. Techniques used for serum IgG4 determination were nephelometry and radial immunodiffusion with thresholds of 130 to 140mg/dL.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity

Data extraction
Data were extracted as 2x2 data and sensitivity, specificity and diagnostic odds ratios (DOR) were reported for each study.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Summary receiver operating characteristic curves were estimated using the Moses-Littenberg model. Pooled sensitivity, specificity and diagnostic odds ratios were estimated, together with their 95% confidence intervals (CIs). Diagnostic odds ratios were pooled using the DerSimonian and Laird random-effects models; methods to pool sensitivity and specificity were not reported. All analyses were conducted for all controls and stratified according to control group (pancreatic cancer or autoimmune disease without pancreatitis). Heterogeneity was assessed using the $X^2$ test.

Results of the review
Ten studies were included in the review. Seven studies assessed the accuracy of serum IgG4 in the diagnosis of autoimmune pancreatitis (159 patients with autoimmune pancreatitis and 1,099 patients in control groups: 304 with
pancreatic cancer, 96 with autoimmune diseases, and 699 with other conditions); four studies assessed the role of IgG4 as a marker for the efficacy of steroid treatment in patients with autoimmune pancreatitis (34 patients).

**IgG4 in diagnosing pancreatitis:** Diagnostic sensitivity ranged from 67 to 100%. Pooled diagnostic sensitivity was 82% (95% CI 76 to 88). Diagnostic specificity ranged from 89 to 100% when all control groups were considered, with a pooled value of 95% (95% CI 93 to 96). Pooled diagnostic specificity was similar when the analysis was restricted to control groups with pancreatic cancer (95%, 95% CI 92 to 98; four studies) and when restricted to those with autoimmune diseases without pancreatitis (96%, 95% CI 90 to 99; five studies). There was strong evidence of heterogeneity in specificity for all analyses (p<0.001), but only weak evidence of heterogeneity for sensitivity (p=0.078).

**IgG4 in monitoring pancreatitis:** All four studies showed a decrease in IgG4 concentrations from baseline values to values after four weeks of steroid treatment. This decrease was found to be statistically significant in two studies (p<0.02).

**Authors’ conclusions**

Serum immunoglobulin G4 was a good marker for autoimmune pancreatitis and its determination should be included in the diagnostic workup of this disease. Heterogeneity between studies means that more studies are needed on the accuracy of serum immunoglobulin G4.

**CRD commentary**

The review addressed a clear objective supported by inclusion criteria defined in terms of population and index test. Details were lacking on reference standard and outcome data were poorly specified. The literature search was limited to electronic databases without additional attempts to locate studies, such as screening bibliographies or contacting experts in the field. In addition, the review was restricted to published English language studies. This meant that it was possible that relevant studies could have been missed and the review may be subject to language and publication bias. Details on the review process were not reported, so it was not possible to determine whether appropriate steps were taken to minimise reviewer bias and errors.

Study quality was not assessed, so the reliability of the included studies was unclear. Few details were provided on the included studies, which made it difficult to determine the generalisability of the review findings. Although heterogeneity was assessed, explanations for the observed heterogeneity were not investigated, so pooled values should be interpreted with caution.

The authors’ conclusions are supported by the data presented, but should be interpreted with extreme caution given possibility of missing studies, failure to assess study quality and heterogeneity between studies.

**Implications of the review for practice and research**

**Practice:** The authors stated that serum immunoglobulin G4 should be included in the diagnostic workup of autoimmune pancreatitis.

**Research:** The authors stated that more studies are needed to better evaluate the true accuracy of serum immunoglobulin G4 in discriminating autoimmune pancreatitis from other autoimmune diseases, and to establish the best method of determining serum immunoglobulin G4 and establishing the best cut-off value for diagnosing autoimmune pancreatitis.

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