Anti-Glomerular Basement Membrane Antibody Diagnostics in a Large Cohort Tertiary Center: Should We Trust Serological Findings?

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ABSTRACT: **Background**: Anti-glomerular basement membrane (GBM) antibody disease, or Goodpasture's disease, is the clinical manifestation of the production of anti-GBM antibodies, which causes rapidly progressive glomerulonephritis with or without pulmonary hemorrhage. Anti-GBM antibody detection is mandatory for the diagnosis of Goodpasture's disease either from the serum or kidney biopsy. Renal biopsy is necessary for disease confirmation; however, in cases in which renal biopsy is not possible or is delayed, serum detection of anti-GBM antibody is the only way for diagnosis.

Objectives: To assess the predictive value of positive anti-GBM antibodies in a clinical setting.

Methods: Data from anti-GBM antibody tests performed at one medical center between 2006 and 2016 were systematically and retrospectively retrieved. We recruited 1914 patients for the study. Continuous variables were computed as mean ± standard deviation, while categorical variables were recorded as percentages where appropriate. Sensitivity and specificity of anti-GBM titers were calculated. Kaplan–Meyer analysis was performed, stratifying survival according to the anti-GBM antibody titers.

Results: Of the 1914 anti-GBM test results detected, 42 were positive, 23 were borderline, 142 were excluded, and 1707 results were negative. Male-to-female ratio was 1:1.2. Sensitivity of anti-GBM test was 41.2% while specificity was 85.4%. Concerning the Kaplan–Meyer analysis, overall survival was 1163.36 ± 180.32 days (median 1058 days).

Conclusions: Our study highlights the lack of sensitivity of serological testing of anti-GBM titers. Comparing survival curves, the survival correlated with anti-GBM titer only in a borderline way. Because highly sensitive bioassays are not routinely used in clinics, renal biopsy is still pivotal for Goodpasture's disease diagnosis.

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KEY WORDS: Anti-glomerular basement membrane (GBM), Goodpasture's disease, rapidly progressive glomerulonephritis, vasculitis, autoimmunity

Serology is the term used to refer to antibody detection in serum or body fluids [1]. These antibodies are generally produced as a response to infection or foreign material, or against self-proteins [2]. There are several techniques for performing serology such as enzyme-linked immunosorbent assay (ELISA), agglutination and complement-fixation [3]. Serological tests are crucial for the diagnosis of many diseases. For some diseases serological tests are the basis for diagnosis. This appreciable way of diagnosis in low-resource countries is still the only way for diagnosis, mainly because of the low costs of these tests and because they do not necessitate the presence of advanced technology.

Autoimmune diseases are especially based on antibody identification and are a branch of medicine based on serology. Antibody detection, by serology, can help clinicians better understand several pathological processes that are difficult to link solely on clinical grounds. For diagnosis, antibody detection should accompany suitable clinical presentation [4]. Anti-glomerular basement membrane (GBM) antibody is an antibody formed against the intrinsic antigen in the GBM [5,6]. The cause that stimulates the production of the anti-GBM antibody is still unclear [5]. The anti-GBM antibody is an immunoglobulin G (IgG) antibody of one of three types, but it can be immunoglobulin A (IgA) or immunoglobulin M (IgM). [7]. It seems that anti-GBM antibodies are directed against type IV collagen found in the glomerular basement membrane [8]. Anti-GBM antibody disease or Goodpasture's disease is the clinical manifestation of the production of the anti-GBM antibody, which causes rapidly progressive glomerulonephritis with or without pulmonary hemorrhage [9]. Anti-GBM antibody detection is mandatory for the diagnosis of Goodpasture's disease either from the serum or kidney biopsy. Renal biopsy is necessary for disease confirmation; however, in cases where renal biopsy is not possible or is delayed, serum detection of anti-GBM antibody is the only way for diagnosis when clinical findings are suggestive of the disease and renal biopsy performance is unfeasible [10]. The sensitivity of this test in detecting the anti-GBM antibody varies according

to the kit used. Both false-positive and false-negative results are not uncommon; hence, renal biopsy is recommended for disease confirmation [11,12]. Moreover, for serological confirmation Western blot analysis is used, especially when renal biopsy is not performed [13]. As a consequence of its rarity, there is scant literature available detailing results of large numbers of patients tested for the anti-GBM antibody. The aim of our study is to summarize our 10 years of experience analyzing positive serological results of the anti-GBM antibody from a large cohort of patients.

PATIENTS AND METHODS

PATIENTS

All anti-GBM antibody tests done at the Zabludowicz Center for Autoimmune Diseases in Sheba Medical Center, Tel Hashomer, Israel during the period 2006–2016 were systematically and retrospectively collected and analyzed.

Anti-GBM antibody titers were tested with commercially available ELISA kits (AESCULISA, Aesku Diagnostics, Wenelsheim, Germany) according to the manufacturer's directions. For qualitative interpretation of the results, optical density of the patient sample was divided by optical density of the cutoff calibrator preparation included in the kit. A ratio > 1.0 was considered as positive. In particular, values were classified as:

- Borderline (anti-GBM 0.1–1)
- Low positive (anti-GBM 1.0–2.0)
- High positive (anti-GBM 2.0–5.0)
- Very high positive (anti-GBM > 5.0

Sheba Medical Center is a 1500-bed tertiary hospital serving a population of more than 1,500,000 people. The center is affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. All patients aged 18 years and older who were tested for the anti-GBM antibody during the study period were included in the present review. Data of patients with a positive anti-GBM antibody test were extracted from the medical records. These data were arranged in ad hoc prepared tables, which included the following information: demographic data (age and gender), disease manifestations, laboratory test results (creatinine, hemoglobin, C-reactive protein, albumin, C3, C4, anti-GBM titer, erythrocyte sedimentation rate, perinuclear anti-neutrophil cytoplasmic antibodies, or cytoplasmic anti-neutrophil cytoplasmic antibodies [c-ANCAs]), radiological findings (X-ray and computed tomography scans of the chest), co-morbidities and renal biopsy findings.

The study was approved by the ethics committee of the Sheba Medical Center.

STATISTICAL ANALYSIS

Continuous variables were computed as mean ± standard deviation, while categorical variables were recorded as percentages where appropriate. For sample proportions, 95% confidence interval (CI) was computed using the Clopper–Pearson exact binomial proportion interval method as fitting. The Kaplan–Meyer analysis was performed stratifying survival according to the anti-GBM antibody titer.

Statistical analysis was performed using IBM SPSS statistics software, version 20 (IBM Corp, Armonk, New York, USA) and MedCalc Statistical Software (version 16.4.3, MedCalc Software, Ostend, Belgium).

Figures with P values < 0.05 were considered statistically significant.

RESULTS

We recruited 1914 samples for the current study. Concerning the serology, 42 were positive, 23 were borderline, 142 samples were excluded, and 1707 produced negative results [Figure 1]. As such, the prevalence of anti-GBM positive samples was 2.2% (95%CI 1.6–3.0%). Excluded results were mainly due to technical challenges including, for example, inadequate blood sample volume. On the basis of the reference values, 28 (66.7%) (95%CI 50.5–80.4%) samples belonged to the first group (low positive anti-GBM antibody titer), while 10 (23.8%) (95%CI 12.1–39.5%) were in the second group (high positive anti-GBM antibody titer), and 4 (9.5%) (95%CI 2.7–22.6%) were in the third group (very high positive anti-GBM antibody titer).

Male-to-female ratio was 1:1.2. Eighteen subjects underwent renal biopsy and received the diagnosis of diffuse crescentic glomerulonephritis, crescentic glomerulonephritis with c-ANCA positive small vessel vasculitis, diffuse proliferative glomerulonephritis, microscopic polyangiitis, focal glomerulosclerosis, and membranous glomerulonephritis. The main characteristics of the subjects included in the current analysis are shown in Table 1.

Concerning the Kaplan–Meyer analysis, survival (in days) was 1060.66 ± 194.72 (median 830), 1646.21 ± 431.24 (median 2060), and 539.50 ± 404.08 (median 8) for group 1, 2 and 3, respectively. Overall survival was 1163.36 ± 180.32 days (median

Figure 1. Flowchart of the inclusion/exclusion criteria of the study population

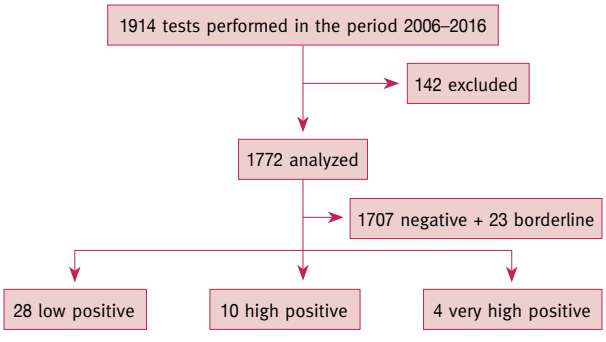


Table 1. Main demographic, clinical and laboratory characteristics of the included sample

Variable	Value
Age (years)	54.36 ± 19.19 (median 54.5, range 19–87)
Gender	
Male	19 (45.2%)
Female	23 (54.8%)
Laboratory exams	
Creatinine	2.86 ± 2.97
Hemoglobin	10.41 ± 3.22
C-reactive protein	76.68 ± 111.98
Albumin	3.26 ± 0.69
C3	110.20 ± 40.50
C4	25.99 ± 12.73
Anti-glomerular basement membrane titer	1.86 ± 1.33
Erythrocyte sedimentation rate	18.76 ± 34.50
Microscopic red blood cells in urine	4 (9.5%); at the stick 50.76 ± 91.77
Radiological exams (X-rays and computerized tomography scan)	
Pleural effusion	6 (14.3%)
Pericardial effusion	2 (4.8%)
Consolidation	1 (2.4%)
Interstitial edema	4 (9.5%)
Interstitial infiltration	6 (14.3%)
Cavitary lesion	1 (2.4%)
Atelectasia	1 (2.4%)
Pulmonary hemorrhage	13 (31.0%)
Symptoms and clinical manifestations	
Vasculitic rash	3 (7.1%)
Joint pain (arthralgia)	9 (21.4%)
Aspecific rash	9 (21.4%)
New-onset acute renal failure	12 (28.6%)
Exacerbations of chronic kidney disease	8 (19.0%)
Shortness of breath	9 (21.4%)
Other respiratory symptoms (hemoptysis/cough)	10 (23.8%)
Neurological symptoms	2 (4.8%)
Fever of unknown origin	3 (7.1%)
Co-morbidities	
No co-morbidity	14 (33.3%)
One co-morbidity	8 (19.0%)
One or more co-morbidity	20 (47.6%)
Diabetes	12 (28.6%)
Hypertension	19 (45.2%)
Chronic kidney disease	5 (11.9%)
Chronic heart failure	5 (11.9%)
Familial Mediterranean fever	1 (2.4%)
Hypothyroidism	4 (9.5%)
Mixed connective tissue diseases	1 (2.4%)
Rheumatoid arthritis	1 (2.4%)
Cirrhosis	3 (7.1%)
Chronic obstructive pulmonary disease	4 (9.5%)
Usual interstitial pneumonia	1 (2.4%)
Glucose-6-phosphate dehydrogenase deficiency	1 (2.4%)
Systemic lupus erythematosus	1 (2.4%)
Ischemic heart disease/peripheral vascular disease	5 (11.9%)
Bipolar disease	1 (2.4%)
Lymphoma	2 (4.8%)
Asthma	2 (4.8%)
Cryoglobulinemia	1 (2.4%)
Neuromuscular weakness	1 (2.4%)
Psoriasis	1 (2.4%)
Anti-phospholipid antibodies syndrome	1 (2.4%)
Treatment	
Pulse steroids	17 (40.5%)
Cyclophosphamide	10 (23.8%)
Plasmapheresis	4 (9.5%)
Dialysis	4 (9.5%)
Outcome	
Goodpasture's disease	17 (40.5%)
Wegener's disease	1 (2.4%)
Microscopic polyangiitis	1 (2.4%)
Renal transplant	2 (4.8%)
Renal failure	21 (50.0%)
Dialysis	9 (21.4%)
Death	5 (11.9%)

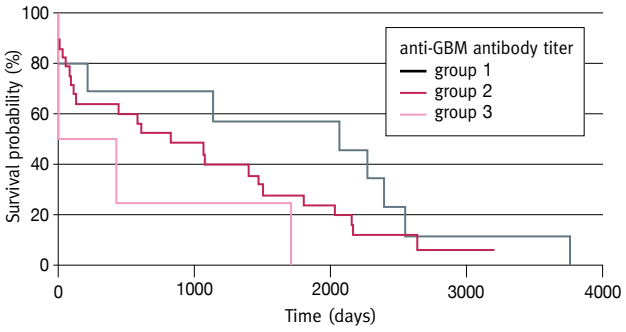
1058). Comparing survival curves, the difference among the three groups was statistically borderline (chi square 4.58, degrees of freedom = 2, $P = 0.1012$). For group 1, hazard ratio (HR) was 0.65 (95%CI 0.33–1.29) and 2.15 (95%CI 0.46–10.07) with respect to groups 2 and 3. In group 2, HR was 1.53 (95%CI 0.77–3.05) and 3.30 (95%CI 0.68–16.10) with respect to groups 1 and 3 [Figure 2].

DISCUSSION

Goodpasture's disease remains a rare entity with a prevalence of approximately 1 case per million people [14]. Usually the natural course of such a disease entity is rather aggressive, which occurs as the result of antibody binding to type IV collagen in the kidney and lungs [15]. The IgG antibody binding represents a type II immunological reaction. Nonetheless other immunoglobulin subtypes have been encountered, including IgM and IgA [16]. In approximately 80% of the patients both organs are affected. Goodpasture's disease, which results in crescentic glomerulonephritis, accounts for up to 10% of the cases of acute renal failure, kidney function deterioration and irreversible damage [17]. The rapid detection of this disease entity is essential due to the nature of the lifesaving treatment modalities that, when used early in the disease course, can be effective and preserve the otherwise irreversible organ injury and failure [18]. The detection of anti-GBM is reliant on ELISA testing and confirmed with Western blot analysis.

Antibody serologic detection is of diagnostic significance, although the presence of false-positive and false-negative results are infrequently encountered [13]. False-negative results could

Figure 2. Kaplan–Meyer analysis performed stratifying survival according to the anti-glomerular basement membrane (GBM) antibody titers



group 1 = low positive titer, group 2 = high positive titer, group 3 = very high positive titer

occur due to the failure of standard anti-GBM ELISA kits in the detection of the less common immunoglobulin subtypes including IgM and IgA subtypes [19]. In contrast false-positive results have been reported due to the presence of polyclonal immunoglobulin in the sera. False-positive results could be excluded by the comparison to negative control or the use of more specific techniques including Western blot analysis [13].

Our work is based on a large series of patients tested for the presence of anti-GBM antibody because of suspected clinical manifestations of Goodpasture's disease. We found no such extensive published study.

Our data, in part, confirm the findings of other researchers. Regarding the general descriptive epidemiology, Li and co-workers [20] reviewed their clinical experience in Hong Kong from 1992 to 2003. They found a female predominance (ratio 2:8) and a patient survival of 70% at 1 year.

Sinico and co-authors [21] retrospectively studied a series of 19 patients with Goodpasture's disease, 41 pathological and 28 normal controls, using different assays. They obtained high values of sensitivity (between 94.7 and 100.0%), and specificity (from 90.9 to 100.0%). Our value of sensitivity is significantly lower [Table 2]. We speculate that this could be due to several reasons: some cases of Goodpasture's disease are characterized by circulating antibodies not properly detected by commercially available immunoassays. Second, these results respect real-life experience, sometimes having a low pre-test probability of the disease and therefore having a negative impact on the accuracy of the test. With regard to this result, Salama and collaborators [13] presented three cases of patients with Goodpasture's disease in which traditional serological techniques failed to confirm the suspected diagnosis. As such, they suggested not to rely completely on serological tests, but to consider renal biopsy as the gold standard to ascertain the diagnosis of Goodpasture's disease. The true prevalence of cases of Goodpasture's disease with undetectable anti-GBM antibodies could be higher than what is commonly expected. Jia and colleagues [22] reported four additional patients with Goodpasture's disease with antibodies undetectable with commercial ELISA assays. Only indirect immunofluorescence managed to detect antibodies, which recognized cryptic and conformation-dependent epitopes. As such, the particular nature of the antigens recognized by these antibodies could explain the failure of classical immunoassays. Ohlsson et al. [12] described four patients with severe, life-threatening and rapidly progressive Goodpasture's disease, in which commercially available ELISA kits failed to detect anti-GBM antibodies.

Table 2. Predictive values of anti-glomerular basement membrane diagnostics in our cohort

Statistics	Value	95% confidence interval
Sensitivity	41.18%	18.44–67.08%
Specificity	85.42%	72.24–93.93%
Positive likelihood ratio	2.82	1.16–6.87
Negative likelihood ratio	0.69	0.45–1.04
Positive predictive value	50.00%	29.12–70.88%
Negative predictive value	80.39%	73.04–86.12%

Concerning the clinical correlates of anti-GBM antibodies, Herody and colleagues [23] assessed 29 patients (18 males, 11 females) aged 6–76 years with anti-GBM disease, of which 14 developed Goodpasture's disease and 16 with end-stage renal failure requiring dialysis. Two patients died. Creatininemia over 600 µmol/l (6.78 mg/dl), oligo-anuria, altered glomeruli, a high percentage of circumferential crescents, circulating anti-GBM antibodies detected by immunofluorescence, and a high level of circulating anti-GBM antibodies evaluated by ELISA predicted an unfavorable renal course. We found only a statistically borderline correlation between anti-GBM antibody titers and survival curve. This result seems to support the statement of Liu and colleagues [24] that the relation between serological findings and clinical-pathological aspects is complex and not always linear, with seronegative Goodpasture's disease a possibility when serological tests do not support a diagnosis of Goodpasture's disease but the clinical suspicion is high.

CONCLUSIONS

Goodpasture's disease has been traditionally defined as a monophasic disease; however, new entities are emerging within this disorder, including syndromes with variable serological findings and seronegative patients. Despite the advancement in the field of serological testing, anti-GBM titers still lack the sensitivity in disease detection. In addition, survival correlation with anti-GBM titer was shown to be statistically borderline significant. Since highly sensitive bioassays are not routinely used in clinics, renal biopsy should be considered the gold standard, and serological findings should be taken "*cum grano salis*" (with a grain of salt).

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Capsule

Internet program for physical activity and exercise capacity in children with juvenile idiopathic arthritis: a multicenter randomized controlled trial

Armbrust et al. evaluated the effects of Rheumates@Work, an internet-based program supplemented with four group sessions aimed at improving physical activity, exercise capacity, health-related quality of life (HRQoL), and participation in children with juvenile idiopathic arthritis. Patients were recruited from three pediatric rheumatology centers in the Netherlands for an observer-blinded, randomized controlled multicenter trial. Physical activity level, time spent at rest and during light and moderate-to-vigorous physical activity (MVPA) were recorded in a diary and with an accelerometer before intervention, after intervention, and at follow-up after 3 and 12 months (intervention group only). Exercise capacity was assessed using the Bruce treadmill protocol. HRQoL was assessed with the Pediatric Quality of Life Inventory generic core scale. Participation in school and in physical education classes were assessed by questionnaire. The intervention group consisted of 28 children, and there were 21 children in the control group. MVPA, exercise capacity, and participating in school and physical education classes improved significantly in the intervention group. HRQoL improved in the control group. No significant differences were found between groups. The effect of Rheumates@Work on physical activity and exercise capacity lasted during the 12 months of follow-up. Improvements in physical activity were significantly better for the cohort starting in winter compared to the summer cohort. The authors conclude that Rheumates@Work had a positive but small effect on physical activity, exercise capacity, and participation in school and physical education class in the intervention group. Improvements lasted for 12 months. Participants who started in winter showed the most improvement. Rheumates@Work had no effect on HRQoL.

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