Immunoglobulin G subclasses and spirometry in patients with chronic obstructive pulmonary disease


ABSTRACT: Immunoglobulin G (IgG) subclass levels were measured in 58 patients with chronic obstructive pulmonary disease (COPD) and in 125 healthy controls. Total IgG values were significantly lower in the 27 COPD patients on steroid therapy compared with patients not taking steroids (8.31(0.14) vs 9.50(0.14), p<0.05), geometric mean (log sm). Total IgG (9.80 (0.14) vs 12.18 (0.16), p<0.005), IgG1 (5.87 (0.19) vs 6.68 (0.12), p<0.05) and IgG2 levels (2.75 (0.21) vs 3.70 (0.20), p<0.005) were significantly reduced in the COPD patients not taking steroids compared with the controls. IgG3 values were significantly elevated in smokers compared with nonsmokers in both the control and COPD groups. Fifteen COPD patients (25.9%) had a low level of one or more subclasses. IgG2 subclass deficiency was the most common, being present in 9 patients. A significant correlation was found between forced expiratory volume in one second (FEV1) and IgG2 subclass levels (r=0.415; p<0.005). IgG subclass deficiencies may contribute to the development and progression of respiratory disease in COPD patients.


The four immunoglobulin G (IgG) subclasses have distinct physicochemical and biological properties. Antibody responses to many antigens occur predominantly in certain subclasses. Normal IgG consists of approximately 70% IgG1, 20% IgG2, 6% IgG3 and 4% IgG4 [1]. IgG subclass deficiencies, other than IgG1 deficiency, are frequently associated with normal total IgG levels [2].

Selective deficiencies of one or more IgG subclasses may be associated with increased susceptibility to recurrent infections, especially sinusoidal infections [3]. Impairment of respiratory function, in particular expiratory flow, has been reported in some patients with IgG subclass deficiency [4]. Rarely, healthy adults may lack one or more IgG subclasses [5].

Much of the published work to date refers to the paediatric population. Adults with chronic obstructive pulmonary disease (COPD) suffer from recurrent chest infections with resulting clinical deterioration. We report the results of measurements of IgG subclass levels and pulmonary function tests in adults with COPD.

Materials and methods

Patients

Serum was collected from 58 patients (45 males and 13 females; age 66±6.9 yrs, mean±sd, range 50–80 yrs) with COPD attending the respiratory clinic at University College Hospital, Galway. All patients tested were clinically stable and none had a recent chest infection. A standard questionnaire was completed for each patient, giving information on the nature, duration and severity of symptoms, smoking habits, the number of courses of antibiotics in the previous year, the number of admissions with respiratory problems and the medications prescribed. A personal or family history of atopy was sought for each patient.

All patients had chronic productive cough for at least three months of the year and a history of cigarette smoking; all had evidence on examination and on spirometry of airflow obstruction. No patient had a clinical diagnosis of asthma or bronchiectasis and none had a history of atopy or of chronic or recurrent chest symptoms in childhood.

Serum was collected from 125 healthy adult volunteers (68 males and 57 females; age 48±5.9 yrs, mean±sd, range 22–81 yrs) none of whom had a history of chronic respiratory disease or recurrent infections.

The study was approved by the local Ethical Committee; all subjects studied were informed of the nature of the study and agreed to participate.

IgG subclasses

Total IgG estimations were carried out using rate nephelometry on the Beckman Automated
Immuonochemistry System. IgG subclasses were measured using mouse monoclonal subclass specific antisera (Oxoid) according to the RID method of Lowe et al. [6] with the following modifications: the RID plates were poured using 1.4% agarose in 0.1 M barbitone buffer, pH 8.6, containing 5% PEG (polyethylene glycol) 4000. The antisera concentrations (clone code) used were as follows: IgG1 -2.65 μl·cm⁻² (JL512), IgG2 -1.25 μl·cm⁻² (HP014), IgG3 -0.40 μl·cm⁻² (ZG4), IgG4 -1.2 μl·cm⁻² (RJ4) +1.2 μl·cm⁻² (GB7B). Human standard serum (Janssen) containing IgG1: 6.1 g·l⁻¹, IgG2: 3.3 g·l⁻¹, IgG3: 0.47 g·l⁻¹ and IgG4: 0.62 g·l⁻¹ was used as control.

Pulmonary function tests

Vital capacity (VC), forced expiratory volume in one second (FEV₁) and the quotient FEV₁/VC expressed as a percentage (FEV₁%) were determined using a bellows spirometer (Vitalograph); the best of three attempts was recorded for each patient. Results were expressed as percentages of the reference values [7].

Statistical methods

A geometric mean was obtained for each subclass. Normal bounds for subclass values were obtained by taking the mean logarithm of the control values ± twice the standard deviation of the logarithms and then getting the antilogarithms of the results. Low IgG subclass levels were designated as those more than 2 below the geometric mean for the control population.

Differences between means were analysed using Student’s t-test or Mann Whitney test, as appropriate, and accepted as significant at p<0.05. The correlations between immunoglobulins and pulmonary function values were calculated with Pearson’s product-moment correlation. The contribution of individual patient characteristics and medication to the severity of pulmonary function impairment was evaluated using stepwise linear regression analysis.

Results

All subclasses were detectable in each subject studied. The percentage distribution of IgG subclasses in the control group was as follows: IgG1 -57.5%, IgG2 -31.8%, IgG3 -4.7% and IgG4 -5.9%. Subclass levels were not significantly different in any age group and no difference was observed between male and female values in either the patient or control groups (data not shown).

Three subjects in the control group had low IgG1 values and 2 of these had low total IgG levels. Three subjects had low IgG3 levels, 2 had low IgG2 and 4 had low IgG4 levels. Nobody had low values in more than one subclass.

The distribution of subclass concentrations in patients with COPD is shown in figure 1. Fifteen COPD patients (25.9%) had a low level of one or more subclasses. IgG2 deficiency was the commonest deficiency detected, being present either alone or in combination in 9 patients. Five patients had isolated low IgG2 levels and 4 had isolated low IgG1 values; 2 patients had low IgG2 and IgG4 levels; 2 had low IgG1 and IgG4; one patient each had combined IgG1 and IgG2 and combined IgG2 and IgG3 deficiencies. No patient had isolated IgG3 or IgG4 deficiency. Eight of the patients with subclass deficiency and 6 other patients had a repeat subclass estimation at a later clinic visit; there was no significant difference between the two measurements.

Twenty seven COPD patients were on steroid medications; 25 were taking inhaled steroids and 2 were on low-dose oral steroids (5 milligrams prednisolone daily). FEV₁ values were lower in patients treated with steroids compared with patients not receiving steroids (37.1±12.4 vs 43.8±23.1 %pred), but the difference was not statistically significant. Total IgG levels were significantly reduced in patients taking steroids compared with those not treated with steroids: mean (log so) 8.31(0.14) vs 9.80(0.14), p<0.05 (table 1); individual subclass levels were lower in patients receiving steroids but not to a statistically significant degree. Compared with controls, COPD patients not receiving steroids had lower levels of total IgG (9.8(0.14) vs 12.18(0.16), p<0.005), IgG1 (5.87(0.19) vs 6.68(0.12), p<0.05) and IgG2 (2.75(0.21) vs 3.70(0.21), p<0.001) (table 1).

Current smokers in both control and COPD groups had significantly elevated IgG3 levels compared with
nonsmokers (including ex-smokers) (table 2). The proportion of current smokers was greater in the COPD group (21/58 vs 21/125). When nonsmokers in the two groups were compared, there was no significant difference in IgG3 levels.

Significant correlations were found between IgG2 and FEV1 (r=+0.42; p<0.005, fig. 2) and between IgG2 and FEV% (r=+0.34; p<0.01). Spirometric values and clinical data in patients with differing IgG2 levels are given in Table 3. There was no significant relationship between the other subclass levels and spirometric values. Stepwise linear regression analysis was performed with FEV1 as the dependent variable to evaluate the contribution of individual patient characteristics, medication and subclass values to the severity of pulmonary impairment. The only significant independent variables were the duration of symptoms (coefficient (SE) -0.99 (0.37), p<0.01) and the IgG2 subclass concentration (5.15(1.152); p<0.005).

Table 1. - IgG subclass levels in controls and COPD patients

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Total IgG</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>125</td>
<td>12.18 (0.16)</td>
<td>6.68 (0.12)</td>
<td>3.70 (0.21)</td>
<td>0.55 (0.30)</td>
<td>0.69 (0.44)</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not treated with steroids</td>
<td>31</td>
<td>9.80 (0.14)</td>
<td>5.87 (0.19)</td>
<td>2.75 (0.21)</td>
<td>0.67 (0.25)</td>
<td>0.60 (0.47)</td>
</tr>
<tr>
<td>vs controls</td>
<td></td>
<td>p&lt;0.005</td>
<td>p&lt;0.05</td>
<td>p&lt;0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Treated with steroids</td>
<td>27</td>
<td>8.31 (0.14)</td>
<td>5.12 (0.15)</td>
<td>2.34 (0.19)</td>
<td>0.56 (0.23)</td>
<td>0.53 (0.39)</td>
</tr>
<tr>
<td>vs not treated with steroids</td>
<td></td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are geometric mean (log so). The normal bounds, given for the control group, represent the geometric mean±2 log so. NS: p>0.05. IgG: immunoglobulin G; COPD: chronic obstructive pulmonary disease.

Table 2. - IgG subclass levels in smokers and nonsmokers (including ex-smokers)

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Total IgG</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>104</td>
<td>12.06 (0.16)</td>
<td>6.64 (0.12)</td>
<td>3.63 (0.20)</td>
<td>0.50 (0.31)</td>
<td>0.70 (0.43)</td>
</tr>
<tr>
<td>Smokers</td>
<td>21</td>
<td>12.79 (0.16)</td>
<td>6.88 (0.13)</td>
<td>4.07 (0.25)</td>
<td>0.86 (0.25)</td>
<td>0.64 (0.47)</td>
</tr>
<tr>
<td>vs nonsmokers</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>p&lt;0.005</td>
<td>NS</td>
</tr>
<tr>
<td>COPD (Not treated with steroids)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>21</td>
<td>9.42 (0.15)</td>
<td>5.71 (0.23)</td>
<td>2.60 (0.25)</td>
<td>0.61 (0.28)</td>
<td>0.52 (0.49)</td>
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<tr>
<td>vs control nonsmokers</td>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers</td>
<td>10</td>
<td>10.64 (0.13)</td>
<td>6.22 (0.11)</td>
<td>3.05 (0.13)</td>
<td>0.82 (0.21)</td>
<td>0.81 (0.42)</td>
</tr>
<tr>
<td>vs control smokers</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>vs COPD nonsmokers</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>COPD (Total)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>37</td>
<td>8.78 (0.16)</td>
<td>5.43 (0.20)</td>
<td>2.38 (0.23)</td>
<td>0.53 (0.26)</td>
<td>0.58 (0.52)</td>
</tr>
<tr>
<td>vs control nonsmokers</td>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.005</td>
<td>p&lt;0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers</td>
<td>21</td>
<td>9.63 (0.12)</td>
<td>5.65 (0.13)</td>
<td>2.88 (0.15)</td>
<td>0.81 (0.20)</td>
<td>0.51 (0.38)</td>
</tr>
<tr>
<td>vs control smokers</td>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>vs COPD nonsmokers</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>p&lt;0.005</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are geometric mean (log so). NS: p>0.05. For other abbreviations, see legend to table 1.
The role of cigarette smoking in the aetiology of COPD is well established, but the host factors that influence susceptibility to COPD are less well understood. Previous studies have reported IgG subclass deficiencies in patients with chronic or severe recurrent chest symptoms [8, 9], including some patients with asthma [10]. We studied IgG subclass levels in patients with a persistent obstructive ventilatory impairment on spirometry and a chronic productive cough. Bronchiectasis and asthma were excluded on clinical grounds and more rigorous investigations were not performed.

Oral corticosteroid therapy increases the catabolism and decreases the synthesis or accumulation. Alveolar macrophages, receptors with greatest affinity for IgG3 [14]. In this study, IgG subclass levels were also reduced but not to a statistically significant degree.

**MERRILL et al.** [13] reported elevated serum levels of IgG1 and IgG3 in smokers; they also reported that the relative levels of IgG3 and IgG4 in lung lavage fluid were higher in smokers, suggesting a degree of local synthesis or accumulation. Alveolar macrophages, present in increased amounts in smokers, display IgG receptors with greatest affinity for IgG3 [14]. In this study, current smokers in both control and patient groups had significantly elevated IgG3, but not IgG1 concentrations compared with nonsmokers (including ex-smokers).

**Isolated IgG1 deficiency and IgG4 deficiency have been reported in patients with severe sinopulmonary infections** [9]. Seven patients in this study had low IgG1 levels (all with low total IgG levels) and 4 had low IgG4 values. However, neither deficiency was associated with more severe lung disease either clinically or on spirometry in our patients.

**Antibodies against capsular polysaccharides,** including those of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, are predominantly of the IgG2 subclass in adults [15]. Low IgG2 levels have been reported in patients with chronic or recurrent chest symptoms [8, 16] and in otherwise healthy adults with community-acquired pneumonia [17]. **BIÖRKANDER et al.** [4] reported significantly decreased FEV1, levels and abnormal single-breath nitrogen tests in IgA deficient patients with low levels of IgG2 or IgG3 and frequent respiratory infections; IgG2 and FEV1 were significantly correlated, suggesting that airflow limitation was more pronounced with decreasing levels of IgG2.

We found IgG2 deficiency in 9 out of 58 patients with COPD. The population studied was older than in previous reports, and none of our patients had a history of chest problems in childhood. As in the study by **BIÖRKANDER et al.** [4], IgG2 levels were significantly correlated with FEV1 (and FEV1%). The subgroup of patients with IgG2 deficiency, either alone or in combination with other subclass deficiencies, had especially severe lung disease, both clinically and on spirometry.

Our patients with COPD and IgG2 deficiency may have a diminished capacity to respond to the polysaccharide antigens of common respiratory pathogens, and this may lead to more frequent infections and hence to worsening of respiratory function. However, some clinically healthy individuals may have very low levels of IgG2 [18]. The question of a relationship between IgG subclass deficiency, recurrent respiratory infections and deterioration in lung function can only be answered by prospective studies. Encouraging reports of the response to immunoglobulin replacement therapy in patients with IgG2 and other subclass
deficiencies [17, 18] emphasize the importance of further evaluating the role of IgG subclass deficiency in the development and progression of respiratory disease.

References

RÉSUMÉ: Les niveaux de sous-classes d'immunoglobulines G (IgG) ont été mesurés chez 58 patients atteints de BPCO et chez 125 sujets bien portants. Les valeurs totales d'IgG sont significativement plus basses chez 27 patients BPCO sous stéroïdes, par comparaison avec les patients sans stéroïdes (8.31 (0.14) versus 9.80 (0.14), p<0.05), moyenne géométrique (log 10). Les IgG totales (9.80 (0.14) versus 12.18 (0.16), p<0.005), les IgG1 (5.87 (0.19) versus 6.68 (0.12), p<0.05) et les taux d'IgG2 (2.73 (0.21) versus 3.70 (0.20), p<0.005), sont réduits de façon significative chez les patients BPCO qui ne prennent pas de stéroïdes, par comparaison avec les sujets contrôles. Les valeurs d'IgG3 sont élevées significativement chez les fumeurs, par comparaison avec les non-fumeurs, à la fois dans les groupes contrôles et BPCO. Quinze patients BPCO (25.9%) ont un niveau bas de l'une ou de plusieurs des sous-classes. La déficience de la sous-classe IgG2 est la plus courante, étant présente chez 9 patients. Une corrélation significative a été découverte entre les VEMS et les niveaux de la sous-classe d'IgG2 (r=0,415, p<0.005). Les déficiences dans les sous-classes d'IgG peuvent contribuer au développement et à la progression des maladies respiratoires chez les patients BPCO.