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# Prevalence of auto-antibodies associated to pulmonary arterial hypertension in scleroderma – A review

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ABSTRACT

The prevalence of auto-antibodies associated to pulmonary arterial hypertension in scleroderma patients was reviewed, based on reports cited in two major scientific databases.

Data were collected on the following types of antibodies: antinuclear, anti-double-stranded DNA, anticentromere, anti-CENP-A, anti-CENP-B, anti-bicaudal D2, anti-nucleolar, anti-Scl-70 (anti-topoisomerase I), anti-topoisomerase II α, anti-RNP, anti-U1RNP, anti-U3RNP, anti-RNA polymerase III, anti-Th/To, anti-histone, antiphospholipid, anti-PmScl, anti-Sm, anti SSA (anti-Ro),anti SSB (La), anti-Ro52 (TRIM 21), anti-Ku, anti-B23, anti-RuvBL1, anti-RuvBL2, anti-fibrin bound tissue plasminogen activator, anti-endothelial cell, anti-phosphatidylserine-prothrombin complex, anti-endothelin-1 type A receptor, anti-angiotensin II type 1 receptor, anti-carbonic anhydrase II, anti-fibroblast, anti-cyclic citrullinated peptide, anti-4-sulfated N-Acetyl-lactosamine, class I and II anti-human leukocyte antigen.

Auto-antibodies were shown by different authors to be associated to this condition, with different prevalence values for each type of auto-antibody. Antinuclear antibodies, anti-centromere antibodies, antiphospholipid antibodies, anti-U3 RNP antibodies and anti-Th/To antibodies would appear to show a particularly important prevalence in scleroderma patients with pulmonary hypertension, appearing in about 8/10 (antinuclear), 1/ 2 (anti-centromere, anti-phospholipid), and 1/4 (anti-U3RNP, anti-Th/To) of patients.

The available evidence points in the direction of a strong association between auto-immune mechanisms and pulmonary hypertension in the setting of scleroderma.

## 1. Introduction

Scleroderma or systemic sclerosis is a systemic disease that may involve not only the skin but also a number of internal organ systems. Concerning the skin, the disease may vary from the limited cutaneous form to the diffuse cutaneous form of systemic sclerosis. The lungs are involved in a significant proportion of scleroderma patients, and both interstitial lung disease and pulmonary arterial hypertension [1] are important forms of disease in this context. Raynaud's phenomenon is also recognized as being a relatively frequent clinical manifestation of this condition, as is gastrointestinal and/or renal involvement.

The pathogenesis of scleroderma is complex and incompletely understood. Fibrosis and vascular changes are believed to play a part in this disease. Several types of auto-antibodies are known to be more or less frequently present in scleroderma patients. This argues in favor of an auto-immune mechanism acting in this disease. Anti-nuclear antibodies, anti-centromere antibodies, anti-topoisomerase I (also known as anti-Scl-70 antibodies) and anti–RNA polymerase III antibodies are well known to be associated with this disease - the latter three having been incorporated into current diagnostic criteria for this disease [2].

In the present review, we aimed at characterizing the prevalence of different types of auto-antibodies in scleroderma patients in association to pulmonary arterial hypertension, by analyzing the published data cited in two major scientific databases. For the purpose of this review, “scleroderma” and “systemic sclerosis” will be taken as the same disease, since different authors may use one or the other expression.

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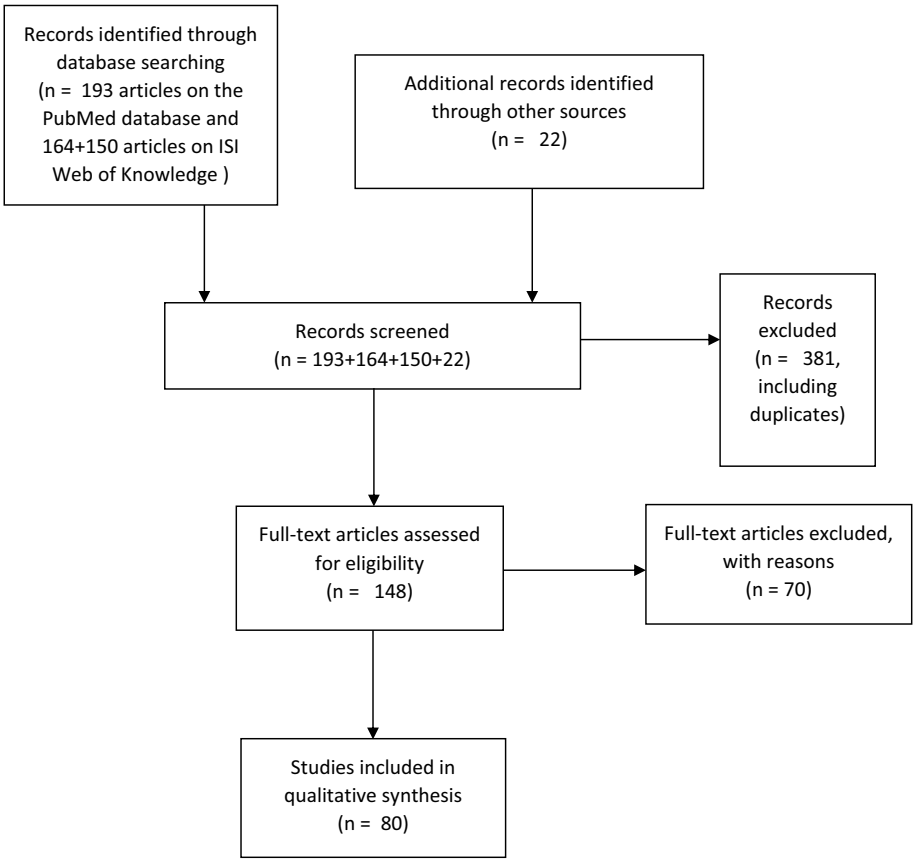


**Fig. 1.** Flowchart showing literature search method. n - number of articles.

## 2. Methods

### 2.1. Search strategy

The study started with a search on two databases, Medline (PubMed) and ISI Web of Knowledge, using the queries: Pubmed - "scleroderma" OR "systemic sclerosis" AND "pulmonary hypertension" AND "antibodies"; ISI Web of Knowledge - "systemic sclerosis" AND "pulmonary hypertension" AND "antibodies"; "scleroderma" AND "pulmonary hypertension" AND "antibodies" (two different searches).

The search took place between June and September 2017, and repeated in early 2018. No articles were excluded based on publication date. The aim of our search was to identify studies evaluating the presence of antibodies in scleroderma patients with pulmonary arterial hypertension.

The queries resulted in 193 articles on the PubMed database and 164/ 150 articles on ISI Web of Knowledge (Fig. 1). Additional studies were found after searching the references of previous review articles and other relevant sources, including articles related to the topic in question as well as articles citing (or cited by) the selected articles.

### 2.2. Inclusion criteria

Only human studies were included, documenting antibody status in association to pulmonary arterial hypertension in scleroderma patients. All antibodies under study were considered of potential interest.

### 2.3. Exclusion criteria

Articles written in languages other than English, French or Spanish, as well as mechanistic and animal studies, were excluded. Case reports and studies containing less than ten subjects were also excluded. Excluded were articles dealing mainly with: other organ systems; other diseases; diagnostic (laboratory) methods; disease nomenclature and diagnostic criteria; guidelines; review articles with no original data.

### 2.4. Data extraction

Study eligibility was individually assessed by two investigators. Different opinions regarding the relevance of articles were solved by consensus between the authors. We aimed at presenting an overview of studies assessing antibody status in association to pulmonary arterial hypertension in scleroderma patients. For this purpose, we prepared a table with the overall data, as well as separate tables regarding the antibodies more widely studied.

### 2.5. Quality assessment

The presence of any given article in at least one of the two databases analyzed was taken as proxy for having been the subject of peer review and therefore of having sufficient quality to merit further analysis.

### 2.6. Calculations

Simple arithmetic calculations are presented in Table 10, automatically obtained using Microsoft Excel 2016 software.

## 3. Results

A total of 80 articles were identified and taken for further analysis (Table 1) concerning patients with scleroderma, pulmonary arterial hypertension and including data on auto-antibodies: two from the decade of 1980 [3,4], nine from the decade of 1990 [5–13], twenty seven from the decade of 2000 [14–40] and forty two from the

**Table 1**
Clinical and laboratory findings in published reports on pulmonary hypertension associated to scleroderma. N-number. ANA – anti-nuclear antibody. RNAP - Anti-ribonucleic acid polymerase III antibody. ACA – Anti-centromere antibody. ATA - Anti-topoisomerase I antibody (also known as anti-Scl-70). ANoA - Anti-nucleolar antibody. Anti-RNP - anti-ribonucleoprotein antibody. ETAR - Anti-endothelin-1 type A receptor antibody. AT1R - Anti-angiotensin II type 1 receptor antibody. CREST syndrome - calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias. For complete references see text.

| Study (year) | Number of patients | Mean or median age (years) | Antibody (ies) under study | Findings concerning pulmonary hypertension |
|---|---|---|---|---|
| Stupi et al. (1986) | 673, 30 with isolated pulmonary hypertension | 57 | Antinuclear antibodies (ANA)<br>Anticentromere antibody (ACA)<br>Anti-Scl-70<br>Anti-RNP<br>Anti-SS-A, anti-SS-B | Antibody positivity in 20 patients with CREST syndrome and catheterization-proven pulmonary hypertension: ANA 7/16; ACA 8/15; anti-Scl-70 0/14; anti-RNP 1/13; Anti-SS-A or anti-SS-B 0/13. |
| Steen et al. (1988) | 397 | 42.2–45.6 years at onset | Anti-Scl-70 | Lung involvement in 34/ 86 ACA+ patients, 42/ 209 ACA -, Anti-Scl-70 – patients, 57/ 102 Anti-Scl-70 + patients. |
| | | | Anticentromere antibody (ACA) | Isolated pulmonary hypertension present:<br>- Limited scleroderma – 14/ 83 ACA+ patients; 14/108 ACA – patients.<br>- Diffuse scleroderma – 0/ 68 Anti-Scl-70 + patients; 0/ 138 Anti-Scl-70 – patients. |
| Okano and Medsger (1990) | 371 | – | Anti-Th | Pulmonary arterial hypertension was seen in 23 % of 14 Anti-Th positive patients with limited cutaneous involvement, not significantly different from the prevalence in Anti-Th negative patients; 3 out of 15 Anti-Th positive patients died with pulmonary hypertension. |
| Kasukawa et al. (1990) | 14 | 44.6 years at onset of pulmonary hypertension | Anti-nRNP<br>Anti-Sm | Anti-nRNP positivity in 6/10 patients with pulmonary hypertension; anti-Sm positivity seen in none of the same 10 patients. |
| Okano et al. (1992) | 416 | – | Anti-U3 small nuclear ribonuclear protein (U3snRNP) | Primary pulmonary arterial hypertension significantly more common in patients positive for anti-U3snRNP than in antibody negative patients. |
| Kuwana et al. (1994) | 275 | 41.7 | Anti-topoisomerase 1 | 16 patients with isolated pulmonary arterial hypertension, 15 with anti-U1-RNP antibodies. |
| | | | Anti-U1-RNP<br>Anticentromere<br>Anti-RNAP<br>Anti-U3 RNP<br>Anti-Ku<br>Anti-Th RNP | Isolated pulmonary arterial hypertension seen in patients:<br>0/ 68 with positive anti-topoisomerase 1 antibodies,<br>18/ 91 positive anti-U1-RNP antibodies,<br>0/ 44 positive anticentromere antibodies,<br>7/14 positive anti-RNAP antibodies,<br>0/ 10 positive anti-U3 RNP antibodies,<br>0/ 7 positive anti-Ku antibodies,<br>0/ 5 positive anti-Th RNP antibodies.<br>(numbers presented as in the original text) |
| Fritzler et al. (1995) | 128 | 50 | Anti-fibrin bound tissue plasminogen activator (tPA) | 25 patients had anti-tPA antibody positivity; 5/ 21 patients with anti-tPA antibody had pulmonary hypertension, to be compared to 6/96 other patients. |
| Ihn et al. (1996) | 80 | – | Anticardiolipin antibodies; | Anticardiolipin antibodies seen in 20 patients (IgG) and 4 patients (IgM); isolated pulmonary hypertension in 20% of the 20 patients, versus 10% in the remaining 60 patients. |
| | | | Beta 2-GPI-dependent anticardiolipin antibodies | Beta 2-GPI-dependent anticardiolipin antibodies positivity in 8 patients; 63% [5] such patients with isolated pulmonary hypertension to be compared to 7% of the remaining 72 patients. |
| Sacks et al. (1996) | 580 limited cutaneous and 677 diffuse cutaneous patients | – | Anti-U3-RNP | - Isolated pulmonary hypertension seen in 60 limited cutaneous and in 14 diffuse cutaneous patients; 6/ 13 such patients with diffuse cutaneous disease and pulmonary hypertension positive for anti U3-RNP antibodies, to be compared to 25/207 (1) with diffuse cutaneous disease without pulmonary hypertension; 2/ 18 limited cutaneous patients with pulmonary hypertension positive for anti U3-RNP antibodies. |
| | | | Anti-centromere | - ACA positivity in 33/ 60 patients with limited cutaneous disease and pulmonary hypertension; |
| | | | Anti-U1-RNP | - anti-U1-RNP positivity in 7/60 such patients.<br>[1] Different numbers presented in the abstract (13/ 244) and in the text (25/ 207). |
| Koh et al. (1996) | 344 patients, 17 with pulmonary hypertension | 52.5 | ANA | ANA positivity in 12 patients out of 15 with pulmonary hypertension |

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**Table 1** (*continued*)

| Study (year) | Number of patients | Mean or median age (years) | Antibody (ies) under study | Findings concerning pulmonary hypertension |
|---|---|---|---|---|
| Negi et al. (1998) | 76 | 32.7 | IgG anti-endothelial cell antibodies | - IgG anti-endothelial cell antibodies positivity in 27.6% of patients, all women - 40% of patients with diffuse disease (16/ 40), versus 13.5% of patients with limited cutaneous disease (5/36).<br>- Pulmonary arterial hypertension more frequent in patients with IgG anti-endothelial cell antibodies positivity (5/21 versus 1/55). |
| Grigolo et al. (2000) | 92 patients, 27.2% with pulmonary hypertension | – | Anti topoisomerase II α | - Anti topoisomerase II α antibody positivity in 21.7% (20/ 92) of patients. Pulmonary hypertension seen in 55% of positive patients, versus 19.4% in antibody-negative patients. |
| | | | Anti topoisomerase I (Scl −70) | - Anti topoisomerase I (Scl −70) positivity in 50% of patients. |
| | | | ACA | - ACA positivity in 27.2% of patients. |
| Gunduz et al. (2001) | 11 patients with pulmonary hypertension and renal crisis; | 54.1 | Anti-Th/To | - Anti-Th/To – 4/11 versus 1/15 |
| | 15 patients with pulmonary hypertension | (group of 11 patients) | Anti–RNA polymerase III | - Anti–RNA polymerase III – 5/11 versus 0/15 |
| | | | Anti–U3 RNP. | - Anti–U3 RNP – 2/11 versus 2/15 |
| | | | Anti–U1 RNP | - Anti–U1 RNP – 1/11 versus 0/15 |
| | | | ACA | - ACA – 0/11 versus 8/15 |
| | | | Anti–topoisomerase I. | - Anti–topoisomerase I – 0/11 versus 0/ 15. |
| Launay et al. (2001) | 67 patients, 25 with pulmonary hypertension, 11 with isolated pulmonary hypertension, 42 without pulmonary hypertension. | 56 | Anticentromere (ACA)<br>Anti-Scl70<br>Antinucleolar (ANoA)<br>Anticardiolipin | Antibody positivity:<br>- ACA – 6/11 versus 14/42<br>- Anti-Scl70– - 0/11 versus 12/ 42<br>- ANoA – 1/11 versus 3/ 42<br>- Anticardiolipin – 8/ 11 versus 15/ 42 |
| Tormey et al. (2001) | 42 out of 1026 patients with anti-fibrillarin antibody positivity | – | Anti-fibrillarin (anti-U3-RNP) | 11 (/42) patients with isolated pulmonary hypertension; 2 patients with pulmonary fibrosis and pulmonary hypertension. |
| Alessandri et al. (2003) | 34 | 51.1 | Anti--carbonic anhydrase II | Higher prevalence of anti-CAII in patients with pulmonary hypertension (45.5%) than in patients without pulmonary hypertension (4.3%). |
| Steen and Medsger (2003) | 106 scleroderma with pulmonary hypertension patients + 106 scleroderma controls | 40.6–40.4 years at onset | Anti-centromere<br>Anti-Th/To<br>Anti–U3 RNP<br>Anti-U1 RNP<br>Anti–Scl-70 | Anti-centromere: cases 43/98, control 42/97<br>Anti-Th/To: cases 15/48, controls 10/34<br>Anti–U3 RNP cases 13/50, controls 1/30<br>Anti-U1 RNP: cases 10/50, controls 9/53<br>Anti–Scl-70: cases 0/88, controls 12/93<br>Anti–U3 RNP associated to pulmonary hypertension, Anti–Scl-70 found to be protective. |
| Hesselstrand et al. (2003) | 276 | 49.2 | Anti-DNA topoisomerase I | Isolated pulmonary hypertension and pulmonary hypertension associated with pulmonary fibrosis seen, respectively, in patients: |
| | | | Anti-U1 RNP | Anti-DNA topoisomerase I positive – 17.6%, 29.4%/ 26; |
| | | | Anti-RNA polymerase I, II and III | Anti-histone positive– 25%, 25%/ 44; |
| | | | Anti-histone | Anti-U1 RNP positive – 19.4%, 29.0%/ 59; |
| | | | | Anti-RNA polymerase I, II and III positive – 25%, 22.2%/ 60. |
| Mitri et al. (2003) | 87 patients with anti-Th/To antibodies and 306 with ACA | 41.5–41 | Anti-Th/To<br>ACA | Pulmonary hypertension seen in 24/ 87 anti-Th/To positive patients and in 59/ 306 ACA positive patients. |
| Ulanet et al. (2003) | 92 | 45.3–54.0 | Anti B23 | Pulmonary hypertension seen in 6/ 10 anti-B23 positive patients and in 20/ 82 B23 antibody negative patients. |
| Antonioli et al. (2003) | 60 | 57 | Anticardiolipin<br>Anti-β2 glycoprotein I<br>Lupus anticoagulant | Two patients with primary pulmonary hypertension. One patient had positive anticardiolipin and anti-β2 glycoprotein I antibodies; the other was anticardiolipin and lupus anticoagulant positive and anti-β2 glycoprotein I antibody negative |
| Hasegawa et al. (2004) | 112 | 40 | Anti-phosphatidylserine-prothrombin complex | Pulmonary hypertension in 56% of 18 antibody positive patients and in 18% of 94 antibody negative patients. |
| Assous et al. (2005) | 108 scleroderma patients, 16 with pulmonary hypertension | | Antiphospholipid<br>Antinuclear<br>Anti-RNP (anti-ribonucleoprotein)<br>Anti-topoisomerase I / anti-centromere | Antibody positivity in 16 patients with pulmonary hypertension: antiphospholipid 7/16; antinuclear 14/16; anti-RNP 4/16; anti-topoisomerase I / anti-centromere 7 and 9/16, respectively. |

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**Table 1** (*continued*)

| Study (year) | Number of patients | Mean or median age (years) | Antibody (ies) under study | Findings concerning pulmonary hypertension |
|---|---|---|---|---|
| Steen (2005) | 1432 | – | ACA<br>Anti-Th/To<br>Anti-PmScl<br>Anti-U1RNP<br>Anti-U3RNP<br>Anti-topoisomerase<br>Anti-RNA polymerase III | Isolated pulmonary hypertension seen in patients with antibody positivity: ACA 19/ 291; anti-Th/To 32/72; anti-PmScl 3/36; anti-U1RNP 14/71; anti-U3RNP 24/55; anti-topoisomerase 2/318; anti- RNA polymerase III 6/120. |
| Hesselstrand et al. (2005) | 227 | 47.2 | ATA | ATA positivity seen at baseline examination in 33.3% /24 patients with tricuspid gradient > 33 mmHg, versus 11% /203 patients with tricuspid gradient ≤ 33 mmHg.<br>ATA positivity seen at follow-up examinations (cumulative) in 31.6% /38 patients with tricuspid gradient > 33 mmHg, versus 9.7% /189 patients with tricuspid gradient ≤ 33 mmHg. |
| Hayakawa et al. (2005) | 103 | 42, 45 | Anti-DNA topoisomerase II α | Pulmonary hypertension seen in none of the 13 patients with anti-DNA topoisomerase II α antibody positivity and in 6 out of 90 patients with antibody negativity |
| Tamby et al. (2005) | 30 scleroderma patients, 10 with pulmonary hypertension | 58.4 (10 patients) | Anti-endothelial cells<br>ANA<br>ACA | Patients with pulmonary hypertension associated scleroderma express anti-endothelial cells antibodies. Antibody positivity: ANA 5/10, ACA 3/10. |
| Tamby et al. (2006) | 30 scleroderma patients, 10 with pulmonary hypertension | 58.4 (10 patients) | Anti-fibroblast<br>Anti-topoisomerase I<br>ANA<br>ACA | Anti-fibroblast antibodies seen in 3/ 10 patients with scleroderma and pulmonary hypertension; anti-topoisomerase I antibodies seen in 2/ 10 patients. ANA and ACA data as reported previously. |
| Steen et al. (2007) | 833 | 42–-43 | Anti-centromere<br>Anti-nucleolar<br>Anti-topoisomerase I | Isolated pulmonary arterial hypertension seen in 55/309 ACA positive patients, in 29/185 ANoA positive patients and in 7/339 ATA positive patients (significantly different). |
| Steen et al. (2008) | 54 scleroderma patients at risk for pulmonary hypertension | 53.2 years | Anti-centromere ($n$ = 13)<br>Anti-nucleolar antibody ($n$ = 19)<br>Anti-Scl-70 ($n$ = 7) | Increases in right ventricular systolic pressure, in exercise echocardiography: Anti-centromere + patients, 17.6 mmHg; Anti-nucleolar + patients, 18.4 mmHg; Anti–Scl-70 + patients, 8.6 mmHg.<br>This latter value is significantly lower than in patients with Anti-centromere antibody. |
| Hamaguchi et al. (2008) | 203 | 46 | Anti-topoisomerase I<br>ACA<br>Anti-U1-RNP<br>Anti-RNAP<br>Anti-Th /To<br>Anti-U3-RNP | Isolated pulmonary hypertension seen in patients with positivity for the antibodies: anti-topoisomerase I, 17% /64; ACA, 7%/ 75; anti-U1-RNP, 20%/10, anti-RNAP, 8%/12; anti-Th /To, 14%/7; anti-U3-RNP, 0/ 5. |
| Kampolis et al. (2008) | 71 | 44.6–43.6 | ACA<br>Anti-Scl-70 | ACA seen in 7/ 16 patients with pulmonary artery systolic pressure slope > /= 2.5 mmHg/year, 9/ 55 patients with slope < 2.5 mmHg/year; corresponding values for anti-Scl-70: 8/16 and 33/55. The presence of ACA was significantly associated with a pulmonary artery systolic pressure rise of ≥ 2.5 mmHg/year. |
| Marie et al. (2008) | 69 | 58 | Anticardiolipin<br>Anti-beta2 glycoprotein I<br>Lupus-like anticoagulant | Pulmonary hypertension seen in 4 out of 13 patients with antiphospholipid antibodies |
| Rozman et al. (2008) | 625 | – | Anti-Ku | Pulmonary hypertension seen in 5/11 anti-Ku positive patients and in 10/38 control patients |
| Hachullah et al. (2009) | 78, 43 with early onset and 35 patients with late onset pulmonary hypertension | 59.2 at pulmonary hypertension diagnosis | Anticentromere<br>Antitopoisomerase I<br>Antinucleolar | ACA positivity in 19 (44%) early onset vs 15 (43%) late onset pulmonary hypertension patients<br>ATA positivity in 7 (16%) early onset vs 6 (17%) late onset pulmonary hypertension patients<br>ANoA positivity in 10 (23%) early onset vs 6 (17%) late onset pulmonary hypertension patients |
| Gupta et al. (2009) | 72 | 35 | Antiphospholipid (anticardiolipin and lupus anticoagulant) | Pulmonary hypertension 0/ 7 patients positive for antiphospholipid antibodies and in 3/ 65 negative patients. |

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**Table 1** (*continued*)

| Study (year) | Number of patients | Mean or median age (years) | Antibody (ies) under study | Findings concerning pulmonary hypertension |
|---|---|---|---|---|
| Boin et al. (2009) | 75 + 75 | 52.5, 53.1 | Anti–β2-glycoprotein I<br>Anticardiolipin<br>ACA | Elevated right ventricular pressure seen in 56/94 patients.<br>Anti–β2-glycoprotein I positivity seen in 27 patients with and in 14 patients without pulmonary hypertension (increased odds ratio).<br>Anticardiolipin positivity seen in 15 patients with and in 13 patients without pulmonary hypertension.<br>ACA positivity seen in 78 patients, 33 of which with pulmonary hypertension. |
| Aggarwal et al. (2009) | 108 + 2471 | 42.8, 47.4 | Anti-U3 RNP | Pulmonary arterial hypertension seen in 27/ 86 patients positive for anti-U3 RNP antibodies and in 239/ 1823 antibody negative patients. |
| Terrier et al. (2010) | 158 | 47.2 | Antifibroblast antibody with anti-α-enolase activity<br>ANA | Pulmonary hypertension in 12/ 35 patients with positive anti-α-enolase antibody and in 20/ 108 negative anti-α-enolase antibody;<br>24 patients positive for ANA, 12 with pulmonary hypertension |
| Meyer et al. (2010) | 319 | 53.8 | Anti-RNA polymerase III antibody | 1 patient with pulmonary hypertension out of 26 positive for RNAP; 13 patients with pulmonary hypertension out of 263 negative for RNAP |
| Launay et al. (2011) | 50 | 61 | Anti-centromere antibody<br>Anti-topoisomerase I antibody | In 50 systemic sclerosis patients with pulmonary arterial hypertension, 29 were positive for anti-centromere antibody and 8 are positive for anti-topoisomerase I antibody. |
| Skare et al. (2011) | 66 | 51.35 | Anti-Scl-70<br>Anti-centromere<br>Anti-U1-RNP | In 66 systemic sclerosis patients 10 were positive for anti-Scl-70 antibody (2 had pulmonary hypertension), 15 were positive for anti-centromere antibody (5 had pulmonary hypertension) and 7 were positive for anti-U1-RNP antibody (2 had pulmonary hypertension). |
| Sharif et al. (2011) | 278 African American patients | 46.9 | Anti-U3-RNP (anti-fibrillarin) | In 50 systemic sclerosis patients positive for anti-U3-RNP antibody, 10% had pulmonary arterial hypertension. |
| Grader Beck et al. (2011) | 181 | 59.3 | Anti-4-sulfated N-Acetyl-lactosamine | Anti-4-sulfated N-Acetyl-lactosamine antibody positivity in 27/ 181 patients, 15 of which with pulmonary arterial hypertension. |
| Riemekasten et al. (2011) | 298 | | Anti-angiotensin II type 1 receptor<br>Anti-endothelin-1 type A receptor | Increased relative risk of pulmonary arterial hypertension with higher levels of either antibody |
| Rodriguez-Reyna et al. (2011) | 139 | 45.3 | ACA<br>Anti-DNA Topo-I (Anti-topoisomerase I)<br>Anti-U1 RNP<br>Anti-PM-Scl<br>Pol III (Anti–RNA polymerase III)<br>Anti-Ku | Pulmonary arterial hypertension present in 75% anti-Ku antibody positive patients versus 23% in anti-Ku negative patients. Remaining antibodies with a non-significant different distribution of pulmonary hypertension between positive and negative patients. |
| Clements et al. (2012) | 279 patients with idiopathic pulmonary arterial hypertension and 228 scleroderma with pulmonary arterial hypertension patients | 56 and 58 years | ANA | Abnormal ANA: 38/140 (27.1%) in idiopathic pulmonary arterial hypertension and 97/114 (85.1%) in scleroderma with pulmonary arterial hypertension.<br>Abnormal ANA more common in scleroderma patients. |
| Hashimoto et al. (2012) | 357 | Median 51 years at diagnosis | Anti-Scl-70 antibody<br>Anti-centromere antibody<br>Anti-U1-RNP antibody | Pulmonary hypertension in 12/68 patients positive for anti-Scl-70 antibody only, 8/105 positive for ACA only and 16/57 are positive for anti-U1-RNP antibody only. |
| Hudson et al. (2012b) | 963 | 55.42 | Anti-Ro52/TRIM21 antibody | Pulmonary hypertension in 26/194 patients positive for anti-Ro52/TRIM21 |
| Hudson et al. (2012) | 802 | 55.78 | Anti-centromere antibody<br>CENP-A antibody<br>CENP-B antibody | Pulmonary hypertension in 38/279 patients positive for ACA, 38/276 positive for CENP-A antibody and 39/286 positive for CENP-B antibody. |
| Graf et al. (2012) | 129 | – | ACA<br>Anti-Scl70<br>Anti-RNA polymerase III<br>Anti-U1RNP<br>Anti-Th/To<br>Anti-Pm/Scl | Pulmonary hypertension seen in:<br>5/51 patients positive for ACA;<br>3/23 patients positive for Anti-Scl70;<br>2/20 patients positive for Anti-RNA polymerase III;<br>4/9 patients positive for Anti-U1RNP;<br>3/8 patients positive for Anti-Th/To;<br>1/9 patients positive for Anti-Pm/Scl. |
| Polimeni et al. (2012) | 78 | 48 | Anti-cyclic citrullinated peptide | No relationship with pulmonary hypertension |
| Koschik et al. (2012) | 2349 + 76 | 40.9, 47.3 | Anti-PM-Scl | Pulmonary arterial hypertension, not secondary to pulmonary fibrosis, in: 3/59 anti-PM-Scl positive patients; 247/ 1688 anti-PM-Scl negative patients |

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**Table 1** (*continued*)

| Study (year) | Number of patients | Mean or median age (years) | Antibody (ies) under study | Findings concerning pulmonary hypertension |
|---|---|---|---|---|
| Touré et al. (2013) | 40 | Median 41 | Anticardiolipin<br>Anti-β2 GPI<br>Lupus anticoagulant | 7 cases of pulmonary hypertension out of 23 patients with antiphospholipid antibodies |
| Lewandowska et al. (2013) | 54 | 55.7 | Anti-endothelial cell | One patient with pulmonary hypertension out of 14 patients positive for anti-endothelial cell antibodies |
| Becker et al. (2014) | 81 | – | Anti-angiotensin receptor type-1 (anti-$AT_1R$)<br>Anti-endothelin receptor type A (anti-ETAR) | In the cohort of systemic sclerosis patients with pulmonary hypertension, 69.1% were positive for anti-$AT_1R$ antibody and 65.4% positive for anti-ETAR antibody |
| Mellal et al. (2014) | 147 | 45.4 | Anticardiolipin | Five patients (33.3%) with pulmonary arterial hypertension / 15 patients with anticardiolipin antibodies (versus only 8.5% in antibody negative patients). |
| Gosh et al. (2014) | 46 | 38.8 | Anti-nuclear<br>Anti-Scl-70<br>Anti-centromere | Pulmonary hypertension seen in 11 patients, 9 of which positive for anti-nuclear antibody, 4 positive for anti-Scl-70 antibody and 2 positive for anti-centromere antibody (the corresponding figures for the 35 patients without pulmonary hypertension being 29, 7 and 7, respectively). Pulmonary hypertension seen in 8/ 38 patients with ANA positivity. |
| Hsu et al. (2014) | 35 | 59.1 | Anti-centromere<br>Anti-Scl-70<br>Anti-nucleolar ANA<br>Anti-U1-RNP | Pulmonary hypertension in 35 patients, 10/35 patients positive for ACA, 2/35 positive for anti-Scl-70 antibody, 10/35 positive for antinucleolar ANA and none positive for anti-U1-RNP antibody. |
| Morrisroe et al. (2014) | 940 | 57.5 | Anticardiolipin | Pulmonary hypertension seen in 124 (13.2%) patients, divided in 20/ 95 patients with and in 104/ 774 patients without anticardiolipin antibodies positivity. |
| Nihtyanova et al. (2014) | 398 | 45, 49 | Anti–topoisomerase I<br>Anti–RNA polymerase III<br>Anti–U3 RNP | In multivariable analysis, anti–RNA polymerase III and anti–U3 RNP antibodies acted as positive predictors for pulmonary hypertension, while the presence of anti–topoisomerase I antibodies reduced the hazard of pulmonary hypertension. |
| Kaji et al. (2014) | 588 | 44.9–58.1 | Anti-RuvBL1/2 antibody | Pulmonary hypertension seen in one patient out of 10 with anti-RuvBL1/2 antibody positivity |
| Salazar et al. (2015) | 2040 | 44.7–44.6 (whole cohort) | ANA | ANA positivity seen in 3041/3249 scleroderma patients.<br>2040 patients evaluated for pulmonary hypertension. Pulmonary hypertension seen in 332/ 1907 ANA positive and in 13/133 ANA negative patients. |
| Tao et al. (2015) | 136 patients, 28 with pulmonary hypertension | 47.1 | Anti-nuclear antibody<br>Anti-nuclear RNP antibody<br>Anti-Sm antibody<br>Anti-Ro/SSA antibody<br>Anti-La/SSB antibody<br>Anti-double-stranded DNA antibody | In 28 systemic sclerosis patients with pulmonary arterial hypertension 26 were positive for anti-nuclear antibody, 11 for anti-nuclear RNP antibody, 6 for anti-Ro/SSA antibody and 2 each for anti-Sm antibody, anti-La/SSB antibody and anti-double-stranded DNA antibody. |
| Hinchcliff et al. (2015) | 162 | 59.8 | Anti-centromere<br>Anti-nucleolar<br>Anti-Scl-70 (anti-topoisomerase I)<br>Anti-RNA polymerase III antibody<br>Anti-U1-RNP antibody | In 162 systemic sclerosis patients with pulmonary hypertension 60 were positive for anti-centromere antibody, 39 positive for anti-nucleolar antibody, 11 positive for anti- Scl-70 antibody, 9 positive for anti-RNA polymerase III antibody, 8 positive for anti-U1-RNP antibody, 28 were positive for non-specific ANAs and 7 were negative for all antibodies. |
| Motegi et al. (2015) | 246 | 64 | Anti-RNA polymerase III antibody<br>Anti-topoisomerase I antibody<br>Anti-centromere antibody | 14 patients positive for anti-RNA polymerase III antibody, 51 positive for anti-topoisomerase I antibody and 97 positive for anti-centromere antibody and, in each group, 1, 9 and 8 have pulmonary hypertension, respectively. |
| Srivastava et al. (2015) | 551 | 51.1–-59.5 | Anti-topoisomerase I antibody<br>Anti-centromere antibody | In 388 patients positive for anti-centromere antibody (91 with diffuse disease and 297 with limited disease) 49 (13 + 36) had pulmonary hypertension. In 163 patients positive for anti-topoisomerase I antibody (111 with diffuse disease and 52 with limited disease) 11 (9 + 2) had pulmonary hypertension. |
| Wodkowski et al. (2015) | 1574 | 55.1 | anti-Ro52/ TRIM21 | Pulmonary hypertension in:<br>- 8% of patients with monospecific anti-Ro52/ TRIM21 antibody;<br>- 20% of overlapping anti-Ro52/ TRIM21 antibody;<br>- 12% of anti-Ro52/ TRIM21 antibody negative patients. |

(*continued on next page*)

**Table 1** (*continued*)

| Study (year) | Number of patients | Mean or median age (years) | Antibody (ies) under study | Findings concerning pulmonary hypertension |
|---|---|---|---|---|
| García-Hernández et al. (2016) | 184 | 57.8 | ACA<br>ATA | Confirmed pulmonary hypertension seen in 25 patients.<br>ACA positive in 16/25 patients, ATA positive in 3/25 patients. |
| Hoa et al. (2016) | 2140 | 55.1 | Anti-Ku | 24 patients had anti-Ku antibodies, of which 2 patients also had pulmonary hypertension. |
| Perosa et al. (2016) | 84 patients with anti-centromeric protein A antibodies | 56.4 | Anti-centromeric protein A | Pulmonary arterial hypertension seen in 4 patients. Increased anti-pc4.2 antibody levels was associated with an increase in systolic pulmonary artery pressure, while an increase in anti-pc14.1 antibody levels was associated with a decrease in systolic pulmonary artery pressure. |
| Sobanski et al. (2016) | 308 patients with scleroderma and pulmonary hypertension | 54.4, 62.7 | Anti–U1 RNP | Anti–U1 RNP antibody positivity seen in 16 patients (292 with antibody negativity). Trend toward better survival in anti–U1 RNP–positive patients. |
| Tozkir et al. (2016) | 46 | 48.1 | Class I and II anti-human leukocyte Antigen (HLA) | Patients with and without anti-HLA antibodies<br>Had similar frequencies of pulmonary hypertension<br>And pulmonary fibrosis |
| Hoffman-Vold et al. (2017) | 279 | 49 | Anti-RNA polymerase III antibody<br>Anti-centromere antibody<br>Anti-topoisomerase I antibody | Pulmonary hypertension seen in 4/33 RNAP positive patients, in 28/134 ACA positive patients and in 5/46 ATA positive patients. |
| Markusse et al. (2017) | 287 | 54 | ACA<br>Anti-Scl-70<br>Anti-RNAP (III)<br>Anti-RNP | Odds ratios of 0.39 for ACA positivity (107 patients), 2.12 for Anti-Scl-70 positivity (69 patients), 1.21 for Anti-RNAP (III) positivity (13 patients) and 2.22 for Anti-RNP positivity (26 patients), all when associated to elevated pulmonary arterial pressure, none of them significant. |
| Michelfelder et al. (2017) | 24 scleroderma patients with pulmonary hypertension and interstitial lung disease and 27 scleroderma patients with pulmonary hypertension | 60, 63 | Anti-endothelin-1 type A receptor<br>Anti-angiotensin II type 1 receptor<br>ANA<br>ACA<br>Anti-Scl-70<br>Anti-PmScl<br>Anti-U1RNP<br>Anti-Pol3 (anti-ribonucleic acid polymerase III) | Autoantibody profiles did not differ in the two groups of patients, with or without interstitial lung disease |
| Tall et al. (2017) | 37 scleroderma patients positive and 139 scleroderma patients negative for Antifibrillarin autoantibodies. | 36.9, 42.9 | Antifibrillarin (anti-U3-RNP) | Pulmonary hypertension seen in 3/35 antifibrillarin positive and in 8/ 139 antifibrillarin negative patients. |
| Carreira et al. (2017) | 1188 | 52.3 | Anti-Scl-70<br>ACA | Overall, pulmonary hypertension seen in 193, not present in 961 patients.<br>Pulmonary hypertension seen in 75, not present in 322 Scl-70 positive patients.<br>Pulmonary hypertension seen in 58, not present in 259 ACA positive patients. |
| Ilgen et al. (2017) | 93 | 50–53 | Anti-angiotensin II type 1 receptor | No correlation between serum levels of antibodies and systolic pulmonary artery pressure measurements |
| Fritzler et al. (2018) | 451 | 55.5 | Anti-bicaudal D2 | Pulmonary hypertension seen in 2/22 patients with single-specificity anti-bicaudal D2 antibody and in 8/94 overlapping anti-bicaudal D2 antibody |

**Table 2**
Antinuclear antibody (ANA) positivity in scleroderma patients and pulmonary arterial hypertension. For complete references see text.

| | |
|---|---|
| Stupi et al. (1986) | ANA positivity in 7 out of 16 patients with CREST syndrome and catheterization-proven pulmonary hypertension |
| Koh et al. (1996) | ANA positivity in 12 patients out of 15 with pulmonary hypertension |
| Assous et al. (2005) | ANA positivity in 14 patients out of 16 with pulmonary hypertension |
| Tamby et al. (2005), (Tamby et al. 2006) | ANA positivity in 5 patients out of 10 patients with pulmonary hypertension (same data in both articles) |
| Terrier et al. (2010) | 24 patients positive for ANA, 12 with pulmonary hypertension |
| Clements et al. (2012) | ANA positivity in 97 patients out of 114 patients with pulmonary hypertension |
| Gosh et al. (2014) | Pulmonary hypertension in 8/ 38 patients with ANA positivity; ANA positivity in 9 out of 11 patients with pulmonary hypertension |
| Salazar et al. (2015) | Pulmonary hypertension in 332 patients out of 1907 ANA-positive patients |
| Tao et al. (2015) | ANA positivity in 26 patients out of 28 with pulmonary hypertension |

2010–2018 period [41–82].

### 3.1. Antinuclear antibodies

The list of research reports including data on antinuclear antibodies (ANA) is presented in Table 2. A vast majority (81%) of scleroderma patients with pulmonary arterial hypertension were positive for ANA. The prevalence of pulmonary hypertension in ANA positive scleroderma patients seems to be significantly smaller (18%).

### 3.2. Anti-double-stranded DNA antibody

Tao et al. studied 28 systemic sclerosis patients with pulmonary arterial hypertension; 2 patients were positive for anti-double-stranded DNA antibody [61].

### 3.3. Anticentromere antibodies

The list of research reports including data on anticentromere antibodies (ACA) is presented in Table 3. Almost half (45%) of scleroderma patients with pulmonary arterial hypertension were positive for ACA, whereas less than one fifth (15%) of ACA positive scleroderma patients had pulmonary arterial hypertension (Table 10).

### 3.4. Anti-CENP-A and anti CENP-B antibodies

Hudson et al. studied 802 scleroderma patients with the Canadian Scleroderma Research Group. Pulmonary hypertension was seen in 38/279 patients positive for anti-centromere antibodies, 38/276 positive for CENP-A antibody and 39/286 positive for CENP-B antibody [49] (CENP-A and CENP-B standing for centromere protein A and centromere protein B). Perosa et al. published further data on anti-CENP-A antibody in this context [67].

### 3.5. Anti-bicaudal D2 antibody

Fritzler et al. found pulmonary hypertension to be present in 2/22 patients with single-specificity anti-bicaudal D2 antibody and in 8/94 overlapping anti-bicaudal D2 antibody (the whole cohort comprising 451 scleroderma patients) [79]. Inflammatory myopathy and interstitial lung disease were more likely to be present in association to this antibody [79].

**Table 3**
Anti-centromere antibody (ACA) positivity in scleroderma patients and pulmonary arterial hypertension. For complete references see text.

| | |
|---|---|
| Stupi et al. (1986) | ACA positivity in 8 out of 15 patients with CREST syndrome and catheterization-proven pulmonary hypertension |
| Steen et al. (1988) | Isolated pulmonary hypertension present in 14/ 83 ACA positive limited scleroderma patients |
| Kuwanaet al. (1994) | Isolated pulmonary arterial hypertension seen in 0/ 44 ACA positive patients |
| Sacks et al. (1996) | ACA positivity in 33/ 60 patients with limited cutaneous disease and pulmonary hypertension |
| Gunduz et al. (2001) | ACA positivity in 0/11 patients with pulmonary hypertension and renal crisis and in 8/15 patients with pulmonary hypertension |
| Launay et al. (2001) | ACA positivity in 6/11 patients with isolated pulmonary hypertension |
| Steen and Medsger (2003) | ACA positivity in 43/98 patients with pulmonary hypertension |
| Mitri et al. (2003) | Pulmonary hypertension seen in 59/306 ACA positive patients |
| Assous et al. (2005) | ACA positivity in 9/16 patients with pulmonary hypertension |
| Steen (2005) | Isolated pulmonary hypertension in 19/291 patients with ACA positivity |
| Tamby et al. (2005), Tamby et al. (2006) | ACA positivity in 3/10 patients with pulmonary hypertension |
| Steen et al. (2007) | Isolated pulmonary arterial hypertension seen in 55 out of 309 ACA positive patients, |
| Hamaguchi et al. (2008) | Isolated pulmonary hypertension seen in 7% of 75 ACA positive patients |
| Kampolis et al. (2008) | ACA positivity seen in 7/ 16 patients with pulmonary artery systolic pressure slope $> / =$ 2.5 mmHg/year, 9/ 55 patients with slope $<$ 2.5 mmHg/year |
| Hachullah et al. (2009) | ACA positivity in 19 (44%) early onset versus 15 (43%) late onsetpulmonary hypertension patients |
| Boin et al. (2009) | Pulmonary hypertension in 33/78 ACA positive patients |
| Launay et al. (2011) | ACA positivity in 29 patients out of 50 with pulmonary hypertension |
| Skare et al. (2011) | Pulmonary hypertension in 5/15 ACA positive patients |
| Hashimoto et al. (2012) | Pulmonary hypertension in 8/105 ACA positive patients |
| Hudson et al. (2012) | Pulmonary hypertension in 38/279 ACA positive patients |
| Graf et al. (2012) | Pulmonary hypertension in 5/51 ACA positive patients |
| Gosh et al. (2014) | ACA positivity in 2 patients out of 11 with pulmonary hypertension |
| Hsu et al. (2014) | ACA positivity in 10 patients out of 35 with pulmonary hypertension |
| Hinchcliff et al. (2015) | ACA positivity in60 patients out of 162 with pulmonary hypertension |
| Motegi et al. (2015) | Pulmonary hypertension in 8/97 ACA positive patients |
| Srivastava et al. (2015) | Pulmonary hypertension in 49/388 ACA positive patients |
| García- Hernández et al. (2016) | ACA positivity in 16 patients out of 25 with pulmonary hypertension |
| Hoffman-Vold et al. (2017) | Pulmonary hypertension in 28/ 134 ACA positive patients |
| Michelfelder et al. (2017) | ACA positivity in 26% of patients with pulmonary hypertension andInterstitial lung disease and in 48% of patients with pulmonary hypertension |
| Carreira et al. (2017) | Pulmonary hypertension seen in 58 (out of 317), not present in 259 (out of 317) ACA positive patients. |

### 3.6. Anti-nucleolar antibodies

Launay et al. described anti-nucleolar antibodies in 1/ 11 scleroderma patients with isolated pulmonary hypertension, to be compared to 3/ 42 patients without pulmonary hypertension [16]. Steen et al. described isolated pulmonary arterial hypertension to be present in 29 out of 185 anti-nucleolar positive patients [28]. Hachullah et al. studied 78 scleroderma patients, and found anti-nucleolar antibody positivity in 10 (23%) early onset versus 6 (17%) late onsetpulmonary hypertension scleroderma patients [32]. Hsu et al. described anti-nucleolar (antinuclear) antibody positivity in 10 out of 35 scleroderma patients with pulmonary hypertension [57]. Hinchcliff et al. described a set of 162 systemic sclerosis patients with pulmonary hypertension, 39 of which were positive for anti-nucleolar antibody [62]. These authors further found no significant association between risk of death and the presence of autoantibodies [62].

### 3.7. Anti-Scl-70 (anti-topoisomerase I) antibodies

About 18% of scleroderma patients with pulmonary hypertension had anti-Scl-70 antibodies positivity, whereas only 5% of scleroderma patients with anti-Scl-70 antibodies positivity had pulmonary hypertension (Table 4).

### 3.8. Anti-topoisomerase II α

Grigolo et al. found anti topoisomerase II α antibody positivity in 21.7% (20/ 92) of scleroderma patients. Pulmonary hypertension was seen in 55% of positive patients, versus 19.4% in antibody-negative patients [14]. Hayakawa et al. studied 103 scleroderma patients and found no case of pulmonary hypertension in the 13 patients with anti-DNA topoisomerase II α antibody positivity, whereas 6 cases were seen in the 90 patients with antibody negativity [37].

### 3.9. Anti-RNP antibodies

Anti-ribonucleoprotein antibodies have been recognized to be associated to pulmonary hypertension by Sharp [83]. Stupi et al. described one case of pulmonary hypertension and anti-RNP antibody positivity in a series of 13 patients with CREST syndrome [3]. Kasukawa et al. described anti-nRNP positivity in 6/10 patients with scleroderma and pulmonary hypertension [6]. Assous et al. described anti-RNP antibody positivity in 4 out of 16 scleroderma patients with pulmonary hypertension [23]. Tao et al. described a series of 28 systemic sclerosis patients with pulmonary arterial hypertension, of which 11 were positive for anti-nuclear RNP antibody [61]. Markusse et al. described 26 scleroderma patients positive for anti-RNP antibody (out of 287 patients); the risk for increased pulmonary arterial pressure was increased if the nailfold videocapillaroscopy pattern was taken into consideration [71].

### 3.10. Anti-U1RNP antibodies

The percentage of scleroderma patients with pulmonary hypertension that had anti-U1RNP antibodies positivity was estimated to be 9%, whereas approximately 22% of scleroderma patients with anti-U1RNP antibodies positivity had pulmonary hypertension (Tables 5 and 10).

### 3.11. Anti-U3RNP antibodies

The presence of anti-U3RNP antibodies in scleroderma patients was studied in several research papers (Table 7). Anti-U3RNP antibodies positivity was seen in about 24% of scleroderma patients with pulmonary hypertension (Table 10). Pulmonary hypertension was present in about 25% of scleroderma patients with anti-U3RNP antibodies positivity (Table 10).

### 3.12. Anti-RNA polymerase III antibodies

The data concerning anti-RNA polymerase III (RNAP) antibodies is

**Table 4**
Anti-Scl-70 (anti-topoisomerase I) antibody positivity in scleroderma patients and pulmonary arterial hypertension. * taken as 5 patients for further calculations. For complete references see text.

| | |
|---|---|
| Stupi et al. (1986) | Anti-Scl-70 positivity in 0 patients out of14 with pulmonary hypertension |
| Steen et al. (1988) | Isolated pulmonary hypertension in 0 /68 anti-Scl-70 positive diffuse scleroderma patients |
| Kuwana et al. (1994) | Isolated pulmonary arterial hypertension seen in 0/ 68 anti-topoisomerase I antibodies positive patients |
| Gunduz et al. (2001) | Anti–topoisomerase I antibodies in0 patients out of 15 with pulmonary hypertension |
| Launay et al. (2001) | Anti-Scl70 positivity in 0 patients out of 11 with pulmonary hypertension |
| Steen and Medsger (2003) | Anti–Scl-70 positivity in 0patients out of 88 with pulmonary hypertension |
| Hesselstrand et al. (2003) | Isolated pulmonary hypertension in 17.6% of 26 anti-DNA topoisomerase I positive patients *; pulmonary hypertension associated to pulmonary fibrosis in 29.4% of same group of patients |
| Assous et al. (2005) | Anti-topoisomerase I antibodies positivity in 7/16 patients with pulmonary hypertension |
| Steen (2005) | Isolated pulmonary hypertension seen in 2/318 anti-topoisomerase positive patients |
| Tamby et al. (2006) | Anti-topoisomerase I antibodies seen in 2/ 10 patients with pulmonary hypertension |
| Steen et al. (2007) | Isolated pulmonary arterial hypertension seen in 7/339 anti-topoisomerase I positive patients |
| Hamaguchi et al. (2008) | Isolated pulmonary hypertension seen in 17% of 64 anti-topoisomerase I positive patients |
| Hachullah et al. (2009) | Anti–topoisomerase I antibodies in7 (16%) early onset versus 6 (17%) late onsetpulmonary hypertension patients |
| Launay et al. (2011) | Anti–topoisomerase I antibodies in 8 patients out of 50 with pulmonary hypertension |
| Skare et al. (2011) | Pulmonary hypertension in 2/ 10 anti-Scl-70 positive patients |
| Hashimoto et al. (2012) | Pulmonary hypertension in 12/68 anti-Scl-70 antibody only positive patients |
| Graf et al. (2012) | Pulmonary hypertension in 3/23 anti-Scl-70 positive patients |
| Gosh et al. (2014) | Anti-Scl-70 positivity in 4 patients out of 11 with pulmonary hypertension |
| Hsu et al. (2014) | Anti-Scl-70 positivity in 2 patients out of 35 with pulmonary hypertension |
| Nihtyanova et al. (2014) | The presence of anti–topoisomerase I antibodies reduced the hazard of pulmonary hypertension. |
| Hinchcliff et al. (2015) | Anti-Scl-70 positivity in 11 patients out of 162 with pulmonary hypertension |
| Motegi et al. (2015) | Pulmonary hypertension in 9/51 anti-topoisomerase I antibody positive patients |
| Srivastava et al. (2015) | Pulmonary hypertension in 11/163 anti-topoisomerase I antibody positive patients |
| García-Hernández et al. (2016) | Anti-topoisomerase I antibody positivity in 3 patients out of 25 with pulmonary hypertension |
| Hoffman-Vold et al. (2017) | Pulmonary hypertension in 5/46 of anti-topoisomerase I antibody positive patients |
| Carreira et al. (2017) | Scl-70 antibody positivity in 75/193 patients with pulmonary hypertension |
| Markusse et al. (2017) | Systolic pulmonary artery pressure was not significantly increased inpatients with anti-Scl-70 antibodies (multivariate logistic regression analysis) |
| Michelfelder et al. (2017) | Anti-Scl-70 antibodies positive in 15% of 27 patients with pulmonary hypertension without Interstitial lung disease |

**Table 5**
Anti-U1RNP antibody positivity in scleroderma patients and pulmonary arterial hypertension. For complete references see text.

| | |
|---|---|
| Kuwanaet al. (1994) | 16 patients with isolated pulmonary arterial hypertension, 15 with anti-U1-RNP antibodies.<br>Isolated pulmonary arterial hypertension in 18 out of 91 patients positive for anti-U1RNP antibodies |
| Sacks et al. (1996) | Anti-U1RNP antibody positivity in 7 out of 60 patients with limited cutaneous disease and pulmonary hypertension |
| Gunduz et al. (2001) | Anti-U1RNP antibody positivity in 1 patient out of 11 with pulmonary hypertension and renal crisis and in 0 patients out of 15 with pulmonary hypertension |
| Hesselstrand et al. (2003) | Isolated pulmonary hypertension and pulmonary hypertension associated with pulmonary fibrosis in 19.4% and in 29.0% of 59 anti-U1 RNP antibody positive patients |
| Steen and Medsger (2003) | Anti-U1RNP antibody positivity in 10 out of 50 patients with systemic sclerosis, limited cutaneous involvement and pulmonary hypertension |
| Steen (2005) | Isolated pulmonary hypertension present in 14/71 anti-U1RNP antibody positive patients. |
| Hamaguchi et al. (2008) | Isolated pulmonary hypertension present in 20% [2]/ 10anti-U1RNP antibody positive patients. |
| Skare et al. (2011) | Pulmonary hypertension present in 2/ 7 anti-U1RNP antibody positive patients. |
| Hashimoto et al. (2012) | Pulmonary hypertension present in 16/ 57 anti-U1RNP antibody positive only patients. |
| Graf et al. (2012) | Pulmonary hypertension present in 4/ 9 anti-U1RNP antibody positive patients. |
| Hsu et al. (2014) | Anti-U1RNP antibody positivity in 0 patients out of 35 with pulmonary hypertension |
| Hinchcliff et al. (2015) | Anti-U1RNP antibody positivity in 8 patients out of 162 with pulmonary hypertension |
| Sobanski et al. (2016) | Anti-U1RNP antibody positivity in 16 patients out of 308 with pulmonary hypertension |
| Michelfelder et al. (2017) | Anti-U1RNP antibody positivity in 16% of 19 patients with pulmonary hypertension and interstitial lung disease versus 14% of 21 patients with pulmonary hypertension. |

**Table 6**
Anti–RNA polymerase III (RNAP) antibodies positivity in scleroderma patients and pulmonary arterial hypertension. For complete references see text.

| | |
|---|---|
| Kuwanaet al. (1994) | Isolated pulmonary arterial hypertension seen in 7/14 anti-RNAP antibodies positive patients. |
| Gunduz et al. (2001) | Anti–RNA polymerase III positivity in 0/15 patients with pulmonary hypertension (versus 5/11 patients with pulmonary hypertension and renal crisis) |
| Hesselstrand et al. (2003) | Isolated pulmonary hypertension seen in 25% of 60 anti-RNA polymerase I, II and III antibodies positive patients(hypertension and pulmonary hypertension associated with pulmonary fibrosis in 22.2% of 60) |
| Steen (2005) | Isolated pulmonary hypertension seen in 6/120 patients with anti- RNA polymerase III antibody positivity |
| Hamaguchi et al. (2008) | Isolated pulmonary hypertension seen in 8% of 12 patients with positivity for the anti-RNAP antibodies |
| Meyer et al. (2010) | Pulmonary hypertension seen in 1/ 26 RNAP antibody positive patients; 13 patients with pulmonary hypertension out of 263 negative for RNAP |
| Graf et al. (2012) | Pulmonary hypertension seen in 2/20 anti-RNA polymerase III positive patients |
| Nihtyanova et al. (2014) | Presence of anti–RNA polymerase III as positive predictor for pulmonary hypertension |
| Hinchcliff et al. (2015) | Anti-RNA polymerase III antibody positivity in 9 out of 162patients with pulmonary hypertension |
| Motegi et al. (2015) | Pulmonary hypertension seen in 1/14 anti-RNA polymerase III antibody positive patients |
| Hoffman-Vold et al. (2017) | Pulmonary hypertension seen in 4/33 RNAP positive patients |
| Markusse et al. (2017) | Patients with RNAPIII positivity did not have an increased risk of pulmonary hypertension; with a severe nailfold videocapillaroscopypattern, this risk was significantly increased |

presented in Table 6. The presence of pulmonary hypertension was estimated to be 12% of antibody positive scleroderma patients, whereas antibody positivity was seen in approximately 5% of scleroderma patients with pulmonary hypertension (Table 10).

### 3.13. Anti-Th/To

The data concerning anti-Th/To antibodies are presented in Table 8. The presence of pulmonary hypertension was estimated to be 33% of antibody positive scleroderma patients, whereas antibody positivity was seen in approximately 25% of scleroderma patients with pulmonary hypertension (Table 10).

### 3.14. Anti-histone antibodies

Anti-histone antibodies are known to be associated to drug-induced systemic lupus erythematosus. In scleroderma patients, Hesselstrand et al. described isolated pulmonary hypertension in 25% of 44 anti-histone positive patients (out of a total number of 276 scleroderma patients) [20]. Anti-histone antibodies were present in 11.6% of 112 scleroderma patients from Italy [84].

### 3.15. Antiphospholipid antibodies

The association between pulmonary arterial hypertension and antibodies associated to the antiphospholipid syndrome in scleroderma patients have been the subject of a number of reports, as shown in Table 9. Overall, a significant number of scleroderma patients with pulmonary hypertension have antiphospholipid antibodies and a significant number of scleroderma patients with antiphospholipid antibodies have pulmonary hypertension.

### 3.16. Anti-PmScl antibodies

Steen reported on isolated pulmonary hypertension in 3 scleroderma patients out of 36 with anti-PmScl antibody positivity [24]. Graf et al. further reported on the topic, describing pulmonary hypertension in 1 patient out of 9 positive for Anti-PmScl antibodies [51].Koschik et al. described the presence of pulmonary arterial hypertension, not secondary to pulmonary fibrosis, in 3 out of 59anti-PmScl antibody positive scleroderma patients and in 247 out of1688 anti-PmScl antibody negative patients [80].

### 3.17. Anti-Sm antibodies

Autoantibodies against Smith antigen (Sm) are currently recognized as important in the diagnosis of systemic lupus erythematosus [70]. Kasukawa et al.reported on 10 scleroderma patients with pulmonary hypertension, none of which with anti-Sm antibodies positivity [6]. Furthermore, Tao et al. reported on a series of 28 systemic sclerosis patients with pulmonary hypertension, 2 of which were positive for anti-Sm antibodies [61].

### 3.18. Anti SSA (anti-Ro) and anti SSB (La) antibodies

Stupi et al. found no patient with positivity for either anti-SSA or anti-SSB antibodies in a series of 13 patients with CREST syndrome and pulmonary hypertension [3]. Tao et al. reported on a series of 28 systemic sclerosis patients with pulmonary hypertension, 6 of which were positive for anti-Ro/SSA antibodies and 2 for anti-La/SSB antibodies

[61].

Low et al. found anti-Ro60 antibodies to be associated with pulmonary arterial hypertension in a study involving several types of diseases, including scleroderma (antibodies to SSA/Ro being directed at Ro52 and at Ro60) [85].

### 3.19. Anti-Ro52 (TRIM 21) antibodies

Hudson et al. studied Anti-Ro52/ TRIM 21 antibodies in 963 scleroderma patients, and found pulmonary hypertension to exist in 26/ 194 patients positive for the antibody [50]. Anti-Ro52/ TRIM 21 antibodies were subsequently shown to be associated to interstitial lung disease and poor survival in scleroderma patients[82]. Pulmonary hypertension was seen in only 8% of patients with monospecific anti-Ro52/TRIM21 antibodies as reported by Wodkowski et al. [82].

### 3.20. Anti-Ku antibodies

Anti-Ku antibodies are found in different types of connective tissue diseases including overlap syndromes. Kuwana et al. reported on the presence of isolated pulmonary arterial hypertension in none of the 7 patients positive for anti-Ku antibodies [8]. Rozman et al. described pulmonary hypertension in 5/11 anti-Ku positive patients and in 10/38 control patients [36]. Hoa et al. reported on 2140 scleroderma patients, 24 of which had anti-Ku antibodies, of which 2 patients also had pulmonary hypertension [66]. Rodriguez-Reyna et al. described pulmonary arterial hypertension as being relatively more frequent in anti-Ku antibody positive patients versus negative patients [81].

### 3.21. Anti-B23 antibody

Ulanet et al. studied 92 scleroderma patients and found pulmonary hypertension in 6/ 10 anti-B23 antibody positive patients and in 20/ 82 B23 antibody negative patients [22], B23 being a nucleolar phosphoprotein.

### 3.22. Anti-RuvBL1 and RuvBL2 antibodies

Kaji et al. described one case of pulmonary hypertension out of 10 patients with anti-RuvBL1/2 antibody positivity [75].

### 3.23. Anti-fibrin bound tissue plasminogen activator (tPA)

Fritzler et al. reported on 25 scleroderma patients with anti-tPA antibody positivity; 5 out of 21 such patients had pulmonary hypertension and 7 had CREST syndrome [9]. Arterial pulmonary hypertension was seen in 6 out of 96 patients in the same cohort without anti-tPA positivity [9].

### 3.24. Anti-phosphatidylserine-prothrombin complex

Hasegawa et al. studied 112 scleroderma patients and found pulmonary hypertension to be present in 56% of 18 antibody positive patients, to be compared to 18% of 94 antibody negative patients [39].

### 3.25. Anti-endothelial cell antibodies

Negi et al. studied a cohort of 76 scleroderma patients, and found IgG anti-endothelial cell antibodies positivity in 27.6% of patients, all women - 40% of patients with diffuse disease (16/ 40), versus 13.5% of patients with limited cutaneous disease (5/36) [12]. Pulmonary arterial hypertension was more frequent in patients with IgG anti-endothelial cell antibodies positivity (5/21 versus 1/55) [12]. Tamby et al. studied 10 cases of pulmonary hypertension associated to scleroderma and found that these patients express anti-endothelial cells antibodies [26]. Lewandowska et al. described one patient with pulmonary hypertension out of 14 scleroderma patients positive for anti-endothelial cell antibodies [53]. In the same series of patients, out of the 15 patients suffering from lung fibrosis, 7 were positive for anti-endothelial cell antibodies [53].

### 3.26. Anti-endothelin-1 type A receptor antibody, anti-angiotensin II type 1 receptor antibody

Riemekasten et al. studied anti-angiotensin II type 1 receptor and anti-endothelin-1 type A receptorantibodies in a cohort of scleroderma patients [77]. These authors noted an increased relative risk of pulmonary arterial hypertension in the presence of higher levels of either antibody. Increased mortality associated to higher levels of these two antibodies was also seen, and they were shown to have biological effects [77,86]. Becker et al. studied a cohort of systemic sclerosis patients with pulmonary hypertension; 69.1% of the patients were positive for anti-angiotensin II type 1 receptor antibody and 65.4% were positive for anti-endothelin type A receptor antibody [54]. Michelfelder et al. studied anti-endothelin-1 type A receptor antibody and anti-angiotensin II type 1 receptor antibody in 24 scleroderma patients with pulmonary hypertension and interstitial lung disease and 27 scleroderma patients with pulmonary hypertension [72]. These authors stated that higher levels of antibodies against angiotensin and endothelin receptors predicted mortality in both groups but could not differentiate between the two groups of patients [72]. Ilgen et al. found no correlation between serum levels of anti-angiotensin II type 1 receptor antibodies and systolic pulmonary artery pressure measurements in scleroderma patients [76].

### 3.27. Anti-carbonic Anhydrase II antibodies

Alessandri et al. found a higher prevalence of anti-carbonic anhydrase II antibodies in scleroderma patients with pulmonary hypertension (45.5%) when compared to in patients without pulmonary hypertension (4.3%) [18].

### 3.28. Antifibroblast antibody

Tamby et al. studied anti-fibroblast antibodies in 30 scleroderma patients; 3 cases out of 10 with pulmonary hypertension had antibody positivity [27]. Terrier et al. studied a set of 158 scleroderma patients.Pulmonary hypertension was seen in 12/ 35 patients with positive antifibroblast antibody with anti-α-enolase activity antibody and in 20/ 108 negative patients [41].

### 3.29. Anti-cyclic citrullinated peptide antibody

Polimeni et al. found no relationship between anti-cyclic citrullinated peptide antibody (CCP; an antibody frequently present in rheumatoid arthritis patients) and pulmonary hypertension in a set of 78 scleroderma patients [52].

### 3.30. Anti-4-sulfated N-Acetyl-lactosamine antibodies

Grader Beck et al. studied 181 scleroderma patients. The anti-4-sulfated *N*-Acetyl-lactosamine antibody positivity was seen in 27 patients, 15 of which with pulmonary arterial hypertension [46].

### 3.31. Class I and II anti-human leukocyte antigen (HLA) antibodies

Tozkir et al. studied 46 scleroderma patients and found that patients with and without anti-HLA antibodies had similar frequencies of pulmonary hypertension and pulmonary fibrosis [69].

## 4. Discussion

Scleroderma is a disease considered to decrease life expectancy [87], and the presence of pulmonary hypertension leads to a further increase in mortality [87,88].Pulmonary arterial hypertension acts as an independent factor for increased mortality in this context [88]. Bryan et al. reported on an association between the presence of anti-topoisomerase antibody and increased mortality in scleroderma patients [89]. Jacobsen et al. pointed at an association between anti-topoisomerase I and anti-RNAP antibody positivity and decreased survival due to scleroderma [90]. The presence of anti-histone antibodies was associated to reduced survival in the study by Hesselstrand et al. [20]. The presence of either anti-Scl-70 (anti-topoisomerase I) or anti-U1 RNP antibodies was associated with reduced survival, compared to the presence of anti-centromere antibodies, in the report by Hissaria et al. [87]. Pulmonary arterial hypertension appears to be more common in patients developing scleroderma later in life, a group of patients with an increased prevalence of anti-centromere antibodies [91]. Conflicting data have been published concerning a possible association between anti-PmScl antibodies and malignancy [92]. Several important areas of uncertainty have been identified concerning this clinical condition [93]. Berger and Steen have discussed the importance and possible physiological and pathological relevance of a number of auto-antibodies in scleroderma patients [94].

In a series of 1188 scleroderma patients, arterial hypertension was present in 17% of the patients [74]. In a further series of 940 scleroderma patients, pulmonary arterial hypertension was present in 13.2% of patients [58]. In yet another large series of scleroderma patients, pulmonary arterial hypertension was present in 14% of 2140 patients [66]. Pulmonary hypertension was present in 17.4% of 1907 ANA-positive scleroderma patients [60]. In the tri-nation (Canada, Australia, USA) cohort of 1574 scleroderma patients reported by Wodkowski et al., pulmonary hypertension was seen in 14% of patients [82].

The evidence reviewed in the present text points at an important prevalence of different types of antibodies in scleroderma patients with pulmonary arterial hypertension. Some types of antibodies were the subject of multiple scientific reports, whereas other types were studied in one single report or in a small number of reports.

Concerning the set of antibodies analyzed in Tables 2 to 9, Table 10 shows that pulmonary hypertension was present in no less than 5% and no more than 33% of the antibody-positive scleroderma patients under study (limited data was available in some cases).

In what concerns the antibody positivity in scleroderma patients with pulmonary hypertension, Table 10 shows that an estimate of 81% of patients have positive antinuclear antibodies, meaning that about 8 patients out of each 10 patients with scleroderma and pulmonary hypertension are positive for this type of antibodies. About or nearly half of patients with scleroderma and pulmonary hypertension were found to be positive for anti-centromere antibodies and for antiphospholipid antibodies (although a much smaller number of patients were studied in this latter case). Anti-U3 RNP antibodies and anti-Th/To antibodies are both above the 20% value for antibody positivity in patients with pulmonary hypertension. Therefore, antinuclear antibodies, anti-centromere antibodies, antiphospholipid antibodies, anti-U3 RNP antibodies and anti-Th/To antibodies would appear to show a particularly important prevalence in scleroderma patients with pulmonary hypertension, appearing in about 8/10, 1/2, and 1/4 patients, respectively. Both anti-centromere antibodies and antiphospholipid antibodies have a value in the right hand side column of Table 10 that is more than double the corresponding value in the left hand side of the column, perhaps allowing one to speculate on a possible role for these two types of antibodies and factors on the pathophysiology of scleroderma-associated pulmonary arterial hypertension. This aspect could be due, of course, to the fact that the values were obtained in different studies corresponding to different populations of patients under study. Hamaguchi, in his 2010 review article, recognized anti-centromere antibodies, anti-Th/To antibodies and anti-U3RNP antibodies to be associated to pulmonary hypertension in scleroderma patients [95], in close parallelism with the prevalence data now presented.Antiphospholipid antibodies were found to be associated to pulmonary hypertension in scleroderma patients in the report by Merashli et al. [96].

Concerning a set of other antibodies reported by different authors in the setting of scleroderma, some have already been studied in some detail, whereas other may merit yet further study, since small series of patients were reported as of the present moment. For example, a significant amount of data regarding anti-Ro52 (TRIM 21) antibodies seem to be available in the context under study.

### 4.1. Limitations

Important limitations exist concerning the present report. Differences in antibody laboratory work and in evaluations of pulmonary arterial hypertension concerning different research reports are evident. These aspects are especially important when reports from different decades are considered together. Patients were studied in different geographical areas, corresponding to different ethnic and cultural backgrounds [94]. The prevalence of the different types of antibodies in different forms of the disease was not explored at full length. Finally, since more than one report exists from some authors/groups, patient overlap may exist between different series, making statistical evaluation difficult.

## 5. Conclusions

In the present review, a number of research reports that deal with auto-antibodies in scleroderma patients with pulmonary hypertension

**Table 7**
Anti-U3 RNP (antifibrillarin) antibodies positivity in scleroderma patients and pulmonary arterial hypertension. For complete references see text.

| | |
|---|---|
| Okano et al. (1992) | Primary pulmonary arterial hypertension significantly more common in patients positive for anti-U3snRNP than in antibody negative patients (Anti-U3 small nuclear ribonuclear protein). |
| Kuwanaet al. (1994) | Isolated pulmonary arterial hypertension seen in 0/ 10 anti-U3 RNP antibodies positive patients |
| Sacks et al. (1996) | Anti-U3 RNP positivity in 6 patients out of 13 patients with diffuse cutaneous disease and pulmonary hypertension; anti-U3 RNP positivity in 2 patients out of 18 with limited cutaneous disease and pulmonary hypertension |
| Gunduz et al. (2001) | Anti-U3 RNP positivity in 2 patients out of 11 with pulmonary hypertension and renal crisis; anti-U3 RNP positivity in 2 patients out of 15 with pulmonary hypertension |
| Tormey et al. (2001) | Isolated pulmonary arterial hypertension seen in 11/ 42anti-U3 RNP antibodies positive patients, in 2 patients with pulmonary fibrosis and pulmonary hypertension |
| Steen and Medsger (2003) | Anti-U3 RNP positivity in 13 patients out of 50 with pulmonary hypertension |
| Steen (2005) | Isolated pulmonary hypertension seen in 24/55 patients with anti-U3RNP antibody positivity |
| Hamaguchi et al. (2008) | Isolated pulmonary hypertension seen in 0/5 patients with anti-U3-RNP antibody positivity |
| Aggarwal et al. (2009) | Pulmonary arterial hypertension seen in 27/ 86 patients positive for anti-U3 RNP antibodies and in 239/ 1823 antibody negative patients |
| Sharif et al. (2011) | Pulmonary arterial hypertension seen in 10% of 50 patients with anti-U3-RNP antibody positivity |
| Nihtyanova et al. (2014) | In multivariable analysis, anti–U3 RNP antibodies acted as a positive predictor for pulmonary hypertension |
| Tall et al. (2017) | Pulmonary hypertension seen in 3/35 antifibrillarin positive and in 8/ 139 antifibrillarin negative patients. |

**Table 8**
Anti-Th/To antibodies associated to the antiphospholipid syndrome in scleroderma patients and pulmonary arterial hypertension. For complete references see text.

| | |
|---|---|
| Okano and Medsger (1990) | Pulmonary arterial hypertension was seen in 23% of 14 Anti-Th positive patients with limited cutaneous involvement |
| Kuwana et al. (1994) | Isolated pulmonary arterial hypertension seen in 0/ 5 patients positive anti-Th RNP antibodies. |
| Gunduz et al. (2001) | Anti-Th/To antibodies seen in 4/11 patients with pulmonary hypertension and renal crisis versus 1/15 patients with pulmonary hypertension |
| Steen and Medsger (2003) | Anti-Th/To positivity seen in 15/48 patients with pulmonary hypertension |
| Mitri et al. (2003) | Pulmonary hypertension seen in 24/ 87 anti-Th/To positive patients |
| Steen (2005) | Isolated pulmonary hypertension seen in 32/72 patients with anti-Th/To antibody positivity |
| Hamaguchi et al. (2008) | Isolated pulmonary hypertension seen in14% of 7 patients with positivity for anti-Th /To antibodies (1 patient) |
| Graf et al. (2012) | Pulmonary hypertension seen in 3/8 patients positive for Anti-Th/To; |

**Table 9**
Antibodies associated to the antiphospholipid syndrome in scleroderma patients and pulmonary arterial hypertension. For complete references see text.

| | |
|---|---|
| Ihn et al. (1996) | Pulmonary hypertension in 20% [4] of 20 patients with IgG anticardiolipin antibodies positivity; pulmonary hypertension in 63% [5] of 8 patients with Beta 2-GPI-dependent anticardiolipin antibodies positivity |
| Launay et al. (2001) | Anticardiolipin antibodies positivity seen in 8 out of 11 patients with isolated pulmonary hypertension. |
| Antonioli et al. (2003) | Two scleroderma patients with primary pulmonary hypertension. One patient had positive anticardiolipin and anti-β2 glycoprotein I antibodies; the other was anticardiolipin and lupus anticoagulant positive and anti-β2 glycoprotein I antibody negative |
| Assous et al. (2005) | Antiphospholipid antibody positivity seenin 7 out of 16 patients with pulmonary hypertension |
| Marie et al. (2008) | Pulmonary hypertension seen in 4 out of 13 patients with antiphospholipid antibodies |
| Gupta et al. (2009) | Pulmonary hypertension seen in 0/ 7 patients positive for antiphospholipid antibodies (anticardiolipin and lupus anticoagulant) |
| Boin et al. (2009) | Anti–β2-glycoprotein I positivity seen in 27 out of 56patients with pulmonary hypertension; anticardiolipin positivity seen in 15 out of 56 patients with pulmonary hypertension |
| Touré et al. (2013) | Pulmonary hypertension seen in 7 cases out of 23 patients with antiphospholipid antibodies |
| Mellal et al. (2014) | Pulmonary arterial hypertension seen in 5 patients (33.3%) out of 15 patients with anticardiolipin antibodies |
| Morrisroe et al. (2014) | Pulmonary hypertension seen in 20 out of 95 patients with anticardiolipin antibodies positivity |

**Table 10**
Estimates of prevalence (%) of pulmonary hypertension in antibody positive patients and of antibody positivity in patients with pulmonary hypertension in scleroderma patients. Numbers inside brackets obtained from studies presented in Tables 2-9.

| Antibodies | Pulmonary hypertension in antibody positive scleroderma patients (%, estimates) | Antibody positivity in scleroderma patients with pulmonary hypertension (%, estimates) |
|---|---|---|
| Anti-nuclear | 18 (352/1969) | 81 (170/210) |
| Anti-centromere | 15 (384/ 2572) | 45 (261/ 586) |
| Anti RNA polymerase III | 12 (37/299) | 5 (9/177) |
| Anti Scl-70 | 5 (67/1244) | 18 (129/735) |
| Anti U3 RNP | 25 (70/283) | 24 (23/96) |
| Anti-U1 RNP | 22 (67/304) | 9 (60/663) |
| Anti-Th/To | 33 (63/193) | 25 (16/63) |
| Antiphospholipid[a] | 25 (43/175) | 51 (42/83) |

[a] In the report by Boin et al. (reference [34]), only the data of anti–β2-glycoprotein I antibodies was considered, since there may be overlap of antibody positivity.

were reviewed. A considerable number of auto-antibodies were shown by different authors to be associated to this condition, with different prevalence values for each type of auto-antibody. The available evidence points in the direction of a strong association between auto-immune mechanisms and pulmonary hypertension in the setting of scleroderma.

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## Conflicts of interest

None to report.

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