Arterial hypertension in systemic sclerosis

Ewa Wielosz, Magdalena Dryglewska, Anna Górak, Ewa Łyś, Maria Majdan

Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Lublin, Poland

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Abstract

Introduction: Arterial hypertension (AH) is common in systemic connective tissue diseases. Aim: To evaluate the incidence of AH in patients with systemic sclerosis (SSc) and to present clinical characteristics of the group diagnosed with AH.

Material and methods: The study involved 108 patients with SSc divided into two groups: with AH (+) – 45 and AH (–) – 63. Moreover, the serological profile, scleroderma renal crisis, involvement of internal organs and mortality were determined. The kidney function was assessed based on creatinine concentration and the estimated glomerular filtration rate (eGFR).

Results: AH was diagnosed in 47/108 SSc patients (41.7%). The age difference among patients was statistically significant and was higher in the AH (+) SSc group (p = 0.026). The incidences of oesophageal involvement (p = 0.011), digital ulcerations (p = 0.017), and mortality (p = 0.019) were found to be significantly higher in the AH (+) SSc group. Scleroderma renal crisis was observed in 9/108 patients (8.3%). The incidence of chronic kidney disease (CKD) was higher in the AH (+) SSc group, both of stage 2 (p = 0.013) and 3 (p = 0.07). Stages 4 and 5 of CKD were found only in the group with AH. Moreover, this group had a higher incidence of elevated uric acid (p = 0.007).

Conclusions: AH is relatively common in patients with SSc and is associated with a significantly more severe course of the disease and higher frequency of renal involvement.

Key words: systemic sclerosis, arterial hypertension, renal involvement.

Introduction

Arterial hypertension (AH) is common in systemic connective tissue diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or systemic sclerosis (SSc) [1]. The mechanism leading to an increased risk of AH in these patients remains unclear; however, it is likely to be related to immune-mediated changes in cardiovascular and renal functions. A number of factors contribute to the development of AH during connective tissue diseases, including impaired systemic vascular function, altered renal haemodynamics, increased oxidative stress and inflammatory cytokines [2]. Vascular lesions are known to play an important role in the deterioration of renal and heart function as well as lead to AH development. On the other hand, AH may deteriorate renal and heart function [3].

Systemic sclerosis is an autoimmune connective disease characterized by immune dysregulation and micro- and macrovascular deformities, which can lead to excessive deposition of collagen, resulting in skin and internal organ fibrosis. During the last few decades, the pathogenesis of SScs has been focused on microvasculopathy and endothelial dysfunction, principally manifested by digital ulcers and Raynaud’s phenomenon, which could cause progressive tissue fibrosis and, finally, organ tissue damage. Recently, different studies have demonstrated an association between endothelial dysfunction, cardiovascular disease (CVD), and atherosclerosis in SSc [4]. Pathological changes include the proliferation of the vascular endothelial or smooth muscle cells, lumen stenosis by collagen accumulation of the vascular intima, vasoconstriction or fragility, and apoptosis. Vascular lesions, the autoimmune disorder and collagen deposition may interact. Although the microvascular disease is a prominent hallmark of SSc, a higher prevalence of the macrovascular disease with AH development and a poorer related prognosis have been reported in SSc than in the general population [5]. Furthermore, subclinical atherosclerosis in SSc patients is more frequent than in a healthy peer population and it is one of the causes of AH development [6]. AH is commonly feared...
in SSc because it often heralds renal impairment. Renal involvement is observed in 60–80% of patients with SSc, while clinically based kidney symptoms in 10–40% [7]. In the majority of cases, chronic renal involvement is found to develop slowly over the course of years, triggering moderate often clinically unapparent renal function loss in 50% of the affected patients [8]. Apart from chronic kidney disease (CKD) with a slow deterioration of the glomerular filtration rate (GFR) and AH development, other forms of kidney involvement in SSc are scleroderma renal crisis (SRC), which affects about 5% of SSc patients with abrupt AH and acute kidney injury (AKI) [9]. One of the basic methods of treating vascular complications in patients with SSc is the use of calcium channel blockers (CCB) and angiotensin-converting enzyme inhibitors (ACEI). Despite the fact that AH is quite common in patients with SSc, there is a group of patients in whom CCB may not occur due to low blood pressure.

Aim
The aim of the study was to evaluate the incidence of AH in a group of patients with SSc and to present clinical characteristics of the group diagnosed with AH.

Material and methods
The cohort was a group of 126 (98 women and 28 men) European Caucasian SSc patients hospitalised consecutively in the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin in 2011–2018. However, 18 patients were excluded due to the coexistence of overlap syndrome with other rheumatic diseases (e.g. SLE, RA, Sjögren syndrome), thus 108 patients were included and evaluated. All patients had given written informed consent to participate in the study according to the Helsinki Declaration of 1975, as revised in 2000. The study design was approved by the ethical committee. All patients fulfilled the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification criteria of SSc [10].

Table 1. Characteristics of the study group

| Parameter          | Value         |
|--------------------|---------------|
| Number of patients | 108           |
| Subtype of SSc:    |               |
| dCSSc              | 57            |
| lCSSc              | 51            |
| Gender             |               |
| Female             | 83            |
| Male               | 25            |
| Age [years]        | 53.9 ±14.0 (19–81) |
| Duration of disease [years] | 5.2 ±5.5 (0–23) |
Arterial hypertension in systemic sclerosis

Scl, anti-Ku, anti-Th/To anti-Ro52 and autoantibodies against the nucleolus-organising region-90 (anti-NOR90). The patients’ sera were analysed at a 1:101 dilution and the autoantibodies were detected using alkaline phosphatase–labelled antihuman IgG. The analysis of results was carried out electronically using EUROLINE Scan (EUROMMUN AG, Lubeck, Germany). Furthermore, the subjects were examined for the presence of antibodies to cardioline (aCL) in IgM and IgG classes, whose concentrations were determined with the use of commercially available enzyme-linked immunosorbent assay (ELISA) kits. To this end, AUTOSTAT II ACA Isotype assay (Hycor Biomedical, Garden Grove, California, U.S.A.) was employed. The results were interpreted as positive when the concentrations were higher than 15 MPL U/ml or GPL U/ml IgM and/or IgG class aCL antibodies. AH was diagnosed in the case of AH history or when systolic blood pressure (SBP) was higher than 140 mm Hg and diastolic blood pressure (DBP) > 90 mm Hg; the sitting test was carried out by manometer on the left arm after 15 min prior rest. The result was a mean of three readings. Mean blood pressure (MBP) was calculated from the formula, DBP + (SBP – DBP)/3. According to the presence of AH, the patients were divided into two groups: with arterial hypertension AH (+) – 45 and otherwise AH (–) – 63 patients. 19 patients had a history of arterial hypertension prior to SSc diagnosis. All patients with AH were treated persistently with ACEI and 28/45 (62 %) were treated with CCB. Moreover, 18/63 (29%) patients with AH were treated with a low dose of CCB.

As regards SSc treatment, 20 patients were treated with intravenous cyclophosphamide, 31 with mycophenolate mofetil and 7 with methotrexate. None of the patients with SSc receives steroids and non-steroidal anti-inflammatory drugs, only patients with overlapping syndrome were treated with low and medium doses of steroids. Furthermore, 14 patients were treated with vasodilators (12 with sildenafil and 2 with i.v. iloprost). Patients receiving urate lowering therapy and those with diabetes mellitus were excluded from me study.

Statistical analysis
All calculations were performed with Statistica v. 10.0 software (StatSoft, Krakow, Poland). The data associations were analysed using the non-parametric χ² test. Multivariable logistic regression was used to analyse potential risk factors. P-value < 0.05 was considered statistically significant.

Results
AH was found in 45/108 SSc patients (41.7%), including 18/45 in the lcSSc group and 27/63 in the dcSSc group. The patients’ age was statistically significantly higher in the AH (+) SSc group, as compared to the AH (–) SSc group (p = 0.026). Additionally, the incidences of oesophageal involvement (p = 0.011), digital ulcerations (p = 0.017) and mortality (p = 0.019) were found to be significantly higher in the AH (+) SSc group. Moreover, there was a tendency, albeit not statistically significant, for a higher prevalence of AH in male patients and in the PAH group. Furthermore, there were no significant intergroup differences regarding the subtype of the disease, duration of the disease, ILD, heart involvement, the prevalence of arthritis or arthralgia, myalgia, calcinosis and neoplastic diseases (Table 2). There were also no significant differences in the immune profile of patients in the AH (+) SSc group compared to the AH (–) SSc group. On the other hand, the prevalence of aCL antibodies was shown to be higher in the AH (+) group than in the AH (–) group (Table 3), so there was renal involvement (in the latter p = 0.03). SRC was observed in 9 out of 108 patients (8.3%) and its occurrence was notably higher in the group of patients with a history of AH (p = 0.006). Furthermore, the incidence of CKD was higher in the AH (+) SSc group, both of stage 2 (p = 0.013) and of stage 3 (p = 0.07). Stages 4 and 5 of CKD were found only in the group with AH. Additionally, this group was characterized by lower eGFR values (0.0013). Moreover, the incidences of hyperuricemia were significantly higher in the AH (+) SSc group (p = 0.007) (Table 4). Multivariate logistic regression analysis showed no independent risk factors for hypertension in the study group of patients with systemic sclerosis.

Discussion
Previous research works have managed to establish that AH is presented in approximately 26–35% of patients with SSc [17–19]. It is also known that AH in SSc has heterogeneous aetiology. There are some indications that vascular changes in SSc are primary to hypertension development and lead to the impairment of functions of internal organs such as kidneys and heart, thereby contributing to hypertension [20]. Found in SSc, myocardial fibrosis and microangiopathy of small heart vessels heavily contribute to disturbances in systolic and/or diastolic activity of the heart with subsequent right and left ventricular failure and the resulting development of hypertension [21]. What is more, the impairment of glomerular filtration in the course of vascular disorders in SSc is a further cause of hypertension [22–24]. On the other hand, hypertension leads to vascular complications, which could contribute to kidney damage or heart failure. In addition, one cannot underestimate the importance of atherosclerotic lesions in small arterioles. Their intensity increases with age both in the population with systemic connective tissue diseases and in the group without systemic diseases, leading to an increase in blood pressure. On the basis of literature data, atherosclerotic lesions in the course of SSc have been found more often than in
Ewa Wielosz, Magdalena Dryglewska, Anna Górak, Ewa Łyś, Maria Majdan

The chronic inflammatory process that accompanies connective tissue systemic diseases, especially inflammatory joint diseases, plays a special role in the development of cardiovascular incidents and hypertension. These results suggest that in comparison with the population devoid of SSc and other systemic connective tissue diseases, the proneness to hypertension is higher among SSc/collagenosis patients. Ryan et al. showed that immune disorders in the course of systemic connective tissue diseases, especially in systemic lupus erythematosus, contribute to an increased cardiovascular risk and the development of hypertension [8]. Regarding the therapy affecting the development of scleroderma renal crisis, it has been documented that the use of calcium channel blockers (CCBs) is associated with a significant reduction in the risk of SRC. CCBs are considered the first-line therapy for the treatment of Raynaud’s phenomenon. Hypoperfusion leading to an impaired glomerular filtration rate in systemic scleroderma activates the RAA system. CCBs counteract the vasoconstriction of angiotensin II on the afferent arterioles, preserving its effect on the efferent arterioles and thus supporting glomerular filtration and counteracting SRC [27]. According to another study, previously diagnosed AH treated with angiotensin converting enzyme inhibitors and glucocorticoids is an independent factor for renal function deterioration and GFR decreases. Therefore, these classes of drugs should be used with caution in patients with systemic sclerosis [28]. As reported in some other studies, since digital ulcers, pulmonary arterial hypertension and scleroderma renal crisis have common physiopathological pathways, the treatment of these phenomena should be similar. Moreover, the influence of vasodilators: endothelin receptor antagonists (ERAs) and phosphodiesterase-5 inhibitors (PDE5i), on the above phenomena was investigated. The results have shown no differences in the incidence of SRC between the patients treated with ERAs and/or PDE5, but the treatment appeared to delay

| Parameter                  | SSc AH (+) – 45 (41.7%) | SSc AH (–) – 63 (58.3%) | p < 0.05 |
|----------------------------|--------------------------|-------------------------|----------|
| Number of patients         | 45 (41.7%)               | 63 (58.3%)              | NS       |
| Subtype of disease:        |                          |                         |          |
| dcSSc                      | 27 (60%)                 | 30 (47.6%)              | NS       |
| lcSSc                      | 18 (40%)                 | 33 (52.4%)              | NS       |
| Gender:                    |                          |                         |          |
| Female                     | 31 (69%)                 | 52 (82.5%)              | NS       |
| Male                       | 14 (31%)                 | 11 (17.5%)              | NS       |
| Age of the study group [years] | 57.4 ±12.5 (19–80) | 51.5 ±14.0 (20–81) | p = 0.0264 |
| Duration of the disease    | 5.7 ±6.2 (0–23)          | 4.8 ±4.9 (0–19)         | NS       |
| Raynaud’s Phenomenon [years] | 5.1 ±4.0 (0–20)  | 7.9 ±15.8 (0–19) | NS       |
| ILD – (HRCT)               | 24 (53.3%)               | 37 (58.7%)              | NS       |
| PAH                        | 15 (33.3%)               | 10 (15.9%)              | p = 0.0346 |
| Decreased DLCO             | 24 (53.3%)               | 30 (47.6%)              | NS       |
| Heart involvement          | 22 (48.9%)               | 23 (36.5%)              | NS       |
| Joint involvement          | 8 (17.8%)                | 16 (25.4%)              | NS       |
| Oesophagus involvement     | 35 (77.7%)               | 34 (54%)                | p = 0.0115 |
| Digital ulcerations        | 17 (37.8%)               | 11 (17.5%)              | p = 0.0174 |
| Calcinosis                 | 9 (20%)                  | 11 (17.5%)              | NS       |
| Myalgia or myositis        | 8 (17.8%)                | 11 (17.5%)              | NS       |
| Neoplastic disease         | 7 (15.5%)                | 7 (11%)                 | NS       |
| Mortality                  | 14 (31.1%)               | 8 (12.7%)               | p = 0.0192 |
| ESR                        | 25 ±23.0 (1–102)         | 18.8 ±14.7 (2–73)       | 0.0925   |
| CRP                        | 8.3 ±10.7 (0–23)         | 7.0 ±11.7 (0.01–67.8)   | NS       |

AH – arterial hypertension, ILD – interstitial lung disease, HRCT – high-resolution computer tomography, DLCO – diffusing capacity for carbon monoxide, PAH – pulmonary arterial hypertension. Data were presented as numbers and percentages. P-value of < 0.05 was considered statistically significant.
Arterial hypertension in systemic sclerosis

The occurrence of SRC [29]. Treatment with Losartan has been shown to reduce the symptoms of vasospasm in Raynaud’s syndrome and in systemic sclerosis, yet to a lesser extent [30].

In our study, hypertension was found in 41.7% of patients with systemic sclerosis. The age of patients and mortality were statistically considerably higher in the group of patients with SSc than in the group without it. In fact, age is a well-known risk factor for arterial hypertension in the general population.

The limitation of our research is the lack of a peer control group with hypertension. There is very little published research on the characteristics of patients with SSc with hypertension in comparison with the group of patients with SSc without hypertension [17, 18, 31]. Kuryata et al. showed that the 5-year risk of developing hypertension in patients with SSc is 20% [31]. Other clinicians have found that a particularly high risk of hypertension occurs in patients over 43 years of age, especially with pulmonary fibrosis, increased inflammatory parameters and the presence of rheumatoid factor. In addition, in the group of patients with SSc with hypertension, proteinuria and a decrease in glomerular filtration were more frequent [31]. In a different study, the same research team shows a significant association between hypertension and limited scleroderma subtype, arthritis, pulmonary fibrosis, gastrointestinal complications and renal dysfunction [18]. The relationship between the limited SSc subtype and the presence of hypertension has also been shown in the German registry of patients with SSc [32].

On the other hand, Si Ahmed-Bouali et al. examined

Table 3. Serological characteristics of the study group with and without arterial hypertension

| Variable                      | SSc AH (+) – 45 | SSc AH (–) – 63 | P < 0.05 |
|-------------------------------|-----------------|----------------|-----------|
| aCL                           | 6 (13.3%)       | 4 (6.3%)       | NS        |
| LAC                           | 2 (4.4%)        | 1 (1.6%)       | NS        |
| Anti-topo I (Scl-70)          | 16 (35.6%)      | 29 (46%)       | NS        |
| Anti-centromere               | 6 (13.3%)       | 15 (23.8%)     | NS        |
| Anti-RNA Pol III              | 9 (15.8%)       | 7 (10%)        | NS        |
| Anti-Th/To                    | 0 (0%)          | 2 (3.2 %)      | NS        |
| Anti-Ku                       | 2 (4.4%)        | 1 (1.6%)       | NS        |
| Anti-PmScI                    | 7 (15.5%)       | 9 (14.3%)      | NS        |
| Anti-NOR-90                   | 3 (6.7%)        | 3 (4.8%)       | NS        |
| Anti-PDGF                     | 0 (0%)          | 0 (0%)         | NS        |
| Anti-SSA/RO52                 | 10 (22.2%)      | 19 (30%)       | NS        |

eCL– anticardiolipin antibodies, LAC – lupus anticoagulant. Data were presented as numbers and percentages. P-value of < 0.05 was considered statistically significant.

Table 4. Renal involvement in the SSc group with and without arterial hypertension

| Parameter                        | SSc AH (+) – 45 | SSc AH (–) – 63 | P < 0.05 |
|----------------------------------|-----------------|----------------|-----------|
| CKD – eGFR:                      |                 |                |           |
| 1 (> 90 ml/min)                  | 8 (17.8%)       | 16 (25%)       | NS        |
| 2 (60–90 ml/min)                 | 17 (37.8%)      | 39 (61.9%)     | p = 0.013 |
| 3 (30–60 ml/min)                 | 10 (22.2%)      | 6 (9.5%)       | p = 0.067 NS |
| 4 (15–30 ml/min)                 | 6 (13.3%)       | 0 (0%)         | p = 0.002 |
| 5 (< 15 ml/min)                  | 3 (6.7%)        | 0 (0%)         | p = 0.037 |
| Serum uric acid levels (higher than 5.7 mg/dl) | 21 (46.7%) | 14 (22.2%) | p = 0.007 |
| Mean serum uric acid concentrations [mg/dl] | 6.1 ±2.2 (3.1–12.7) | 4.99 ±1.9 (2.1–14.5) | p = 0.007 |
| Mean serum creatinine concentrations [mg/dl] | 1.4 ±1.2 (0.5–6.2) | 0.8 ±0.2 (0.4–1.4) | p = 0.0036 |
| Presence of scleroderma renal crisis (SRC) | 8 (17.8%) | 1 (1.6%) | p = 0.0027 |
| Renal involvement                | 25 (46.7%)      | 13 (20.6%)     | p = 0.033 |
| Proteinuria                      | 8 (17.8%)       | 6 (9.5%)       | NS        |
| Erythrocyturia                   | 5 (11.1%)       | 8 (12.7%)      | NS        |
| CKD – eGFR:                      |                 |                |           |
| 1 (> 90 ml/min)                  | 105.75          | 101.21         |           |
| 2 (60–90 ml/min)                 | 77.55           | 69.78          |           |
| 3 (30–60 ml/min)                 | 50.09           | 50.33          |           |
| 4 (15–30 ml/min)                 | 23.26           | –              |           |
| 5 (< 15 ml/min)                  | 6.54            | –              | NS        |

CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate. Data were presented as numbers and percentages. P-value of < 0.05 was considered statistically significant.
Our results demonstrate that oesophageal involvement and renal complications are much more common in the group of patients in whom scleroderma coexists with hypertension. The hypertension group of patients was characterised by a significantly higher incidence of scleroderma renal crisis and chronic kidney disease in stages 2 and 3. On the other hand, chronic kidney disease in stages 4 and 5 was found only in the group of patients with SSc with concomitant hypertension. These findings can be explained by the coexistence of scleroderma and hypertensive nephropathy in this group of patients.

Moreover, the SSc group with AH characterized by lower eGFR values compare to the SSc group without AH. However, AH is a well-known factor for vascular damage and could lead to deterioration of renal function.

Significantly higher serum uric acid levels in hypertension patients may be associated with an increased risk of cardiovascular incidents and death. Simpson et al. showed that an increase in serum uric acid concentration of 1 mg/dl increases the risk of death by 14% in patients with SSc [33]. Analysing a group of patients with hypertension, it was found that the occurrence of fingertip ulcers in the group is more frequent compared to patients without hypertension. Hypertensive vasculopathy and scleroderma vasculopathy may be related to the observed overlap of vascular disorders.

Interestingly, the analysis of the serological profile of SSc patients with hypertension has demonstrated a low frequency of anti-Sci-70 and anti-SS-A antibodies, but it was not statistically significant. No supporting literature data could be identified, apart from a more frequent occurrence of the rheumatoid factor in patients with SSc with hypertension [31].

Nonetheless, a higher incidence of antiphospholipid antibodies has been reported in patients with SSc with hypertension and renal impairment [34–37]. Merashli et al. showed that patients with SSc with antiphospholipid antibodies are more likely to suffer from pulmonary arterial hypertension, finger ulcers and kidney involvement [35]. Our previous work also showed that proteinuria, hypertension and deterioration of glomerular filtration are more common in patients with SSc with antiphospholipid antibodies [36, 37]. One of the probable causes may be thrombotic microangiopathy in patients with SSc who do not meet the criteria for antiphospholipid syndrome. In the present study, one of the markers for antiphospholipid antibodies, anticardiolipin antibodies, were more common in the group of patients with SSc with hypertension, but these changes were not statistically significant.

Conclusions
We identified the presence of CVD risk factors to be associated with higher disease activity and disability. This knowledge can help practicing rheumatologists to identify patients at risk who may benefit from closer follow-up or tailored therapeutic strategies, according to their CVD status. This could facilitate the prevention of CVD events by heightened attention to CVD risk factor control and help to improve SSc treatment targets. Further longitudinal studies are needed to confirm our findings and to evaluate specific barriers and facilitators of SSc response measures in cases of CVD comorbidity.

Conflict of interest
The authors declare no conflict of interest.

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