Primary *versus* systemic sclerosis-associated Raynaud's phenomenon: relationship with clinical and environmental factors

E. Favoino[1], M. Prete[2], V. Liakouli[3], A. Sisto[4], A. Corrado[5], P. Leone[2], G. Lisco[4], M. Vomero[6,7], E. Biancalana[8], E. Chiara[8], G. Emmi[8], V. Racanelli[9], A. Marcoccia[10], R.D. Grembiale[11], F.P. Cantatore[5], L. Navarini[6,7], P. Ruscitti[12], F. Ciccia[3], R. Giacomelli[6,7], F. Perosa[4]

[1]Laboratory of Cellular and Molecular Immunology, and [2]Internal Medicine Unit, Department of Interdisciplinary Medicine, University of Bari Medical School, Bari; [3]Rheumatology Section, Department of Precision Medicine, University of Campania Luigi Vanvitelli, Naples; [4]Rheumatic and Systemic Autoimmune Diseases Unit, Department of Interdisciplinary Medicine, University of Bari Medical School, Bari; [5]Rheumatology Unit, Department of Medical and Surgery Sciences, University of Foggia; [6]Clinical and Research Section of Rheumatology and Clinical Immunology, Fondazione Policlinico Campus Bio-Medico, Rome; [7]Rheumatology and Clinical Immunology, Department of Medicine, University of Rome Campus Biomedico, School of Medicine, Rome; [8]Department of Experimental and Clinical Medicine, University of Florence; [9]Centre for Medical Sciences, University of Trento and Internal Medicine Division, Santa Chiara Hospital, Provincial Health Care Agency (APSS), Trento; [10]Department of Medical Area, Vascular Disease and Immunology Unit, Sandro Pertini Hospital, Rome; [11]Rheumatology Research Unit, Department of Health Sciences, University of Catanzaro Magna Graecia, Catanzaro; [12]Rheumatology Unit, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy.

Abstract

Objective

Raynaud's phenomenon (RP) can be induced by stress and environmental factors, occurring as a primary disease (pRP) or associated with connective tissue disease. RP is seen in more than 95% of patients with systemic sclerosis (SSc) and may precede its diagnosis by several years. Accordingly, there is a clear need to identify those patients with RP who will eventually develop connective tissue disease, including SSc. The aim of this case-control study was to assess the association of SSc-RP versus pRP with respect to environmental factors, lifestyle habits, and clinical setting.

Methods

A questionnaire was used to collect current data from 180 patients with SSc-RP and 103 with pRP. Statistical analyses were performed to identify possible risk factors for SSc-RP.

Results

SSc-RP was found to be inversely associated with living in urban area (OR=0.37; p<0.001), computer use (OR=0.38, p<0.001), contraceptive use (OR=0.32; p=0.017), habitual alcohol use (OR=0.35; p=0.029), and hepatitis B virus vaccine (OR=0.09; p=0.011), while it was directly associated to cold sensitivity (OR=3.48; p=0.001), lower quality of life (OR=2.69; p<0.001), finger pain (OR=3.03; p<0.001) and autoimmune hypothyroidism (OR=3.62; p=0.007). All associations were supported by either multivariate and/or multivariable analyses.

Conclusion

This study revealed differences in lifestyle and preventive health behaviours between SSc-RP and pRP, and also suggests that patients with pRP and autoimmune hypothyroidism should be strictly monitored for any clinical changes that may indicate SSc onset. Further investigations are needed to prospectively evaluate autoimmune hypothyroidism as a predisposing condition for SSc-RP.

Key words

primary Raynaud's phenomenon, systemic sclerosis-associated Raynaud's phenomenon, environmental factors, clinical factors, autoimmune hypothyroidism

Elvira Favoino, PhD
Marcella Prete, MD, PhD
Vasiliki Liakouli, MD, PhD
Adriana Sisto, MD
Ada Corrado, MD, PhD
Patrizia Leone, PhD
Giuseppe Lisco, MD
Marta Vomero, PhD
Edoardo Biancalana, MD
Emanuele Chiara, MD
Giacomo Emmi, MD, PhD
Vito Racanelli, MD, PhD
Antonella Marcoccia, MD
Rosa Daniela Grembiale, MD
Francesco Paolo Cantatore, MD, PhD
Luca Navarini, MD
Piero Ruscitti, MD, PhD
Francesco Ciccia, MD, PhD
Roberto Giacomelli, MD, PhD
Federico Perosa, MD, PhD

Please address correspondence to:
Elvira Favoino
Dipartimento Interdisciplinare di Medicina (DIM),
Laboratorio di Immunologia Cellulare e Molecolare
Università di Bari Scuola Medica,
Piazza G. Cesare 11,
70124 Bari, Italy.
E-mail: elvira.favoino@uniba.it

and to:
Federico Perosa
Dipartimento Interdisciplinare di Medicina (DIM),
UO di Malattie Reumatiche e Autoimmuni Sistemiche
Università di Bari Scuola Medica,
Piazza G. Cesare 11,
70124 Bari, Italy.
E-mail: federico.perosa@uniba.it

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Introduction

Raynaud's phenomenon (RP) is a vasospastic disorder characterised by episodic vasospasm of the digits that may be accompanied by finger numbness and pain in response to cold or emotional stimuli (1). RP is classified as primary (pRP) or secondary (sRP) on the basis of the absence or presence of an underlying disease, respectively (2, 3). Among systemic immune-mediated rheumatic diseases, systemic sclerosis (SSc) and mixed connective tissue diseases, are those most strongly associated with RP. RP can also occur in systemic lupus erythematosus, rheumatoid arthritis, myositis, and some vasculopathies (*e.g.* Buerger's disease) (2). The prevalence of RP in the general population ranges from 3 to 5%, with pRP accounting for 80–90% of cases (4). The misdiagnosis of secondary RP as pRP is estimated to occur in 12% to 20% of patients (1, 5, 6). In SSc, RP is the most frequent manifestation, present in >95% of this population, and it precedes other SSc clinical manifestations by weeks to several years (7). Factors suggesting an incipient SSc-RP include positivity for antinuclear and SSc-specific autoantibodies, puffy fingers, an abnormal nailfold capillaroscopy, and/or digital ulcers (DUs) (8-11). But before these signs show up, an earlier detection of SSc-RP is desirable for patient management as it enables a closer follow-up, with the possibility of timely treatment and better outcomes. Criteria for predicting the evolution from pRP to SSc-RP are therefore needed. This case-control study evaluated environmental factors, lifestyle habits and/or clinical settings more often associated with SSc-RP than with pRP but which in the latter may represent factors suggesting a closer monitoring for a potential evolution to SSc-RP.

Materials and methods

Patients and controls

From 2020 to 2022, 180 consecutive patients with SSc-RP patients satisfying the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc (12) and 166 patients with a diagnosis of pRP patients, according to LeRoy criteria (13), were recruited in seven Italian rheumatology units (Bari, Foggia, Naples, Catanzaro, L'Aquila, Rome, Florence). A subgroup of 103 pRP patients frequency matched for age to SSc-RP was selected for the case-control study. All participants were systematically interviewed using a previously validated, anonymous, self-administered questionnaire designed to assess the influence of social, demographic, environmental, and work-related factors and/or lifestyle habits on RP (14).

Inclusion criteria

The inclusion criterion was participant aged >18 years who provided voluntary informed consent to participate in this study.

Exclusion criteria

The exclusion criteria included pRP patients aged outside the age range of the SSc-RP group, and patients with missing data.

Statistical analyses

The sample size for this study was calculated using G*Power software (v. 3.1.9.7 for Windows) based on a 0.80 power, a 0.25 effect size, and a 0.05 alpha error.

Statistical analyses were performed using SPSS software (v. 21 for Windows). Variables with missing data were excluded from the analysis.

All data were dichotomised; the only continuous variables were age and hours spent at the computer. For those variables, the Mann-Whitney U-test was used to compare differences between two groups. Fisher's exact test was used to test the associations between dichotomised variables. Correction for multiple comparison was performed using the Benjamini-Hochberg method for false discovery rates.

Variable with a statistically significant association at Fisher's exact test was analysed by multivariable logistic regression where by sex and age were included as confounding variables. Then, the identified sex- and age-independent variables were run together for a multivariable logistic regression analysis to establish their possible interdepend-

ency, the outcome being pRP *versus* SSc-RP. For all tests, a p-value<0.05 indicated statistical significance.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethical Committee of the University of Bari Medical School (n. 6017/C.E., 25/11/2019). Informed consent was obtained from all subjects included in the study.

Results

This case-control study comprised 283 Caucasian patients with RP, of whom 180 (63.6%) with SSc-RP and 103 (36.4%) with pRP. The questionnaire response rate was 100%. The socio-demographic characteristics, lifestyle habits, and general health information of the study patients are described in Table I.

Variables occurring with a at least 1.5-fold higher percentage in SSc-RP than in pRP patients were: 'DUs' (pRP, 0% *vs*. SSc-RP, 57.8%), 'finger pain' (pRP 31.1%; SSc-RP 57.8%), 'widowed' (pRP, 4.9% *vs*. SSc-RP, 8.3%), 'autoimmune hypothyroidism' (pRP 4.9%; SSc-RP 15.6%) 'tuberculosis infection' (pRP 1%; SSc-RP 5.0%), and 'HPV vaccine' (pRP 1%; SSc-RP 1.7%).

Variables similarly distributed between the two groups were: 'familial autoimmune diseases', 'cold sensitivity', 'married', 'divorced/separated', 'mood', 'perfume', 'iodine-based compounds', 'chlorine-based compounds', 'alcohol-based compounds', and 'seasonal flu vaccine'.

Variables occurring with at least 1.5-fold higher percentage in pRP than in SSc-RP were: 'urban area' (pRP 51.5%; SSc-RP 28.4%), 'single' (pRP 23.3%; SSc-RP 10.0%), 'computer use (>4 hrs/day)' (pRP 39.8%; SSc-RP 20.0%), 'contraceptive use' (pRP 12.6%; SSc-RP 4.4%), 'habitual alcohol use' (pRP 11.7%; SSc-RP 4.4%), 'venereal diseases' (pRP 5.8%; SSc-RP 2.8%), 'HBV vaccine' (pRP 5.8%; SSc-RP 0.6%), and 'pneumococcal or meningococcal vaccine' (pRP 2.9%; SSc-RP 1.1%) (Table I).

According to Fisher's exact test, the percentage of females was significantly higher in the SSc-RP group than in the pRP group (OR=6.03; p<0.001), as was the presence of DUs (p<0.001) and finger pain (OR= 3.03; p<0.001), sensitivity to cold (OR=3.48; p=0.001), the impairment of QoL (OR=2.69; p<0.001), the use of hair dye (OR=2.59; p=0.001), and the presence of autoimmune hypothyroidism" (OR=3.62; p=0.007). On the other hand, the percentage of the following items was significantly lower in the SSc-RP group than in the pRP group: "urban area" (OR= 0.37; p<0.001), 'sin-

Table I. Clinical characteristics of 103 patients with primary Raynaud's phenomenon (pRP) and 180 patients with Raynaud's phenomenon associated with systemic sclerosis (SSc-RP).

Variables grouped	Specific variable	pRP	SSc-RP
		no. (%)	
General characteristics	Age (mean±SD)	56.61±9.89	58.45±12.62
	Female	76 (73.8)	170 (94.4)
	Familial RP	16 (15.5)	21 (11.7)
	Familial autoimmune diseases	22 (21.4)	37 (20.6)
RP-related	Cold sensitivity	81 (78.6)	167 (92.8)
Disease-related	DUs (in the present or past)	0 (0)	104 (57.8)
	Quality of life affected	55 (53.4)	135 (75)
	Finger pain	32 (31.1)	104 (57.8)
Living areas	Urban area[a)]	53 (51.5)	51 (28.3)
Family status:	Single	24 (23.3)	18 (10.0)
	Married	68 (66.0)	131 (72.8)
	Divorced/separated	8 (7.8)	14 (7.8)
	Widowed	5 (4.9)	15 (8.3)
Mood	Euthymic	41 (39.8)	66 (36.7)
	Anxious	45 (43.7)	72 (40.0)
	Depressed	8 (7.8)	19 (10.6)
	Stressed out	17 (16.5)	24 (13.3)
Work habits	Computer use (>4 hrs/day)	41 (39.8)	36 (20.0)
	Exposure to work-environment-related toxic substance/s[b)]	12 (11.7)	17 (9.4)
Habits of daily living / use of, or contact with	Sodium hypochlorite-based compounds	30 (29.1)	64 (35.6)
	Perfume	47 (45.6)	75 (41.7)
	Nail polish	20 (19.4)	27 (15.0)
	Hair dye	60 (58.3)	141 (78.3)
Disinfectants	H_2O_2-based	35 (34.0)	53 (29.4)
	Iodine-based	1 (1)	3 (1.7)
	Chlorine -based	17 (16.5)	32 (17.8)
	Alcohol -based	12 (11.7)	26 (14.4)
Sexual-related habit	Contraceptives	13 (12.6)	8 (4.4)
Playing musical instruments	String[c)] and or percussion	4 (3.9)	10 (5.6)
Substance use	Nicotine (smoker)[d)]	26 (25.2)	35 (19.4)
	Alcohol	12 (11.7)	8 (4.4)
	Drug	1 (1.0)	2 (1.1)
Medical history	Therapeutic Drug/s	43 (41.7)	96 (53.3)
	General surgery	51 (49.5)	110 (61.1)
	Cosmetic surgery	1 (1.0)	1 (0.5)
	Prosthesis	32 (31.1)	45 (25)
	Contact lenses	14 (13.6)	18 (10.0)
Other diseases	Autoimmune hypothyroidism	5 (4.9)	28 (15.6)
	Dermatitis	26 (25.2)	31 (17.2)
	Recurrent infections	9 (8.7)	24 (13.3)
	Tuberculosis	1 (1.0)	9 (5.0)
	Venereal diseases	6 (5.8)	5 (2.8)
Vaccine (other than mandatory)	Seasonal flu	17 (16.5)	35 (19.4)
	Hepatitis A virus	0 (0.0)	3 (1.7)
	Hepatitis B virus	6 (5.6)	1 (0.6)
	Human papilloma virus	1 (1.0)	3 (1.7)
	Pneumococcal or meningococcal	3 (2.9)	2 (1.1)
	Tuberculosis	1 (1.0)	3 (1.7)

[a)](> 20,000 inhabitants) and/or airport areas *vs*. town or rural area.
[b)]Housewife, housemaid, laboratory technician, hairdresser, metallurgical worker, and agricultural worker were considered jobs with a risk of exposure to toxic substances, whereas student, office worker, doctor, teacher, and lawyer were not.
[c)]Piano, guitar, etc.
[d)]Including those who quit smoking within the last five years.

Table II. Fisher's exact test to identify dichotomised variables with a statistically higher (odds ratio; OR >1) or lower (OR <1) prevalence in Raynaud's phenomenon (RP) secondary to systemic sclerosis than in primary RP.

Variable	c2[a]	OR (95% CI)[b]	*p*[c]	BHC $p<0.001$[d]
Female	24.6	6.03 (2.78-13.10)	<0.001	Yes
DUs	94.72	NA	<0.001	Yes
Cold sensitivity	12.08	3.48 (1.67-7.27)	0.001	Yes
QoL affected	14.00	2.69 (1.59-4.56)	<0.001	Yes
Finger pain	18.44	3.03 (1.81-5.06)	<0.001	Yes
Urban area	14.55	0.37 (0.22-0.62)	<0.001	Yes
Single	8.92	0.37 (0.19-0.72)	0.005	No
Hair dye use	12.83	2.59 (1.52-4.39)	0.001	Yes
Computer use	12.77	0.38 (0.22-0.65)	<0.001	Yes
Contraceptive use	6.30	0.32 (0.12-0.81)	0.017	No
Habitual alcohol use	5.23	0.35 (0.13-0.89)	0.029	No
Hepatitis B virus vaccine	7.48	0.09 (0.01-0.76)	0.011	No
Autoimmune hypothyroidism	7.32	3.62 (1.35-9.70)	0.007	No

[a]Pearson's chi-squared (c^2).
[b]OD: odds ratio; CI: confidence interval.
[c]Fisher's exact *p* test.
[d]Following Benjamini-Hochberg correction (BHC) for multiple comparisons; $p<0.001$ was considered statistically significant.
DUs: digital ulcers; NA: not applicable; QoL: quality of life.

Table III. Logistic regression analyses of the interdependency of variables statistically associated with Raynaud's phenomenon (RP) secondary to systemic sclerosis (SSc-RP) (OR>1) *vs*. primary Raynaud's phenomenon (pRP).

Variable/s	Multivariable[a]		Multivariable[b]	
	OR (95% CI)	*p*	OR (95% CI)	*p*
DUs	NA[c]	0.996	NA[c]	0.996
Cold sensitivity	2.55 (1.15-5.65)	0.021	1.30 (0.43-3.91)	0.634
QoL affected	2.11 (1.86-3.77)	0.011	0.90 (0.38-2.11)	0.812
Finger pain	2.97 (1.73-5.11)	<0.001	0.83 (0.35-1.93)	0.670
Urban area	0.39 (0.23-0.66)	0.001	0.75 (0.36-1.54)	0.435
Single	**0.35 (0.17-0.74)**	**0.006**	**0.32 (0.11-0.90)**	**0.032**
Hair dye use	1.39 (0.71-2.71)	0.335		
Computer use	0.42 (0.23-0.75)	0.004	0.62 (0.26-1.48)	0.287
Contraceptive use	0.31 (0.12-0.80)	0.016	0.34 (0.08-1.32)	0.121
Habitual alcohol use	**0.42 (0.15-1.11)**	**0.083**		
Hepatitis B virus vaccine	0.07(0.01-0.66)	0.002	0.15 (0.01-1.56)	0.115
Autoimmune hypothyroidism	**2.82 (1.04-7.67)**	**0.042**	**3.61 (1.09-11.87)**	**0.035**

[a]Variables statistically associated with SSc-RP according to Fisher's exact test were analysed by multivariable logistic regression, adjusting each variable for age and sex, based on the outcome of pRP *vs*. SSc-RP.
[b]Age- and sex-independent variables statistically associated with SSc-RP according to Fisher's exact test were analysed by multivariable logistic regression. Sex and age were used as confounding variables.
[c]The presence of DUs was not recorded in any pRP patient.
CI: confidence interval; DUs: digital ulcers; NA: not applicable; QoL: quality of life.
A $p<0.05$ was considered statistically significant.

gle' (OR=0.37; $p=0.005$), 'computer use' (OR=0.38; $p<0.001$), 'contraceptive use' (OR=0.32; $p=0.017$), 'habitual alcohol use' (OR=0.35; $p=0.029$), and 'HBV vaccine' (OR=0.09; $p=0.011$).

After statistical correction for multiple comparisons, the factors that remained statistically significant were: 'female', 'DUs', 'cold sensitivity', 'QoL affected', 'finger pain', 'urban area', 'hair dye use' and 'computer use' (Table II).

The analysis of the relationship between 'DUs' and 'cold sensitivity' performed in the whole cohort, revealed a direct association between the two items ($p=0.005$, Pearson's chi-squared = 7.71) (Table I).

A multivariable analysis was performed to evaluate whether the associations identified as statistically significant in the Fisher's exact were influenced by sex or age. As shown in Table III, the association of SSc-RP with 'hair dye use' and 'habitual alcohol use' was lost after adjustment for confounding variables, while the associations between SSc-RP and 'cold sensitivity', 'QoL affected', 'finger pain', 'urban area', 'single', 'computer use', 'contraceptive use', 'HBV vaccine', and 'autoimmune hypothyroidism' remained statistically significant, indicating their independence of either sex or age.

In the multivariable analysis, performed to estimate the association between age- and sex-independent variables and the outcome (SSc-RP), the variables that remained significantly associated with SSc-RP were 'single' (OR=0.32; $p=0.032$), and 'autoimmune hypothyroidism' (OR=3.61; $p=0.035$) (Table III).

Discussion

The present case-control study is the first to compare patients with SSc-RP and pRP in terms of environmental factors, lifestyle habits, and clinical setting. The QoL of RP patients was also assessed, and the results showed that it was lower in patients with SSc-RP than in those with pRP. The finding that a higher proportion of SSc-RP patients complains of RP-related symptoms, such as cold sensitivity and finger pain, may account for the low QoL reported by this group. These data are in accordance with the few studies that investigated disease-specific QoL in pRP and sRP (15, 16). Specifically, in a survey study including 443 subjects (from 15 countries) with self-reported RP (sRP 34%; pRP 43%), RP-related QoL was lower in patients with SSc-RP than in those with pRP (15). Similarly, in a smaller cohort of 101 patients with RP (60 pRP, 41 sRP), Fábián *et al*. demonstrated that sRP had a worse quality of life than pRP (16). This higher perception of cold and finger pain by SSc-RP patients, along with the presence of DUs, may underlie the inverse association between SSc-RP and computer use.

The reason of the lower prevalence of SSc-RP patients living in urban area is unknown. It is known that SSc patients are more susceptible to cold and ambient temperature changes than pRP because of the underlying vasculopathy

and related fibrosis (17, 18). Recently, it has been demonstrated in SSc that RP is worsened not only by cold temperature but also by hot temperature compounded by air conditioning (19). Outdoor temperature differences between countryside and urban area are related to different style of lives conditioned by the ways to control indoor comfort temperatures (20). Extreme temperatures (cold/hot) represent a real RP environmental factor that deserves a better evaluation between SSc-RP and pRP. One possibility to explain the lower prevalence of SSc-RP patients living in urban area is the presence of undefined country-related environmental factor(s), which may favour the onset of SSc; alternatively it may be linked to the choice of SSc-RP patients to live in countryside to reduce stress, anxiety and depression, which are known to be more common in sRP than in pRP (16). On the other hand, the higher prevalence of pRP patients living in urban area suggests that air pollution may be a potential risk factor for pRP development. This hypothesis is supported by our previous study indicating a direct association of living in urban area with pRP patients as compared to healthy individuals (14).

The higher proportion of HBV unvaccinated patients in SSc-RP than in pRP patients suggests that the former either are less aware of this type of vaccination, or, more likely, they avoid HBV vaccination "for the erroneous belief that vaccine may worsen autoimmunity", as discussed in previous investigations (21-24). Similarly, the prevalence of hormonal contraceptive use in SSc-RP lower than in pRP patients may reflect the fact that SSc-associated physical conditions reduce sexual activity and or libido; however, it may also be the case that SSc-RP patients may be concerned about possible detrimental effect of oestrogen and progestin treatment, or oestrogen effects during the fertile age, in enhancing the risk of RP (25-27) or in exacerbating B cell immune response (28, 29).

Alcohol consumption was lower in the SSc-RP group than in the pRP group. This association was found to be sex-dependent, given the higher prevalence of male patients in the pRP group and corroborated by previous Italian study showing that alcohol consumption was higher in males than females (30).

In our study, the status of 'single' was more prevalent in pRP than in the age-matched SSc group. These findings are in agreement with the results obtained by a previous meta-analysis study demonstrating that 'married' was associated with a lower risk of pRP than being single/separated/divorced/widowed as compared with healthy population (6). It is likely that 'single' individual may experience anxiety and emotional stress for their singlehood status, key triggers for RP episodes (1), though we cannot exclude that this association may be due to confounding bias.

Of particular interest is the finding of a direct association between SSc-RP and autoimmune hypothyroidism. Autoimmune hypothyroidism is often observed in poly-autoimmunity patients (31, 32). Some studies have reported a high prevalence of autoimmune hypothyroidism in SSc patients (33-37). Specifically, a North American study of 56 SSc patients and 56 healthy individuals matched by age and sex found a high prevalence of autoimmune hypothyroidism in the SSc cohort (33). In a European multicentre study, the prevalence of autoimmune thyroiditis in 585 French and 547 Italian patients with SSc was higher than in the respective general populations (35). Similar findings were reported by Biro *et al*. for 119 Hungarian SSc patients (34), and by Posselt *et al*. in a cross-sectional observational study of 58 SSc patients in Brazil (38). A longitudinal study of 179 SSc patients and 179 matched controls showed a significantly higher incidence of thyroid peroxidase antibody positivity in SSc patients (36). Finally, a recent meta-analysis concluded that, worldwide, SSc was significantly associated with an increased risk of autoimmune hypothyroidism (37). Only one study found a lower risk of hypothyroidism among SSc patients with serum anti-thyroid-peroxidase positivity (39).

In all the above-mentioned studies, general population (34, 35), healthy subjects (33, 36, 38) or osteoarthritis patients (39) were used as controls. By contrast, in the present investigation pRP was used as control population, thus providing straightforward information on the difference in the prevalence of autoimmune thyroiditis between SSc-RP and pRP patients.

The results of our study suggest that patients with pRP and autoimmune hypothyroidism may be prone to developing SSc-RP and should therefore be closely monitored by nailfold capillaroscopy (40) and detection of SSc-specific autoantibodies to allow an early diagnosis and prompt treatment of SSc. However, this study has some limitations, including the limited number of patients, the recall bias and the lack of detailed information related to thyroid function. Future research is needed to assess the external validity of our findings. Finally, a longitudinal prospective observation will establish the impact of RP duration on environmental and clinical outcomes and whether autoimmune thyroiditis in pRP is able to sign subjects at very early stage for an evolution into SSc-RP.

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