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Relevance of serum angiogenic cytokines in adult patients with dermatomyositis

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Abstract

Background: Until now, there are few studies evaluating serum levels of angiogenic cytokines in dermatomyositis (DM). Therefore, the aims of the present study were: (a) to analyze systematically and simultaneously serum levels of angiogenin (ANG), angiopoietin (ANGPT)-1, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-1 and − 2, platelet derived growth factor (PDGF)-AA and -BB in DM; (b) to correlate the serum level of these cytokines with the DM clinical and laboratory features.

Methods: This is a cross sectional study, in which 48 patients with DM aged 18 to 45 years were gender-, age- and ethnicity-matched with 48 healthy individuals (control group). The serum levels of cytokines analyses were performed by multiplex immunoassay. The parameters of DM activity were based on the scores established by the International Myositis Assessment & Clinical Studies Group.

Results: The mean ages, gender frequencies and ethnicities were comparable between the patients with DM and the control group. A significantly higher serum FGF-1 and FGF-2 levels ($P < 0.001$ and $P < 0.001$, respectively), lower VEGF and PDGF-AA levels ($P = 0.009$ and $P = 0.022$), and comparable ANG, ANGPT-1 and PDGF-BB levels were observed in DM patients compared to controls. There was a tendency for cytokines (with the exceptions of VEGF and PDGF-BB) to correlate positively with the DM activity parameters, whereas FGF-2 correlated inversely. Moreover, FGF-1 strongly correlated with DM cutaneous manifestations.

Conclusions: The present data provide the relevance of different serum angiogenic cytokines in patients with DM. Additional studies will be needed to validate the data obtained in this work.

Keywords: Angiogenesis, Cytokines, Dermatomyositis, Idiopathic inflammatory myopathies, Myositis

Background

Dermatomyositis (DM) is an autoimmune inflammatory myopathy characterized by a subacute onset and progressive skeletal muscle weakness. The disease is associated with typical cutaneous manifestations, including heliotrope and/or Gottron's papules [1–7]. The cornerstone of DM physiopathogenesis involves vascular disturbances and a primarily humoral immune response [4–6], and can involve multiple cytokines related to mechanisms ranging from inflammation to angiogenesis.

Several serum angiogenic cytokines have been described in the literature, including: angiogenin (ANG), angiopoietin-1 (ANGPT-1), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) types 1 and 2, and platelet-derived growth factor (PDGF-AA e PDGF-BB). However, these serum angiogenic cytokines have been scarcely assessed in DM [8–14]. For instance, Kuwahara [8] observed high ANG mRNA expression in the skin tissue of patients with active DM but no significant increase in the serum ANG level. Nevertheless, the authors described a positive correlation between the serum ANG and aldolase levels.

High serum VEGF levels have been noted in DM and polymyositis (PM) [9–11]. However, as a limitation, these data are based on a series of cases, involving individuals mostly ≥40 years of age with no detailed treatment information.

Kadono et al. [13] observed an elevated serum FGF-2 level in DM patients that correlated with the serum creatine phosphokinase (CPK) level and pulmonary fibrosis.

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However, this study assessed only 7 untreated female patients ≥50 years of age.

The serum ANGPT-1 levels were normal in patients with DM in a unique study in the literature [12]; however, although additional information concerning the association between values and clinical or laboratory parameters was provided, no date concerning the serum FGF-1 and PDGFs, there are no data evaluating serum levels were available for these patients.

Therefore, the aim of the present research was to assess simultaneously and systematically the serum ANG, ANGPT-1, VEGF, FGF (types 1 and 2), PDGF-AA and PDGF-BB levels in DM patients. Additionally, we sought to correlate the serum levels of these cytokines with demographic, clinical, laboratory, and therapeutic factors and comorbidities of patients with DM.

Methods

A cross-sectional study was performed at a single centre. The study included 60 consecutive patients with DM (age ≥ 18 and ≤ 45 years) enrolled from 2012 to 2014 who fulfilled all of the Bohan and Peter criteria items [1, 2] and were regularly followed at our outpatient myopathy unit. Patients with cancer-associated myositis, clinically amyopathic DM and overlapped myositis were not included in the study.

The study was approved by the local ethics committee (HCFMUSP - CAPPesq number 1.545.393) and all patients signed the informed consent form.

To avoid possible factors that could interfere with serum cytokine analysis, patients with > 10 years of DM disease ($n = 8$) and tobacco habits ($n = 4$) were excluded. Moreover, no cases of acute and/or chronic infections, liver and renal diseases, menopause, diabetes mellitus, non-controlled chronic systemic arterial hypertension, myocardial infarction, ischemic stroke, alcohol consumption and claudication vascular symptoms were included. Therefore, 48 patients with DM were assessed, and 48 age, gender and ethnicity-matched healthy volunteers were recruited as a control group during the same period.

All participants underwent a clinical evaluation that included a standardized interview, and their charts were extensively reviewed.

Demographic data were collected, including the current age, gender, ethnicity, waist circumference, weight and body mass index [BMI, weight/height^2 (kg/m^2)]. The clinical and laboratory data included the age at disease onset, disease duration, muscle enzyme serum levels [CPK: reference value 26–308 U/L, aldolase: < 7.5 U/L, alanine aminotransferase (ALT): < 41 U/L, aspartate aminotransferase (AST): < 37 U/L, lactate dehydrogenase (LDH): 240–480 U/L)], and clinical manifestations [articular (arthralgia or arthritis), pulmonary (moderated or severe subjective dyspnea associated simultaneously with confirmed "ground-glass" on high-resolution chest computed tomography) activity, and cutaneous (Gottron's papules, heliotrope rash, ulcers, vasculitis, "shawl" sign, "V-neck" sign, facial rash, Raynaud's phenomenon, and calcinosis].

The disease status was evaluated using the following questionnaires and scores: global assessment of the disease (by the physician and the patient) through the visual analogue scale (VAS) [15–17], Manual Muscle Testing (MMT-8) [18], Health Assessment Quality (HAQ) [19].

Therapy data included the use of immunosuppressives and, glucocorticoids (current and cumulative doses).

Cytokine assessment. A blood sample (10 mL of blood) obtained from each participant after a 12-h overnight fast was immediately (< 30 min) centrifuged at 3000 rpm for 10 min at 4 °C. The serum was stored at − 80 °C prior analysis of the cytokines ANG, ANGPT-1, VEGF, FGF-1, FGF-2, PDGF-AA and PDGF-BB. The analysis was performed using the Luminex 200- xMAP Technology (Millipore, USA), as described elsewhere [20].

Statistical analysis. The Kolmogorov-Smirnov test was used to evaluate the distribution of each parameter. The demographic and clinical features were expressed as the mean ± standard deviation (SD) for continuous variables or as frequencies and percentages (%) for categorical variables. The median (25th - 75th interquartile range) was calculated for continuous variables that were non-normally distributed. Comparisons between the patient and control parameters were made using Student's *t*-test or the Mann-Whitney test for continuous variables, whereas the Chi-square test or Fisher's exact test was used to evaluate categorical variables. The correlations among the parameters were analysed by Spearman's correlation. All of the analyses were performed using the SPSS 15.0 statistical software (Chicago, USA). A $P < 0.05$ was considered to indicate statistical significance.

Results

Forty-eight patients with DM and 48 controls were evaluated. As expected, the mean age, gender frequency and ethnicity were similar between the groups (Table 1). The mean age at disease onset was 30.9 years, with 5.0 months of symptoms prior to diagnosis and median disease duration of 1.0 year.

The articular, pulmonary and cutaneous involvements were present in 29.2, 35.4 and 100% of the cases, respectively.

The disease status parameters are shown in Table 1. As expected, all muscle enzymes were significantly higher in the patients with DM than in the controls.

Table 1 General features of patients with dermatomyositis and health individuals

Parameters	DM (*n* = 48)	Control (n = 48)	*P* value
Age (years)	33.3 ± 7.6	35.8 ± 8.2	1.000
White ethnicity	36 (75.0)	32 (66.7)	0.501
Female gender	36 (75.0)	36 (75.0)	1.000
Age at disease onset (years)	30.9 ± 7.4	–	–
Duration: diagnosis - symptoms (months)	5.0 (2.3–8.5)	–	–
Disease duration (years)	1 (0–4)	–	–
Clinical cumulative manifestations			
Articular involvement	14 (29.2)	–	–
Pulmonary involvement	17 (35.4)	–	–
Cutaneous involvement	48 (100.0)	–	–
Gottron's papules	47 (97.9)	–	–
Heliotrope rash	40 (83.3)	–	–
Facial rash	30 (62.5)	–	–
Raynaud' phenomenon	24 (50.0)	–	–
"V-neck" sign	15 (31.3)	–	–
Ulcers	10 (20.8)	–	–
Vasculitis	10 (20.8)	–	–
"Shawl" sign	8 (16.7)	–	–
Calcinosis	0	–	–
MMT-8 (0–80)	78 (71–80)		
HAQ (0.00–3.00)	0.36 (0.00–2.00)	–	–
Patient VAS (0–10 mm)	5 (1–6)	–	–
Physician VAS (0–10 mm)	4 (1–5)	–	–
Creatine phosphokinase (U/L)	200 (93–960)	100 (81–161)	0.002
Aldolase (U/L)	5.9 (4.1–12.9)	3.6 (3.1–4.3)	< 0.001
Lactic dehydrogenase (U/L)	412 (347–597)	323 (296–381)	< 0.001
Alanine aminotransferase (U/L)	25 (16–60)	17 (13–21)	< 0.001
Aspartate aminotransferase (U/L)	25 (19–52)	19 (16–22)	< 0.001
Prednisone			
Current use	34 (70.8)	–	–
Current dose (mg/day)	20.0 (3.1–50.0)	–	–
Cumulative dose[a] (mg)	645 (90–2103)	–	–
Cumulative dose[b] (g)	15.5 (5.8–27.8)	–	–
Immunosupressive/imunmodulatory[c]			–
None	20 (41.7)	–	–
One	11 (22.9)	–	–
Two	17 (35.4)	–	–

Results expressed as percentage (%), mean ± standard deviation, median (25th - 75th interquartile range)
DM dermatomyositis, *HAQ* Health Assessment Questionnaire, *MMT* Muscle Manual Testing, *VAS* visual analogue score
[a] Last 3 months; [b] since the begin of treatment; [c] imunossupressive / imunomodulatory: azathioprine (2–3 mg/kg/day), methotrexate (15–25 mg/week), cyclosporine (1.5–2.5 mg/kg/day), mycophenolate mofetil (2–3 g/day), rituximab (1 g, intravenous, at baseline and after one month - first cycle - and this schema was repeated after six months), cyclophosphamide (0.5–1.0 g/m^2 body surface), leflunomide (20 mg/day) and/or intravenous human immunoglobulin (2 g/kg, daily, two consecutive days)

Regarding drug treatment, 70.8% of the patients were using prednisone with a mean dose of 20.0 mg/day. The median cumulative dose of prednisone was 645 mg (over the last three months of blood collection) and 15.5 g (since the onset of disease symptoms). Approximately half of the patients were using at least

one immunosuppressive or immunomodulatory drug, including azathioprine (2–3 mg/kg/day), methotrexate (15–25 mg/week), cyclosporine (1.5–2.5 mg/kg/day), mycophenolate mofetil (2–3 g/day), rituximab [1 g, intravenous, at baseline and after one month (first cycle); this scheme was repeated after six months], cyclophosphamide (0.5–1.0 g/m^2 body surface), leflunomide (20 mg/day) and/or human intravenous immunoglobulin (2 g/kg, daily, two consecutive days) (Table 1).

The serum levels of the angiogenic cytokines (ANG, ANGPT-1 and PDGF-BB) were comparable between the groups (Table 2). The FGF-1 and FGF-2 levels were elevated, whereas the VEGF and PDGF-AA levels were decreased in the patients with DM compared to the control group.

Table 3 shows only the significant correlations between the angiogenic cytokines analysed in the present study and the demographic, clinical, laboratory and therapeutic parameters shown previously in Table 1. Moreover, the correlations between the cytokines themselves were also analysed. All data refer to patients with DM.

The FGF-1 serum levels were moderately correlated with the cutaneous clinical manifestations (facial rash, "V-neck" sign and "shawl" sign) as well as some disease activity parameters (patient and physician VAS, and muscle enzymes) and were inversely correlated with the disease duration and cumulative prednisone dose. Additionally, the serum FGF-1 levels positively correlated with the serum ANG, ANGPT-1 and PDGF-AA levels and negatively correlated with the FGF-2 levels.

FGF-2 tended to be inversely correlated with the disease activity parameters (patient and physician VAS, MMT-8, and muscle enzymes) and serum FGF-1, ANG, ANGPT-1, PDGF-AA and PDGF-BB levels. A positive correlation was found between the serum FGF-2 levels and the cumulative prednisone dose.

Table 2 Serum levels of angiogenic cytokines in patients with dermatomyositis and healthy individuals

Parameters	DM (n = 48)	Control (n = 48)	*P* value
ANG (ng/mL)	4383 (3588–7251)	3931 (2735–5397)	0.138
ANGPT-1 (ng/mL)	8576 (4964–13,060)	8080 (5785–9609)	0.224
VEGF (ng/mL)	28.6 (5.8–49.3)	38.6 (21.3–72.6)	0.009
FGF-1 (ng/mL)	3.1 (1.8–14.9)	0.7 (0.4–1.8)	< 0.001
FGF-2 (ng/mL)	1.6 (0.6–3.1)	0.3 (0.0–0.9)	< 0.001
PDGF-AA (ng/mL)	545 (304–797)	654 (411–1083)	0.022
PDGF-BB (ng/mL)	2039 (1539–2506)	2107 (1752–2465)	0.358

Results expressed as median (25th - 75th interquartile range)
ANG angiogenin, *ANGPT-1* angiopoietin-1, *DM* dermatomyositis, *FGF* fibroblast growth factor, *PDGF* platelet-derived growth factor, *VEGF* vascular endothelial growth factor

Low serum PDGF-AA and VEGF levels were observed in patients with DM. No correlation was found between the VEGF level and the disease activity parameters or treatment data. However, the serum PDFG-AA, and FGF-1 levels were positively correlated with the DM disease parameters (physician VAS, MMT-8, HAQ, and muscle enzymes) and inversely correlated with the disease duration and cumulative prednisone dose. A positive correlation between the PDGF level and the serum ANG, ANGPT-1 and PDGF-AA levels and a negative correlation with the FGF-2 level were also observed.

ANG, ANGPT-1 and PDGF-BB were not elevated in DM. However, the correlations among the serum levels of these cytokines and the other parameters generally followed the same profiles observed for FGF-1 and PDGF-AA.

Discussion

This study is the first to systematically and simultaneously analyse the serum levels of several angiogenic cytokines in patients with DM.

The great advantage of the present study was its use of rigorous selection criteria for patients. Additionally, we excluded confounding factors that could interfere with the evaluation and interpretation of the angiogenic cytokines.

FGF-1 was positively correlated with the cutaneous clinical manifestations and some disease activity parameters, which was in contrast with FGF-2. We also observed lower FGF-1 levels in the patients with longer disease duration and a cumulative utilization of prednisone.

Both FGF-1 and -2 act in several cellular processes and specifically, in angiogenesis, they induce cell proliferation and the physical organization of endothelial cells into tubular structures [21–24]. Due to their specific biological functions and roles, FGFs have the potential for application to induce the regeneration of a wide spectrum of tissues [24].

By combining these known actions of FGF-1 with our findings, we propose that this cytokine may be involved in the physiopathogenesis of cutaneous manifestations in active DM patients, because patients with more cutaneous lesions, a shorter duration of disease or long-term treatment have higher serum FGF-1 levels. Further studies of cutaneous biopsies to evaluate local levels of FGF-1 or its genic expression could corroborate this hypothesis.

FGF-2 has a more powerful healing action than FGF-1. Indeed, blockage of FGF-2 activity is almost completely impairs wound angiogenesis [25]. Moreover, some in vitro and in vivo studies have demonstrated that FGF-2 promotes stem cell recruitment during the muscle regeneration process [26].

Table 3 Spearman's correlation between angiogenic cytokines and diferent disease parameters

	ANG		ANGPT-1		FGF-1		FGF-2		VEGF		PDGF-AA		PDGF-BB	
	rho	*P*	*rho*	*P*	*rho*	*P*	*rho*	*P*	*rho*	*P*	*rho*	*P*	*rho*	*P*
Current age			0.289	0.018							0.399	0.018		
Age at disease onset			0.401	0.005	0.295	0.042					0.416	0.003		
Disease duration			−0.448	0.001	−0.394	0.006					−0.326	0.024	−0.411	0.004
Body mass index									0.317	0.028				
Facial rash	0.387	0.021			0.367	0.010								
"V-neck" sign					0.338	0.019								
"Shawl" sign			0.355	0.013	0.343	0.017								
Pulmonary involvement	0.435	0.009												
Patient VAS	0.410	0.014	0.326	0.024	0.351	0.014	−0.364	0.012						
Physician VAS	0.476	0.004	0.387	0.007	0.341	0.018	−0.385	0.007			0.324	0.025		
MMT-8			−0.470	0.001			−0.413	0.004			−0.457	0.001	−0.382	0.008
HAQ			0.400	0.005							0.338	0.019		
Creatine phosphokinase			0.315	0.035										
Aldolase			0.537	< 0.001	0.397	0.009	−0.344	0.028			0.469	0.002	0.478	0.002
Lactic dehydrogenase					0.339	0.023								
Aspartate aminotransferase					0.429	0.004	−0.398	0.008			0.363	0.016	0.324	0.034
Alanine aminotransferase					0.379	0.010								
Cyclosporin			−0.309	0.032										
Prednisone (current use)			0.463	0.001	0.342	0.017					0.478	0.001	0.510	< 0.001
Prednisone (cumulative[a])			−0.390	0.006	−0.399	0.005	0.301	0.040			−0.315	0.029		
ANG	1.000		0.366	0.001	0.512	< 0.001	−0.594	< 0.001			0.408	0.004		
ANGPT-1	0.360	0.034	1.000		0.502	< 0.001	−0.453	0.001			0.820	< 0.001	0.725	< 0.001
FGF-1	0.344	0.034	0.502	< 0.001	1.000		−0.376	0.009			0.437	0.002		
FGF-2			−0.543	0.001	−0.376	0.009	1.000				−0.459	0.001	−0.391	0.007
VEGF									1.000					
PDGF-AA			0.820	< 0.001	0.437	0.002	−0.459	0.001			1.000		0.720	< 0.001
PDGF-BB			0.725	< 0.001			−0.391	0.007			0.720	< 0.001		1.000

ANG angiogenin, *ANGPT-1* angiopoietin-1, *FGF* fibroblast growth factor, *HAQ* Health Assessment Questionnaire, *MMT* Muscle Manual Testing, *P P* value, *PDGF* platelet-derived growth factor-AA and BB; *Rho*: Spearmen's correlation, *VAS* visual analogue scores, *VEGF* vascular endothelial growth factor
[a]Since the disease onset symptoms

A negative correlation between the serum FGF-2 level and the disease activity parameters and a positive correlation with the cumulative prednisone dose were noted. One possible explanation for this finding is that FGF-1 and FGF-2 are continuously released into the bloodstream by muscle and endothelial tissues due to myofibrillar necrosis. Alternatively, the muscle regeneration process and fibrosis that occur during the evolution of disease or its treatment may maintain the elevated FGF-2 level due to its potent cure and regeneration actions. This phenomenon would make FGF-2 a marker of the muscular healing process in DM patients.

We found an inverse pattern of correlation between FGF-1 and -2 (positive and negative, respectively) and the other angiogenic cytokines evaluated. We conclude that there are mechanisms that up and down-regulate FGF-1 and FGF-2 during the different stages of disease progression with a more established counter-regulation in chronic or adequately treated cases.

PDGF-AA and PDGF-BB promote the maturation of blood vessels through the recruitment and adhesion of mural cells by specific interactions with their receptors PDGF-Rαα (positive mitotic signals) and PDGF-Rββ (positive and negative mitotic signals). Both cytokines can promote and inhibit chemotaxis and cell growth [27], and their behavior depends on the context.

In this study, the correlations between the PDGF-AA level and the clinical and laboratory parameters in DM patients had the same pattern as FGF-1 with the exception of the cutaneous manifestations. FGF-1 has been shown to induce the expression of PDGF-AA in endothelial cells through an unknown mechanism [28]. Thus,

in active DM, these cytokines may interact in a synergistic manner to potentiate their angiogenic actions through interactions with their receptors.

One possible explanation for the reduction in the VEGF serum levels in DM patients is that most of our patients were in an early stage of the disease, were well treated and were controlled symptomatically; therefore, little inflammatory infiltration was present and the capillary efficiency was more established. Another probable hypothesis is that the release of this cytokine by endothelial and inflammatory cells occurred initially at sites of greater inflammation, such as the muscle and/or skin, without the need for blood transport [10]. Thus, local measurement of VEGF in these tissues and an analysis of its gene expression patterns are needed in future studies.

The serum PDGF- BB, ANG and ANGPT-1 levels were correlated with the DM disease parameters, similar to FGF-1.

As discussed above, the PDGFs interact with specific receptors, and PDGF-BB has an affinity for all PDGF-R heterodimers [27]. Similarly, other cytokines, such as FGF-2, have an activation/inhibition relationship with PDGF [29]. The cytokine profile found in this study shows an increase of FGF-2 in DM patients, which may have inhibitory effects on PDGF-BB.

In agreement with our results, only one study evaluated the serum ANG levels in DM patients [8] and found no significant difference in the ANG levels between groups. However, the authors observed high gene expression of ANG in the analysed skin biopsies which suggests in situ inflammatory activity control more than a systemic control.

ANGPT-1 also interacts with other cytokines, such as VEGF, on endothelial cells to inhibit leukocyte adhesion the expression of some specific cell adhesion molecules [30]. Another important antagonist of ANGPT-1 is ANGPT-2 [31]. The interaction with inhibitory factors, such as ANGPT-2, may allow the serum levels to remain similar the levels observed in healthy people, as shown in our results.

Considering that the cytokines with the highest serum levels evaluated in this work were FGF-1 and FGF-2 and the correlation of these cytokine levels with the treatment received, we cannot exclude the possibility that the immunosuppressive treatment may have influenced the results by interfering with the inflammatory and angiogenic processes.

Among the limitations of the present study were the transversal nature and the analysis of the serum levels of the cytokines performed in a single measurement, because the serum profiles could have changed during the evolution of the disease and the establishment of treatment.

Conclusions

In summary, we found an increase in the serum FGF-1 and FGF-2 levels, a decrease in the VEGF and PDGF-AA levels, and comparable ANG, ANGPT-1 and PDGF-BB levels in patients with DM and the healthy controls. The FGF-1, PDGF-AA, ANG and AGPT-1 levels showed a positive correlation with the disease activity parameters, which was in contrast to the FGF-2 level. Moreover, FGF-1 and FGF-2 correlated positively with the cutaneous DM manifestations and cumulative prednisone dose, respectively. These data provide the possible involvement of angiogenic cytokines in DM disease.

Abbreviations

ALT: Alanine aminotransferase; ANG: Angiogenin; ANGPT: Angiopoietin; AST: Aspartate aminotransferase; BMI: Body mass index; CPK: Creatine phosphokinase; DM: Dermatomyositis; FGF: Fibroblast growth factor; HAQ: Health Assessment Quality; LDH: Lactate dehydrogenase; MMT: Manual muscle testing; PDGF: Platelet derived growth factor; SD: Standard deviation; VAS: Visual analogue scale; VEGF: Vascular endothelial growth factor

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Authors' contributions

All authors contributed equally to write and review the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the local ethics committee (HCFMUSP - CAPPesq number 1.545.393) and all patients signed the informed consent form.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no conflicts of interest.

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