ORIGINAL RESEARCH ARTICLE

Cardiovascular Therapeutics

Growth Arrest-Specific 6 and Cardiometabolic Risk Factors in Patients with Psoriasis

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SUMMARY

Objectives: An increased risk for cardiovascular disease with psoriasis has been reported. Growth Arrest-Specific 6 (GAS6) amplifies pro-inflammatory endothelial cell activation via TAM receptors. However, it also inhibits inflammation by multiple mechanisms including phagocytosis. The objective of this study was to investigate whether plasma GAS6 levels are associated with conventional cardiometabolic (CM) risk factors in patients with psoriasis. **Methods:** Forty patients diagnosed with psoriasis (22 male, mean age: 43.3 ± 13.8 years) and 40 age-/sex-matched healthy controls (22 male, mean age: 39.3 ± 8.9 years) were included in the study. CM risk factors (hypertension, hyperlipidemia, diabetes mellitus, and cigarette smoking) were identified. GAS6 levels were measured by ELISA. **Results:** There were no significant differences between the plasma GAS6 levels of patients with psoriasis compared to the control group (6.6 ± 2.0 ng/mL, 7.6 ± 2.8 ng/mL, respectively, $P > 0.05$). However, GAS6 levels of patients with psoriasis having a smoking history (n = 11) were significantly lower than both patients with psoriasis who had no smoking history (n = 29) and controls (5.5 ± 1.7 ng/mL, 6.9 ± 1.9 ng/mL, 7.6 ± 2.8 ng/mL, respectively, $P < 0.05$). Similarly, psoriasis patients with at least one CM risk factor showed lower GAS6 levels compared to subjects without any CM risk factor (5.7 ± 1.7 ng/mL, 7.3 ± 2.0 ng/mL, $P < 0.01$). There was no correlation between the GAS6 level, disease duration or PASI score ($r = 0.150$, -0.150, and $P = 0.310$, 0.398, respectively). **Conclusions:** This pilot study provides the first evidence in humans for an association between low plasma GAS6 levels and conventional risk factors in psoriasis. Further large scale, prospective studies are needed to confirm these results.

Introduction

Psoriasis is an inflammatory skin disease affecting approximately 125 million patients worldwide [1]. An increased risk for cardiovascular disease (CVD) associated with psoriasis has been documented in observational studies [2,3].

The molecular mechanisms for increased cardiometabolic (CM) risk in psoriasis have yet to be described. Studies have reported an increased prevalence of conventional CM risk criteria including cigarette smoking, hypertension (HT), hyperlipidemia (HL), and diabetes mellitus (DM) in psoriasis [4,5]. The question remains whether the increased prevalence of CVD in psoriasis is solely related to the increased prevalence of conventional CM risk criteria or new vascular biomarkers are necessary to assess vascular health in these patients [5]. Both clinical and basic research provide extensive evidence suggesting that the observed association is mediated through physiological mechanisms including vascular calcification, modification of the lipid profile, coagulation, thrombosis, and inflammation [6].

Growth Arrest-Specific 6 (GAS6) is a vitamin K-dependent protein (VKDP) which is expressed by diverse tissues such as endothelial cells, smooth muscle cells, and bone marrow. It has been reported that GAS6 is involved in the pathogenesis of inflammation and thrombosis, which relate to CVD including venous thromboembolism and atherosclerosis [7]. Animal model studies indicated that inhibition of VKDP with warfarin induces widespread vascular calcification [7,8]. Recombinant human GAS6 significantly inhibited apoptosis and calcification of vascular smooth muscle cells [9].

Skin lesions in psoriasis are characterized by hyperproliferation of keratinocytes, epidermal hyperplasia, and inflammatory

cytokine milieu [10]. Inflammation in psoriasis is triggered by cutaneous lymphocyte infiltration and activation. Inflammatory cells generate molecules that start the pathogenic cascade leading to characteristic plaque formation in psoriasis. GAS6 is a ligand for TAM receptors (Tyro3, Axl, Mer), a family of receptor tyrosine kinases. GAS6 and TAM receptors have emerged as potent negative regulators of innate immune responses [11]. They have a role in immune response and removal of apoptotic cells. Following phagocytosis of apoptotic cells or the induction of T-cell-dependent adaptive immune responses, ligand-induced TAM signaling dampens proinflammatory cytokine production and thus prevents exaggerated or prolonged inflammation [12]. GAS6 knock-out mice were found to be protected from thrombosis [13], and TAM receptor knock-out mice developed autoimmunity [14].

Szász et al. [15] studied expression of GAS6 in psoriasis skin lesions in mice. They found that the mRNAs of TAM receptors and GAS6 are downregulated in psoriatic epidermis, and mRNA of GAS6 was negatively correlated with the expression of proinflammatory mediators in psoriasiform skin. It could be hypothesized that plasma GAS6 levels are associated with conventional CM risk factors in patients with psoriasis.

Materials and Methods

Study Population

Forty consecutive patients with a diagnosis of psoriasis followed by the Dermatology outpatient clinics were enrolled into the study. The diagnosis of psoriasis was based on dermatological examination. The severity of the psoriasis was evaluated by "The Psoriasis Area Severity Index" (PASI score: 0–72, >10 indicating moderate–severe disease) scale in all patients [16]. Conventional CM risk factors (hypertension, hyperlipidemia, diabetes mellitus, and cigarette smoking) were identified. HT was defined as systolic and/or diastolic blood pressure ≥140/90 mmHg, previously diagnosed HT, or use of any antihypertensive medications. DM was defined as fasting plasma glucose levels more than 126 mg/dL in ≥3 measurements, previously diagnosed DM or the use of antidiabetic medications such as oral antidiabetic agents or insulin. HL was defined as serum total cholesterol ≥200 mg/dL, serum triglyceride ≥150 mg/dL, low-density lipoprotein cholesterol ≥130 mg/dL, previously diagnosed HL, or the use of lipid-lowering medication. Smoking status was defined as a history of tobacco use at the time of admission or in the half-year prior to the visit. Patients with other inflammatory conditions including typical rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and gout, any evidence of coronary artery disease (CAD), left ventricular (LV) systolic dysfunction (LV ejection fraction <55%), valvular heart disease, cardiomyopathy, arrhythmias, or conduction disorders were excluded from the study. None of patients with psoriasis were on anticoagulation therapy or vitamin K supplementation. After exclusion criteria, the remaining 40 patients with psoriasis were included in the study.

As a control group, 40 age-/sex-matched healthy volunteers were included in the study. All volunteers enrolled in the study filled out a health questionnaire. As a part of the Mediterranean lifestyle, their habitual food consumption included fruit and green leafy vegetables, a good source of vitamin K. Volunteers were excluded if they had systemic connective tissue disease, any evidence of systemic infection, CAD, HT, DM, HL, cardiomyopathy, arrhythmias, or conduction disorders. Other criteria for exclusion were as follows: the use of anticoagulation therapy or vitamin K supplementation, smoking, alcohol consumption, drug or vitamin, or any chronic disease. The investigation complies with the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee, and all participants gave written informed consent before participating.

ELISA of plasma GAS6

Venous blood samples were collected into vacuum tubes containing 3.2% Na-citrate between 8:00 A.M. and 10:30 A.M. following an overnight fasting. After centrifugation at 2300 *g* for 15 min at room temperature, the plasma aliquots were stored at −80°C before analysis. The human GAS6 sandwich ELISA development kit (R&D Systems, Inc., Minneapolis, MN, USA) and a Substrate Reagent Pack (Color reagent A&B) (R&D Systems, Inc.) were used to measure plasma GAS6 levels. ELISA was performed in line with our previous publications [17,18]. The human GAS6 sandwich ELISA development kit (R&D) was designed for the analysis of cell culture supernatants and was not optimized by the manufacturers for analysis of human plasma when we started first time. We have optimized and validated the method. To optimize the ELISA method, the following parameters were tested: Type of antibody; capture antibody concentration; dilution solution; dilution ratio of samples and calibrators; blocking agent (BSA or nonfat dry milk), and incubation time and temperature. In summary, the following optimal conditions were identified. Dilution solution for samples and calibrators was PBST containing 1 mM EDTA and 1% BSA. Dilution ratio of samples and calibrators was 1/40. Capture antibody concentration was 4 μg/mL, and blocking solution was 5% BSA in PBST. Incubation time during antigen antibody interaction (both capture and detection antibodies) was 1 h at 37°C. After analytical validation studies of the method, samples were analyzed.

Statistical Analyses

Statistical analyses were performed using SPSS 16.0 statistical package for Windows (Chicago, IL, USA). Continuous data were expressed as mean ± standard deviation, while categorical data were presented as a percentage. The chi-square test was used for comparison of categorical variables, while Student's *t*-test, one-way ANOVA, or Mann–Whitney *U*-test were used to compare parametric and nonparametric continuous variables, respectively. Normal distribution was assessed by Kolmogorov–Smirnov test. Correlation analysis was performed by Pearson's or Spearman's correlation test. Logistic regression analysis was performed to determine the independent predictors of the presence of CM risk factors (HT, HL, DM, and cigarette smoking) in patients with psoriasis. A value of $P < 0.05$ was considered statistically significant.

Results

Forty patients with psoriasis (22 male, mean age: 43.3 ± 13.8 years) and 40 healthy controls (22 male, mean age:

39.3 ± 8.9 years) were enrolled in the study. The mean disease duration of patients with psoriasis was 153.3 ± 112.7 months, and the mean PASI score of the patients with psoriasis was 14.5 ± 9.3. Previous medications of patients with psoriasis were as follows: topical treatment in 22.5%, oral retinoid in 20%, photo(chemo)therapy in 5%, methotrexate in 27.5%, cyclosporine in 5%, etanercept in 10%, and infliximab in 7.5% of cases. Six patients had psoriatic arthritis. The baseline characteristics and clinical data of the study population are shown in Table 1.

Intra-assay variation was found to be 12.63% at a mean concentration of 5.20 ± 0.66 ng/mL for GAS6 ELISA method. Inter-assay variation was 13.97% at a mean concentration of 9.17 ± 1.28 ng/mL. Recovery was evaluated by addition of GAS6 into human plasma at five different concentrations (40, 20, 10, 5, and 2.5 ng/mL). The mean recovery was 104%.

There were no significant differences between the plasma GAS6 levels of patients with psoriasis compared to the control group (6.6 ± 2.0 ng/mL, 7.6 ± 2.8 ng/mL, respectively, $P > 0.05$). However, GAS6 levels of patients with psoriasis who had a smoking history (n = 11) were significantly lower than both patients with psoriasis who had no smoking history (n = 29) and controls (5.5 ± 1.7 ng/mL, 6.9 ± 1.9 ng/mL, 7.6 ± 2.8 ng/mL, respectively, $P < 0.05$) (Figure 1). There was no correlation between the GAS6 level, disease duration, or PASI score ($r = 0.150$, -0.150, and $P = 0.310$, 0.398, respectively).

Patients with psoriasis were evaluated for the presence of conventional CM risk factors including HT, HL, DM, and cigarette smoking. Patients with one or more CM risk factors had significantly lower GAS6 levels compared to the patients without CM risk factor (5.7 ± 1.7 vs. 7.3 ± 2.0 ng/mL, $P < 0.01$) (Figure 2). Correlation analysis revealed that the number of CM risk factors (HT, DM, HL, or cigarette smoking) was inversely correlated with GAS6 levels ($r = -0.335$, $P = 0.034$). Logistic regression analysis was performed to determine the predictors of the presence of CM risk in patients with psoriasis (Table 2). Plasma GAS6 levels independently predicted the presence of CM risk factors in patients with psoriasis.

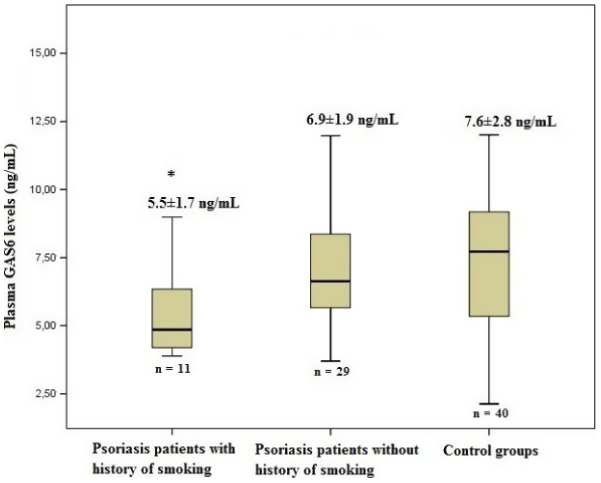

Figure 1 Comparison of GAS6 levels among psoriasis patients with smoking history, psoriasis patients without smoking history and controls. *$P < 0.05$.

Discussion

In this article, we studied a novel vascular and endothelial biomarker of GAS6, together with conventional CM risk factors, in patients with psoriasis. Although substantial advances have been made in defining the molecular mechanisms of psoriasis, major issues remain unresolved. These include the status of the disease as epithelial or immunologic, the autoimmune root of the inflammation, the balance of cutaneous versus systemic factors. Also the role of genetic versus environmental influences on disease initiation, progression, and response to therapy are not clear [19]. Psoriasis is characterized by excessive growth and aberrant differentiation of keratinocytes [20]. The trigger of the keratinocyte response is thought to be activation of the cellular immune system, with T cells, dendritic cells, and various immune-related cytokines and chemokines contributing to pathogenesis. The precise molecular mechanisms for increased CM risk in psoriasis remain unclear.

Psoriasis might be the optimum milieu to observe the biological effects of GAS6. Vascular inflammation and/or the conventional CM risk factors may result in an increased CM risk in patients with

Table 1 Baseline characteristics and clinical data of the study population

	Patients with psoriasis (n = 40)	Control group (n = 40)	*P* value
Age, years	43.3 ± 13.8	39.3 ± 8.9	0.130
Male gender, n (%)	22 (55)	22 (55)	1.0
Hypertension, n (%)	6 (15)	0 (0)	**0.010**
Diabetes mellitus, n (%)	4 (10)	0 (0)	**0.041**
Hyperlipidemia, n (%)	11 (27.5)	0 (0)	**<0.001**
Smoking, n (%)	11 (27.5)	0 (0)	**<0.001**

Data are presented as mean ± standard deviation or number of patient (%). Bold values indicate statistical significance $P < 0.05$.

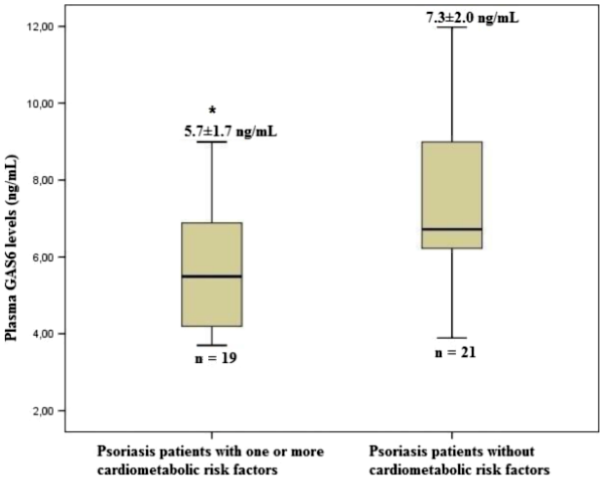

Figure 2 Comparison of GAS6 levels between psoriasis patients with or without cardiometabolic risk factors. *$P < 0.05$.

Table 2 Logistic regression analysis to determine the independent predictors of the presence of cardiometabolic risk factors in patients with psoriasis

	Odds ratio (OR)	95% Confidence interval for OR	*P* value
Age (years)	0.976	0.917–1.038	0.431
Gender (male)	0.205	0.036–1.172	0.075
Duration of psoriasis (months)	1.000	0.993–1.007	0.997
PASI Scores	1.044	0.951–1.147	0.366
GAS6 Levels (ng/mL)	1.781	1.014–3.126	**0.044**

GAS6, Growth Arrest-Specific 6; PASI, Psoriasis Area Severity Index.

psoriasis. In this pilot study, we compared plasma GAS6 protein levels between patients with psoriasis and healthy controls. Plasma GAS6 levels were lower in patients with psoriasis who with at least one CM risk factor such as hypertension, hyperlipidemia, diabetes mellitus, and cigarette smoking than patients with psoriasis who have no CM risk factors, as well as healthy controls (Figure 2).

Our findings support our hypothesis, and the results of Szász et al. [15], an animal model of psoriasis, in which GAS6 was downregulated. Szász et al. studied only mRNAs, not protein patterns. Swindell et al. [21] compared five mouse models of psoriasis. Correspondence to the human disease was strong with respect to the genes involved in epidermal development and keratinization. However, immune- and inflammation-associated gene expression was more variable between models as compared to the human variant of the disease.

The possible mechanisms between vascular risk and psoriasis are the focus of clinical and basic research [22]. The initiation of atherosclerosis is characterized by activation of the vascular endothelium [23]. We previously reported that patients with psoriasis had reduced vascular function [24]. We used an oscillometric technique for the assessment of arterial stiffness parameters and cardiovascular hemodynamics in patients with psoriasis. Patients with psoriasis had significantly higher pulse wave velocity and augmentation index compared to the controls. One possible mechanism is that patients with psoriasis have a higher prevalence of CM risk factors such as DM, HL, and HT [25]. Psoriasis is a chronic inflammatory skin disease. Experimental and clinical data indicate that chronic inflammation is an important risk factor of CVD and accelerated atherosclerosis [26]. Inflammatory markers such as C-reactive protein (CRP) levels are increased in patients with psoriasis compared with controls [6]. In a recent study, Balta et al. [27] demonstrated that patients with psoriasis had higher arterial stiffness which correlated with age, diastolic blood pressure, high-sensitive CRP and body mass index ($P < 0.05$). Yiu et al. [28] reported that high-sensitive CRP was an independent predictor of arterial stiffness in patients with psoriasis. Mechanisms including genetic susceptibility, inflammation, hemostasis dysregulation, and hyperhomocysteinemia provide a link between psoriasis and atherosclerosis [29]. Inflammation, CRP, and a biomarker of vascular calcification, osteopontin, modulate vascular changes in patients with psoriasis. Cao et al. reported that serum myeloperoxidase (MPO) level was elevated 2.5-fold ($P < 0.001$) in patients with psoriasis and correlated with coronary artery calcification, carotid plaque, carotid intima-media thickness and flow-mediated dilation, but did not correlate with psoriasis severity [30].

The coagulation factors are well-known VKDPs, which require carboxylation to become biologically active. GAS6 has no function in the coagulation cascade although it shares 44% homology with protein S, an anticoagulant protein [31]. Warfarin prevents the activation of GAS6, and in animals, induces vascular calcification [7]. GAS6 has favorable effects on leukocyte sequestration and migration, platelet aggregation and hematopoiesis to proliferation, apoptosis, and phagocytosis. All of these functions are associated with conditions of injury, inflammation, and repair [32]. GAS6 and its receptors are involved in the pathogenesis of vascular calcification, vasculitis, and atherosclerosis [33]. Vascular smooth muscle cells continuously produce GAS6 to protect vascular damage. GAS6 regulates both apoptosis and migration of smooth muscle cells into areas of vascular damage. Therefore, a failure to activate GAS6 leads to vascular damage and also forms the coronary calcification [7]. Previous studies have demonstrated that there is a close relationship between decreased GAS6 levels and CAD. Lee et al. [34] reports that the expression of GAS6 considerably higher in the left internal mammary artery (LIMA) than the aorta in patients with undergoing coronary artery bypass grafting (CABG). The higher expression of GAS6 in the LIMA compared to aorta may explain the less frequent atherosclerotic events in the LIMA than other arteries. In another study, GAS6 levels are reported to be significantly lower in patients with undergoing CABG than controls [35]. Jiang et al. [36] reports that the median plasma GAS6 levels are significantly lower in patients with acute coronary syndrome than healthy controls. GAS6 is highly expressed by endothelial cells in atherosclerosis-prone areas of the vascular tree. There is evidence that GAS6 has a pivotal role in endothelial cell activation and participates in the interactions between endothelial cells, platelets, and leukocytes during inflammation [37].

GAS6/TAM receptor signaling amplifies pro-inflammatory endothelial cell activation. In contrast to supporting the inflammatory response, this signaling inhibits inflammation by multiple mechanisms including phagocytosis. The clearance of apoptotic cells is critical for both tissue homeostasis and the resolution of inflammation. TAM receptors are expressed on phagocytes such as dendritic cells and macrophages. GAS6 binds to both TAM receptors on the surface of phagocytes and to the phosphatidylserine expressed on the surface of apoptotic cells [12].

Mouse model studies have led to contradictory results regarding the pro- or antiatherogenic properties of GAS6, and relatively few data are available in human pathophysiology [38,39]. GAS6 did not affect adhesion of granulocytes to resting endothelial cells, while it inhibited granulocyte adhesion to tumor necrosis factor-alpha-activated endothelial cells [40].

The signaling pathways activated during the removal of apoptotic cells versus Toll-like receptor inhibition remain to be contrasted [41]. As mentioned above, the GAS6/TAM receptor signaling plays a role in a variety of diverse, and even controversial, cellular mechanisms such as proliferation, differentiation, development, survival, crosstalk, and apoptosis.

Recently, plasma GAS6 is reported to be elevated in patients with SLE [42–45] and severe sepsis [46]. SLE is an autoimmune

disease, characterized by a deficiency in the clearance of apoptotic cells by macrophages. Some studies indicated that GAS6 is associated with a SLE disease activity score [42,43] whereas others showed only with specific clinical manifestations [44,45]. Similar to some other autoimmune diseases, in this article we have not found correlation between the GAS6 level, disease duration or PASI score. However, psoriasis patients with at least one CM risk factor showed lower GAS6 levels compared to subjects without any CM risk factor. As the function of GAS6 remains largely undetermined and controversial, it is difficult to interpret plasma GAS6 levels in psoriasis with our current understanding of GAS6/TAM signaling. There is an urgent need for comprehensive studies to better understand the underlying mechanisms and clinicpathologic correlations for psoriasis and atherosclerosis in humans.

Study Limitations

Our study has several limitations. Little is known on the distribution of GAS6, particularly, its relation to various CM risk factors. Firstly, this study is cross-sectional and the sample size is small. Although we measure GAS6 in this cross-sectional study, we do not have follow-up, and therefore, we do not have prospective change in GAS6 levels in these patients. Many confusing variables can affect GAS6 levels in patients with psoriasis. In this study, we did not observe any discerning correlation between GAS6 levels and echocardiographic indices of aortic calcification, that is, aortic flow velocity. Future large scale, prospective studies are needed to confirm that low plasma levels of GAS6 may be a novel biomarker of CM risk in patients with psoriasis.

Conclusions

This study provides, to the best our knowledge, the first evidence in human for an association between plasma GAS6 levels and conventional risk factors in psoriasis. Our study indicates that psoriasis patients with CM risk have low plasma GAS6 levels. This pilot study may cause further studies to elucidate the central role of GAS6 in the pathophysiology of coronary calcification in psoriasis and smoking.

Acknowledgment

None.

Conflict of Interest

The authors declare no conflict of interest.

Author contributions

All the authors have contributed equally to this article.

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