Original Article

The Role of Salusins and Interleukin 12 Family in the Rosacea Pathogenesis

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Abstract

Aim: Salusins and recently discovered interleukin (IL)-12 family members (IL-35 and IL-39) have been investigated in various disorders associated with chronic inflammation. The aim of this study was to evaluate the roles of salusin-alpha (α), salusin-beta (β), IL-35, and IL-39 in the pathogenesis of rosacea. **Methods:** This study is a single-center, prospective case–control study performed in a tertiary healthcare institution. Salusin-α, salusin-β, IL-35, and IL-39 were analyzed by enzyme-linked immunosorbent assay method from venous blood of 50 rosacea patients who did not receive any treatment and 50 age-matched healthy controls, and the test results were compared between the two groups as statistically. **Results:** Patients in the rosacea group (female:male ratio = 1.9:1; median age: 56 years) had significantly higher mean salusin-α, IL-35, and IL-39 levels compared with the control group (female:male ratio = 2.1:1; median age: 41 years). There was no statistically significant difference between the two groups in terms of salusin-β levels. **Conclusion:** The increased vascularity and Th1-mediated inflammation might be possible explanations for the elevated salusin-α and IL-39 levels in rosacea patients. On the other hand, the higher mean IL-35 level detected in the same group was an unexpected finding due to the immunosuppressive effect of the cytokine. Recently, targeted therapies have become popular in many inflammatory diseases. In this context, salusins, IL-35, and IL-39 seem to be possible molecules that could be modified for therapeutic reasons in the future in the treatment of rosacea.

Keywords: Interleukin 12, interleukin 35, interleukin 39, rosacea, salusin-α, salusin-β

Introduction

Rosacea is a chronic inflammatory cutaneous disorder that usually occurs in adults between 20 and 50 years old.[1-3] The etiopathogenesis of rosacea is poorly understood. Genetic predisposition, environmental triggers, immune dysregulation, inflammatory reactions to cutaneous microorganisms, neurovascular dysregulation, and vascular dysfunction are the possible underlying factors. Various triggers are known to aggravate rosacea symptoms, such as ultraviolet exposure, diet, smoking, alcohol consumption, obesity, and stress.[4-7]

In addition, rosacea has been associated with several disorders such as inflammatory bowel disease, malignancies, metabolic, autoimmune, allergic, urogenital, and cardiovascular disease (CVD).[8,9] However, there is no clear explanation for these associations. The chronic inflammatory nature of rosacea and the vascular dysfunction in its pathogenesis might play a central role in the development of comorbid disorders.[8]

Salusin-alpha (α) and salusin-beta (β) are mediators that were first identified in the human embryo and are expressed in a variety of tissues, including vascular tissues.[10] In studies conducted on psoriasis vulgaris, rheumatoid arthritis (RA), and CVD, it has been reported that salusin levels differed in patient groups compared with the controls.[11-13] Thus, there may be changes in salusin levels in rosacea, as well.

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Interleukin (IL)-35 and IL-39 are recently discovered ILs belonging to the IL-12 family.[14,15] IL-35 generates an immunosuppressive effect by increasing T-regulatory (Treg) cell proliferation and inhibiting T-helper (Th) 17 cell differentiation.[15] IL-39 is another proinflammatory cytokine whose expression is increased in some chronic inflammatory skin disorders such as psoriasis and atopic dermatitis.[16]

To the best of our knowledge, the salusin-α, salusin-β, IL-35, and IL-39 levels have not been studied in patients with rosacea. We aimed to define the relationship between the levels of salusin-α, salusin-β, IL-35, IL-39, and rosacea.

Materials and Methods

Fifty patients with rosacea who were followed up at 2–3 months intervals in our tertiary dermatology outpatient clinic were enrolled in the study as the patient group, whereas 50 subjects from a similar age group were included in the control group. None of the subjects in the patient group had received topical or systemic treatment for rosacea. The exclusion criteria were tobacco consumption (including passive smoking), history of any chronic inflammatory disorder, known malignancy or active acute/chronic infection, and use of corticosteroids or other immunosuppressive therapy. Written and verbal consent of the patients, who voluntarily agreed to participate, was taken before the study.

Serum samples were obtained from the patients and the control group from the venous blood. Salusin-α, salusin-β, IL-35, and IL-39 were studied by enzyme-linked immunosorbent assay method. The test results were statistically compared between the two groups. SPSS program for Windows, Version 14.0. (SPSS Inc., Chicago, IL, USA) was used for the statistical evaluation, and $P < 0.05$ was accepted as statistically significant.

The study has been approved by the Ethics Committee of Çanakkale Onsekiz Mart University Faculty of Medicine (approval date/number: 23.09.2020/12-29). The financial source of the study was provided by Çanakkale Onsekiz Mart University Scientific Research Projects Unit with project number 3542.

Results

The demographic profile and clinical characteristics of the subjects in the rosacea and control groups are summarized in Tables 1 and 2, respectively.

Among 50 patients in the rosacea group, 33 were female, and 17 were male (female:male ratio = 1.9:1). The median age of the rosacea group was 56 years (age range: 32–79). In the control group, 34 were female, and 16 were male (female:male ratio = 2.1:1), with a median age of 41 years (age range: 28–70). Hypertension (HT) (n = 5; 10%), diabetes mellitus (DM) (n = 5; 10%), and hyperlipidemia (HL) (n = 1; 2%) diagnoses were present in the patient group.

The median disease duration in rosacea patients was 8.5 years (range: 1–35 years). Erythematotelangiectatic rosacea (n = 38;76%) was the predominant subtype, whereas ocular rosacea was the least commonly observed phenotype (n = 3; 6%). The Malar region was exclusively involved.

The mean salusin-α, IL-35, and IL-39 levels were significantly higher in the rosacea group compared with the control group. However, there was no statistically significant difference between the two groups regarding salusin-β levels [Figure 1 and Table 3].

Discussion

Salusins are recently discovered bioactive peptides associated with oxidative stress. They are biosynthesized from prosalusin under the influence of tumor necrosis factor (TNF)-α, which is generated by triggered inflammatory cells.[17,18] Conflicting results were presented in the literature regarding the salusin levels in the context of disorders, in which oxidative stress and TNF-α play a significant role. These are particularly CVD and other inflammatory disorders such as RA, multiple sclerosis, and psoriasis, which are demonstrated to coexist with rosacea.[10,11,13,19-21]

The antiatherogenic effect of salusin-α and proatherogenic effect of salusin-β have been established in the light of the study reporting elevated salusin-β and reduced salusin-α levels in atherosclerotic diseases.[21] Correspondingly, Erden *et al.*[11] observed lower salusin-α and higher salusin-β levels in psoriasis patients compared with the control group.

Table 1: Demographic characteristics of the rosacea and control groups

Characteristics	Rosacea (n = 50)	Control (n = 50)	P value
Age (years) median (range)	56 (32–79)	41 (28–70)	**<0.001**
Gender, *n* (%)			
Female	33 (66)	34 (68)	0.832
Male	17 (34)	16 (32)	
Concomitant disease, *n* (%)			
DM	5 (10)	0 (0)	**<0.001**
HT	5 (10)	0 (0)	
HL	1(2)	0 (0)	
Family history, *n* (%)			
Yes	50 (100)	50 (100)	
No	0 (0)	0 (0)	
Smoker, *n* (%)			
Yes	50 (100)	50 (100)	
No	0 (0)	0 (0)	
Alcohol intake, *n* (%)			
Yes	50 (100)	50 (100)	
No	0 (0)	0 (0)	

DM: diabetes mellitus, HL: hyperlipidemia, HT: hypertension, SD: standard deviation.

Statistically significant values are highlighted in bold

Rosacea is a systemic disorder that might coincide with other inflammatory disorders. Vascular dysregulation, immune function impairment, increased oxidative stress, and TNF-α are implicated in its pathogenesis.[1-4] A meta-analysis of 13 studies on 50,442 subjects evaluating the relationship between rosacea and metabolic syndrome revealed an association of rosacea with HT and HL. However, no clear relation was identified with DM or CVD.[22] In our rosacea patients, DM (n = 5), HT (n = 5), and HL (n = 1) diagnoses were present, whereas they were not detected in the control group. Spoendlin *et al.*[23] reported decreased rosacea risk in patients with advanced DM. Since vasodilation is a major component of rosacea, they attributed this finding to insufficient vasodilatation frequently encountered in these patients.[23] In another study, the ultrasonographical examination of the vascular structures in the facial region of rosacea patients reported no occlusion, unlike in atherosclerosis, but an increased dermal and hypodermal vascularity compared with the control group.[24] This might be a possible explanation for the elevated salusin-α levels in our rosacea patients.

Table 2: Disease characteristics of the rosacea group

Parameters	Values
Age of onset (years) median (range)	44 (27–61)
Disease duration (years) median (range)	8.5 (1–35)
Rosacea subtype, *n* (%)	
Erythematotelangiectatic	38 (76)
Papulopustular	4 (8)
Ocular	3 (6)
Phymatous	5 (10)
Anatomical localization of lesions, *n* (%)	
Forehead	24 (48)
Nose	46 (92)
Malar region	50 (100)
Chin	21 (42)
Eyes	3 (6)
Others	0 (0)
Treatment use for rosacea in the last 3 months, n (%)	
No	50 (100)
Yes	0 (0)

SD: standard deviation

Similarly, Özgen *et al.*[13] observed high salusin-α levels in RA and Behçet disease (BD), whereas in another study, they conducted on systemic lupus erythematosus (SLE) and systemic sclerosis (SS) patients salusin-α levels were reported to be low.[25] Researchers have suggested that salusin-α might play a role in the inflammatory pathway of Th1-mediated diseases because RA and BD are Th1-dependent, whereas SLE and SS are Th2-dependent.[13] Th1-mediated inflammation in the rosacea pathogenesis might be another reason for the elevated salusin-α levels in the rosacea group of our study.

Besides their impact on the hemodynamic system and atherosclerosis pathogenesis, salusins exhibit mitogenic activities. Salusin-β induces the expression of growth-related genes such as c-myc and c-fos.[17] It also stimulates the proliferation of vascular smooth muscle cells, fibroblasts, and muscle cells.[17] The antiapoptotic effects of the salusins were established in the study of Xiao-Hong *et al.*[26] as well. Considering the high salusin-α levels in our study, it might be suggested that salusins stimulate the growth and proliferation of inflammatory cells and induce inflammation by inhibiting apoptosis in rosacea. Meanwhile, the augmented vascularization in areas of intense erythema may be attributed to the same mechanism.

Another major outcome of our study was the higher levels of IL-35 and IL-39 in the rosacea group compared with the control group. IL-35 is among the recently identified members of the IL-12 family. It is mainly secreted from

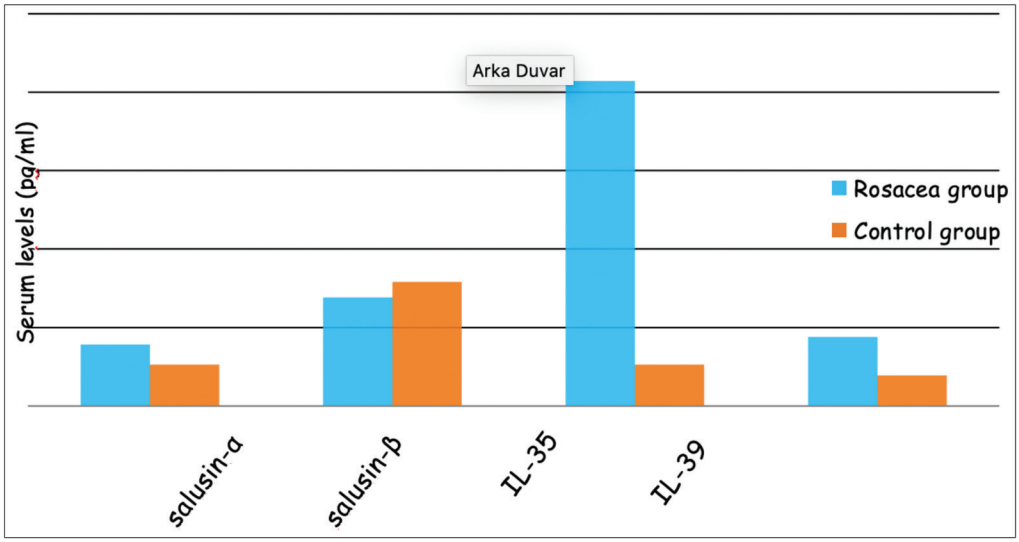

Figure 1: Salusin-alpha, salusin-beta, interleukin-35, and interleukin-39 levels in rosacea and control groups

Table 3: Comparison of rosacea and control groups regarding salusin-alpha, salusin-beta, interleukin-35, and interleukin-39 levels

Variables	Rosacea	Control	Total	*P* value
	n = 50 (50%)	*n* = 50 (50%)	*n* = 100	
Salusin-alpha[a] (pg/mL)	784.532 ± 272.112	529.972 ± 198.694	254.559 ± 47.649	**<0.05**
Salusin-beta[a] (pg/mL)	1386.508 ± 516.870	1585.547 ± 263.436	413.759 ± 98.343	0.414
Interleukin-35[a] (pg/mL)	4142.590 ± 662.478	529.972 ± 198.694	2557.043 ± 100.82	**<0.05**
Interleukin-39[a] (pg/mL)	881.561 ± 358.634	391.597 ± 104.891	489.963 ± 52.843	**<0.05**

[a]Data represented as mean ± SD.

Statistically significant values are highlighted in bold

Treg cells. By increasing Treg proliferation and preventing Th17 differentiation, IL-35 suppresses the release of IL-17 and consequently causes immunosuppression.[27,28] Thus, it has been investigated in disorders such as RA, psoriasis, SLE, SS, and dermatomyositis, in which Th17 plays a role in the inflammatory cascade, and contradictory results have been reported.

The majority of the studies on psoriasis and RA showed low levels of IL-35, as expected.[29-33] On the other hand, in several reports of SLE, SS, and dermatomyositis patients, IL-35 was detected at higher levels than controls.[34] In two further studies, patients with inactive SLE were shown to have higher IL-35 values than the ones with active SLE,[35,36] whereas Qiu *et al*.[37] noted a decline in IL-35 levels in their SLE patients following systemic corticosteroid therapy. A similar inconsistency prevails regarding IL-35 levels in the setting of SS. The higher IL-35 levels were detected in SS patients with pulmonary fibrosis compared with individuals without pulmonary fibrosis.[38] However, another study revealed elevated IL-35 levels in early phase SS compared with the late phase.[39]

Similar to SLE patients, Zdanowska *et al*.[31] observed a reduction in IL-35 levels in psoriasis patients managed with adalimumab therapy compared with pretreatment values. The conflicting data on the IL-35 levels in the disorders mentioned above with similar pathogenetic mechanisms might be due to the fluctuations in the disease activity and immunosuppressive treatments employed. The significantly higher mean IL-35 level in our rosacea patients was also an unexpected finding, which necessitates further investigation.

IL-39 is another newly discovered member of the IL-12 family. It has a heterodimeric structure consisting of IL-23p19 and Ebi3 subunits. Unlike IL-35, IL-39 has a proinflammatory effect. IL-39 is mainly secreted from B cells stimulated with lipopolysaccharide, whereas other immune cells such as dendritic cells and macrophages have been reported to express IL-39 mRNA.[40,41]

A limited number of studies are present on IL-39 in the literature, each highlighting a different action of the molecule. Luo *et al*.[41] reported an increase in IL-39 levels in patients with acute coronary syndrome compared with the control group. The Ebi3 subunit was detected at lower levels in SS patients than the controls in another study. The authors concluded that this led to increased collagen deposition and fibrosis.[42] IL-39 levels were significantly higher in the rosacea group in our study, which had been expected due to its proinflammatory effect.

The limitation of our study is the limited number of patients, whereas the prospective case-control design is its main strength.

Conclusion

The increased vascularity and Th1-mediated inflammation might be possible explanations for the elevated salusin-α and IL-39 levels in rosacea patients, whereas the higher mean IL-35 level detected in the same group was an unexpected finding. The targeted therapies have become popular for inflammatory disorders as the underlying pathogenetic mechanisms are increasingly clarified. Salusins, IL-35, and IL-39 seem to be possible molecules that might be modified for therapeutic reasons in the future. Further large-scale studies are warranted to draw more precise conclusions.

Ethical statement

The study was approved by the Clinical Research Ethics Committee of Çanakkale Onsekiz Mart University Rectorate (approval date: 23.09.2020, approval no:12-29)

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflict of interest

There are no conflicts of interest.

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