Evaluation of Serum Fetuin-A and Osteoprotegerin Levels in Patients with Psoriasis

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Abstract Psoriasis patients are determined to have a high ratio of coronary artery calcification. Fetuin-A and osteoprotegerin are systemic calcification inhibitors and related to vascular calcification and cardiovascular mortality. In this study we investigated the relationship between fetuin-A and osteoprotegerin levels in psoriasis patients. The study included 40 healthy volunteers and 40 psoriasis patients. Venous blood were collected from healthy volunteers and psoriasis patients in order to search the fetuin-A and osteoprotegerin levels. Disease severity were grouped as mild, moderate and severe according to psoriasis area and severity index (PASI). The relationship between fetuin-A and osteoprotegerin levels and clinical features as sex, PASI and presence of psoriatic arthritis were analyzed. Fetuin-A levels in psoriasis patients were statistically lower than the control group ($p < 0.001$). In serum osteoprotegerin levels, no statistically significant difference was found in two groups ($p > 0.05$). Serum fetuin-A and osteoprotegerin level differences were not statistically significant between patients with psoriatic arthritis history and those without. When we grouped patients in respect of their sexes fetuin-A and osteoprotegerin levels of males and females were not significantly

different ($p > 0.05$). No correlation was detected between the ages and PASI scores and the fetuin-A and osteoprotegerin levels of patients. As a result fetuin-A levels in psoriasis patients are found to be low but not related to disease severity. In the light of our results we concluded that fetuin-A may have a role in psoriasis pathogenesis and may contribute to the calcification process developed in psoriasis.

Keywords Psoriasis · Fetuin-A · Osteoprotegerin

Introduction

Psoriasis is one of the inflammatory skin diseases, which is characterized by sharply demarcated, erythematous squamous plaques. Genetical, immunological and environmental factors are thought to play a role in the etiology. Characteristics of psoriasis are hyperproliferation of keratinocytes, infiltration of inflammatory cell in dermis and epidermis, vasodilatation of dermal vessels [1]. While the patients with psoriasis were analyzed in terms of coronary calcification, which is related to cardiovascular disease progression, was determined to have a high risk [2].

Changes which affect calcium and phosphate levels in the extracellular fluid, are risk factors for pathological calcification and mineralization. Fetuin-A is a glycoprotein that is known as $\alpha 2$ -Heremans-Schmid and can attach to the cationic calcium ions [3]. Fetuin-A can prevent calcification by forming soluble complexes with calcium and phosphate, which are called “calciprotein particles”. For this reason, Fetuin-A has been proposed as an endogenous inhibitor of pathological mineralization or calcification of soft tissues [4, 5]. Studies with mice devoid of fetuin-A suggested that, more soft tissue calcification has occurred.

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The low level of Fetuin-A has been also found to be associated with vascular calcification [4, 6].

Osteoprotegerin is a glycoprotein from the family of TNF receptors (TNFR) which are defined in the regulation of bone resorption [7]. It has been shown that osteoprotegerin is synthesized in different cell types such as great media of the arteries, coronary artery smooth muscle and vascular endothelial cells [8, 9]. Osteoprotegerin can be found as soluble in both circulation and wall of vessels. The function of this molecule is known as inhibition of osteoclastic differentiation and activation by connecting to the receptor activator nuclear kappa B (RANK) molecules which locate on osteoclastic precursors and prevent the interaction of RANKL and RANK [7, 10]. Synthesis of osteoprotegerin can be increased by endothelial cell injury, intimal hyperplasia, smooth muscle cell hypertrophy and calcification secondary to advanced plaques in the vascular system [11]. Large artery calcifications are determined in osteoprotegerin-deficient mice [8].

Our aim is to investigate the changes of levels in the blood of these two molecules that play an important role in the metabolism of calcification, in patients with psoriasis.

Materials and Methods

The study population consisted of 40 psoriasis patients (20 males and 20 females) all of whom had been referred to the Department of Dermatology. Forty healthy control subjects were also enrolled in the present study. The subjects with present or past history of any disease like atherosclerosis, coronary heart disease, diabetes mellitus, chronic renal disease, chronic liver disease, any systemic therapy persons etc. were excluded from the study. This research project was approved by institutional ethical committee. The volunteers and the psoriasis patients were properly informed about the project and included in the research work after their consent. The patients enrolled in the present study were questioned regarding age, gender, age of onset, duration of disease, height, weight, body mass index (BMI). BMI was calculated as weight/height (kg/m^2). The control group comprised age, sex, and BMI matched individuals who did not have any systemic or neurological diseases.

The disease, psoriasis was diagnosed by clinical signs and symptoms as Auspitz sign, erythema, itching, thickening and scaling of the skin. Histopathological examination was done whenever needed to confirm the psoriasis. Psoriasis Area and Severity Index (PASI) score was used to determine the severity and patients were grouped as mild, moderate and severe psoriasis. Blood samples were collected at 09.00–10.00 in the morning after an overnight fast to avoid any effects associated with circadian rhythm.

Samples were centrifuged at $3000 \times g$ for 5 min. The sera obtained were transferred to eppendorf tubes and frozen at -80°C until the day of analysis. Serum fetuin-A levels were studied using a Human Fetuin-A kit (Booster, CA, USA) by the enzyme-linked immunosorbent assay (ELISA) method according to the manufacturer's instructions. Serum osteoprotegerin levels were studied using a Human osteoprotegerin kit (Booster, CA, USA) by the ELISA method according to the manufacturer's instructions.

All data were expressed as mean $\pm$ SD. Statistical analysis were performed using the SPSS (Statistical Package for Social Sciences Inc., Chicago, IL, USA) 13.0 software package. Analysis of variance was used to estimate the difference between means. The Student-*t* test was used to compare two independent means, and the χ^2 test was used to compare categorical variables. The correlation between clinical and biochemical parameters was calculated using Pearson's correlation coefficient. *p* value <0.05 was considered statistically significant.

Results

The study population consisted of 40 patients with psoriasis who presented at the Dermatology Polyclinics. Forty healthy volunteers were also included in the control group. The mean ages of the participants were 42.7 ± 14.0 years for the patients with psoriasis and 43.0 ± 11.0 years for the control subjects. The female-to-male ratio (F/M) was 20/20 in all groups. There were no significant differences between the groups in terms of mean age or gender ($p > 0.05$). Similarly, there was no significant difference in BMI between the psoriasis and control groups ($p > 0.05$). The demographic characteristics and clinical findings of the two groups are presented in Table 1.

The duration of the disease in psoriasis patients ranged from 1 to 40 years (mean: 13.8 ± 12.0 years). In addition, arthritis involvement was observed in 15 patients (37.5 %). The PASI scores of the patients ranged from 1 to 22 (median: 5.51). PASI scores are presented in Table 2.

The mean serum fetuin-A level was 12.0 ± 2.2 ng/ml in the psoriasis group and 14.6 ± 2.4 ng/ml in the healthy control group, and this difference was significant ($p < 0.001$) (Fig. 1).

The mean serum osteoprotegerin level was 279.3 ± 24.8 pg/ml in the psoriasis group and 273.9 ± 26.3 pg/ml in the healthy control group ($p > 0.05$). There was no significant difference in osteoprotegerin between the psoriasis and control groups ($p > 0.05$) (Fig. 2).

In psoriasis patients, fetuin-A and osteoprotegerin were not significantly related to age or with psoriasis severity as

Table 1 Demographical and clinical findings of groups

		Psoriasis (n = 40)	Controls (n = 40)	<i>p</i>
Age (years)		42.7 ± 14.0 (40.5)	43.1 ± 11.0 (44.0)	0.902
Sex	Female (n:20/20)	40.6 ± 13.8 (40.0)	42.2 ± 11.0 (44.5)	0.341
	Male (n:20/20)	44.9 ± 14.2 (40.5)	43.9 ± 11.2 (43.5)	0.632
BMI (kg/m ²)		28.0 ± 5.52 (26.0)	27.0 ± 5.0 (26.4)	0.402

Mean ± SD (median)

BMI body mass index

Table 2 PASI scores of patients with psoriasis

PASI	n	%
<3 (Mild psoriasis)	14	35
3–15 (Moderate psoriasis)	20	50
>15 (Severe psoriasis)	6	15
Total	40	100

PASI psoriasis area and severity index

Table 3 In psoriasis patients correlation coefficients with serum fetuin-A and osteoprotegerin concentrations

	<i>r</i>	<i>p</i>
Fetuin-A—PASI	0.110	0.501
Osteoprotegerin—PASI	0.186	0.250
Fetuin-A—Age	0.213	0.187
Osteoprotegerin—Age	0.260	0.105
Fetuin-A—Osteoprotegerin	0.008	0.963

PASI psoriasis area and severity index

Fig. 1 Serum fetuin-A levels **Fig. 2** Serum osteoprotegerin levels

measured by PASI (Spearman's rank correlation) (Table 3).

Discussion

Psoriasis is a chronic, inflammatory, skin disease which is characterized by erythematous squamous plaques. Despite being one of the most studied disease in dermatology, etiopathogenesis has not been fully elucidated [1].

In the studies, it was determined that the epidermis had got the presence of a calcium gradient. The high calcium content of the granular layer, low calcium content of basal and spinous layers were also found in these studies [12]. According to the degradation of calcium gradient, increased proliferation is observed in the epidermis of patients with psoriasis [13, 14]. A study of Karvonen et al. [15] has shown that psoriatic keratinocytes have lower levels of ionized calcium stores than normal keratinocytes. Patients' keratinocytes, with lesions and non lesions have the same risk of a congenital defect in calcium metabolism, and this defect in lesional cells were observed to be more.

Fetuin-A is an important, systemic calcification inhibitor, which is synthesized in the liver, has a high affinity for calcium and phosphate. Low fetuin-A serum levels were observed in patients with diabetes, chronic renal failure, hemodialysis and coronary artery disease [4, 16, 17]. In addition, it was determined that fetuin-A deficient

mice could develop soft tissue calcification [6]. Some studies have shown that when fetuin-A deficient mice fed with phosphor and vitamin D-rich diet, they would have diffuse calcifications [18].

The levels of serum fetuin-A in patients with systemic lupus erythematosus (SLE) has been reported as low and to be associated with the activity of the disease [19]. Calcium and inorganic phosphate levels were found to be higher in SLE patients than in healthy controls. A negative correlation was found between fetuin A levels and vascular complications in patients with SLE that was thought to be a marker for vascular diseases [19]. In a study of patients with pseudoxanthoma elasticum, fetuin-A levels were found to be lower than the control group. While the patients were analyzed in terms of gender, higher fetuin-A levels were determined in women. From here, the authors have been suggested that fetuin-A levels could be changed by gender [3]. In juvenile dermatomyositis with or without calcification, no significant differences were observed in the fetuin-A levels among healthy controls. Fetuin-A levels were found to be lower in inverse proportion with age, in children. The early age calcification in patients with juvenile dermatomyositis could have been related with the levels of fetuin A and it was thought that fetuin-A could contribute to the etiology of ectopic calcification [20].

Uysal et al. [21] reported that serum fetuin A levels were elevated in patients with psoriasis in comparison with the healthy individuals. In addition, fetuin A concentrations were positively correlated with PASI score. Gerdes et al. [22] found significant decreased fetuin A levels in all patients with psoriasis compared to controls. They did not find any influence of sex, age and BMI on fetuin A. Also, they did not show any correlation between PASI score and fetuin A levels. They suggest that inflammation may cause this reduction because fetuin A is known as a negative acute phase protein. Our study revealed that fetuin-A levels were significantly lower in patients with psoriasis compared to the control group. However, patients with psoriasis were assessed by the PASI score, which is indicating the severity of disease, it was not observed a significant correlation between PASI scores and fetuin-A levels. These results suggest that, reduction in the levels of fetuin-A develops independently from the severity of psoriasis. However, in our study, fetuin-A levels of the patients were regardless of gender of them. In our study, we could not determine a statistically significant relationship between age and fetuin-A levels and we suggested that age is an ineffective factor on fetuin-A levels in patients with psoriasis.

Osteoprotegerin is synthesized by osteoblasts and bone marrow stromal cells. Furthermore, apart from osteoblasts, it can be synthesized by most tissues such as the cardiovascular system, kidney, lung, gut, bone marrow and by hematopoietic and immune cells [23]. Osteoprotegerin is

defined as a receptor activator of RANK for bone marrow stromal osteoblast and endothelial cells [7]. It competes with RANKL, for the appropriate receptor which is known as RANK. Osteoprotegerin can be found as soluble in both circulation and wall of vessels and may prevent osteoclastogenesis by inhibiting RANKL-RANK interaction, connecting to RANK on osteoclast precursor molecules [7, 10]. Some investigators have shown that osteoprotegerin can be produced in vitro by endothelial cells and smooth muscle cells. In addition, it is also determined that osteoprotegerin of endothelial cells has a role of protection of endothelial cells by binding apoptosis inducing ligand which is related to the tumor necrosis factor [8].

Osteoprotegerin levels have been studied on autoimmune and inflammatory disease such as ankylosing spondylitis, systemic lupus erythematosus, atherosclerosis, cardiomyopathy and chronic hepatitis [24]. In a study of Kwok and his colleagues, osteoprotegerin serum levels were found to be higher in patients with SLE, than in healthy controls [25]. Gris and his colleagues reported that serum osteoprotegerin levels increased in psoriatic arthritis and ankylosing spondylitis [26]. In a study of İlhan and his colleagues, osteoprotegerin serum levels were significantly higher in patients with Behçet, than in healthy controls [27]. In addition, severe osteoporosis and vascular calcification have been shown to improve in the aorta and renal artery of osteoprotegerin deficient mice [28]. Attia and his colleagues have studied at osteoprotegerin serum levels in patients with or without psoriatic arthritis and they have found to be higher in psoriasis patients than in the controls [29].

While these patients were analyzed in terms of arthritis, a statistically significant difference was not found between levels of osteoprotegerin. In the study of Hofbauer et al. [24], it was found that there was not a statistically significant difference in osteoprotegerin serum levels between patients with psoriatic arthritis and control groups. However, when the patients with psoriatic arthritis were evaluated in terms of gender, it was found to be higher levels of osteoprotegerin in female patients than in male patients.

In our study, there is not a statistically significant difference in terms of osteoprotegerin levels between the psoriasis patients and the control group. In addition, when it is analyzed according to the gender, symptoms of arthritis and PASI score that indicates the disease severity, there is not statistically significant relationship between osteoprotegerin levels and those factors. However, low fetuin A levels with insignificant changes in osteoprotegrin indicates that fetuin A levels probably decrease due to the inflammation.

In conclusion, serum fetuin-A levels are detected lower in patients with psoriasis. The difference of osteoprotegerin levels was not detected between the patients with psoriasis and the healthy control group. Also, there are no statistically significant difference patients with psoriasis

and controls compared gender, severity of disease and in terms of arthritis. Further studies to elucidate the link between psoriasis and calcification is required.

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Compliance with ethical standards

Conflict of interest No conflict of interest was declared by the author.

Ethics committee approval Ethics committee approval was received for this study.

Informed consent N/A.

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