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The levels of serum pentraxin3, CRP, fetuin-A, and insulin in patients with psoriasis

S. UYSAL[1], F.M. YILMAZ[1,2], K. KARATOPRAK[1], F. ARTÜZ[3], N.U. CUMBUL[3]

[1]Clinic of Biochemistry, Ankara Numune Education and Research Hospital, Ankara, Turkey
[2]Department of Biochemistry, Yıldırım Beyazıt University Medical Faculty, Ankara, Turkey
[3]Clinic of Dermatology, Ankara Numune Education and Research Hospital, Ankara, Turkey

Abstract. – OBJECTIVE: The objective of this study was to evaluate the relationship between disease severity and biochemical parameters such as pentraxin3, CRP, fetuin-A, insulin and HOMA-IR levels in patients with psoriasis.

PATIENTS AND METHODS: This study included 58 patients with psoriasis and 30 healthy controls admitted to Ankara Numune Teaching and Research Hospital between January 2011-August 2012. Serum pentraxin3, CRP, fetuin-A and insulin concentrations were determined. Also, HOMA-IR values were calculated.

RESULTS: The serum values for CRP, insulin, HOMA-IR, pentraxin-3 and fetuin-A in patients with psoriasis were elevated than control subjects (*p* values = 0.002, 0.003, 0.003, 0.006 vs 0.007, respectively). According to the PASI score, patients were divided into three groups, minimal, moderate and severe psoriasis. There were positive correlation between the levels of CRP and insulin, HOMA-IR, PASI score. In addition, PASI score values were positively correlated with insulin, HOMA-IR and fetuin-A levels.

CONCLUSIONS: Elevated levels of pentraxin3, CRP, fetuin-A, insulin and HOMA-IR might play a role in the pathogenesis of psoriasis. Higher CRP, fetuin-A, insulin and HOMA-IR concentrations were associated with the severity of the psoriasis.

Key Words:
Psoriasis, PASI score, Pentraxin3, C-reactive protein, Fetuin-A, Insulin, HOMA-IR.

Introduction

Psoriasis is a chronic, inherited, and autoimmune inflammatory skin disorder affecting approximately 2-3% of the general population. The pathogenesis of psoriasis is not well understood, but genetic, environmental and immunologic factors are known to be involved in the development of the disease[1,2].

Psoriasis is associated with an increased risk of systemic chronic comorbidities such as diabetes mellitus, obesity, hypertension and metabolic syndrome[3]. Patients with psoriasis also have a high prevalence of cardiovascular disease (CVD)[4]. It has been suggested that inflammatory process which is shown with the elevation of C-reactive protein (CRP) contributes development of CVD in psoriatic patients[5].

The long pentraxin, pentraxin-3 (PTX-3), is an inflammatory marker and a member of pentraxin superfamily which contains CRP and serum amyloid P. Some inflammatory mediators like lipopolysaccaride (LPS), IL-1β and TNF-α induces PTX-3 production at dendritic cells, macrophages, fibroblasts, vascular endothelial cells, adipocytes and other tissues. PTX-3 not only regulates inflammatory responses, but plays an important role in innate immunity and female fertility[6,7]. Several studies have examined that plasma PTX3 concentrations are increased in patients with CVD[8,9]. Moreover, patients with severe psoriasis are reported to have higher PTX3 levels than healthy controls and mild psoriasis[7].

Fetuin-A is a glycoprotein synthesized by the liver which induces insulin resistance inhibiting the insulin receptor tyrosine kinase in hepatocytes and skeletal muscle cells. High circulating fetuin-A has been linked to obesity, insulin resistance, risk of diabetes, in patients with non-alcoholic liver disease and chronic kidney disease[10]. There is an inverse correlation between fetuin-A concentrations and calcified coronary artery disease; however, the role of fetuin-A in cardiovascular system is still a bit unclear[11].

As a low grade systemic inflammatory disease obesity may contribute to development and worsening of psoriasis. The adipose tissue can lead to insulin resistance by producing adipokines and cytokines[12].

Therefore, we speculated that PTX3, CRP, fetuin-A, insulin and HOMA-IR might also have a role in the pathogenesis of psoriasis. The aim of

Corresponding Author: Sema Uysal, MD; e-mail: dr_semauysal@hotmail.com

this study was to evaluate a possible link between the severity of the disease and these parameters in psoriatic patients.

Patients and Methods

Patients

This study was conducted at Ankara Numune Teaching and Research Hospital between January 2011-August 2012 with approval of the local Ethics Committee and suitable with the Declaration of Helsinki. All individuals provided written informed acceptance. Fifty-eight patients {32 women and 26 men, median age (min-max) 43.5 (18-71)} with the diagnosis of psoriasis, and thirty age-matched healthy controls (15 women and 15 men, median age (min-max) 39 (20-68), were included in our study. The cases with psoriasis were looked over and diagnosed by the dermatologists based on clinical examination. The severity of the disease was assessed according to Psoriasis Area and Severity Index (PASI) and the patients with psoriasis were divided into three groups: 12 patients with minimal psoriasis (PASI < 3), 30 patients with moderate psoriasis (PASI = 3-10) and 16 patients with severe psoriasis (PASI > 10). PASI score ranged from 1.2 to 33.6 and median for PASI was 5.75. The exclusion criteria were: acute circumstance such as abdominal pain, febrile illness, history of myocardial infarction and cerebrovascular accident, other auto-immune diseases, malignancy, pregnancy and breastfeeding. The age and gender of matched healthy subjects also were examined by the dermatologists who have assured that the control subjects have not any psoriatic lesions or psoriasis history.

Laboratory Analysis

After a 12-hour fasting period, peripheral venous blood samples were collected, centrifuged at 4000 rpm for 10 minutes and stored at -80°C. All samples were thawed only once before analyses. C-reactive protein (CRP), glucose, total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL), uric acid, and insulin levels were determined. Serum CRP, glucose, uric acid and lipid parameters were analysed in a Roche Modular P analyser with the original reagents (Cobas P800, Roche Diagnostics, Mannheim, Germany). Low density lipoprotein (LDL) levels were calculated using the Friedewald formula[13]. We measured insulin levels by an electrochemiluminescent method in a Roche Cobas e601 analyzer with reagents from the manufacturer (Roche Diagnostics, Mannheim, Germany). Pentraxin 3 and fetuin-A serum levels were determined quantitatively by enzyme linked immunesorbent assay (ELISA) with an ELISA microplate strip washer (ELX50; BioTek Instruments, Vinooski, VT, USA) and ELISA microplate reader (ELX808; BioTek Instruments, USA). Pentraxin 3 was studied using a commercially available kit from R&D Systems (Minneapolis, MN, USA). In this assay system, the intra-assay and inter-assay coefficient of variation were always under 10%. The minimum detectable dose of pentraxin 3 ranged from 0.007-0.116 ng/mL. The concentration of fetuin-A was measured with ELISA kits from Epitope Diagnostics (San Diego, CA, USA). The analytical sensitivity of the human fetuin-A ELISA as determined by the 95% confidence limit on 20 duplicate determination of zero standard was 5.0 ng/mL. The inter-assay and intra-assay coefficients of variation for in fetuin-A were 6.8% and 5.5%, respectively.

Statistical Analysis

A statistical analysis was performed using IBM SPSS Statistics Version 17 (SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normality by the Kolmogorov-Smirnov test/Shapiro-Wilk test. Values were presented as mean ± standard deviations or, in the case of non-normally distributed data, as median with data range (minimum to maximum). Chi-square test was used for intergroup comparisons. Independent Samples *t* test or Mann-Whitney U-test was used for comparison between the two groups. The mean differences among groups were compared by one-way ANOVA. Otherwise, the Kruskal-Wallis test was used for comparisons of median values. When the p values from the one-way ANOVA or Kruskal-Wallis test statistics were statistically significant, a *post hoc* Tukey HSD or Conover's non-parametric multiple comparison test were used to determine which groups differed from which others. Spearman's rank correlation test was used for correlation and relation between indicated parameters. A p value < 0.05 was considered to indicate statistical significance. The Bonferroni adjustment was used for all multiple comparisons, to control type I errors.

Results

58 patients with psoriasis and 30 healthy subjects were included in this study. There were no sig-

nificant differences for age and sex among groups (Table I). Distribution of clinical types of patients were as follows: 70.7% of patients with plaque type (n = 41), 15.5% palmoplantar type (n = 9), 12.1% guttate type (n = 7) and 1.7% inverse type (n = 1). There were 8 patients with psoriatic arthritis (13.79%). The number of untreated patients was 6 (10.3%). 38 of 52 patients were treated with topical corticosteroid (65.5%), 8 patients were treated systemic therapy (13.8%) and 6 patients were treated with narrow-band UVB radiation (NB-UVB) (10.3%). Methotrexate, cyclosporine or combined these drugs were systemic therapy styles.

Demographic and biochemical findings of the subjects with psoriasis and control group are shown in Table I. The levels of PTX3, fetuin-A, CRP, insulin, and HOMA-IR levels were statistically higher in patients compared to the control group ($p = 0.006$, $p = 0.007$, $p = 0.002$, $p = 0.003$, and $p = 0.003$ respectively, Table I). We accepted 2.7 for the reference value of HOMA-IR. Serum uric acid, TG, total cholesterol and LDL cholesterol concentrations were higher in the patients with psoriasis than control group, but the differences were not statistically meaningful ($p > 0.05$). The median values of fasting glucose for patient and control groups were 91 and 91.5, respectively. In addition, the levels of HDL cholesterol were significantly lower in patient group compared with the control group ($p = 0.007$).

Patients group with psoriasis was separated into three groups (minimal, moderate and severe psoriasis) according to the PASI score; and compared with each other. As shown in Table II, it was considered that the serum insulin, HOMA-IR median values were significantly higher in the severe group than the control group, as well as CRP levels ($p = 0.006$, $p = 0.011$ and $p < 0.001$, respectively). Serum CRP concentrations were increased in severe psoriasis group compared to the minimal group ($p = 0.008$) (Table II).

Serum insulin levels were found to be positively correlated with CRP concentrations and PASI score in psoriatic patients and control subjects ($r = 0.246$, $p = 0.021$ and $r = 0.319$, $p = 0.002$, respectively). HOMA-IR values showed significant correlations with CRP concentrations and also PASI score ($r = 0.243$, $p = 0.022$ and $r = 0.314$, $p = 0.003$, respectively). The levels of serum CRP were positively correlated with PASI score ($r = 0.437$, $p < 0.001$). Fetuin-A concentrations were significantly correlated with PASI score ($r = 0.247$, $p = 0.002$. Serum PTX3 levels were not correlated with PASI score or any other biochemical parameters.

Discussion

Psoriasis is known to be associated with several disturbances including CVD, hypertension, dyslipidemia, atherosclerosis, type 2 diabetes mellitus, obesity, cerebrovascular events, osteoporosis, chronic obstructive pulmonary disease, cancer and depression[14]. It has been understood that psoriasis is not only a hyperkeratotic disorder of keratinocytes. A dysregulation of the immune system which is mediated by cytokines is also in-

Table I. Comparison of study parameters treatment among the groups.

	Control (n = 30)	Psoriasis (n = 58)	*p* value
Age	39 (20-68)	43.5 (18-71)	0.57
Sex (female/male)	15/15	32/26	0.65
Fasting glucose (mg/dL)	91.5 (66-103)	91 (72-145)	0.29
Uric acid (mg/dL)	4.66 ± 0.93	4.93 ± 1.09	0.26
Triglyceride (mg/dL)	106 (50-323)	121.5 (37-297)	0.17
Total cholesterol (mg/dL)	173 (111-204)	181.5 (120-338)	0.54
HDL cholesterol (mg/dL)	52 (17-73)	46 (30-92)	0.007*
LDL cholesterol (mg/dL)	105.2 (34-188.2)	110.1 (45-230.8)	0.53
CRP (mg/L)	1.42 (0.34-2.94)	1.85 (0.75-8.90)	0.002*
Insulin (μIU/mL)	6.12 (3.91-17.63)	9.64 (1.87-23.02)	0.003*
HOMA-IR	1.33 (0.64-4.35)	2.20 (0.61-6.75)	0.003*
Pentraxin3 (ng/mL)	2.86 (1.11-4.94)	3.36 (1.16-7.72)	0.006*
Fetuin-A (g/L)	0.29 (0.21-0.39)	0.36 (0.20-0.44)	0.007*

HOMA-IR: homeostasis model assessment of insulin resistance, CRP: C-reactive protein.
*$p < 0.05$ was considered to be statistically significant

Table II. Comparison of biochemical parameters among the three different psoriasis and control groups.

	Control (n = 30)	Minimal (n = 12)	Moderate (n = 30)	Severe (n = 16)	*p*
Fasting glucose (mg/dL)	91.5 (66-103)	91 (72-106)	91.5 (77-117)	93 (74-145)	0.41[a]
Uric acid (mg/dL)	4.66 ± 0.93	4.59 ± 1.2	5.15 ± 0.93	4.77 ± 1.27	0.23[b]
Triglyceride (mg/dL)	106 (50-323)	91.5 (49-242)	119 (37-262)	172 (82-297)	0.024[a]
Total cholesterol (mg/dL)	173 (111-264)	170.5 (120-234)	177 (131-300)	205.5 (127-338)	0.41[a]
HDL (mg/dL)	52 (17-73)	48.5 (30-67)	48 (31-92)	44.5 (31-80)	0.096[a]
LDL (mg/dL)	105.2 (34-188.2)	92.5 (62-158)	110.1 (77-194)	114 (45-238.8)	0.57[a]
CRP(mg/L)	1.42 (0.34-2.94)c	1.60 (0.83-6.20)d	1.79 (0.93-8.73)	3.78 (0.75-8.90)[c,d]	<0.001[a]
Insulin (μIU/mL)	6.12 (3.91-17.63)e	10.31 (4.18-21.5)	9.03 (4.44-23.02)	14.1 (1.87-22.58)[e]	0.006[a]
HOMA-IR	1.33 (0.64-4.35)f	2.18 (0.94-4.49)	2.08 (0.84-5.80)	3.30 (0.61-6.75)f	0.011[a]
Pentraxin3 (ng/mL)	2.86 (1.11-4.94)	4.77 (1.32-7.38)	3.36 (1.32-7.22)	3.29 (1.16-7.72)	0.071[a]
Fetuin (g/L)	0.29 (0.21-0.39)	0.30 (0.28-0.40)	0.37 (0.20-0.44)	0.33 (0.21-0.42)	0.004[a]

Footnote: a: Kruskal Wallis test, b: One-way analysis of variance, according to Bonferroni adjustment of $p < 0.0125$ was considered to be statistically significant, c: There was a statistically significant difference between the control and severity psoriasis groups ($p < 0.001$), d: There was a statistically significant difference between the mild psoriasis and severity psoriasis groups ($p = 0.008$), e: There was a statistically significant difference between the control and severity psoriasis groups ($p = 0.003$), f: There was a statistically significant difference between the control and severity psoriasis groups $p = 0.007$), g: There was a statistically significant difference between the control and moderaty psoriasis groups ($p = 0.001$).

volved in the pathophysiology of the disease. The classification of the disease, therefore, has changed from 'skin disease' to a 'T-cell mediated disease'. T cells seem to play a crucial role by contributing to the development of systemic involvement. It is still of interest whether development and worsening of these comorbidities can be prevented by the control of the disease and inflammatory processes. It can be speculated that the systemic inflammation that is involved in psoriatic pathology contributes to immunological and metabolic alterations that exaggerate and sustain psoriasis, and can play an important role in the development of co-morbidities. The systemic inflammatory pathways may guide to treating the disease and improving clinical outcomes[15]. Therefore, the studies for the new inflammatory mediators can lead to develop new therapeutic targets.

Some immunological mediators and proinflammatory cytokines such as TNF-α and IL-6 contribute to formation of psoriatic lesions or atherosclerotic plaques which induce releasing of CRP (4). It has been suggested that there is a link between the concentration of CRP and CVD, insulin resistance, diabetes mellitus and metabolic syndrome[16]. Isha et al[17] reported that serum CRP and uric acid levels were elevated by more than 20 folds in patients with psoriasis in comparison with the healthy indi-

viduals. They also showed that after 12 weeks treatment, CRP concentrations were diminished approximately 50% of the initial value. In our study, median value for CRP was found to be increased in patients with psoriasis than control group. In addition, CRP concentrations were positively correlated with insulin, HOMA-IR and PASI score. Severe psoriasis group had higher median value for CRP than moderate and mild psoriasis groups. According to our results, CRP appeared to be a marker for severity of the psoriasis.

PTX-3 is known as long pentraxin, differs from classical short proteins [CRP and serum amyloid P component (SAP)] with the presence of an unrelated long N-terminal domain coupled to the C-terminal pentraxin domain, gene organization, chromosomal localization (chromosome 3q25) and cellular source. It is synthesized by various kinds of cells, mostly by dendritic cells, macrophages, fibroblasts, activated endothelia, and by other tissues. The inflammatory cytokines like IL-6 and IL-1 induce the production of classical short pentraxins (CRP and SAP). PTX3 has similar structure and functions like CRP which is recognized as an acute phase reactant. Higher PTX3 levels were found during infections, autoimmune disorders, inflamatory states and various vasculitis[7]. Due to the fact that psoriasis represents a systemic inflammatory disease, several studies observed PTX3 and CRP levels in psoriatic patients[7,18]. These reports suggested that the serum concentrations of both parameters increased in patients with psoriasis. In the present study, we also determined higher PTX3 levels in psoriatic patients than healthy subjects.

Obesity is considered as a low-grade systemic inflammatory disease which leads to increased risk of developing psoriasis and worsening of the disease. The adipose tissue acts as a part of the innate immune system and generates adipokines and cytokines which impair the balance of resistance/sensitivity to insulin[12]. In a cross-sectional study, insulin resistance was found in non-obese psoriatic patients[19]. Our results support the presence of disturbed insulin sensitivity in patients with psoriasis. The insulin and HOMA-IR levels were increased in patient group than healthy participants. These parameters were higher in severe psoriasis group than control group. Insulin and HOMA-IR levels were correlated positively with disease activity of psoriasis indicated as PASI score. These data assert that insulin and HOMA-IR can be used as potential markers for worsening of the psoriasis.

Fetuin-A [also called alpha2-Heremans Schmid glycoprotein (AHSG)] is a multifunctional protein involved in the regulation of insulin sensitivity. As an inducer of insulin resistance, fetuin-A inhibits insulin receptor tyrosine kinase activity by blocking autophosphorylation of tyrosine kinase and insulin receptor substrate-1 (IRS-1). Elevated levels of fetuin-A is associated with obesity, diabetes mellitus, hypertriglyceridemia and metabolic syndrome[10,20]. Brix et al[21] showed a reduction of the concentration of fetuin-A after gastric bypass surgery and weight loss in morbid obese patients. To our knowledge, this is the first study to determine the levels of fetuin-A in patients with psoriasis. We observed higher fetuin-A concentrations in patients with psoriasis than control group. Moreover, there was a positive correlation between fetuin-A levels and PASI score.

In this study there is the lack of data about body mass index (BMI) of the individuals. It is known that BMI may be associated with insulin resistance.

As a result, psoriasis is a complex disorder and immunologic and inflammatory factors are known to be involved in the development of the disease. It is thought that there is a possible link between the underlying systemic inflammatory pathways that is involved the pathogenesis of psoriasis and the development of co-morbid diseases. The investigators emphasizes the importance for early and effective therapy of psoriasis. Therefore, studies for the new mediators can also lead to develop new therapeutic targets.

Conclusions

The biochemical markers studied will provide important contributions to optimize medical treatment and recruit clinical outcomes in patients with psoriasis. Further researches with a great number of psoriasis should confirm our results in order to dissect the role of the enhancement of clearance of these parameters in the pathogenesis of the disease.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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