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Serum Midkine Levels in Patients with Psoriasis

Psöriyazisli Hastalarda Serum Midkin Seviyeleri

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ABSTRACT Objectives: Midkine is a heparin-binding growth factor which functions in development and repair mechanisms. It also has roles in tumor growth, invasion and angiogenesis in cancer cells. Recently, higher serum midkine levels were detected in inflammatory diseases such as rheumatoid arthritis, inflammatory bowel diseases, atherosclerosis and obesity. In the present study, we aimed to investigate serum midkine levels in patients with psoriasis. We also tried to reveal if there is a relationship between serum midkine levels and psoriasis disease activity. **Material and Methods:** Forty-five patients with psoriasis and age, sex-matched healthy controls were enrolled in the study. Serum midkine level, complete blood count, fasting serum glucose level, lipid profile (HDL, LDL, triglyceride, cholesterol), CRP (C-reactive protein), serum liver function tests (ALT; AST) and kidney function tests (urea and creatinine) were studied. Psoriasis area severity index (PASI) scores and body mass indexes were calculated for each patient. **Results:** We found significantly higher serum midkine levels in patients with psoriasis compared to control group. There was no correlation between serum midkine levels and PASI scores. Serum midkine levels were correlated with serum triglyceride levels in patients with psoriasis. **Conclusion:** This study showed that serum midkine levels were significantly higher in psoriatic patients than controls. As midkine is only correlated with serum triglyceride level and not correlated with PASI, we think serum midkine is not an ideal serum marker for the evaluation of psoriasis activity.

Keywords: Midkine; psoriasis; metabolic syndrome; inflammation

ÖZET Amaç: Midkin, büyüme, gelişme ve tamir mekanizmalarında görevli bir büyüme faktörüdür. Ayrıca, kanser hücrelerinde tümör büyümesi, invazyon ve anjiyogenezden sorumludur. Son zamanlarda, romatoid artrit, inflamatuar bağırsak hastalıkları, ateroskleroz ve obezite gibi bircok inflamatuvar hastalıkta yüksek serum midkin seviyeleri tespit edilmiştir. Çalışmamızda, psöriyazisli hastalarda serum midkin seviyesini ve bu seviyelerin hastalık aktivitesi ile ilişkisini belirlemeyi hedefledik. **Gereç ve Yöntemler:** Psöriyazis tanısı almış 45 hasta ile yaş ve cinsiyet açısından eşleşmiş kontroller çalışmaya dahil edildi. Tüm hasta ve kontrollerde, serum midkin seviyeleri, tam kan sayımı, açlık kan şekeri, lipid profili (HDL, LDL, trigliserit, kolesterol), CRP (C reaktif protein), serum karaciğer testleri (ALT, AST) ve böbrek fonksiyon testleri (üre, kreatinin) çalışıldı. Her hasta için psöriyazis alan şiddet indeksi (PAŞİ) skorları ve vücut kitle indeksleri (VKİ) hesaplandı. **Bulgular:** Psöriyazisli hastalarda kontrol grubuna göre belirgin olarak daha yüksek serum midkin seviyeleri saptadık. Serum midkin seviyeleri ile PAŞİ skorları arasında korelasyon gözlemlemedik. Psöriyazisli hastalarda serum midkin seviyelerinin serum trigliserit seviyeleri ile korelasyon göstermekteydi. **Sonuç:** Bu çalışmada psöriyazisli hastalarda kontrollere göre istatistiksel olarak anlamlı seviyede daha yüksek serum midkine seviyeleri saptandı. Ancak serum midkin seviyelerinin trigliserit seviyeleri ile korelasyon gösterip, PAŞİ skorları ile korele olmaması nedeniyle, serum midkin seviyelerinin psöriyazis aktivitesi ve takibinde ideal bir belirteç olmadığını düşünmekteyiz.

Anahtar Kelimeler: Midkin; psöriyazis; metabolik sendrom; inflamasyon

Midkine (MK) is a multifunctional molecule functioning in the developmental period of the fetus. It was first discovered in embryonic carcinoma cells with increased expression in early stages of differentiation.[1] In adults, MK is expressed in limited sites such as epidermis, kidney, lymphocytes and gut.[2] MK has critical function in development and repair mechanisms in normal cells as well as tumor growth, invasion and angiogenesis in cancer cells.[3,4] Various studies have shown that tumor prognosis is worse in the patients with higher MK levels.[5-7] Moreover, higher serum MK levels were detected in various inflammatory diseases such as rheumatoid arthritis, inflammatory bowel diseases, atherosclerosis and

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obesity. It has been argued that targeting MK might be a novel way to treat diseases with high expression of MK.[8-10]

Psoriasis is a systemic inflammatory disease that may be seen along with various comorbidities such as diabetes, obesity and coronary arterial disease.[11] Chronic inflammatory state in psoriasis has been supported with the presence of higher levels of inflammatory markers such as CRP and uric acid.[12,13] In a previous study, higher expression of MK was shown in the tissue samples of patients with psoriasis resulting from hyperkeratinization process.[14] However, there is no data on the relationship between serum MK levels and psoriasis severity. In the present study, we aimed to investigate the relationship of serum MK levels with clinical parameters in psoriatic patients.

MATERIAL AND METHODS

A total of 45 patients with psoriasis who presented to our department between September 2014 and June 2015 were included in the study. Psoriatic patients with the history of coexisting comorbidities, which may affect the level of inflammatory markers, such as malignancy, liver disease and pregnancy were excluded from the study. Also, the patients who were on systemic treatment for psoriasis during the one last month were excluded as these treatments may interfere with the levels of inflammatory markers. However, patients on skin directed therapies for psoriasis including phototherapy (without systemic retinoids) and topical treatments were included. All patients were tested for complete blood count, fasting serum glucose, lipid profile (HDL, LDL, triglyceride, cholesterol), C-reactive protein (CRP), renal (urea, creatinine) and hepatic biochemical tests (ALT, AST). An enzyme double- antibody indirect immunoassay with human MK ELISA kit was used to measure serum MK levels (Assay Biotechnology, California USA). Disease severity was calculated according to Psoriasis Area Severity Index (PASI) scoring system. Types of psoriasis were recorded. Body mass index (BMI) was calculated. For reference, we included 23 age and sex matched healthy subjects. The study was conducted in accordance with the principles set forth in the Helskinki Declaration 2008. Informed consents were obtained from all participants or their legal guardians. The protocol of the study was approved by Ankara Numune Training and Research Hospital Institutional Review Board (Date: 07/05/2014 No: 20796219/ E-14-176).

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp. Chi-square test was used to analyze age and sex differences between patient group and controls. Kolmogorov–Smirnov/Shapiro-Wilk tests were used to check for the normal distribution of data. Mean values between patient and control group were compared using independent samples t tests when variables showed normal distribution. When parametric test assumptions were not available for some variables, the comparisons of two independent groups were performed by Mann-Whitney U test. Pearson correlation analysis was used to calculate correlations between MK and other mean values in patient group. Where parameters did not show a normal distribution, Spearman analysis was used. In order to perform the analysis of covariance (ANCOVA), the natural log transformation of serum MK levels was applied for the normality assumption to be met due to the skewness of the variables in each group. ANCOVA was used to determine the difference of serum ln MK levels between the groups while controlling for triglyceride levels.

RESULTS

Our study included 45 patients with psoriasis and 23 healthy age and sex correlated subjects. Demographic characteristics and laboratory values of the patients were summarized in Table 1. The patient group included 34 patients with classic type of psoriasis, 6 patients with guttate and 5 patients with palmoplantar psoriasis. Of 45 patients, 19 patients were over-weight and 11 patients were obese. Median serum MK levels in patient and control groups were 1.84 (0.24-22) and 1,01 (0.23-4.49); respectively. We detected significantly higher serum MK levels in the patients with psoriasis (p=0.047) (Table 1). Post hoc power analysis was used to evaluate the significant difference obtained with serum MK level and an acceptable power

TABLE 1: Main characteristics and serum midkine levels of patient and control groups.

	Patient group (n=45)	Control group (n=23)	p
Age, years (Median, min-max)	37 (11-77)	36 (16-52)	.062
Male/Female (n)	26/19	12/11	.66
Body mass index, (Median, min-max)	27.5 (18-41.5)	25 (20.2-29.9)	.085
Midkine (pg/mL), (Median, min-max)	1.84 (0.24- 22)	1.01 (0.23- 4.49)	.047

SD, Standart deviation.

TABLE 2: Correlation of serum midkine levels with clinical and laboratory findings in psoriatic patients.

		vs MK	
	Median, min-max	p	r
Age, years	37 (11-77)	0.379	0.134
Body mass index	27.5 (18-41.5)	0.805	0.038
Age at onset, years	28 (5-75)	0.781	0.043
Disease duration, years	5 (0.1-38)	0.867	0.026
PASI	7 (2.2-36.3)	0.759	-0.047
CRP (mg/L)	2 (0- 94)	0.174	-0.206
Glucose (ng/mL)	98 (74-121)	0.646	0.070
Triglyceride (mg/dL)	118 (37-611)	**0.017***	**0.354**
LDL (mg/dL)	127 (54-227)	0.283	0.163
Total cholesterol (mg/dL)	191 (129-353)	0.126	0.232
HDL (mg/dL)	45 (30-79)	0.983	0.003
Hemoglobin (g/dL)	14.3 (11-17,8)	0.365	-0.138
Thrombocyte (mm^3)	$249x10^3$($165x10^3$-$880x10^3$)	0.484	-0.107
Neutrophil (mm^3)	4.6 (2.2-10.6)	0.520	-0.098
Lymphocyte (mm^3)	2.3 (1- 4.1)	0.367	0.138
N/L ratio	1.91 (0.8- 6)	0.180	-0.204
ALT	20 (9-131)	0.135	-0.226
AST	20 (12-57)	0.819	-0.036
Creatinine	0.79 (0.47-1.15)	0.562	-0.089

SD: Standart deviation, MK: Midkine, PASI: Psoriasis area severity index, N/L: Neutrophil/lymphocyte, CRP: C-reactive protein, LDL: Low density lipoprotein, HDL: High density lipoprotein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.

value of 68.5% were calculated. Among the screened laboratory tests described in the materials and methods section, only triglyceride levels were correlated with serum MK levels in the patients with psoriasis (r=0.354, p=0.017). There were also no correlation between serum MK levels and age, disease duration, age at onset, PASI and BMI (Table 2).

Since serum MK and triglyceride levels were correlated, we performed an ANCOVA in order to control for triglyceride levels to determine if there is a significant difference of ln serum MK levels between groups. This analysis revealed no difference in ln serum MK levels between patient and control groups. Triglyceride was significantly related to the ln serum MK levels (p=0.006) and there was no significant difference between ln serum MK levels (p=0.068).

DISCUSSION

To the best of our knowledge, this is the first study evaluating the relationship between serum MK level and psoriasis severity. Epidermis is one of the few sites where MK is normally present in healthy individuals.[15] In 2013, Monma et al. showed staining with

MK in the upper epidermal layers of psoriatic skin samples, and they thought that this expression might be due to hyperkeratinization process seen in psoriatic patients.[14] Hitherto, serum and tissue levels of MK were mostly studied for various malignancies such as neuroblastoma, oral and esophaegal squamous cell carcinoma, breast and pancreatic cancers.[16-18] Recently, some studies have also shown this relevance in inflammatory diseases like rheumatoid arthritis, ulcerative colitis, Chron's disease and obesity.[2,8]

Our study showed significantly higher levels of serum MK in patients with psoriasis comparing to the controls. In psoriatic patients, we have not found any correlation between serum MK level and BMI in contrast to a prior study that showed a positive correlation between serum MK level and BMI.[10] However, serum MK level was found to be correlated with elevated triglyceride level. Accordingly, ANCOVA with triglyceride level as a covariate, revealed no difference in serum MK level between groups showing us that this difference may rely on metabolic disturbances which is frequently seen in psoriatic patients. We could consider that higher levels of serum MK might be a useful clue to distinguish psoriatic patients who may have metabolic syndrome in order to make further work up, since metabolic syndrome generally shows elevated triglyceride concentration.[19,20] We did not find any correlation between serum MK level and PASI. Of note, it has been shown in many studies that PASI is not correlated with metabolic syndrome.[20-23]

New data has recently emerged showing MK has an important function in the steps of inflammation which also functions in the pathogenesis of both psoriasis and metabolic syndrome.[24,25] It is thought that MK might function in inflammation pathways via recruiting inflammatory cells including neutrophils and macrophages by inducing monocyte chemoattractant protein-1 (MCP-1).[26,27] Plus, in stimulated cells, it was found that TNF-α and IL-6 correlated with MK secretion levels.[24] In 2014, Fan et al. showed that MK is expressed in adipocytes and MK contributes to impairment in insulin signaling in these cells. In these study, TNF-α treatment resulted increase in MK expression in adipocytes. They also observed increased serum MK levels in obese individuals.[10,28] Currently, MK is considered as a candidate therapeutic target for insulin resistance and other inflammatory conditions.[2,8,24]

CONCLUSION

Our results show that MK has a limited value in the activation process of psoriasis. Serum MK level is significantly higher in psoriatic patients than controls. However, this difference was considered mainly as a result of metabolic disturbances seen in psoriasis patients. Since we couldn't show any correlation between disease severity and serum MK level, in the follow up, it is obvious that the response to any treatment couldn't be gauged just using serum MK level. This might be a result of relatively low numbers of patients included in our study indicating the necessity of larger cohorts in future studies.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Seda Pürnak, Ferda Artüz, Turan Turhan;* ***Design:*** *Seda Pürnak, Ferda Artüz, Turan Turhan;* ***Control/Supervision:*** *Seda Pürnak;* ***Data Collection and/or Processing:*** *Seda Pürnak, Bağdagül Çakır, Seray Külcü Çakmak;* ***Analysis and/or Interpretation:*** *Seda Pürnak;* ***Literature Review:*** *Seda Pürnak;* ***Writing the Article:*** *Seda Pürnak;* ***Critical Review:*** *Seda Pürnak, Ferda Artüz, Turan Turhan, Bağdagül Çakır, Seray Külcü Çakmak;* ***References and Fundings:*** *Seda Pürnak, Turan Turhan, Ferda Artüz;* ***Materials:*** *Seda Pürnak, Bağdagül Çakır, Seray Külcü Çakmak.*

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