Original Investigation
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A cross-sectional study investigating association of liver diseases in moderate to severe psoriasis patients

Orta-şiddetli psoriazisli hastalarda karaciğer hastalıkları birlikteliğini araştıran kesitsel bir çalışma

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Abstract

Background and Design: Non-alcoholic fatty liver disease (NAFLD), which is a systemic comorbidity of psoriasis, is the most common liver disease in population with risk of cirrhosis progression. The aim of this study was to investigate the frequency and risk factors of NAFLD in moderate-severe psoriasis patients.
Materials and Methods: Patients aged 18 years and older, who were followed up with a diagnosis of moderate to severe psoriasis at Hacettepe University Faculty of Medicine, Department of Dermatology and Venereology between 2015 and 2016, were included. Demographic and disease-related data (age, sex, age at psoriasis onset, alcohol use, family history of psoriasis, psoriatic arthritis history), and associating systemic diseases were reviewed. Liver function tests (LFT) were evaluated during routine examinations. Evaluation of gastroenterology consultations was reviewed with indications (positive hepatitis markers, elevated LFT, liver disease history). Abdominal, liver and biliary system ultrasonography results were assessed. Descriptive stastistics were evaluated by cross-table and chi-square test. The difference between the two means was evaluated by t-tests. P value less than 0.05 were accepted as statistically significant.
Results: Two hundred and sixty-six patients with moderate-severe psoriasis were included. %12 of the patients (n=31) had elevated LFT. Abdominal ultrasonography was performed in 77% (n=24) of patients who were evaluated by gastroenterology department for LFT elevation. NAFLD was found in 65% (n=20) of patients with high LFT. The incidence of coronary artery disease, hypertension and hyperlipidemia was significantly higher in patients with high LFT compared to patients with normal LFT (p=0.003, p=0.011 and p=0.001, respectively). Examination and laboratory values were compared according to presence of elevation in LFT; uric acid levels were statistically higher in psoriatic patients with high LFT (p=0.002). The mean waist circumference in patient group with elevated LFT and in group with normal LFT was found to be 108.3±9.6 cm and 98.2±15.4 cm, respectively. The difference was statistically significant (p=0.005).
Conclusion: NAFLD should be kept in mind as a frequent and important cause of elevated LFT observed in psoriasis patients. The presence of comorbidities such as cardiovascular diseases, hypertension and hyperlipidemia, which are frequently observed in psoriasis patients diagnosed with NAFLD, should be investigated. We recommend measurement of waist circumference and blood pressure and parameters including fasting blood glucose, lipid profile and uric acid in terms of metabolic syndrome.
Keywords: Psoriasis, non-alcoholic fatty liver disease, metabolic syndrome, hypertension, waist circumference

Öz

Amaç: Psoriazisin sistemik komorbiditelerinden olan non-alkolik yağlı karaciğer hastalığı (NAYKH), toplumda görülen en sık karaciğer hastalığıdır ve siroza ilerleme riski taşımaktadır. Bu çalışmanın amacı orta-şiddetli psoriazis tanısı ile takip edilen hastalarda NAYKH sıklığını ve bu komorbidite ile ilişkili olabilecek risk faktörlerini araştırmak olarak belirlenmiştir.
Gereç ve Yöntem: Hacettepe Üniversitesi Deri ve Zührevi Hastalıklar Anabilim Dalı polikliniklerinde 2015-2016 yılları arasında orta-şiddetli psoriazis tanısı ile izlenmiş 18 yaş ve üzerindeki hastalar çalışmaya dahil edildi. Hastalara ait demografik ve hastalık ilişkili veriler (yaş, cinsiyet, hastalık başlangıç yaşı, alkol kullanım öyküsü, ailede psoriazis varlığı, psoriatik artrit varlığı), mevcut olabilecek sistemik hastalıklara (diabetes mellitus, hiperlipidemi, hipertansiyon, enfeksiyöz ve diğer karaciğer hastalıkları) dair veriler toplandı. Rutin tetkikleri sırasında bakılmış olan

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karaciğer fonksiyon testleri (KCFT) değerlendirildi. Hastalardan endikasyon dahilinde (hepatit belirteçlerinde pozitiflik, KCFT'de bozukluk, bilinen karaciğer hastalığı öyküsü) istenilmiş olan gastroenteroloji bölüm konsültasyon sonuçları incelendi. Hastalara endikasyon dahilinde istenilmiş olan abdominal, karaciğer ve biliyer sistem ultrasonografi sonuçları gözden geçirildi. Tanımlayıcı istatistikler, çapraz tablo ve ki-kare testi ile, iki ortalama arasındaki fark t-testi ile değerlendirildi. 0,005'ten küçük olan p değerleri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışmamıza dahil edilme ve dışlanma kriterlerine uyan 266 orta-şiddetli psoriazis hastası dahil edildi. Hastaların %12'sinde (n=31), yapılmış olan rutin değerlendirmeleri sırasında bakılan KCFT'de yükseklik olduğu saptandı. KCFT yüksekliği nedeni ile gastroenteroloji bölümüne konsülte edilmiş olan hastaların %77'sine (n=24) abdominal ultrasonografi yapıldı. Bu hastaların %65'inde (n=20) NAYKH olduğu saptandı. KCFT'si yüksek olan hastalarda koroner arter hastalığı, hipertansiyon ve hiperlipidemi sıklığı, KCFT'si normal olan hasta grubuna göre anlamlı olarak daha yüksekti (p=0,003, p=0,011, p=0,001). KCFT yüksekliği olan psoriazisli hastalarda ürik asit düzeylerinin istatistiksel anlamlı düzeyde daha yüksek olduğu görüldü (p=0,002). Bel çevresi KCFT yüksekliği saptanan hasta grubunda 108,3±9,6 cm iken, KCFT'si normal olan grupta 98,2±15,4 cm olarak bulundu, aradaki fark istatistiksel olarak anlamlı bulundu (p=0,005).

Sonuç: Psoriazis hastalarında gözlenen KCFT yüksekliğinin sık ve önemli bir sebebi olarak NAYKH akılda tutulmalıdır. NAYKH tanısı alan psoriazis hastalarında görülme sıklığı yüksek olan kardiyovasküler hastalıklar, hipertansiyon ve hiperlipidemi gibi komorbiditelerin varlığı açısından hastaların değerlendirilmeleri gerekmektedir. Bu hastaların muayeneleri sırasında bel çevresi ve kan basıncı ölçümü yapılması ve laboratuvar incelemelerinde metabolik sendrom açısından bakılması gerekli olan açlık kan şekeri ölçümü, açlık lipit profili ve ürik asit düzeyi gibi diğer parametrelere dikkat edilmesi gerekmektedir.

Anahtar Kelimeler: Psoriazis, non-alkolik yağlı karaciğer hastalığı, metabolik sendrom, hipertansiyon, bel çevresi

Introduction

Psoriasis is a chronic, recurrent inflammatory skin disease with a frequency range of 0.5-2% in various populations[1]. Psoriasis is considered a disease with significant comorbidities due to systemic inflammatory effects[1,2]. The main systemic comorbidities of psoriasis are non-alcoholic fatty liver disease (NAFLD), metabolic syndrome and cardiovascular diseases[1,3]. Although systemic psoriatic comorbidities are considered to be due to increased systemic inflammation in psoriasis, the pathogenesis and predisposing factors for these diseases are still unclear[4]. NAFLD, one of the systemic comorbidities of psoriasis, is the most common liver disease in the population and carries the risk of progression to cirrhosis[5]. NAFLD diagnosis can be made with characteristic findings in ultrasonographic examination performed after excluding secondary non-alcoholic causes[5,6].

In the light of the literature, the aim of this study was to investigate the frequency of NAFLD and risk factors associated with this comorbidity in patients followed with a diagnosis of moderate to severe psoriasis.

Materials and Methods

Patients aged 18 years of age and older, who were followed up with moderate and severe psoriasis at Hacettepe University Hospital between 2015 and 2016, were included in the study. Exclusion criteria were presence of excessive alcohol consumption defined by the patient (greater than 7 cups/week) and systemic drug use (corticosteroids, anabolic steroids, birth control pills, diabetes mellitus, dietary supplement with lipid supplementation, etc.) that may be associated with FLD in the past 6 months. Patients with a psoriasis activity severity index (PASI) score of 10 or greater and with lesions in specific anatomical areas (face, hand, foot, genital region) with a plan of systemic medical treatment were defined as having severe psoriasis and patients with a PASI score of 5-10, but with a dermatology quality of life index score of 10 or more were defined as having moderate psoriasis. Demographic and disease-related data (age, sex, age at onset, history of alcohol use, presence of family history of psoriasis, presence of psoriatic arthritis) and data concerning possible systemic diseases (diabetes mellitus, hyperlipidemia, hypertension, infectious and other liver diseases) were collected. Liver function tests (LFTs) assessed during routine examinations were evaluated. The consultation results of gastroenterology department were reviewed from the patients within indications (positive for hepatitis markers, elevated LFT, known liver disease story). Abdominal, liver and biliary system ultrasonography results were reviewed within the disease indications. This study was done by Hacettepe University Non-Interventional Clinical Research Ethics Committee with numbered permission (approval number: GO-17/315-16). Infomed consent was taken from all patients.

Statistical Analysis

Data analysis was made with SPSS 23. Descriptive statistics were analyzed by cross-tabs and chi-square test, the difference between the two means was assessed by Student's t-test. A p value of less than 0.005 was considered statistically significant.

Results

Two hundred and sixty-six moderate and severe psoriasis patients, who met the inclusion, were included in this study. 12% of the patients (n=31) were found to have elevated LFT (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, total and direct bilirubin) during the routine evaluations. The mean age of the patients with elevated LFT was 49.2±13.5 yrs. The mean age of the patients with high LFT was significantly higher than the group with normal LFT (p=0.03). Of these patients, 32% were female (n=10) and 68% (n=21) were male. The mean age of psoriasis onset was 27.2±14.0 years. There was no significant difference between the two groups in terms of age at onset of psoriasis and gender (p=0.36 and p=0.98, respectively) (Table 1) 55% (n=17) of patients with elevated LFT had used methotrexate previously. Four patients were still using methotrexate as monotherapy and 2 patients were using methotrexate

Table 1. Comparison of demographic characteristics according to the presence or absence of elevation in liver function tests in patients with moderate and severe psoriasis

Demographic and clinical features	LFT elevation (-) (n=235, 88%)	LFT elevation (+) (n=31, 12%)	p
Age	43.3±14.8	49.2±13.5	0.03
Gender (F/M)	95/140	10/21	0.36
Age at psoriasis onset	27.3±15.3	27.2±14.0	0.98

LFT: Liver function tests, F: Female, M: Male

in combination therapy at doses of 7.5-15 mg/week. It was determined that the cumulative dose of methotrexate in these patients was 705±591 mg and that the mean dose was below the limit of 1.5 g for liver biopsy. In addition, it was observed that among patients with elevated LFT, 1 patient was using acitretin as monotherapy and 1 patient were using acitretin treatment in combination therapy at 10-25 mg/day. Hepatitis B positivity was present in only 1 of the patients with elevated LFT, whereas serologic markers for hepatitis B and C in other patients were negative.

Abdominal ultrasonography was performed in 77% (n=24) of the patients for whom gastroenterology department was consulted for LFT elevation. Ultrasonographic examination revealed that NAFLD was found in 65% (n=20) of patients with psoriasis with elevated LFT. For the whole patient group, elevated LFT was found in 12% (n=31) and NAFLD frequency was found to be 8% (n=20) in patients with moderate to severe psoriasis (Table 2).

Table 2. Results of abdominal ultrasonography in patients with moderate and severe psoriasis with elevated liver function tests

Results of abdominal ultrasonography	n	%
Hepatosteatosis and hepatomegaly	13	54%
Hepatosteatosis	7	29%
Hepatomegaly	2	8%
Normal	2	8%

Table 3 Comparison of smoking status and systemic comorbidities according to liver function tests in patients with moderate and severe psoriasis

Comorbidities	LFT elevation (-)	LFT elevation (+)	p
Diabetes mellitus	35, 15.6%	9, 29%	0.06
Hypertension	37, 16.5%	11, 35.4%	0.011
Coronoary artery disease	8, 3.6%	5, 16.1%	0.003
Hyperlipidemia	41, 18.3%	15, 48.3%	0.001
Smoking	70, 37%	12, 5.2%	0.15

Table 4. Comparison of physical examination and laboratory parameters s according to presence of liver function test elevation in patients with moderate and severe psoriasis

Physical and laboratory parameters	LFT elevation (-) (mean ± SD)	LFT elevation (+) (mean ± SD)	p
Uric acid	5.6±1.5	6.6±1.5	0.002
LDL	146.2±37.9	142.5±44.2	0.64
HDL	47.4±11.0	44.5±11.8	0.22
Waist circumference	98.2±15.4	108.3±9.6	0.005
Body mass index	28.0±5.7	29.7±4.2	0.34

SD: Standard deviation, LDL: low density lipoprotein, HDL: high density lipoprotein

The incidence of coronary artery disease, hypertension and hyperlipidemia was significantly higher in patients with psoriasis with higher LFT than in patients with psoriasis with normal LFT. There was no significant difference between the two groups in terms of presence of diabetes mellitus and smoking (Table 3).

When laboratory values were compared according to the presence of elevated LFT in patients with psoriasis, the uric acid levels were found to be statistically significantly higher in psoriatic patients with high LFT (p=0.002). The mean waist circumference was found to be 108 cm in the patient group with elevated LFT, and 98 cm in the normal LFT group, the difference being statistically significant (p=0.005). There was no significant difference between the two groups in terms of low density lipoprotein, high density lipoprotein (HDL) and body mass index (BMI) (Table 4).

Discussion

NAFLD is an important and frequent liver disease that has recently been understood more clearly with the studies performed[3-6]. NAFLD is regarded as a multisystem disease that can affect the liver and other organ systems as well, due to irregularities developing in metabolic and immunological pathways[6]. The association of psoriasis and NAFLD is striking due to the studies that have been carried out in different populations since 2009[7-9]. This association is thought to be related to the influence of common inflammatory and immunological pathways. The non-esterified fatty acids and proinflammatory adipocytokines from the inflammatory fatty tissue are secreted proportionally to the increased BMI and waist circumference in psoriasis and NAFLD, this increase cytokines such as hepatocyte-derived tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and C-reactive protein, the vasoactive and thrombogenic molecules such as plasminogen activator inhibitor-1, Transforming growth factor beta, and fibrinogen. Molecules that cause vicious cycle between psoriatic skin and fatty liver tissue are thought to be especially TNF-α, IL-6 and IL-17[6]. There is evidence that these cytokines also cause insulin resistance, predisposing to diabetes mellitus which is one of the metabolic syndrome components[10].

Recent studies have reported that about 50% of patients with psoriasis had NAFLD[6-9]. In our study, this rate was found to be 65% in the group of patients with high LFT. It has also been shown that NAFLD was associated with psoriasis severity. However, the relationship between NAFLD and psoriasis severity has not been clearly examined in our study in which only the findings of moderate and severe patients were evaluated.

In a study conducted by Abedini et al.[11] and colleagues, 47% of metabolic syndrome, 17% of hypertension and 16% of abnormal LFT were found in psoriatic patients with NAFLD. In addition, waist circumference, BMI, PASI score, fasting lipid levels and fasting blood sugar levels were significantly increased in psoriatic patients with NAFLD. Logistic regression analyses also revealed that waist circumference, PASI scores, abnormal LFT, hypertension, and history of smoking were predictive factors to ensure the level of NAFLD[11]. The study of Dağ et al.[12] supported the view that the increased prevalence of NAFLD could be directly related to the increased frequency of metabolic syndrome in psoriasis patients. In our study, it was shown that NAFLD was an important and frequent cause of LFT elevation in patients with moderate-severe psoriasis in accordance with the

literature. The findings in our study including the cumulative dose of methotrexate used in the LFT group being significantly lower than that of the clinical doses, and the use of psoriasis drugs such as acitretin was only in 2 patients supported that the development of LFT elevation in psoriasis was due to NAFLD rather than usage of hepatotoxic drugs. As a matter of fact, the rate of NAFLD was found to be 65% for this patient group. In addition, the incidence of comorbidities, such as cardiovascular disease, hypertension, hyperlipidemia and high waist circumference, were found to be significantly higher in the patient group with high LFT levels in accordance with the literature. Another significant difference in our study was the laboratory value of uric acid. Elevation of uric acid is known as a laboratory anomaly that can be detected by increase in the epidermal turnover rate in psoriasis[12]. There is considerable evidence that increased uric acid levels are associated with metabolic syndrome and cardiovascular disease[11]. Elevated serum uric acid levels have been shown to be associated with increased triglyceride levels, decreased HDL, and increased blood pressure[13,14]. In our study, it was thought that the elevation of uric acid observed in patients with LFT elevation may be a sign of very important diseases such as cardiovascular diseases, NAFLD and concomitant cardiovascular diseases, and that uric acid levels in psoriasis patients may be assessed and even followed for these comorbidities. There is a need for studies to be carried out for this purpose in order to obtain more precise information in this regard.

Study Limitation

Since our study was a retrospective study, patients without elevated liver function tests were not evaluated in the gastroenterology department and were not assessed for hepatosteatosis which may be present even in these patients; for this reason it is estimated that the incidence of real comorbidity is higher for NAFLD in patients with moderate to severe psoriasis. It is thought that prospective studies in this subject may increase awareness of the disease with high incidence and preventive treatment approaches.

Conclusion

Psoriasis is a disease with complications due to significant systemic comorbidities. NAFLD should be kept in mind as a frequent and important reason for LFT elevation observed in patients with psoriasis. Patients should be assessed for cardiovascular disease, hypertension and hyperlipidemia, which are known to be associated with an increased risk in patients with psoriasis who receive a diagnosis of NAFLD. High waist circumference measurement in patients with psoriasis with elevated LFT, increased uric acid level and presence of hyperlipidemia pose a risk for NAFLD. For this reason, we recommend evaluating fasting blood glucose, fasting lipid profile, and uric acid levels, waist circumference and blood pressure during the examination of patients with psoriasis and in the laboratory examinations in terms of metabolic syndrome.
We emphasize the importance of distinguishing psoriasis patients who are candidates for this disease since NAFLD patients should avoid the use of hepatotoxic agents in the management of chronic treatments for patients with psoriasis and, we assume that routine follow-ups in the gastroenterology section are required.

Ethics

Ethics Committee Approval: Hacettepe University Non-Interventional Clinical Research Ethics Committee with numbered permission (approval number: GO-17/315-16).
Informed Consent: Infomed consent was taken from all patients.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.D., D.M., N.A., H.Ş., Concept: S.D., Design: S.D., Data Collection or Processing: S.D., D.M., Analysis or Interpretation: S.D., D.M., N.A., H.Ş., Literature Search: S.D., D.M., Writing: S.D.
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