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Araştırma Makalesi / Research Article

Evaluation of Trp/Kyn/IDO Relevance with Autoimmune Rheumatological Diseases

Otoimmün Romatolojik Hastalıklarla Trp/Kyn/IDO İlişkisinin Değerlendirilmesi

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Öz

Amaç: Kinurenin metabolizması bağışıklık yanıtını uyaran ve düzenleyen güçlü bir mekanizmaya sahiptir. İndolamin 2-3 dioksijenaz (IDO) enzimi, triptofanın (Trp) kinurenine (Kyn) parçalanmasında rol oynar ve hücresel bağışıklık yanıtını düzenlemede etkin bir role oynar. Bu çalışma, otoimmün romatolojik hastalıklar sınıfından olan psoriatik artrit (PsA), primer Sjögren sendromu (pSS) ve romatoid artrit (RA)'li hastalarda Kyn, Trp ve IDO düzeylerini değerlendirmeyi amaçlamaktadır.
Gereç ve Yöntem: Çalışmaya kendi sınıflandırma kriterlerine göre RA (n=20), PsA (n=18) ve PS (n=19) tanısı almış hastalar dahil edildi. Serum Kyn (mmol/L) ve Trp (mmol/L) düzeyleri HPLC-UV kullanılarak ölçüldü. İDO düzeyleri Kyn/Trp oranına göre hesaplandı.
Bulgular: PsA grubu için Trp ve Kyn'nin ortalama ve standart hata değerleri sırasıyla 0.048±0.002 ve 0.039±0.004; pSS grubu için sırasıyla 0.042±0.003 ve 0.020±0.001; RA grubu için sırasıyla 0.042±0.002 ve 0.026±0.001 idi. Grupların Kyn/Trp (İDO) değerleri pSS için 0.53±0.047, RA için 0.653±0.035 ve PsA için 0.857±0.099 olarak hesaplandı.
Sonuç: Günümüzde bozulmuş Trp metabolizması hastalık oluşum mekanizmasında önemli bir rol oynadığı kabul edilmektedir. Çeşitli patolojik koşullar altında bağışıklık aktivasyon dereceleri arasındaki ilişki Trp, Kyn ve IDO ölçülerek belirlenebilir. Çalışmamızda Trp değerleri pSS ve RA gruplarında aynıydı ancak PsA grubunda daha yüksekti; aynı zamanda Kyn/Trp oranı PsA'da en yüksekti. PSS grubunda diğer gruplara göre daha düşük Kyn ve IDO seviyeleri gözlemledik.
Anahtar Kelimeler: İndolamin-2,3-dioksijenaz (İDO), Kinürenin, Triptofan, Otoimmün romatolojik hastalıklar.

Abstract

Objective: The kynurenine pathway is a potent mechanism that stimulates and regulates the immune response. The enzyme indoleamine 2-3 dioxygenase (IDO) plays a role in the degradation of tryptophan (Trp) to kynurenine (Kyn), which can be determined in blood samples, and has an efficient role in arranging the cellular immune response. This study aimed to evaluate Kyn, Trp and IDO levels in patients with psoriatic arthritis (PsA), primary Sjögren's syndrome (pSS) and rheumatoid arthritis (RA), which are all autoimmune rheumatological diseases.
Materials and Methods: According to the classification criteria, patients diagnosed with RA (n=20), PsA (n=18) and pSS (n=19) were included in this study. Serum levels of Kyn (mmol/L) and Trp (mmol/L) were determined using HPLC-UV. IDO levels were calculated according to the Kyn/Trp ratio.
Results: The mean and standard error values of Trp and Kyn for the PsA group were 0.048±0.002 and 0.039±0.004, respectively; for the pSS group, they were 0.042±0.003 and 0.020±0.001, respectively; and for the RA group, they were 0.042±0.002 and 0.026±0.001, respectively. The Kyn/Trp (IDO) values of the groups were calculated as 0.53±0.047 for pSS, 0.653±0.035 for RA, and 0.857±0.099 for PsA.
Conclusion: Currently, abnormal Trp metabolism is considered a universal mechanism of disease causation. The relationship between the degrees of immune activation can be determined by measuring Trp, Kyn, and IDO under various pathological conditions. In our study, Trp values were the same in the pSS and RA groups but were higher in the PsA group; at the same time, the Kyn/Trp ratio was highest in PsA. We observed lower Kyn and IDO levels in the pSS group than in the other groups.
Keywords: Indoleamine-2,3-dioxygenase (IDO), Kynurenine, Tryptophan, Autoimmune rheumatological diseases.

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INTRODUCTION

The major mechanism by which the uncontrolled production of cytokines causes disease is through excess or unbalanced tryptophan (Trp) metabolism through the kynurenine pathway. Rheumatoid arthritis, psoriatic arthritis and primary Sjögren's syndrome are systemic, autoimmune, and chronic inflammatory rheumatic diseases. Primary Sjögren's syndrome (pSS) is described as the inflammation of all exocrine glands, particularly the lacrimal and salivary glands. Psoriatic arthritis (PsA) is a disease that develops together with the skin disease called psoriasis (psoriasis) and progresses with joint inflammation. Rheumatoid arthritis (RA) is the most widespread chronic inflammatory and systemic autoimmune disease that causes arthritis in the joints and can affect many joints at the same time.

Tryptophan (Trp), which is used in protein synthesis, as well as oxidation (kynurenine), decarboxylation and hydroxylation (melatonin and serotonin), transamination, and deamination (indican), is reducible to different biomolecules and an amino acid that plays role in cell metabolism. [1,2]. The main degradation-way of tryptophan is Kynurenine (Kyn) pathway. The pyrrole ring of tryptophan is oxidized to form N-Formyl kynurenine. This, in turn, is metabolized to kynurenine, kynurenic acid and anthranilic acid.

The enzymes indoleamine-2,3-dioxygenase-1 (IDO-1), IDO-2 and TRP-2,3-dioxygenase (TDO) are known to catalyze the degradation of Trp into Kyn [3,4]. These three enzymes catalyze the same reaction, but show the differs such as substrate specificity, type of induction and in their localization [5–8].

Tryptophan-2,3-dioxygenase can be found mainly in the liver and stimulated by Trp, tyrosine, histidine and glucocorticoids. In contrast, IDO is commonly determined in many tissues and is modulated by many immunological signaling complexes, including tumor necrosis factors, , inflammatory cytokines, type II interferons (INF-γ) and lipopolysaccharides. IDO activity is minimal in non-pathological conditions. However, activation of the enzyme leads to increased degradation of Trp to Kyn [6–8].

Indoleamine-2,3-dioxygenase-1 is the initial enzyme in which catalyzes oxidative destruction in the non-hepatic tissues of tryptophan and is a speed-limiter agent in tryptophan metabolism. The activity of this enzyme results in the consumption of the essential amino acid tryptophan. [9].

Determination of the Kyn/Trp ratio can be used to track the activation status of cellular immunity and IDO. It can provide information about in different diseases involved with T cell activation such as autoimmune disorders, viral infections, cancer [10–13]. Upregulation of IDO expression has been associated with a poor clinical outcome. It is thought that it can be used in disease activity monitoring.

In general, rheumatic diseases can act upon the whole body by affecting the musculoskeletal system, joints, connective tissue and indirectly many organs and systems. Therefore, its scope is quite wide and includes about 200 diseases. We would like to contribute to these studies with a research from Turkey. Trp/Kyn balance and IDO levels were evaluated in these three autoimmune, and chronic inflammatory rheumatic diseases. In this study, we tried to determine the levels of IDO levels used as an display of autoimmunity in these chronic autoimmune diseases, and if differences are found, we aim to use them in the follow-up of diseases. With the study, we used HPLC method of the measurement of Trp and Kyn levels.

MATERIAL AND METHODS

Study population

In the study, 19 patients diagnosed with primary Sjogren Syndrome who met the 2012 American College of Rheumatology classification criteria for Sjögren's syndrome, 18 patients diagnosed with psoriasis who fulfilled the Classification criteria for Psoriatic Arthritis and 20 patients diagnosed with Rheumatoid Arthritis who fulfilled the 2010 ACR/EULAR criteria were taken from follow-up patients who agreed to participate voluntarily.

Patients with one of the following concominant diseases were excluded: additional rheumatic disease, such as autoimmune hepatitis, primary biliary cholangitis, Hashimoto thyroiditis, comorbid chronic diseases, such as hypertension, dyslipidemia, hypothyroidism, chronic kidney disease, diabetes mellitus, obesity (body mass index >30), malignancies, history of cardiovascular or cerebrovascular

disease, active smoker, outside the age range of 25-60 years, inability to give written informed consent. The demographic, clinical and laboratory information of the patients were registered.

Ethics Statement

The study protocol was approved by the Local Research Ethics Committee (Zekai Tahir Burak Women's Health, Training and Research Hospital- 60/2017). Written informed consent was obtained from all participants according to the principles of the Helsinki Declaration.

Sample collection

Blood samples were take in tubes. The samples were centrifuged at 3,000x g for 10 min. Serum samples were stored at − 80 °C until analyses were performed after were aliquoted into Eppendorf tubes..

Determination of tryptophan and kynurenine levels

L-kynurenine (Sigma Aldrich Corp., USA, MA), L-tryptophan (Sigma Aldrich Corp., USA, MA), trichloroacetic acid (Merck), HPLC gradient grade acetonitrile (Sigma Aldrich Corp., USA, MA), Inertsil ODS-3 (150mm x4.6mm x5µm) analytical column were used in this study.
Shimadzu brand Prominence LC-20A Modular HPLC System consisting of System Control Unit CBM-20A, Pump LC-20AT, On-line Degas Unit DGU-20A, Column Oven CTO-20A, Auto Sampler SIL-20A, Photo-diode Array (PDA) detector SPD-M20A modules were used for analysis.
Chromatographic separation was performed using a Inertsil ODS-3 (150 mm x 4.6 mm x 5 µm) reversed-phase analytical column and the column temperature was maintained at 25°C. The isocratic method was selected and the mobile phase consisted of, 15mmol/L acetate buffer (pH:4) solution containing 15% acetonitrile. The flow rate was 0.8 ml/min and total run time was 10 minutes. UV(PDA) detector was used in the study. Wavelengths of 360 nm for Kynurenine and 278 nm for Tryptophan were chosen.
Stock solutions of kynurenine and tryptophan were prepared in methanol. Standard dilutions were prepared within a concentration range of 0.1-1.2 mmol/L with the mobile phase and analyzed in HPLC-PDA device. The calibration line was drawn by comparing the obtained area (y) values against known concentrations (x). Both of calibration curves were obtained with R2 values of 0.99.
For sample preparation, 26 microliters of 40% perchloric acid was put into 200 microliters of serum. It was centrifuged at 12.000 rpm for 10 minutes after a 30 s vortex. 5 microliters supernatant was given to the HPLC device.

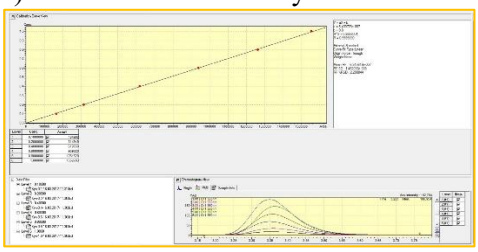
Statistical analysis

Chromatographic data was evaluate used Shimadzu LabSolutions software. SPSS version-16-software (SPSS Inc., Chicago, IL, USA) was used for general descriptive statistics on results. Mann Whitney U test was used to compare data between groups in the study. The results were evaluated at the 95% confidence interval and the significance level was $p<0.05$.

RESULTS

Serum levels of Kyn (mmol/L), Trp (mmol/L) were measured using HPLC-UV. The ratio of Kyn/Trp concentrations was calculated and used to estimate Indoleamine 2,3-dioxygenase activity [14] in Figures 1a and 1b show the calibration curves for Kyn and Trp, respectively.

a)calibration curve for Kyn.



b) calibration curve for Trp

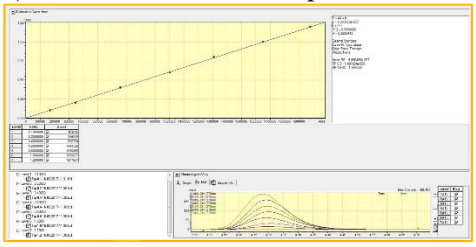


Figure 1: Calibration curve for the linearity test of standards of a) kynurenine and b) tryptophan.

In patients with pSS, the mean Trp level was 0.042 mmol/L, and the mean Kyn level was 0.020 mmol/L. The mean was calculated to be 0.042 mmol/L for Trp and 0.026 mmol/L for Kyn in the RA group. In patients with PsA, Trp levels had a mean of 0.048 mmol/L, and Kyn levels had a mean of 0.039 mmol/L. The values of the patient groups are shown in Figure 2, and descriptive statistics values are shown in Table 1.

Table 1 : Descriptive statistics values of between chronic inflammatory rheumatic diseases groups

Groups	PsA (n = 18) mean ± SD	RA (n = 20) mean ± SD	pSS (n = 19) mean ± SD
Trp (mmol/L)	0.0482 ± 0.0096	0.0418 ± 0.0084	0.0417 ± 0.0111
Kyn (mmol/L)	0.0393 ± 0.0156	0.0262 ± 0.0029	0.0198 ± 0.0022
Kyn/Trp	0.857 ± 0.422	0.653 ± 0.158	0.525 ± 0.209

SD: Standard Deviation ; *Trp:* Tryptophan;*Kyn:* Kynurenine;*PsA:* Psoriatic Arthritis;*RA:* Rheumatoid Arthritis;*pSS:* Sjogren's Syndrome

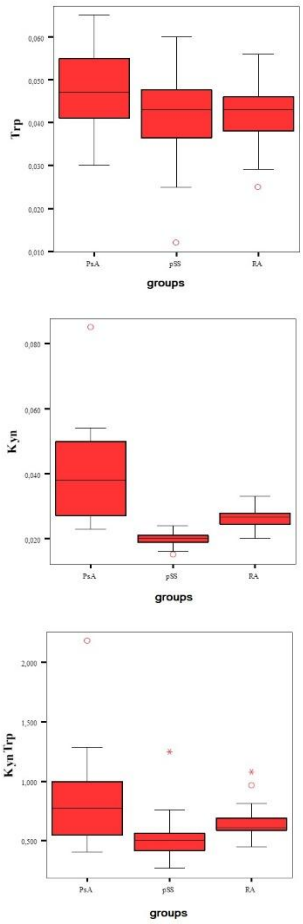


Figure 1 : The laboratory results of between chronic inflammatory rheumatic diseases groups

Trp levels were similar in RA and pSS, while higher levels were observed in PSA. Kyn levels were lower in the SS group than in the other groups. K/T ratios were the lowest in pSS among the groups. A comparison of the analysis between variables is shown in Table 2.

Table 2 : Compare of between-group variables

Groups		PsA			RA			pSS		
		Trp	Kyn	Kyn/Trp	Trp	Kyn	Kyn/Trp	Trp	Kyn	Kyn/Trp
PsA	Trp	-								
	Kyn	x	-							
	Kyn/Trp	x	x	-						
RA	Trp	0.065	x	x	-					
	Kyn	x	0.003	x	x	-				
	Kyn/Trp	x	x	0.096	x	x	-			
pSS	Trp	0.114	x	x	0.899	x	x	-		
	Kyn	x	0.00	x	x	0.00	x	x	-	
	Kyn/Trp	x	x	0.002	x	x	0.001	x	x	-

Trp: Tryptophan;*Kyn:* Kynurenine;*PsA:* Psoriatic Arthritis;*RA:* Rheumatoid Arthritis;*pSS:* Sjogren's Syndrome, *p*< 0.05

DISCUSSIONS and CONCLUSION

In our study, blood Kyn levels were lower in the PSS group than in the other groups, and statistical significance was found in the comparison between groups ($p<0.001$). The Trp/Kyn ratio values were also lower in the pSS group, and a statistically significant difference was found in the comparison between groups ($p<0.05$). IDO activity was lower than that in other groups. As IDO is known to be upregulated in response to inflammatory conditions, this could be interpreted as less inflammation in pSS among our disease groups and suggests that IDO can be used as a disease activity marker.

The organism has no immune response to its own structures. This condition is called self-tolerance or immune tolerance. Uncontrolled response of the body to its own structures as a result of disturbances in the mechanisms of tolerance, systemic or organ-specific 'autoimmune diseases' can occur with autoimmune reactions and tissue/organ damage. Therefore, critical enzymes along amino acid-degradation pathway may be important for keeping autoimmunity under control [15]. It is thought that changes in Kyn/Trp balance and increased levels of Kyn with the destruction of Trp to Kyn indicate immune activity. IDO activity is minimal in non-pathological conditions [8,16].

Depending on pathophysiological conditions such as inflammation and infection, the expression of IDO is upregulated, and the degradation of Trp to Kyn increases in extrahepatic tissues [17]. Inflammatory cytokines increase the activity and expression of IDO,

causing a decrease in Trp in the blood and tissues and an increase in the metabolites of Kyn [18]. IDO activation, mediated by pro-inflammatory cytokines such as interferon- γ, can trigger immunosuppression and tolerance [19–21]. Situated generally in immune cells, IDO plays an important role as a signaling molecule that modulates immune responses. IDO has enzymatic activity in the cytoplasm, while it has transcriptional activity in the nucleus [22–25]. Studies on immune activation have clearly shown the importance of Kyn pathway products and IDO regulation. Increased metabolism of Trp has been observed in some autoimmune diseases [26,27]. Many studies have shown that the Trp/Kyn/IDO-1,2/TDO2 metabolic pathway mediates the pathogenesis and progress of autoimmune diseases.

Increased metabolism of Trp has been observed in a few autoimmune disorders. In patients with primary Sjögren's syndrome, the plasma Kyn level and the Kyn/Trp ratio were higher then those in the control group without autoimmune symptoms [28]. Additionally, many other studies have shown a possible association between abnormalities of Trp metabolism and rheumatoid arthritis and many other autoimmune disorders [26,29,30]. In another study, the irreguler concentration of Trp metabolites, which is defined by high Kyn/Trp ratios in serum and urine, was shown in RA patients. Also, disease activity and clinical symptoms showed a positive correlation with decreased Trp and increased Kyn levels [31–33].

In the intergroup evaluation in our study, the Kyn/Trp ratio was highest in PsA. Although RA is known to have a worse prognosis among these three groups of diseases, in our results, IDO was higher in the PsA group. However, a marginally significant was found in the comparison of Kyn/Trp ratio between RA and PsA groups (p=0.096). Trp and Kyn levels of this group were also higher than the other groups.

Studies in patients with SS have approved that Kyn pathway can be stimulated by interferon-y and other cytokines by activating IDO [22]. Another study of patients with pSS, IDO appears to be a more possible activator of increased Trp breakdown in pSS, as IDO is known to be upregulated in response to inflammatory conditions [28,34].

Another study, have been shown for a possible relationship of IDO with the pathogenesis of RA. It was found that the serum concentrations of decreased Trp and increased Kyn, respectively, in serum samples of RA patients compared to healthy controls [35–37]. The lack of the tryptophan, is the most likely consequence of immune activation releated in the pathogenesis of the disease in patients with RA [16,38].

In our study in three different disease groups, blood Trp values were the similar in the pSS and RA groups, but higher in the PsA group. Similar results were obtained while Trp values were expected to be lower due to the more widespread effects of RA in the body.

In most studies, upregulation of IDO expression has been associated with a poor clinical outcome. A decreased level of Trp and a high level of Kyn indicate a high level of IDO activity. The deficiency of Trp in these patients is most likely due to immune activation, which is related in the pathogenesis of the disease. It has been proposed that clarify the process of tryptophan metabolism in immune regulation may contribute for novel immunotherapeutic advances to treatment to autoimmune diseases[10,34]. Therefore, inhibition of IDO by chemicals has become a therapeutic target for cancer or autoimmune diseases or AIDS treatment[12,19,39,40].

In our study, we observed that blood Kyn and IDO levels in pSS were lower than the other groups, and there was a statistically significant difference between IDO levels in the comparison between groups ($p<0.05$). IDO levels are minimal in non-pathological conditions. Lower IDO levels in pSS compared to other groups may be associated with disease activity. As a result, a comprehensive assessment of the function of IDO in the immunomodulatory procedure can help to obtain IDO inhibitors as optimal drugs.

In our study, we found various differences between the groups in terms of Trp, Kyn and IDO levels. This may not be sufficient for intergroup comparison. We believe that there is a need to work with larger groups in order to use IDO as a disease activity monitoring marker.

A few limitations of this study should be noted. The small example size and the cross-sectional design are important limitation of our study. A larger sample size may be needed to clarify the activity and mechanism of IDO in systemic autoimmune diseases that are heterogeneous diseases. Our results do not provide sufficient results to investigate

potential causality and disease duration, disease activity, and treatment response, as well as changes in these variables. Future studies may focus on easy sampling materials and noninvasive methods to study the metabolic pathways of Trp, Kyn, and IDO.

The kynurenine pathway is a potent mechanism to stimulate and regulating an immune response. In this pathway, the degradation of tryptophan is increased and kynurenine metabolites are produced as a result. In addition, metabolites of this pathway can synergize or antagonize each other's effects with their different natural features. By evaluating the levels of Trp, Kyn and the Kyn/Trp ratio, the degree of immune activation under different pathophysiological conditions can be defined, and the correlation between the kynurenine pathway and autoimmune disease states can be determined. Nevertheless, numerous studies are still required to completely determine the complex relationships of IDO, Trp, Kyn and their metabolites, both among themselves and in the whole organism.

Statements and Declarations

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Conflicts of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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