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Tryptophan degradation and neopterin levels by aging

Abstract: Increased neopterin concentrations and altered tryptophan degradation are observed in diseases concomitant with cellular immune activation. This may be involved in the pathogenesis of several age-related disorders such as neurodegenerative disorders, autoimmune diseases, cardiovascular system disorders and malignancies. Therefore, in the present study, the evaluation of immune system activation by determination of tryptophan degradation and serum neopterin levels was carried out in volunteers aged ≥65 and <65 years old. The kynurenine-to-tryptophan ratio was calculated to estimate indoleamine-(2,3)-dioxygenase (IDO) activity. Tryptophan levels in the elderly (53.1±1.6 μmol/L) were lower than individuals under 65 years (61.4±2.2 μmol/L), whereas kynurenine concentrations in geriatrics and adults were 5.0±0.2 μmol/L and 4.3±0.2 μmol/L, respectively (both $p<0.05$). The kynurenine-to-tryptophan ratio was also significantly higher in geriatrics (92.1±3.2) than adults (73.5±2.8) ($p<0.05$). Neopterin levels were slightly higher in geriatrics compared to adults under 65 years old ($p>0.05$). Effects of gender, smoking habit, pathology and drug use on measured parameters were also evaluated. In conclusion, our findings show that aging is associated with immune activation, and immune activation may be induced by the number of existing pathologies as well as the number of drugs used.

Keywords: elderly; immunomodulation; kynurenine pathway; neopterin.

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Introduction

Aging is characterized by impairment in defense functions and repair processes that provide functional integration between cells and organs. Therefore, this physiological term is associated with progressive increases in the number of disorders and diseases and eventually death [1, 2]. According to the World Health Organization (WHO), most developed countries have accepted the chronological age of 65 years as the definition of elder person [3]. Changes in body composition, organ functions and significant pharmaco-/toxico-kinetic and pharmaco-/toxico-dynamic changes occur with advancing age [4]. One of the most important changes that develop with age is a decrease in immunocompetence [5]. This may be involved in the pathogenesis of several age-related disorders such as neurodegenerative disorders, autoimmune diseases, cardiovascular system disorders, psychiatric complications and malignancies [6, 7]. These diseases also correlate well with two immune-related changes: tryptophan (trp) degradation [8] and neopterin (neop) release [9].

Trp is an essential amino acid which is critical in several metabolic functions. It is a constituent of proteins and also the precursor of two important biosynthetic pathways: the generation of neurotransmitter serotonin and formation of kynurenine (kyn) derivatives and nicotinamide adenine dinucleotides [10]. Trp metabolism mainly occurs through the kyn pathway in the body. Oxidation of trp to kyn is catalyzed by tryptophan pyrrolase (tryptophan 2,3-dioxygenase, TDO) mainly in the liver and by indoleamine 2,3-dioxygenase (IDO) in extrahepatic tissues. With the effect of TDO, blood trp concentration decreases and kyn levels and hence the kyn/trp ratio increases. However, this increase is usually small and not affected by immune activation. IDO is highly inducible by proinflammatory cytokines. The most potent inducer of IDO is interferon-gamma (IFN-γ) produced by T cells (Figure 1) [11–14]. To confirm that trp degradation is held by IDO rather than TDO, it is necessary to demonstrate a concomitant increase of immune system activation markers such as neop [15].

Neop, mainly synthesized by activated macrophages, is a marker of inflammation and immune system

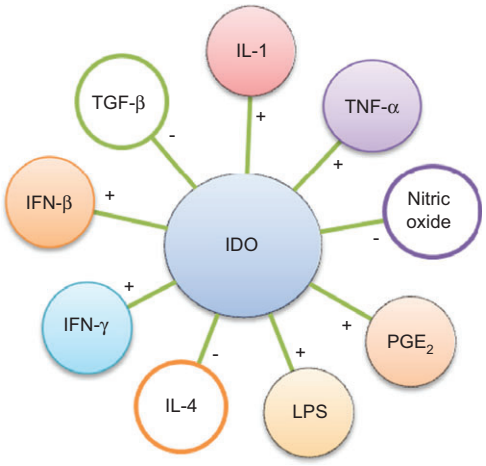

Figure 1 Effect of cytokines or other immune regulatory factors on IDO.
Abbreviations: IL, interleukin; TNF-α, tumor necrosis factor-alpha; LPS, lipopolysaccharide; PGE2, prostaglandin E2; TGF-β, transforming growth factor-beta.

activation. It exists in biological fluids and tissues in reduced and oxidized forms. Production of neop provides prognostic information in inflammation-induced diseases. Neop concentration reflects both the activation of cellular immunity and endogenous release of IFN-γ and the level of oxidative stress caused by activation of the immune system [16, 17].

The frequency of immune system dysfunction generally increases with age. The major aim of the present study was to assess alteration(s) of the immune system in the elderly by measuring trp, kyn and neop levels as a marker for immune activation. Profiles of the parameters by aging were also determined. Additionally, the effects of gender, smoking habit, pathology and drug use on measured parameters were evaluated.

Materials and methods

Study groups and sample collection

Blood samples were collected from 94 volunteers, aged 24–88 years, admitted to the Department of Physical Medicine and Rehabilitation and/or Geriatric Unit in Hacettepe University Adult Hospital. A percentage of participants were employees from the Faculty of Pharmacy, Hacettepe University. Participants were primarily divided into two main groups: <65 years (n=46) and ≥65 years (n=48). The main age groups were divided into subgroups for further evaluation. Participants were also classified according to gender (47 female, 47 male), smoking habit (smokers, n=24) and their chronic diseases.

The participants recruited to the study were questioned whether they had any pathology/health problems and used any chronic medication. Individuals with one, two and three or more diseases were grouped. In total, 35 participants reported no treatment, whereas 59 participants declared using one or more medications. According to the questioning forms, commonly used drugs were antihypertensive agents (n=42) and antiplatelets (n=26). The distribution of other agents were anti-osteoporosis drugs (n=12), oral antidiabetics (n=11), diuretics (n=10), antihyperlipidemics (n=8), acid pump inhibitors (n=6), venoprotector prescriptions (n=3), antiepileptics (n=2), antidepressants (n=2), oral contraceptives (n=1) and non-steroidal anti-inflammatory drugs (n=1). Others included drugs for the treatment of hypothyroidism (n=1), schizophrenia (n=1), dementia (n=1), benign prostatic hyperplasia (n=1) or asthma (n=1).

Following the collection of blood specimens, sera were separated by centrifugation and stored at –20°C until analysis.

The principles of the Ethical Committee of the University in accordance to the Helsinki Declaration were followed during the entire study (# 04/04–5).

Determination of tryptophan degradation and kynurenine pathway

Serum trp and kyn measurements were performed by high-performance liquid chromatography (HPLC) using reversed phase C18 columns. Protein was precipitated by trichloroacetic acid. Trp concentration was monitored by detection of its natural fluorescence (285 nm excitation and 365 nm emission wavelength) and kyn was measured by using UV absorption at 360 nm [18]. The kyn/trp ratio was calculated to assess IDO activity.

Measurement of neopterin levels

Neop concentrations in serum samples were measured by using a commercially available quantitative enzyme-linked immunosorbent assay (ELISA) system (DRG Instruments GmbH, Marburg, Germany) according to the manufacturer's instructions.

Statistical analysis

Results were expressed as standard error of the mean (SEM). The differences among groups were evaluated with Kruskal-Wallis analysis of variance; comparison between two independent groups was detected using the Mann-Whitney U-test. Correlations of the parameters were analyzed using Spearman's nonparametric correlation test. A p-value <0.05 was considered statistically significant.

Results

All results are presented in Tables 1 and 2 including detailed characteristics of the subgroups. There were no significant differences between genders in the measured parameters ($p > 0.05$).

Table 1 Characteristics of the groups and concentrations of the measured parameters.

Groups	n	Gender (F/M)	Age (years)	Tryptophan (µmol/L)	Kynurenine (µmol/L)	Kyn/Trp	Neopterin (nmol/L)
							Mean±SEM (min–max)
Total	94	47/47	55.9±2.0 (24–88)	57.1±1.4 (10.5–94.1)	4.7±0.1 (0.8–8.4)	82.5±2.3 (42.2–135.8)	12.0±0. 8 (2.7–28.4)
Gender							
Male	47		57.1±3.0 (26–88)	56.78±2.14 (10.5–87.1)	4.66±0.20 (0.8–7.8)	82.56±3.55 (43.0–135.8)	11.8±0.9 (4.0–28.4)
Female	47		54.7±2.6 (24–86)	57.47±1.84 (34.4–94.1)	4.71±0.18 (2.2–8.4)	82.53±3.02 (42.2–119.6)	12.2±1.0 (2.7–26.5)
Age, years							
<65	46	26/20	38.6±1.0 (24–63)	61.4±2.2 (10.5–94.1)	4.3±0.2 (0.8–7.8)	73.5±2.8 (42.2–115.6)	11.4±1.0 (2.7–26.5)
≥65	48	21/27	72.5±0.8 (65–88)	53.1±1.6[a](33.8–82.8)	5.0±0.2[a] (2.3–8.4)	92.1±3.2[a] (43.0–135.8)	12.5±0.9 (3.6–28.4)
Age subgroup, years							
19–44	32	13/19	32.0±1.0 (24–44)	60.7±2.8 (10.5–94.1)	3.9±0.2 (0.8–5.7)	65.6±2.4 (42.2–95.3)	9.6±1.0 (2.7–24.3)
45–64	14	13/1	53.7±1.5 (45–63)	62.8±3.5 (37.3–94.1)	5.4±0.4 (3.4–7.8)	90.8±5.0[b] (56.6–115.6)	16.1±1.8[b] (7.2–26.5)
65–74	31	17/14	69.5±0.5 (65–74)	53.9±1.7[b,c] (40.8–71.7)	5.0±0.2[b] (2.3–7.7)	92.3±3.6[b] (43.0–127.1)	11.6±1.2[b,c] (3.6–28.4)
≥75	17	4/13	78.2±1.0 (75–88)	51.5±3.4[b,c](33.8–82.8)	5.0±0.3[b] (3.6–8.4)	91.6±6.3[b] (55.6–135.8)	14.3±1.5[b] (5.1–26.6)
Smoking status							
Non-smoker	70	40/30	59.8±2.1 (24–86)	57.9±1.5 (34.4–94.1)	4.9±0.2 (2.2–8.4)	85.0±2.80 (42.2–135.8)	11.8±0.8 (2.7–28.4)
Smoker	24	7/17	43.5±3.7 (26–80)	55.4±3.6 (10.5–94.1)	4.1±0.2[d] (0.8–5. 7)	74.6±3.83 (43.0–103.7)	12.0±1.4 (4.4–26.6)

[a]$p<0.05$, compared to <65 years; [b]$p<0.05$, compared to 19–44 years, [c]$p<0.05$, compared to 45–64 years subgroup; [d]$p<0.05$, compared to non-smokers.

The results were compared between the groups aged ≥65 years old as geriatric and aged <65 years old as non-geriatric. Serum trp levels of the geriatric group were significantly lower than in the younger group (p=0.001). Both levels of kyn and kyn/trp were found to be higher in the geriatric group compared with the younger group (p=0.007 and p<0.001, respectively). The neop levels in the geriatric group were also slightly higher than in the younger group but the difference was not significant (Table 1).

Adults were separated into two subgroups aged 19–44 years and middle-aged 45–64 years. Geriatrics were also divided into two subgroups aged 65–74 years and ≥75 years. Parameters of age subgroups were compared and serum kyn/trp ratio and neop levels of adults aged 19–44 years were found to be significantly lower than the geriatric subgroups and the middle-aged adult group (all p<0.05).

Trp levels decreased (p<0.05), whereas neop and kyn levels and kyn/trp increased by age (all p<0.05, Figure 2). Detailed statistical results of correlation analyses are displayed in Table 3.

Smoking habit did not alter trp and neop levels and IDO activity (all p>0.05). However, kyn levels were lower in smokers than non-smokers (p=0.034).

The effects of existing pathologies and the number of drugs used on neop, trp and kyn levels and kyn/trp are presented in Table 2. Individuals with hypertension (HT) had lower trp levels than those without HT (p=0.015). By contrast, mean kyn and neop levels and kyn/trp were significantly increased in patients with HT (all p<0.05). Patients with osteoporosis (OP) were found to have significantly lower trp levels compared to the group without OP (p=0.031), but the other measured parameters were not different between the individuals with and without OP (all p>0.05). In patients with type 2 diabetes mellitus (DM), levels of trp and kyn/trp were found to be significantly higher than those without DM (p=0.040 and p=0.012, respectively). There was no significant difference in kyn and trp levels (both p>0.05). Trp levels in patients with hyperlipidemia (HL) were significantly lower than those without HL (p=0.026). However, kyn and neop levels and kyn/trp were not different between individuals with and without HL (all p>0.05).

Correlations between the parameters are presented in Table 3. A strong positive correlation was detected between kyn/trp and neopterin, kyn and neop concentrations and a weaker but still significant negative association between trp and neop levels when assessed in all participants. Furthermore, a correlation between neop concentrations and the kyn/trp ratio was found in HT, OP and HL groups.

Table 2 Chronic conditions, number of existing pathologies, number of drug used and concentrations of the measured parameters.

Groups	n	Gender (F/M)	Age (years)	Tryptophan (µmol/L)	Kynurenine (µmol/L)	Kyn/Trp	Neopterin (nmol/L)
							Mean±SEM (min–max)
Chronic conditions							
Hypertension	+ (48)	28/20	68.9±1.4 (45–88)	54.7±1.9[a] (33.8–94.1)	5.1±0.2[a] (3.3–8.4)	92.7±2.7[a] (56.6–134.5)	13.7±1.0[a] (4.0–28.4)
	– (46)	19/27	42.4±2.6 (24–78)	59.7±2.0 (10.5–94.1)	4.2±0.2 (0.8–7.2)	72.4±3.1 (42.2–135.8)	10.4±0.9 (2.7–26.5)
Osteoporosis	+ (19)	15/4	71.2±2.0 (50–86)	51.5±2.7[a] (33.8–71.7)	5.0±0.3 (3.3–8.42)	89.6±4.5 (68.1–134.5)	12.3±1.5 (4.0–26.6)
	– (75)	32/43	52.1±2.2 (24–88)	58.5±1.6 (10.5–94.1)	4.6±0.2 (0.8–7.8)	81.0±2.6 (42.2–135.8)	11.9±0.8 (2.7–28.4)
Type II diabetes	+ (17)	11/6	65.2±2.9 (31–84)	51.7±2.6[a] (34.8–71.7)	4.9±0.2 (3.6–7.0)	94.6±5.1[a] (59.4–134.5)	13.9±1.5 (3.6–26.5)
	– (77)	36/41	53.9±2.3 (24–88)	58.3±1.6 (10.5–94.1)	4.6±0.2 (0.8–8.4)	80.1±2.5 (42.2–135.8)	11.5±0.8 (2.7–28.4)
Hyperlipidemia	+ (12)	6/6	72.2±1.3 (65–78)	50.8±2.3[a] (42.3–67.0)	4.6±0.2 (3.3–5.7)	91.2±3.9 (68.1–111.1)	10.4±1.7 (4.0–17.3)
	– (82)	41/41	53.6±2.2 (24–88)	58.1±1.6 (10.5–94.1)	4.7±0.2 (0.8–8.4)	81.2±2.6 (42.2–135.8)	12.2±0.7 (2.7–28.4)
Number of existing pathologies							
0	30	13/17	34.5±2.0 (24–73)	59.2±2.9 (10.5–94.1)	4.0±0.2 (0.8–6.2)	69.3±3.3 (42.2–119.6)	9.6±1.1 (2.7–2.3)
1	20	10/10	57.1±3.7 (26–80)	60.6±3.1 (33.8–94.1)	4.7±0.3 (2.3–7.8)	79.4±5.1 (43.0–115.6)	12.8±1.7 (4.4–26.6)
2	18	10/8	67.2±2.4 (48–88)	57.6±2.9 (40.8–82.8)	5.6±0.3[b,c] (3.6–8.4)	92.4±4.9[b] (56.6–124.3)	13.9±1.4[b] (3.6–24.6)
≥3	26	14/12	72.0±1.3 (51–86)	51.7±2.1[b,c] (34.4–71.7)	5.0±0.2[b] (3.3–7.7)	94.3±3.8[b,c] (68.1–135.8)	13.0±1.3[b] (4.0–28.4)
Number of drugs used							
0	35	13/22	40.1±2.9 (24–88)	57.4±2.5 (10.5–94.1)	4.0± 0.2 (0.8–6.2)	70.0±3.4 (42.2–119.6)	9.9±1.0 (2.7–24.3)
1	19	13/6	57.8±4.0 (28–80)	58.4±3.0 (33.8–87.1)	5.0±0.3[d] (3.4–8.4)	82.1±4.4[d] (53.6–113.4)	13.8±1.5[d] (4.8–26.6)
2	17	7/10	70.0±2.2 (45–84)	55.1±3.1 (34.8–82.8)	5.1±0.3[d] (3.3–7.8)	94.2±4.1[d] (68.1–134.5)	11.3±1.3 (4.0–17.5)
≥3	23	14/9	68.0±2.1 (48–86)	57.2±2.9 (34.4–94.1)	5.1±0.2[d] (3.6–7.7)	93.2±4.8[d] (56.6–135.8)	14.2±1.5[d] (3.6–28.4)

[a]$p<0.05$, compared to without disease; [b]$p<0.05$, compared to existing no pathology; [c]$p<0.05$, compared to existing 1 pathology; [d]$p<0.05$, compared to no drug used.

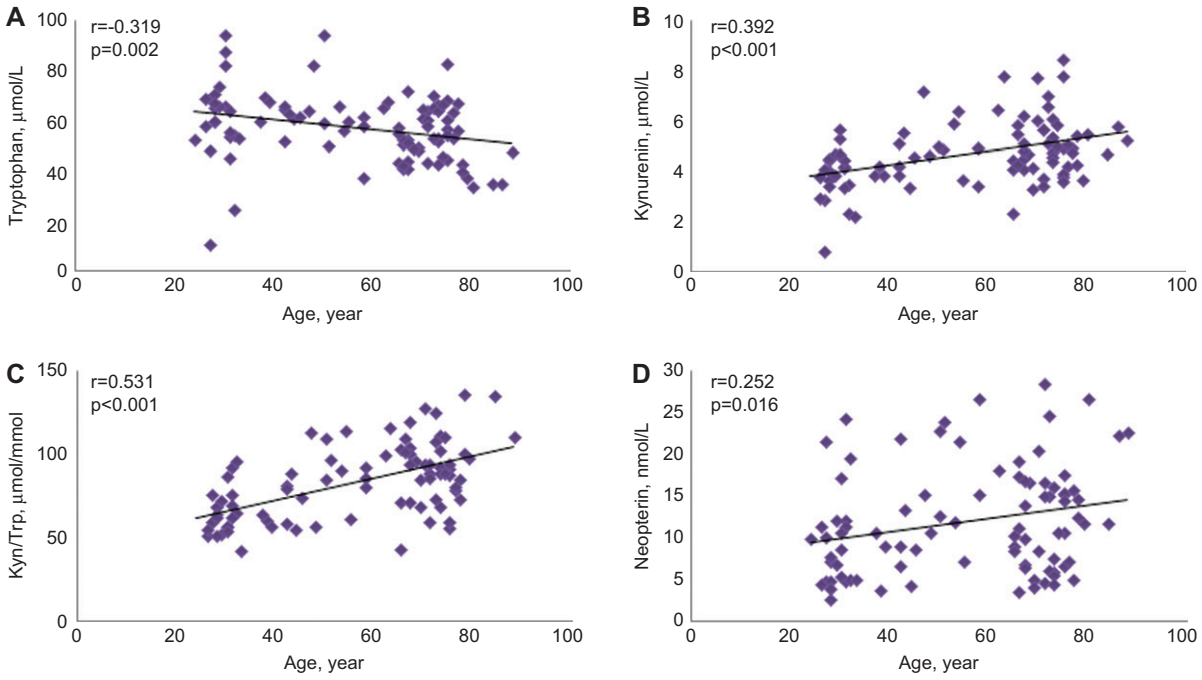

Figure 2 Alteration of serum tryptophan (A), kynurenine (B), Kyn/Trp (C) and neopterin (D) concentrations by age (*p<0.05).

Discussion

Aging is a complex period of life with different structural and functional changes. Many changes of systems and processes occur in our body as aging [19–21]. It is well known that any alteration in immune status may play a role in the etiology of disorders. In addition to conventional parameters, neop levels and trp degradation also change with age as a result of immune modulation [22]. As shown in Table 3, increases in trp degradation strongly correlate with neop levels, an early marker of T cell activation, showing that trp degradation is held by IDO rather than TDO. In the present study, trp levels in the elderly were found to be 13% lower than <65-year-old individuals, whereas kyn concentrations were 16% higher. As a result of these findings, kyn/trp was also increased in geriatrics compared to

Table 3 Correlations between the measured parameters in groups.

Groups	Parameters R (p-value)			
	Neop-Trp	Neop-Kyn	Neop-Kyn/Trp	Trp-Kyn
All participants	−0.224 (0.034)[a]	0.349 (0.001)[a]	0.470 (<0.001)[a]	0.204 (0.053)
Age, years				
<65	−0.151 (0.328)	0.472 (0.002)[a]	0.595 (<0.001)[a]	0.413 (0.005)[a]
≥65	−0.293 (0.048)[a]	0.206 (0.174)	0.407 (0.008)[a]	0.271 (0.065)
Age subgroups, years				
19–44	−0.183 (0.315)	0.248 (0.179)	0.359 (0.047)[a]	0.574 (0.001)[a]
45–64	−0.161 (0.618)	0.445 (0.170)	0.566 (0.055)	0.429 (0.144)
65–74	−0.176 (0.351)	0.208 (0.279)	0.450 (0.016)[a]	0.444 (0.014)[a]
≥75	−0.359 (0.172)	0.421 (0.105)	0.335 (0.263)	-0.049 (0.852)
Chronic conditions				
Hypertension	−0.167 (0.279)	0.268 (0.082)	0.428 (0.006)[a]	0.435 (0.002)[a]
Osteoporosis	−0.280 (0.261)	0.740 (<0.001)[a]	0.575 (0.025)[a]	0.209 (0.391)
Types II diabetes	−0.009 (0.974)	0.155 (0.568)	0.234 (0.401)	0.374 (0.154)
Hyperlipidemia	−0.445 (0.170)	0.091 (0.790)	0.727 (0.011)[a]	0.524 (0.080)

[a]p<0.05.

adults. This increase in trp degradation may result with the overproduction of neuroactive kyn derivatives [23, 24]. By contrast, changes in trp degradation may reduce serotonin biosynthesis and decrease serum serotonin biosynthesis, which may contribute to impaired quality of life in the older age group [25–28]. Similar to trp degradation with age, neopterin levels were found to be approximately 10% elevated in the ≥65-year-old group in comparison with the <65-year-old group. In this study, average neop levels were almost twice as high as other reports using different brand ELISAs. Most of these assays appear to use the same cut-off value of 10–11 nmol/L [29, 30]. It can be suggested that an individual cut-off value needs to be defined by the user when this particular assay is applied.

There are conflicting results with regard to changes in trp degradation and gender. Although we found no differences, kyn concentration in women has been shown to be higher than men and this change has been suggested to be possibly related to hormonal conditions [15]. By contrast, according to Werner et al., there were no differences in serum neop levels between genders [31].

In the present study, smoking showed no effect on measured parameters. However, in the literature, some studies with large populations reported lower neop [30, 32] and lower kyn/trp [33, 34] in smokers versus non-smokers. In our case, the number of participants was rather small compared to previous studies, and two subgroups have disparate volunteer numbers.

In the geriatric population, decreased trp concentrations and increased kyn concentrations in parallel with neop production have been described in various prevalent diseases [9, 35]. In the groups with HT, OP and HL, there was a positive correlation between neop and kyn/trp. Among these diseases, correlations of neop with kyn/trp concentrations were stronger for participants with HT.

We observed an increase in the number of existing pathologies, as well as the number of drugs used by age. Furthermore, immune activation in individuals using medication was apparent. It was observed that drug use has an effect on both trp degradation and neop levels. These results reflect that the number of existing disorders increases with age followed by increases in the number of medications, which arise as changes in immune activation. Besides, polypharmacy is well known to be very common in the geriatric population [36].

There is a lack of data regarding pteridine levels in the geriatric population in Turkey. Our aim was to initiate and broaden pteridine studies in different age or disease groups in Turkey. In the present study, the groups aged ≥65 and <65 years old were compared, and neop levels, as well as trp degradation was determined to be higher in the elderly. As in other age groups, evaluation of immune system activation with pteridine pathway related parameters in the geriatric population and routine measurements of early markers in the immune system may contribute to the implementation of effective treatment approaches and will allow reduction and prevention of potential health problems.

In conclusion, in accordance with previous studies [34, 37], our findings suggest that aging is associated with immune activation which may lead to enhanced degradation of trp and neop production, and immune activation seems to be induced by the number of existing pathologies as well as the number of drugs used. Given the growing number of elderly people worldwide, the results of this study on a geriatric population in Turkey may contribute to further research related to this subject area.

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