

# Negative correlation between TNF- $\alpha$ and triglyceride levels in patients with cerebral infarction

Hikmet Sacmaci<sup>1</sup>, Murat Cakir<sup>2</sup>, Seda Sabah Ozcan<sup>3</sup>

<sup>1</sup>Department of Neurology, Faculty of Medicine, Bozok University, Yozgat, Turkey

<sup>2</sup>Department of Physiology, Faculty of Medicine, Bozok University, Yozgat, Turkey

<sup>3</sup>Department of Medical Biology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey

Copyright@Author(s) - Available online at [www.annalsmedres.org](http://www.annalsmedres.org)

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



## Abstract

**Aim:** To investigate the interactions between tumor necrosis factor-alpha (TNF- $\alpha$ ) and blood lipid levels in patients with acute cerebral infarction.

**Materials and Methods:** A total of 43 cerebral infarction patients who applied to the neurology and emergency department of our faculty were included in cross-sectional matched case-control study, and the results were compared with 41 controls who had similar age and comorbidities. In addition to fasting serum lipids, serum glucose, C-reactive protein and hemogram were analyzed as well. Classification of infarct was made. An enzyme-linked immunosorbent test was used to determine baseline plasma TNF- $\alpha$  levels at the time of first admission and potential correlations between the groups were analyzed.

**Results:** Compared to the control group, the cerebral ischemia group had a higher median TNF- $\alpha$  level (23.53; range, 21.74-43.29 ng/L vs. 23.00; range, 20.62-37.34 ng/L); however, the difference was not significant ( $p > 0.05$ ). Groups were similar regarding blood lipid values ( $p > 0.05$ ). In the patient group, TNF- $\alpha$  level showed a negative correlation with triglyceride (TG) and TG / HDL cholesterol (HDL-C) ( $\rho = -0.319$   $p = 0.037$  and  $\rho = -0.321$   $p = 0.036$ ), whereas no significant correlation was determined in the control group ( $p > 0.05$ ), on the other hand plasma level of TNF- $\alpha$  was positively correlated with the National Health Stroke Scale score ( $\rho = 0.455$   $p = 0.002$ ).

**Conclusions:** Our cross-sectional study revealed an interaction between decreased TG and TG / HDL-C and a high concentration of TNF- $\alpha$  in cerebral infarction for the first time. The importance of our finding is that it provides useful preliminary information, which is necessary for further research in this field.

**Keywords:** Cerebral infarction; inflammation response; triglyceride; tumor necrosis factor alpha

## INTRODUCTION

Although acute cerebral infarction (ACI) is one of the most common causes of permanent disability all over the world, our knowledge on the issue is still limited today (1). Immune cells could become active following a stroke and subsequently, they mediate the entry of peripheral immune cells into the brain parenchyma through the injured blood-brain barrier, with high levels of pro-inflammatory cytokine release (2). Neuroinflammation induces further damage that results in cell death; however, it also has a beneficial function that boosts healing. This inflammatory response occurs in all subtypes of stroke, though it is more common in cardioembolic stroke (3).

Tumor necrosis factor-alpha (TNF- $\alpha$ ) is the primary pleiotropic cytokine that induces stimulation under various pathological and physiological conditions and is associated with inflammation and other immune

responses (4). It has pro-inflammatory properties that increase neural damage in cerebral ischemia (5). It has been underscored in recent findings that TNF- $\alpha$  has significant effects on cerebral ischemia (6). TNF- $\alpha$  is produced by both neurons and microglia in the brain following stroke and plays a key role in all stages of stroke-related brain damage (7). TNF- $\alpha$  can trigger ischemic injury in multiple directions; however, there are studies evaluating the level differently within hours and days after stroke (8).

Dyslipidemia is an alterable risk factor and is associated with a 1.8 to 2.6-fold increased risk of stroke. Conventional lipid parameters, which are represented by increased triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and decreased high-density lipoprotein cholesterol (HDL-C) concentrations, have been identified as risk factors and predictors for cardiovascular disease and cerebral infarction (9).

Received: 09.04.2021 Accepted: 30.06.2021 Available online: 19.08.2021

Corresponding Author: Hikmet Sacmaci, Department of Neurology, Faculty of Medicine, Bozok University, Yozgat, Turkey

E-mail: [hsacmaci@hotmail.com](mailto:hsacmaci@hotmail.com)

In patients with hypercholesterolemia, increased plasma TNF- $\alpha$  levels were accompanied by increased LDL-C and TC concentrations. Besides, it has been found that in hyperlipidemic patients, TNF- $\alpha$  levels are positively correlated with TC and TG concentrations whereas it is negatively correlated with HDL-C concentration (10). Inflammatory mechanisms play a critical role in the atherosclerosis process. Previous studies have shown that TNF- $\alpha$  and some cytokines are increased in atherosclerosis (11). Increasing evidence suggests that TNF- $\alpha$  has an important function in the neuroimmunological development of stroke and has both toxic and protective roles in the damaged brain (3). Yet, there are few data related to the effects of TNF- $\alpha$  on lipid metabolism in stroke patients.

The mechanism of immune activation after stroke is one of the subjects that continue to be investigated in ACI, where primary and secondary protection modalities are crucial. The aim of this study was to investigate the inflammatory properties of plasma TNF- $\alpha$  values and their potential effects on blood lipid values in patients with cerebral infarction as well as the potential interactions between them.

## MATERIALS and METHODS

### Study design and participants

This research is a matched cross-sectional case-control study that includes patients with acute ischemic stroke who were admitted to the Neurology Department of a tertiary training hospital in the central Anatolian region. The ethical approval was obtained from the Ethics Committee; the informed consent form was signed by the patients and/or family members (2017-KAEK-189\_2021.03.10\_06).

Throughout the study, 50 patients who were diagnosed with cerebrovascular disease were hospitalized. 43 patients had a confirmed diagnosis of stroke, and they had complete imaging studies; 40 of the patients were discharged with full recovery, 1 of them underwent thrombolytic therapy and 3 patients died. The control group consisted of 41 age- and sex-matched subjects who had no known brain disease and had vascular risk factors similar to the patient group.

Demographic information, etiology, stroke location, laboratory and imaging results of the patients included in the study were recorded. Risk factors for ischemic stroke were recorded, including comorbidities of heart diseases, hypertension, carotid artery plaques, diabetes mellitus etc. National Institute of Health Stroke Scale (NIHSS) scores range between 0 and 42, and the scores are considered as follows; 0-1: normal, 2-4: mild neurological impairment, 5-15: moderate neurological impairment, 16-20: severe neurological disorder, and 21-42: extremely severe neurological disorder.

Individuals with clinically significant infections, inflammatory diseases, collagen vascular diseases, malignant or autoimmune diseases, severe head trauma or surgical intervention in the last 6 months, or severe

heart, kidney, or liver failure, as well as individuals with mental illness were excluded from the study.

In our study, which was conducted in accordance with the subtypes of Framingham and TOAST (The Trial of Org 10172 in Acute Stroke Treatment) criteria, the etiological assessment of ischemic stroke patients were performed via clinical findings, electrocardiography (ECG), transthoracic echocardiography (ECHO), magnetic resonance imaging (MRI), ultrasonography of extracranial veins (the lumen diameter at the largest stenosis point and then the normal part of the artery outside the carotid bulb, the percentage of stenosis, the ratio of these two measurements using the view that shows the largest stenosis) and MRA, if necessary. Among our patient group, atherothrombosis was considered as the etiology in 31 (72%) patients, based on the patients' medical history and other ischemic risk factors as well as based on the examinations. The etiology was decided to be cardioembolic in the remaining 14 patients (28%), based on the medical history, ECG, and ECHO results.

### Laboratory tests

#### Blood Lipids

Regarding the TC, LDL-C, TG and HDL-C levels, for both groups, the mean values were determined based on the laboratory reference values (TC < 200 mg/dl; HDL-C > 45 mg/dl, LDL-C > 130, TG 0-200 mg/dl). The plasma atherogenic index (PAI) was calculated by taking the logarithm of the TG / HDL cholesterol ratio.

#### Plasma TNF- $\alpha$ Levels

Blood samples for plasma TNF- $\alpha$  levels were collected via venipuncture at the first 24-hours of hospitalization. Within the first 30 minutes, the plasma was separated by centrifuging the samples for 5 minutes at 3000 rpm and the samples were stored at -80°C by the Faculty of Medicine Physiology Department. TNF- $\alpha$  concentration in plasma was analyzed by an enzyme-linked immunosorbent assay (ELISA) technique in accordance with the protocol of the kit (Cat.no: E0082Hu, Shanghai China).

#### Statistical Analysis

The software of SPSS 18.0 was used for the statistical analysis. Descriptive statistics (mean, std. deviation, median, interquartile range etc.) were presented for numerical variables of the sample, which was divided into two groups as study and control groups. The conformity of continuous variables to distribution with normality properties were determined by the Shapiro-Wilk test. Independent Sample t-test and Mann-Whitney U (for non-parametric data) test were used for the comparisons between the two groups when the variables had a normal distribution. Categorical variables were expressed as the number of cases/percentages, and the  $\chi^2$  test was used to compare the two groups. Spearman (nonparametric) and Pearson (parametric) tests were used to calculate the correlation coefficients. The results were considered statistically significant at  $p < 0,05$ .

## RESULTS

Forty-three patients who had been hospitalized on the first day of ischemic stroke were included in the study. Of these, 22 patients were female, which accounted for 51% of all subjects. The median age and interquartile range values of the subjects and controls were 72 (64-78); 69 (50-88), respectively, and the condition of similarity between groups was met. Besides, no significant difference was detected between the two groups regarding body mass index, gender, presence of hypertension, cerebrovascular disease, diabetes history, coronary artery disease, or comorbidities associated with these diseases ( $p > 0.05$ ). In the patient group, 23 patients (53.5%) had small vessel stroke, 11 patients (25.6%) had a cardioembolic stroke, and 9 patients (20.9%) had large vessel infarction. Moreover, the median and percentiles of the patients' NIHSS scores were 5 (3-10).

No significant difference was determined between the groups regarding the values of fasting glucose, LDL-C,

HDL-C, TG, TC and CRP, and white blood cell and platelet values in hemogram. Compared to the control group, plasma TNF- $\alpha$  levels were higher in the patient group, but the difference was not significant ( $p = 0.560$ ). Table 1 shows the clinical and baseline laboratory values of the participants in the groups. Plasma TNF- $\alpha$  level was also measured at similar levels in our patient group who were classified according to TOAST ( $p = 0.293$ ). A significant positive correlation was determined between TNF- $\alpha$  and NIHSS score, as presented in (Table 2) ( $\rho = 0.455$ ,  $p = 0.002$ ).

Separate correlation analysis between TNF- $\alpha$  and blood lipids did not show significant correlations in all subjects but revealed a significant negative correlation between plasma TNF- $\alpha$  level and the scores of TG and PAI in the patient group ( $\rho = -0.319$ ,  $p = 0.037$ ;  $r = -0.321$ ,  $p = 0.036$ ). The correlations between TNF- $\alpha$  and blood lipids are presented in Table 2.

**Table 1. General demographic characteristics of participants and the distribution of serum lipids and plasma TNF-alpha levels**

Variables	Case (n = 43)	Control (n = 41)	Test statistics	P
Age	72 (64-78)	69 (50-88)	U: 849 Z: -653	0.514
Gender				
Male	21(49%)	19 (46%)	X2: 0.052	0.819
Female	22 (51%)	22 (53%)		
BMI (kg/m <sup>2</sup> )	27.68 (26.03-29.64)	27.77 (26.12-30.46)	U: 885.50 Z:-337	0.736
Vascular risk factors, n (%)			X2: 8.169	0.417
None	14 (33%)	17 (40%)		
HT	9 (21%)	12 (28%)		
DM	2 (5%)	1 (2%)		
HT-DM	11 (26%)	5 (12%)		
CAD	3 (7%)	2 (5%)		
HT-CAD	2 (5%)	1(2%)		
Prior stroke	0	2 (2%)		
HT- Prior stroke	2 (5%)	1 (2%)		
HT-DM-CAD	0	2 (%)		
White-blood cell	8.09 (5.93-11.04)	7.34 (6.41-8.94)	U:765.50 Z:-1.709	0.299
Hemoglobine	13.22±2.03	14.20±1.74	t: -2.367	0.020
Platelet	219.23±73.41	228.46±56.42	t: -0.644	0.521
Glucose (mg/dL)	111.60 (96.30-160.80)	107.50 (93.70-122)		
Total cholesterol (mg/dL)	173.40±30.37	172.92±35.19	t: 0.063	0.950
Triglycerides (mM) (mg/dL)	113.80 (81-167)	140 (90.85-184.25)	U: 538.00	0.326
LDL (mg/dL)	106.47±29.12	101.84±32.27	t:0.633	0.529
HDL (mg/dL)	40.83±8.80	43.36±9.35	t: -1.167	0.247
PAI	0.48±0.24	0.51±0.27	t: -0.553	0.582
CRP (mg/L)	4.12 (2.17-11.09)	3.15 (1.76-6.40)	U: 658.00	0.185
TNF	23.53 (21.74-43.29)	23.00 (20.62-37.34)	U: 857.00 Z: -0.583	0.560
NIHSS	5 (3-10)			

BMI, Body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein, TNF- $\alpha$ , tumor necrosis factor-alpha; PAI, Plasma atherogenic index. Data are mean  $\pm$  SEM.pvalues were calculated using Fisher's exact test or Student's t test, as appropriate

Table 2. Correlations between plasma lipids and TNF alpha in our groups

	r/rho coefficient	p	r/rho coefficient	p
Glucose (mg/dL)	-0.067	0.669	-0.152	0.382
Total cholesterol (mg/dL)	0.052	0.742	0.119	0.546
Triglycerides (mM) (mg/dL)	-0.319	<b>0.037</b>	0.266	0.164
LDL (mg/dL)	0.008	0.962	0.036	0.857
HDL (mg/dL)	0.015	0.922	-0.029	0.883
PAI	-0.321	<b>0.036</b>	0.237	0.216
NIHSS	0.455	<b>0.002</b>	-	-

PAI: Plasma atherogenic index, NIHSS: National Institute of Health Stroke Scale

## DISCUSSION

This study showed a significant negative correlation between TNF- $\alpha$  and TG / atherogenic index in the patient group, while there was no significant correlation between blood lipid profile and TNF- $\alpha$  level in the control group. Moreover, in the patient group, TNF- $\alpha$  showed a significant positive relationship with the NIHSS score. Dyslipidemia, which is observed in patients with ACI, and its impact on death risk have been described in previous studies and dyslipidemia has been demonstrated as a correctable risk factor. It has been suggested in the literature that TNF- $\alpha$ , which is known as the proinflammatory cytokine, provides modulation by participating in a complex neuroinflammatory course, which is characterized by neuroprotective and neurotoxic features and plays a central role in cerebral infarction (7).

Hyperlipidemia, oxidative stress and inflammation lead to the initiation and development of atherosclerosis (12). Previous reports have revealed that atherosclerosis is associated with high serum concentrations of TG, TC and LDL-C (13). Other reports have suggested that excess LDL-C could be oxidized, and foam cells may induce the formation of atherosclerotic plaques (12). Abnormal lipid metabolism can lead to various problems in signal transduction and inflammation process (14). Besides, pro-inflammatory mediators circulating in peripheral blood vessels could induce atherosclerosis or de-stabilize atherosclerotic plaque, hence increasing the odds of ischemic stroke (15).

It has also been found that TNF- $\alpha$ , which is a pleiotropic cytokine, plays a crucial role in promoting and accelerating the progression of atherosclerosis (10). For example, they may not only contribute to the endothelial dysfunction and coagulation process, but also indirectly contribute to the process of vascular diseases (16). The potential correlation between TNF- $\alpha$  and hyperlipidemia in various disease groups has been investigated. Espinoza et al. observed a positive association between TNF- $\alpha$  and plasma triglycerides in patients receiving peritoneal dialysis (17). On the other hand, Stepanova et al. did not determine a significant correlation between TG level and TNF- $\alpha$  concentration in relatively few patients receiving

peritoneal dialysis (18). There are limited studies in the literature regarding the interactions between blood lipids and TNF- $\alpha$  in patients with ACI. In our study, no significant difference was found between the groups in terms of TNF- $\alpha$  levels. Furthermore, TNF- $\alpha$  showed a negative correlation with TG in the patient group.

In addition, another study revealed that TNF- $\alpha$  released from the brain can increase apoptosis by the ischemic process (19). The impact of ischemia-induced cerebral tissue inflammation on serum levels of cytokines has been examined by Emsley et al (20). It has been underscored that TNF- $\alpha$  is associated with early worsening of stroke and poor prognosis. Consistent with this information, similarly, a positive correlation was shown between TNF- $\alpha$  and NIHSS in our study. It has been discussed that the cytokine level, which does not make any difference initially, could reach a significant level after a few days to a few months in acute stroke patients. The reason for the lack of difference in TNF- $\alpha$  levels in our study may be due to the short plasma half-life of cytokines, low serum concentration responses, and methodological features (21).

It has been revealed by Zhao et al. that the cytokine, which has multifaceted interactions, increases the flow of adipocyte cholesterol when administered in a certain dose range, but reduces the efflux at higher concentrations (22). On the other hand, contradictory results have been observed on the lipid profile in some diseases for which anti-TNF therapy is implemented. Some studies have shown that anti-TNF therapy is significantly associated with an increase in HDL levels and not with changes in other lipid parameters (LDL, TG, TC) (23, 24). On the contrary, some data suggested that anti-TNF therapy was significantly associated with an increase in TG levels (25, 26). We consider that the association of TNF- $\alpha$  with blood lipids in terms of both neuroprotection and neurotoxicity may be crucial for patients with ACI.

Cumulative data suggest that TNF- $\alpha$  may impair the regulation of energy metabolism and lipid metabolism in some pathological conditions (27). Therefore, TNF- $\alpha$  may be a treatment target for some diseases. Although treatment with agents that block TNF- $\alpha$  actions in acute

inflammatory conditions such as sepsis has been proven to exacerbate the disease, this therapy has been found to be very useful in the case of chronic inflammation (28). In addition, plasma cholesterol concentration has been shown to be consistently suppressed in all acute situations associated with elevated TNF- $\alpha$  levels (28). In experimental observations, anti-TNF agents successfully treat experimental stroke, and this offers a positive approach to successful treatment options (29). Eventually, multifaceted interactions between TNF- $\alpha$ , blood lipids, and ischemic stroke could provide us with crucial data which can guide us in treatment.

In our correlation analysis, TNF- $\alpha$  levels show a negative correlation with TG and PAI. Albeit TNF- $\alpha$  induced hyperlipidemia is well known as cytokines-induced hyperlipidemia, genetic variations in TNF- $\alpha$  may have an impact on the type of these dyslipidemic changes (30). Normally, TNF- $\alpha$  administered exogenously may lead to hyperlipidemia in the healthy population, yet the negative correlation of TNF- $\alpha$  in patients with ACI might also have occurred due to early assessment of the data.

## LIMITATIONS

The main limitation of this study is the small number of study participants. For the reliability of the results, it is considerably important to provide a data set on large sample groups and by eliminating vascular risk factors. In addition to that, cytokine levels were measured only once. Repeated measurements could contribute to the analysis of results from different perspectives. As a third limitation, we did not assess the CSF concentrations of cytokines. Lastly, no correlational analysis was conducted and provided regarding the long-term follow-up of the patients. Ischemic stroke is a complex disease. In this study, we did not put forward a definitive impact of the correlation between TNF- $\alpha$  and dyslipidemia in patients with ACI, considering that the patient series was generated by removing serious infections particularly during the period of pandemic and the study had a cross-sectional design. However, we are of the opinion that it has provided remarkable information for further studies on this subject.

## CONCLUSION

In conclusion, our cross-sectional study showed that in a close interaction range between high TG and atherogenic index with cerebral infarction and low TNF- $\alpha$  levels; this may be an indication for different studies on the importance of TNF- $\alpha$  in cerebral infarction. In addition, we consider our work to provide useful preliminary information that is essential for further research in this field and forms the basis for large-scale research.

*Competing Interests: The authors declare that they have no competing interest.*

*Financial Disclosure: There are no financial supports.*

*Ethical Approval: Approval for the study was obtained from the institutional Review board at Bozok University clinical research Ethics Committee (2017-KAEK-189\_2021.03.10\_06).*

## REFERENCES

1. Shan Y, Hu J, Lv H, et al. miR-221 Exerts Neuroprotective Effects in Ischemic Stroke by Inhibiting the Proinflammatory Response. *J Stroke Cerebrovasc Dis* 2021;30:105489.
2. Roth S, Yang J, Cramer JV, et al. Detection of cytokine-induced sickness behavior after ischemic stroke by an optimized behavioral assessment battery. *Brain Behav Immun* 2021;91:668-72.
3. Maida CD, Norrito RL, Daidone M, et al. Neuroinflammatory Mechanisms in Ischemic Stroke: Focus on Cardioembolic Stroke, Background, and Therapeutic Approaches. *Int J Mol Sci* 2020;21.
4. Postal M, Lapa AT, Sinicato NA, et al. Depressive symptoms are associated with tumor necrosis factor alpha in systemic lupus erythematosus. *J Neuroinflammation* 2016;13:1-7.
5. Lambertsen KL, Finsen B, Clausen BH. Post-stroke inflammation-target or tool for therapy? *Acta Neuropathol* 2019;137:693-714.
6. Lin SY, Wang YY, Chang CY, et al. TNF- $\alpha$  Receptor Inhibitor Alleviates Metabolic and Inflammatory Changes in a Rat Model of Ischemic Stroke 2021;10.
7. Pawluk H, Woźniak A, Grzešek G. The Role of Selected Pro-Inflammatory Cytokines in Pathogenesis of Ischemic Stroke 2020;15:469-84.
8. Lasek-Bal A, Jedrzejowska-Szypulka H, Student S, et al. The importance of selected markers of inflammation and blood-brain barrier damage for short-term ischemic stroke prognosis. *J Physiol Pharmacol* 2019;70.
9. Kloska A, Malinowska M, Gabig-Cimińska M, et al. Lipids and Lipid Mediators Associated with the Risk and Pathology of Ischemic Stroke. *Int J Mol Sci* 2020;21.
10. Chen X, Xun K, Chen L, et al. TNF-alpha, a potent lipid metabolism regulator. *Cell Biochem Funct* 2009;27:407-16.
11. Soeki T, Sata M. Inflammatory biomarkers and atherosclerosis. *Int Heart J* 2016;15-346.
12. Jiang Y, Dai M, Nie WJ, et al. Effects of the ethanol extract of black mulberry (*Morus nigra* L.) fruit on experimental atherosclerosis in rats. *J Ethnopharmacol* 2017;200:228-35.
13. Subramani C, Rajakkannu A, Rathinam A, et al. Anti-atherosclerotic activity of root bark of *Premna integrifolia* Linn. in high fat diet induced atherosclerosis model rats. *J Pharm Anal* 2017;7:123-8.
14. Wymann MP, Schneider R. Lipid signalling in disease. *Nat Rev Mol Cell Biol* 2008;9:162-76.
15. Wytrykowska A, Prośba-Mackiewicz M, Nyka WM. IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 levels in gingival fluid and serum of patients with ischemic stroke. *J Oral Sci* 2016;58:509-13.
16. Hahn BH, Grossman J, Ansell BJ, et al. Altered lipoprotein metabolism in chronic inflammatory states: proinflammatory high-density lipoprotein and accelerated atherosclerosis in systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Res Ther* 2008;10:213.

17. Espinoza M, Aguilera A, Auxiliadora Bajo M, et al. Tumor necrosis factor alpha as a uremic toxin: correlation with neuropathy, left ventricular hypertrophy, anemia, and hypertriglyceridemia in peritoneal dialysis patients. *Adv Perit Dial* 1999;15:82-6.
18. Stepanova N, Driianska V, Savchenko S. Dyslipidemia and Intraperitoneal Inflammation Axis in Peritoneal Dialysis Patients: A Cross-Sectional Pilot Study. *Kidney Dis (Basel)* 2020;6:35-42.
19. Sumbria RK, Boado RJ, Partridge WM. Brain protection from stroke with intravenous TNF $\alpha$  decoy receptor-Trojan horse fusion protein. *J Cereb Blood Flow Metab* 2012;32:1933-8.
20. Emsley HC, Tyrrell PJ. Inflammation and infection in clinical stroke. *J Cereb Blood Flow Metab* 2002;22:1399-419.
21. Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. *Int J Mol Sci* 2019;20:6008.
22. Zhao SP, Dong SZ. Effect of tumor necrosis factor alpha on cholesterol efflux in adipocytes. *Clin Chim Acta* 2008;389:67-71.
23. Chen DY, Chen YM, Hsieh TY, et al. Significant effects of biologic therapy on lipid profiles and insulin resistance in patients with rheumatoid arthritis. *Arthritis Res Ther* 2015;17:52.
24. Ehsani AH, Mortazavi H, Balighi K, et al. Changes in body mass index and lipid profile in psoriatic patients after treatment with standard protocol of infliximab. *Acta Medica Iranica* 2016:570-5.
25. Hassan S, Milman U, Feld J, et al. Effects of anti-TNF- $\alpha$  treatment on lipid profile in rheumatic diseases: an analytical cohort study. *Arthritis Research & Therapy* 2016;18:1-9.
26. Ferraz Filho AC, dos Santos LP, Silva MB, et al. Lipid profile and anti-TNF- $\alpha$  use. *Revista Brasileira de Reumatologia (English Edition)* 2013;53:444-7.
27. Shi J, Fan J, Su Q, et al. Cytokines and abnormal glucose and lipid metabolism. *Front Endocrinol* 2019;10:703.
28. Popa C, Netea MG, van Riel PL, et al. The role of TNF-alpha in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. *J Lipid Res* 2007;48:751-62.
29. Clark IA, Vissel B. Broader Insights into Understanding Tumor Necrosis Factor and Neurodegenerative Disease Pathogenesis Infer New Therapeutic Approaches. *J Alzheimers Dis* 2021;79:931-48.
30. Patel R, Palit SP, Rathwa N, et al. Genetic variants of tumor necrosis factor- $\alpha$  and its levels: A correlation with dyslipidemia and type 2 diabetes susceptibility. *Clin Nutr* 2019;38:1414-22.