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Evaluation of Early Diagnosis via Some Blood Parameters in Alzheimer Type Dementia and Type 2 Diabetes Mellitus Patients

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ABSTRACT

Aim: Alzheimer's disease is a neurodegenerative disease with cognitive loss, which does not have a curative treatment and a blood-based biomarker to make a definitive diagnosis. There is a strong relationship between Alzheimer's disease and type 2 diabetes mellitus. Neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios are recommended parameters as inflammation markers. It was aimed to compare blood parameters and their ratios to each other in terms of their potential to provide early diagnosis in patients with Alzheimer's disease and type 2 diabetes mellitus.

Material and Methods: 80 healthy controls, 47 type 2 diabetes mellitus and 45 Alzheimer's type dementia patients were included in this study. Various blood parameters and their ratios to each other were scanned. One way ANOVA and post hoc Scheffe tests were used for statistical analysis.

Results: Serum iron levels were lower in type 2 diabetes mellitus (53.21±29.28 μg/dL) and Alzheimer's disease (61.26±21.69 μg/dL) groups compared to the control (76.96±30.99 μg/dL) (p=0.001). Lymphocyte numbers were lower in type 2 diabetes mellitus (1.94±0.79 count.10^3) and Alzheimer's disease (1.84±0.68 count.10^3) groups compared to the control (2.25±1.03 count.10^3) (p=0.032). Monocyte-lymphocyte ratio were significantly higher in type 2 diabetes mellitus (0.3±0.18) and Alzheimer's disease (0.28±0.11) groups compared to the control (0.24±0.1) (p=0.039).

Conclusion: The high monocyte-lymphocyte ratio can be considered as an indicator of systemic inflammation in Alzheimer's disease and type 2 diabetes mellitus. In conclusion, serum iron levels, lymphocyte numbers and monocyte-lymphocyte ratio as inflammation markers can be useful for the early diagnosis of type 2 diabetes mellitus and Alzheimer's disease.

Keywords: *Alzheimer's disease, Type 2 diabetes mellitus, Lymphocyte numbers, Serum iron levels, Monocyte lymphocyte ratio*

Alzheimer Tipi Demans ve Tip 2 Diabetes Mellitus Hastalarında Bazı Kan Parametreleri Aracılığıyla Erken Tanının Değerlendirilmesi

ÖZ

Amaç: Alzheimer hastalığı, küratif bir tedavisi ve kesin tanı koyduracak kan bazlı bir biyobelirteci olmayan, bilişsel kayıpla seyreden nörodejeneratif bir hastalıktır. Alzheimer hastalığı ile tip 2 diabetes mellitus arasında güçlü bir ilişki vardır. Nötrofil-lenfosit, trombosit-lenfosit ve monosit-lenfosit oranları inflamasyon belirteçleri olarak önerilen parametrelerdir. Bu çalışmada Alzheimer hastalığı ve tip 2 diabetes mellitus hastalarında kan parametreleri ve oranlarının erken tanı sağlama potansiyelleri açısından birbirleriyle karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya 80 sağlıklı kontrol, 47 tip 2 diabetes mellitus ve 45 Alzheimer tipi demans hastası dahil edildi. Çeşitli kan parametreleri ve bunların birbirlerine oranları retrospektif olarak tarandı. İstatistiksel analiz için tek yönlü ANOVA ve post hoc Scheffe testleri kullanıldı.

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Bulgular: Serum demir düzeyleri tip 2 diabetes mellitus (53.21±29.28 µg/dL) ve Alzheimer hastalığı (61.26±21.69 µg/dL) gruplarında kontrole (76.96±30.99 µg/dL) kıyasla daha düşüktü (p=0.001). Lenfosit sayıları tip 2 diabetes mellitus (1.94±0.79 sayım.10^3) ve Alzheimer hastalığı (1.84±0.68 sayım.10^3) gruplarında kontrole (2.25±1.03 sayım.10^3) göre daha düşüktü (p=0.032). Monosit-lenfosit oranı ise tip 2 diabetes mellitus (0.3±0.18) ve Alzheimer hastalığı (0.28±0.11) gruplarında kontrole (0.24±0.1) göre anlamlı olarak yüksekti (p=0.039).

Sonuç: Yüksek monosit-lenfosit oranı Alzheimer hastalığı ve tip 2 diabetes mellitusta sistemik inflamasyonun bir göstergesi olarak kabul edilebilir. Sonuç olarak, inflamasyon belirteçleri olarak serum demir düzeyi, lenfosit sayısı ve monosit-lenfosit oranı tip 2 diabetes mellitus ve Alzheimer hastalığının erken tanısı için yararlı belirteçler olabilir.

Anahtar Sözcükler: *Alzheimer hastalığı, Tip 2 diabetes mellitus, Lenfosit sayısı, Serum demir düzeyi, Monosit lenfosit oranı*

INTRODUCTION

Alzheimer's disease (AD) with advanced cognitive loss is the most common neurodegenerative disease. Nowadays the number of people affected by AD is common. Despite the developing technology and health facilities, there is no curative treatment agent and blood-based minimally invasive biomarker for AD (1). Current treatments are aimed at slowing the progression of the disease. There are also difficulties in diagnosis, since there is no biomarker that can provide a definitive diagnosis (2).

Acetylcholine esterase inhibitors such as donepezil, rivastigmine, galantamine, and memantine, an N-methyl D-aspartate (NMDA) receptor antagonist, are used in the treatment of AD. These treatments are mostly aimed at slowing the course of the disease and there is a problem about the tolerance to drugs (3,4). The efficacy of the monoclonal antibody aducanumab, which was approved by the US Food and Drug Administration (FDA) in 2021, in the treatment of the disease is controversial (4). Lecanemab, another anti - amyloid β (Aβ) monoclonal antibody approved by the FDA in 2023, targets the Aβ peptide accumulated in AD. It is stated that the benefit of lecanemab in AD should demonstrate via clinical studies (5,6). There is currently no complete curative treatment for AD. Early diagnosis and initiation of treatment with current drugs are important but there is no accepted biomarker that alone can make a definitive diagnosis for AD. Although various biomarkers have been tried for the diagnosis of AD, these options do not meet the criteria of high specificity and sensitivity and remain far from making a definitive diagnosis (7). The fact that the biomarkers considered for AD are blood-based and minimally invasive will provide a great advantage in terms of ease of application (8). Therefore, various blood parameters and their ratios to each other are evaluated for their potential as a biomarker for AD.

There is a strong relationship between AD and type 2 diabetes mellitus (type 2 DM). The function of the phosphoinositide 3 kinase (PI3K)/protein kinase B (Akt)/ the mechanistic target of rapamycin (mTOR) signaling pathway is impaired for both diseases (9,10). The risk of developing AD in type 2 DM patients was found to be higher than in healthy individuals (11). In addition, there are problems in iron metabolism in both AD and type 2 DM (12,13). Iron accumulation has been shown in senile amyloid plaques in Alzheimer's patients, and the increase in iron causes oxidative stress through the fenton reaction (14). The indirect decrease in serum iron as a result of iron accumulation in the brain may be a guide in the diagnosis of AD and type 2 DM. In addition, low serum iron is considered as an inflammatory response (15). When combined with low serum iron, blood cell ratios and the patient's clinic, it can be very useful for the diagnosis of AD and type 2 DM.

Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR) are the recommended parameters as inflammation markers (16,17,18). Peripheral leukocytes are modulated by inflammatory cytokines and chemokines released from damaged tissues. At the same time, peripheral leukocytes can affect damaged tissues. It is accepted that the number of lymphocytes has a neuroprotective effect and contributes to the development of neurological function (19). Therefore, blood cells and their ratios to each other are evaluated in order to diagnose diseases. In particular, the ratio of blood cells to each other seems to be more distinctive than the evaluation of individual cell numbers (16). Especially for AD, which is a blood-based biomarker search, blood cell counts and their ratios to each other are thought to be helpful in the diagnosis (20).

In this study, it was aimed to compare iron-related blood parameters, blood cell counts and their ratios to each other between type 2 DM and Alzheimer's patients with age and sex matched controls. It is desired to have information about the relationship between type 2 DM and AD and to evaluate the potential of use of these parameters in referral of patients with dementia risk for further examinations when necessary.

MATERIAL and METHODS

The blood tests of patients and controls who are treated at Kutahya Health Sciences University Evliya Celebi Training and Research Hospital between 1 December 2017 and 1 December 2022 were retrospectively screened for this study. Ethical approval was obtained from the Ethics Committee of Non-Interventional Clinical Researches of Kutahya Health Sciences University, dated 22.06.2022 and numbered 2022/07-06. In this study, which we conducted as a retrospective archive investigation, informed consent was not required. The individuals included in the study are described in Figure 1. The study was conducted in accordance with the Decleration of Helsinki.

In this study, 80 healthy controls, 47 type 2 DM patients and 45 Alzheimer's patients were included. Groups were selected between 50-90 years old. Age and gender-matched people were included in this study (Table 1). Blood tests given by the patients between 9 and 12 am in the morning were examined. The control group consists of healthy individuals, without diagnosis of type 2 DM and AD. The type 2 DM group consists of patients diagnosed with diabetes without AD, and the AD group consists of patients diagnosed with AD without diabetes. All groups were not diagnosed with chronic heart, liver and kidney disease or malignancy. People with this chronic disease were excluded from the study.

Serum iron, hemoglobin, hematocrit, mean erytrocyte hemoglobin (MCH), mean erytrocyte concentration (MCHC), white blood cell (WBC), red blood cell (RBC), neutrophil, lymphocyte, platelet, monocyte, NLR, PLR, MLR, RBC/Lymphocyte, C reactive protein (CRP), fasting blood glucose and glycosylated hemoglobin (HbA1c) values of patients and healthy controls were investigated. Blood parameters were determined in the hospital laboratory using an autoanalyzer.

Statistical analysis was provided with the IBM Statistical Package of the Social Science (SPSS) program with version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Quantitative data were given as Mean ± Standard Deviation. The conformity of the data to the normal distrubition was determined by the Kolmogorov - Smirnov test. One-way analysis of variance (one-way ANOVA) and post hoc Scheffe tests were used to analyze the data in groups. Statistical power analysis was performed with G*Power 3.1 and showed that the power level for all tests was larger than 80% for the reported significance levels. A value of $p<0.05$ was considered as statistically significant.

RESULTS

While there was no significant difference between the groups in terms of hemoglobin, hematocrit, MCH and MCHC levels ($p>0.05$), serum iron levels was lower in both

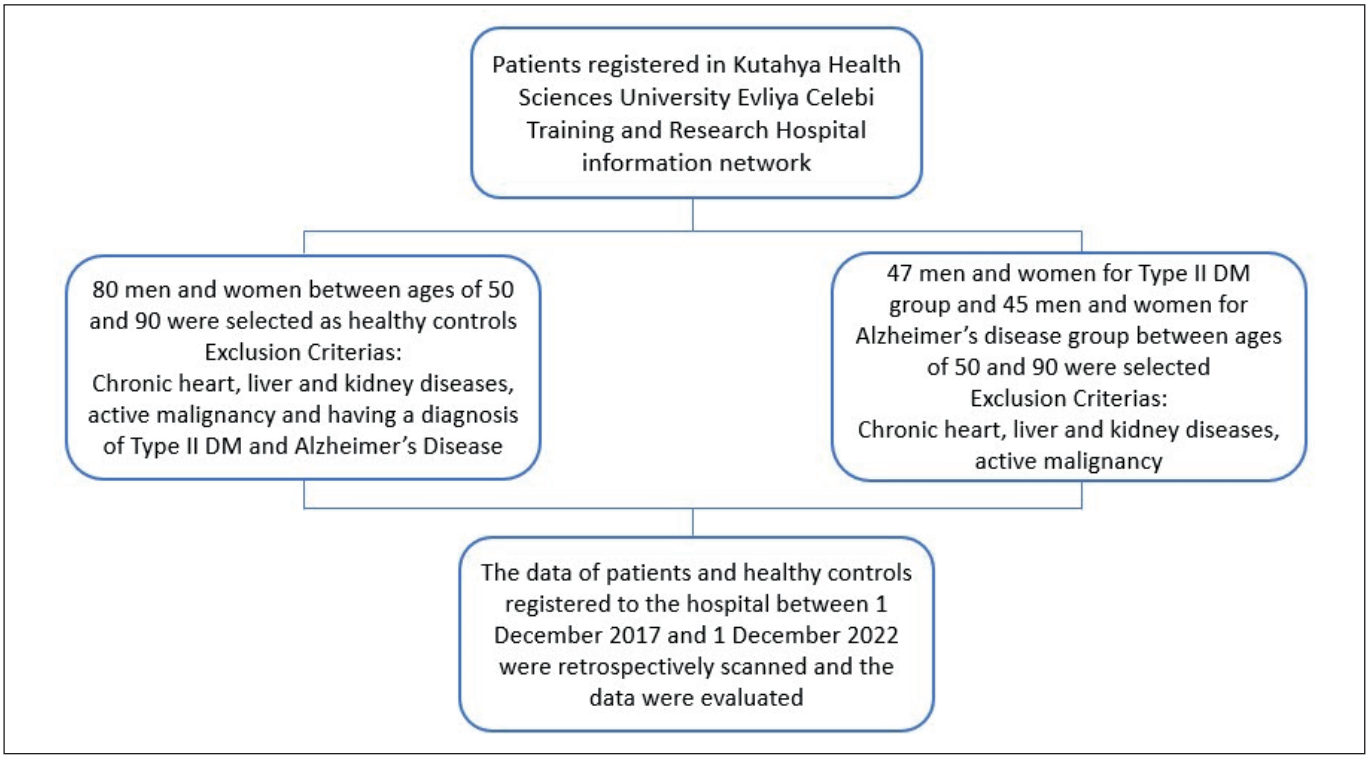

Figure 1. Workflow of the retrospective cohort study and the inclusion and exclusion of individuals.

Table 1: Age-gender characteristics, some blood parameters, ratios and p values.

Characteristics	Control (n=80)	Type 2 DM (n=47)	Alzheimer's (n=45)	p
Age * years	77 (50-90)	79 (52-87)	82 (59-90)	0.341
Gender **	39/41	22/25	21/24	0.897
Serum Fe (µg/dL±SD)	76.96 ± 30.99	53.21 ± 29.28 ▲	61.26 ± 21.69 ▲	0.001
Hemoglobin (g/dL±SD)	13.65 ± 1.54	13.21 ± 2.34	13.50 ± 2.01	0.445
Hematocrit (%±SD)	40.25 ± 4.35	39.45 ± 6.06	39.62 ± 5.84	0.549
MCH (pg±SD)	30.09 ± 7.46	29.28 ± 2.43	29.46 ± 3.77	0.691
MCHC (g/dL±SD)	33.71 ± 1.38	33.32 ± 1.59	33.05 ± 1.53	0.053
WBC (Count.10^3±SD)	7.64 ± 2.51	8.2 ± 2.69	7.96 ± 3.07	0.529
RBC (Count.10^6±SD)	4.69 ± 0.55	4.54 ± 0.76	4.68 ± 0.77	0.475
Neutrophil (Count.10^3±SD)	4.78 ± 2.29	5.50 ± 2.61	5.46 ± 3.02	0.212
Lymphocyte (Count.10^3±SD)	2.25 ± 1.03	1.94 ± 0.79 ▲	1.84 ± 0.68 ▲	0.032
Platelet (Count.10^3±SD)	266.61 ± 66.14	170.70 ± 88.52	238.95 ± 67.13	0.071
Monocyte (Count.10^3±SD)	0.48 ± 0.14	0.51 ± 0.18	0.48 ± 0.19	0.630
NLR±SD	2.76 ± 1.02	3.6 ± 1.65	3.46 ± 1.08	0.197
PLR±SD	143.83 ± 90.66	169.01 ± 93.03	142.65 ± 62.15	0.265
MLR±SD	0.24 ± 0.1	0.3 ± 0.18 ▲	0.28 ± 0.11 ▲	0.039
RBC/Lymphocyte±SD	2.45 ± 1.04	2.82 ± 1.32	2.86 ± 1.1	0.095
CRP (mg/L±SD)	5.91 ± 3.24	19.2 ± 7.63 ▲	12.04 ± 5.64 ▲	0.001
FBG (mg/dL±SD)	97.15 ± 15.93	164.38 ± 43.65 ▲ •	111.84 ± 31.15	0.001
HbA1c (%±SD)	5.26 ± 0.74	7.55 ± 1.65 ▲ •	5.63 ± 0.91	0.001

* Mean value and minimum-maximum values. ** Male/Female, **SD:** Standart deviation

Type 2 DM: Type 2 Diabetes Mellitus, **Serum Fe:** Serum Iron, **MCH:** Mean Corpuscular Hemoglobin, **MCHC:** Mean Corpuscular Hemoglobin Concentration, **WBC:** White Blood Cell, **RBC:** Red Blood Cell, **NLR:** Neutrophil - Lymphocyte Ratio, **PLR:** Platelet - Lymphocyte Ratio, **MLR:** Monocyte - Lymphocyte Ratio, **CRP:** C Reactive Protein, **FBG:** Fasting Blood Glucose, **HbA1c:** Glycosylated Hemoglobin

▲ Significant difference compared to the control group ($p<0.05$)

• Significant difference compared to the Alzheimer's Disease group ($p<0.05$)

type 2 DM group and AD group compared to the control (p=0.001). Serum iron levels was lower in type 2 DM group than in AD group (p>0.05), but this difference is not statistically significant (Table 1).

White blood cells, RBC, neutrophil, platelet and monocyte levels did not differ significantly between the groups (p>0.05). Lymphocyte numbers were significantly lower in type 2 DM group and AD group compared to the control group (p=0.032). There was no significant difference between the type 2 DM group and the AD group in terms of lymphocyte number, but it was found to be slightly lower in the AD group (Table 1).

When we focus on the NLR, MLR, PLR and RBC/Lymphocyte, calculated by the ratio of blood cells to each other, there was only a significant difference between the groups in MLR. Monocyte-lymphocyte ratio was significantly higher in type 2 DM group and AD group than the control (p=0.039) (Table 1).

C reactive protein levels were also higher in type 2 DM group and AD group compared to the control (p=0.001). Also type 2 DM group had higher CRP values according to AD group but this difference is not statistically significant. Fasting blood glucose was significantly higher in type 2 DM group compared to both control and AD groups (p=0.001). Although there was a minimal increase in fasting blood glucose in AD group compared to control, it was not statistically significant (p>0.05). HbA1c levels were similar to fasting blood glucose levels and were significantly higher in the type 2 DM group than in the other two groups (p=0.001) (Table 1) (Figure 2).

DISCUSSION

There are many studies about the relationship between iron and inflammation, but the biological mechanisms underlying the effect of inflammation on iron status indicators are not fully understood yet. However, it is clear that serum iron and its associated parameters are affected by inflammatory

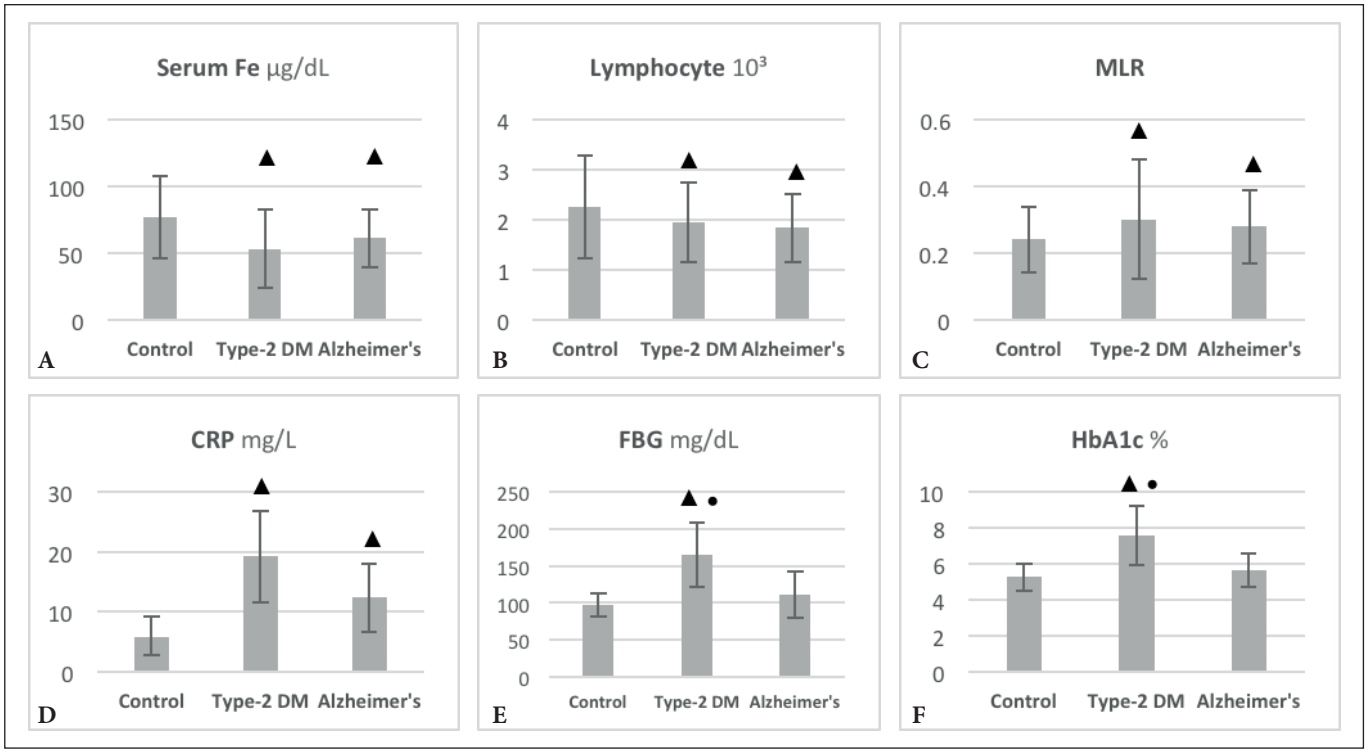

Figure 2. Blood parameter graphics of groups. **A)** Serum Fe levels. **B)** Lymphocyte levels. **C)** Monocyte - lymphocyte ratio levels. **D)** CRP levels. **E)** Fasting blood glucose levels. F. HbA1c levels.

▲ *Significant difference compared to the control group (p<0.05)*

• *Significant difference compared to the Alzheimer's Disease group (p<0.05)*

conditions (21). Inflammatory processes are very important in type 2 DM. Increasing blood glucose seen in DM, excessive fat storage in tissues and oxidative stress associated with free radicals are directly related to inflammatory processes (22). Neuroinflammation also aggravates protein deposits and the development of AD (23). Therefore, changes in the level of inflammatory markers are expected in these diseases.

Decrease in serum iron levels may be related to inflammatory processes in type 2 DM and AD patients in our study. There are studies about anemia in AD. For example Hare et al. found that serum iron levels were low in AD, and it was even emphasized that there was an idiopathic anemia in Alzheimer's patients. They explained this decrease with the desaturation of transferrin, an iron carrier protein (24). Alzheimer's patients also have dysregulation of a group of metals such as iron, zinc, copper and magnessium. In addition to the deterioration of iron homeostasis, accumulation of iron in cerebral amyloid plaques in AD has been shown (25). The accumulation of iron in brain plaques may cause low serum iron levels.

There are various studies in the literature regarding the relationship between type 2 DM and iron. Iron affects glucose metabolism, and glucose metabolism also affects several iron metabolic pathways. For this reason, the relationship between them is called bidirectional. These mechanisms are affected by inflammatory cytokines and oxidative stress. Studies have reported that the increase in tissue iron is associated with type 2 DM (26).

Increased tissue iron is a risk factor for type 2 DM and affects many of the key features of the disease, such as decreased insulin secretion and insulin resistance. This occurs when the tissue iron levels reaches the pathological level (27). It is stated that adipocyte iron is closely associated with insulin resistance. However, it is emphasized that serum iron and iron-related parameters are variable in type 2 DM with the effect of inflammation. The tissue iron can induces the formation of toxic free radicals in type 2 DM (28). As a potent oxidant, iron can accelerate the production of a large number of reactive oxygen radicals involved in regulating the signal transduction process of pancreatic β-islet cells. Thereby iron negatively affects insulin secretion and interfering with the glucose metabolism process (29).

A significant decrease in HbA1c levels was found after iron treatment in the non-diabetic population in Coban et al.'s study (30). In another study, it was shown that the frequency

of iron deficiency anemia increased in type 2 DM patients, and it was stated that the frequency of anemia increased even more in diabetes patients with chronic kidney disease (31). As a result, iron deficiency or excess causes dysfunction in the body, and one of them can be considered as type 2 DM (32,33).

Monocyte-lymphocyte ratio was found to be significantly higher in type 2 DM and AD groups in our data from NLR, MLR and PLR, which are the parameters recommended to be used as inflammation markers. In type 2 DM and AD, which are chronic diseases, the elevation in MLR can be considered as an indicator of systemic inflammation. The high CRP levels in these diseases support this idea.

One study showed that high NLR is a risk factor for the development of diabetic nephropathy and major cardiac events in type 2 DM patients (34). Therefore, these ratios show that they can also give information about the prognosis of the patients. There are studies demonstrating that NLR, PLR and MLR in Alzheimer's patients are different from healthy controls (35,36). However, there are also studies evaluating these ratios in various diseases and finding no significant results (37,38). Additional confounding factors such as drug use or small sample size may be effective in these studies. As a matter of fact, we did not detect any significant changes in NLR and PLR in our study.

There is no blood-based marker that can provide a definitive diagnosis in AD. Considering the role of inflammation in the pathogenesis of AD, it is assumed that routine blood parameters may have diagnostic and predictive value in Alzheimer's patients (39). The lower lymphocyte numbers in Alzheimer's patients compared to the control can be explained by the migration of lymphocytes, which play a role in inflammatory mechanisms, to the brain. In AD, lymphocytes cross the blood-brain barrier and reach the brain and participate in the development processes of AD. Therefore, it is argued that the blood lymphocyte numbers are low in AD (40). As a matter of fact, in our data, low lymphocyte numbers in AD may be the result of inflammatory processes. Similarly, the low lymphocyte numbers found in our data in type 2 DM can be explained by the inflammatory hypothesis.

Fasting blood glucose and HbA1c levels were higher in type 2 DM group than both control and AD group. There are also studies that explain the deterioration in glucose metabolism in Alzheimer's patients (41,42). In our study, although there was a minimal blood glucose and HbA1c elevation in AD group, this was not statistically significant. The Alzheimer's patients included in our study were followed up and using medication. We think that examining the data of Alzheimer's patients in the new diagnosis period and not under regular doctor control may yield better results.

As a result, serum iron level, lymphocyte numbers and MLR can be combined with clinical findings of patients and may be biomarkers that can be used in the diagnosis of type 2 DM and AD. It has been concluded that in these diseases in which the inflammatory process is important, these parameters related to inflammation may be beneficial in diagnosis and prognosis in the light of the patient's anamnesis.

This study has some limitations. If the evaluated blood parameters are compared with the cognitive test scores and cranial imaging examinations of Alzheimer's patients and found to be correlated, it may be possible to reach clearer conclusions. It would also be valuable to evaluate this single-center study with a multi-center and larger sample size. In addition, whether the drugs used by patient groups have an effect on blood parameters is one of the topics we plan to investigate in future studies.

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Author's Contributions
All authors provided developing the hypothesis and study design. All authors performed the literature review. **Esra Tekin** and **Sibel Canbaz Kabay** took part in the data collection and data evaluation. **Esra Tekin** and **Ayşegül Küçük** took part in the statistical analysis and writing of the article. All authors have read and approved the submission.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
None.

Ethical Approve and Informed Consent
Ethical approval was obtained from the Ethics Committee of Non-Interventional Clinical Researches of Kutahya Health Sciences University, dated 22.06.2022 and numbered 2022/07-06.

Review Process
Extremely peer-reviewed.

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