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RESEARCH ARTICLE EN

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Role of soluble fractalkine, GFAP and CD163 in cognitive functions after open heart surgery in diabetic and non-diabetic patients

Year 2022, Volume 13, Issue 4, 565 - 573, 01.10.2022

Arif OZBAY Sureyya BARUN Aybeniz CİVAN KAHVE Abdullah ÖZER Özlem GÜLBAHAR Hasan DAĞLI Seçil ÖZKAN Dilek ERER

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Abstract

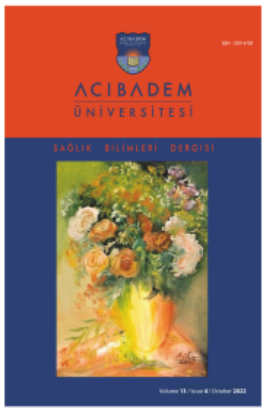
Purpose: In this study, the relationship between postoperative cognitive functions and serum fractalkine, Glial Fibrillar Acidic Protein (GFAP) and Cluster of differentiation 163 (CD163) levels in diabetic and non-diabetic patients after open heart surgery was evaluated. Methods and Materials: This research was planned prospectively as observational clinical study. Cognitive functions, fractalkine, GFAP and CD163 levels were evaluated with preoperative day 1 and postoperative day 7 in 44 patients. Minimental test (MM) was used to evaluate cognitive functions. Results: A positive correlation was found between preoperative CD163 concentrations and postoperative MM test scores in non-diabetic patients (r=0.536, p=0.010). There was also a positive correlation between postoperative CD163 concentrations and postoperative MM Test scores in non-diabetics (r=0.461, p=0.031). In diabetic patients, a positive correlation was found between preoperative and postoperative GFAP concentrations (r=0.792, p<0.001). Conclusion: The underlying mechanisms of Postoperative cognitive dysfunction (POCD) are thought to be different in non-diabetic and diabetic patients. Evidence suggesting that preoperative serum CD163 levels may be a candidate for biomarkers directly related to postoperative cognitive performance in non-diabetic patients. In order to prevent POCD, which is associated with mortality, it is important to determine the predictors before surgery and to select the surgical method and anesthetics according to the risk assessment.

Keywords

cognitive functions, inflammation, CD163, fractalkine, GFAP, heart surgery

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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Psychiatry / Psikiyatri

Role of Soluble Fractalkine, GFAP and CD163 in Cognitive Functions After Open Heart Surgery in Diabetic and Non-diabetic Patients

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ABSTRACT

Purpose: In this study, the relationship between postoperative cognitive functions and serum fractalkine, Glial Fibrillar Acidic Protein (GFAP) and Cluster of differentiation 163 (CD163) levels in diabetic and non-diabetic patients after open heart surgery was evaluated.

Methods and Materials: This research was planned prospectively as observational clinical study. Cognitive functions, fractalkine, GFAP and CD163 levels were evaluated with preoperative day 1 and postoperative day 7 in 44 patients. Minimental test (MM) was used to evaluate cognitive functions.

Results: A positive correlation was found between preoperative CD163 concentrations and postoperative MM test scores in non-diabetic patients (r=0.536, p=0.010). There was also a positive correlation between postoperative CD163 concentrations and postoperative MM Test scores in non-diabetics (r=0.461, p=0.031). In diabetic patients, a positive correlation was found between preoperative and postoperative GFAP concentrations (r=0.792, p<0.001).

Conclusion: The underlying mechanisms of Postoperative cognitive dysfunction (POCD) are thought to be different in non-diabetic and diabetic patients. Evidence suggesting that preoperative serum CD163 levels may be a candidate for biomarkers directly related to postoperative cognitive performance in non-diabetic patients. In order to prevent POCD, which is associated with mortality, it is important to determine the predictors before surgery and to select the surgical method and anesthetics according to the risk assessment.

Keywords: cognitive functions, inflammation, CD163, fractalkine, GFAP, heart surgery

Research registration: April 20, 2021 with number 6759. (*https://www.researchregistry.com/browse-the-registry#home/registrationdetails/607ed790f296b7001ba00501/*)

Açık Kalp Cerrahisi Sonrası Diyabetik ve Diyabetik Olmayan Hastalarda Bilişsel İşlevlerde Fraktalkin, GFAP ve CD163'ün Rolü

ÖZET

Amaç: Bu çalışmada, diyabetik ve diyabetik olmayan hastalarda açık kalp cerrahisi sonrası postoperatif bilişsel fonksiyonlar ile serum fraktalkin, Glial Fibrillar Asidik Protein (GFAP) ve Cluster of Different 163 (CD163) düzeyleri arasındaki ilişki değerlendirildi.

Yöntem: Bu araştırma prospektif olarak gözlemsel klinik bir çalışma olarak planlandı. 44 hastada ameliyat öncesi 1. gün ve ameliyat sonrası 7. gün bilişsel işlevler, fraktalkin, GFAP ve CD163 düzeyleri değerlendirildi. Bilişsel işlevleri değerlendirmek için minimental test (MM) kullanıldı.

Bulgular: Diyabetik olmayan hastalarda preoperatif CD163 konsantrasyonları ile postoperatif MM testi skorları arasında pozitif korelasyon bulundu (r=0.536, p=0.010). Ayrıca diyabetik olmayanlarda postoperatif CD163 konsantrasyonları ile postoperatif MM Testi skorları arasında pozitif bir korelasyon vardı (r=0.461, p=0.031). Diyabetik hastalarda preoperatif ve postoperatif GFAP konsantrasyonları arasında pozitif bir korelasyon bulundu (r=0,792, p<0,00).

Sonuç: Postoperatif bilişsel işlev bozukluğunun (POCD) altında yatan mekanizmaların diyabetik olmayan ve diyabetik hastalarda farklı olduğu düşünülmektedir. Çalışmamız verileri, preoperatif serum CD163 seviyelerinin diyabetik olmayan hastalarda postoperatif bilişsel performansla doğrudan ilişkili biyobelirteçler için aday olabileceğini düşündürmektedir. Mortalite ile ilişkili olan POCD'yi önlemek için cerrahi öncesi öngörücülerin belirlenmesi ve risk değerlendirmesine göre cerrahi yöntem ve anesteziklerin seçilmesi önemlidir.

Anahtar Kelimeler: bilişsel işlevler, inflamasyon, CD163, fraktalkine, GFAP, kalp cerrahisi

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Postoperative cognitive dysfunction (POCD), after anesthesia and surgery is a recognized clinical phenomenon (1) . It was defined for the first time in 1955 under the name of "negative cerebral effects of anesthesia on old people" (2). Postoperative cognitive dysfunction is a clinical condition that lowers a person's quality of life by causing concentration, memory, language use disorders and learning disabilities (3,4). Early studies focused on POCD after cardiac surgery. Shaw et al. identified rates of POCD of 79% at 7 days after surgery, with 38% showing significant symptoms of neuropsychological impairment (5). In subsequent studies, it has been reported that POCD may occur after any type of cardiac and non-cardiac surgery (6). However, it is known that patients undergoing cardiac surgery have a higher risk of developing POCD compared to other operations (7,8). Postoperative cognitive dysfunction rates range from 27% to 66% after cardiac surgery (9,10) while highly variable rates were reported in which non-cardiac surgeries (6). It can lead to consequences such as loss of independence, quality of life, withdrawal from the community, and loss of work and social security (11). In addition, mortality rates were shown to increase in a 8.5-year follow-up study (12). In favor of the role of inflammatory response in POCD, preoperative administration of dexamethasone has been shown to reduce the inflammatory response and the risk of early POCD after cardiac surgery (13).

One of the major mechanisms responsible for the development of POCD is neuroinflammation and activation in astrocytes and microglia. It has been demonstrated by clinical and experimental studies in postoperative period (14,15). Inflammatory mediators in the central nervous system (CNS) can also affect memory and learning through direct or indirect mechanisms (16,17). In one study, inhibition of pro-inflammatory cytokine (IL-6) release in the brain has been reported to improve post-operative memory disorders (18).

Fractalkine or CX3CL1 is a chemokine molecule and is involved in both peripheral and central inflammatory processes (18). The synthesis site in the CNS is neurons and has receptors on microglia (CX3CR1). Soluble fractalkine released by neurons causes activation of microglial cells and leukocytes in the systemic circulation (19,20). Different results have been reported in the literature that fractalkine has both neuroprotective and neurotoxic effects (21). It has been suggested that in Alzheimer's Disease (AD), which is accompanied by cognitive and memory impairment, the level of fractalkine decreases and plays a role in neuroinflammatory processes in the disease (22,23).

Glial Fibrillar Acidic Protein (GFAP) is a marker showing astrocyte activation in neuroinflammatory events. GFAP serum levels are elevated in neuroinflammatory processes (24). In addition, a positive correlation has been reported between POCD and serum GFAP levels after non-cardiac surgery (25).

Cluster of differentiation 163 (CD163) is a marker expressed in microglia cells and showing activation. It is stated that CD163 plays a role in regulating the adaptive immune response and measuring in inflammation-related diseases in tissue or serum may be guiding in terms of the severity and prognosis of the disease (26).

Diabetes mellitus (DM) is a disease that can cause neuroinflammatory changes (27). Some patients have been shown to have impaired cognitive function, but their pathophysiology is not fully understood. Hyperglycemia, vascular disease, hypoglycemia and insulin resistance are thought to play a role in neuroinflammation (16). There are differences in neuroinflammatory mechanisms due to persistent hyperglycemia in diabetic patients. Persistent hyperglycemia-related polyol pathway, protein kinase C (PKC) pathway, mitogen-activated protein kinases (MAPK) pathway are activated and production of advanced glycation end products (AGEs) increase in DM. Thus, inflammatory mediators are released directly or indirectly (28). These mediators stimulate the generation of inflammatory mediators and activation of transcription factor NF-κB which is a potent inducer of inflammatory processes (29). These AGEs act on various receptors present on microglia and macrophages stimulate production of cytokines and chemo attractant proteins (30). Inflammation also affects the structural features of neuron by the glycosylation of myelin protein. Thus, antigenicity varies and monocyte, macrophage and neutrophil infiltration occurs from the blood circulation and activate the glial cells of the nervous system (27,31).

In a meta-analysis comparing patients with diabetic and patients with non-diabetic, the risk of developing POCD was reported to be higher in diabetics (32). In experimental models, an increase in microglial activation and intercellular adhesion molecule-1 (ICAM-1) expression was detected in neuropathological analysis in the brain of diabetic animals (33).

The role of centrally soluble fractalkine, GFAP and CD163 and its relationship with cognitive dysfunction in neuroinflammatory changes after cardiac surgery have not

been previously investigated. In this study, the relationship between preoperative and postoperative fractalkine, GFAP and CD163 levels and cognitive functions was evaluated in diabetic and non-diabetic patients in order to detect the difference in inflammatory processes.

MATERIAL AND METHODS

Sample Selection

This research is a prospective and observational clinical study. It was performed Gazi University Faculty of Medicine Hospital, Department of Cardiovascular Surgery between the dates May 16, 2018 and January 21, 2019. Individuals who had undergone open heart surgery within the specified date range, who met the inclusion criteria and volunteered to participate in the study were included in the study. Power analysis was performed to calculate the minimum number of patients. There was no sample study in the literature investigating the relationship between cognition and neuroinflammatory markers in diabetic and non-diabetic patient groups who underwent open heart surgery. Therefore, other studies involving patient and control groups in which these markers were studied were used in power calculation. Using the mean ± SD values of a study with Fractalkine, taking 80% power and ratio of sample size: 1 at 95% confidence interval (2-sided; patient group: 1.881±1.372, control group: 0.969±655), the patient group for 22, the control group for 22, and the total group for 44 were calculated (34).

Using the mean ± SD values of a study with CD163, taking 80% power and ratio of sample size: 1 at 95% confidence interval (2-sided; patient group: 85.7±29.3, control group: 57.8±20.6), the patient group for 13, the control group for 13, and the total group for 26 were calculated (35). The study started on May 16, 2018 and the study was terminated when the number of patients in both groups reached 22 (January 21, 2019).

22 diabetic and 22 non-diabetic volunteers aged 40 years and older who underwent cardiopulmonary-bypass surgery (CPB) were included in the study. Coronary artery bypass graft (n:28), valve replacement (n:4), coronary artery bypass graft plus valve replacement (n:11) and intracardiac mass excision (n:1) were performed underwent CPB. Those with a known autoimmune disease, active infection, and neuropsychiatric disease were excluded from the study. In order to evaluate cognitive functions, preoperative day before and on postoperative 7th day, MM was performed. Serum fractalkine, GFAP and CD163 levels were measured simultaneously.

Biochemical Methods

Blood samples taken from patients were taken into standard yellow capped tubes, centrifuged at +4 ° C for 10 minutes at 4000 rpm and frozen at -80 ° C until working. Fractalkine, GFAP and CD16 ELISA kits were purchased from Cloud-Clone Corp USA. While preparing the reagents, 1 ml of standard dilution was added to the stock standard to dissolve. Serial dilutions were then made. The working protocol of the kits was performed as follows.

a. Prepared samples were pipetted into 7 standard and 1 blind 100 microliter plate wells. The plate was covered and incubated at 37 ° C for 1 hour.

b. After incubation, the wells were completely emptied. No washing was done at this stage.

c. Reagent A working solution, prepared 100 microliters, was pipetted into all wells. It was incubated for 1 hour at 37 ° C.

d. At this stage, all wells were washed 3 times with 350 microliter wash solution.

e. Reagent B working solution, prepared 100 microliters, was pipetted into all wells. It was incubated for 30 minutes at 37 ° C.

f. Step 4 was repeated. Washing was done 5 times.

g. 90 microliters of substrate solution was added to all wells. It was incubated at 37 ° C, hiding from light for 15 minutes.

h. 50 microliters of stop solution was added to all wells. It was gently mixed. It was taught in 450 nm ELISA reader. By drawing the standard curve graphs, the concentration of all samples was calculated.

Anesthesia Protocol

The anesthesia protocol of all patients included in the study was the same. Following standard monitoring of American Anesthesia Society (ASA), anesthesia was induced with 5-7 mg/kg thiopental-sodium, endotracheal intubation was performed after muscle relaxation with 0.6 mg/kg rocuronium. In the maintenance of anesthesia, sevoflurane was used at a concentration of 1 minimum alveolar concentration (about 2%) and remifentanil infusion at a dose of 0.05-0.2 mcg/kg/min. Skeletal muscle relaxation was maintained by using rocuronium as a 10 mg bolus every 45 minutes.

Cardiac Surgery Procedure

During in cardiac surgery can be performed with on pump CPB. Perfusion is conventionally performed by the on-pump, non-pulsatile cardiopulmonary bypass technique. For cardiopulmonary bypass, the patients were anticoagulated with 300-400 U/kg of heparin to achieve an activated clotting time (ACT) greater than 400 seconds. CPB was initiated following cannulation of the aorta and the right atrium. A Stockert SIII non-pulsatile roller pump (Stockert Instrumente GmbH) and a membrane type oxygenator (Dideco Compact Flo Evo, Sorin Group, Mirandola, Italy) were used. The pump prime solution contained 1000-1500 mL of lactated Ringer's solution to maintain a hematocrit level of 26±2 %. Pump flow was set at 2.2-2.4 L/m2/minute to maintain the mean non-pulsatile arterial pressure between 50-70 mmHg. The body temperatures of the patients were cooled down to 30°C. For myocardial protection, potassium blood cardioplegic solution was administered every 20 minutes and, additionally, cold (4°C) Isolyte S solution was applied topically to the surface of the heart at the same intervals. Cross-clamp time (minutes) and CPB time (minutes) were recorded.

Statistical Analysis

Research data was evaluated through SPSS 22.0 statistical software. Descriptive statistics are presented as mean (±) standard deviation, median (min; max). Parametric and non-parametric distribution properties of all data were examined with Shapiro-Wilks Tests and histogram distributions. Wilcoxon Test, Mann Whitney U Test and Spearman Correlation Test were used as appropriate statistical methods. Statistical significance was accepted as $p < 0.05$.

The Equator Network Guideline (the reporting of studies conducted using observational routinely collected health data statement) was followed in the preparation of this article and presentation of clinical data (36). In error, we did not prospectively register this trial, but we have registered it retrospectively at the Research Registry (https://www.researchregistry.com/), with registration date April 20,2021 and registration number 6759.

RESULTS

Total of 44 patients who participated in the study, 29 (65.9%) were male and 15 (%34.1) were female, and the mean age was 62.8±9.47 (min: 46, max: 84). The mean (±) standard deviation, median (min; max) values of the patients' pre-op and post-op CD163, fractalkine, GFAP levels and MM Test scores are shown in Table 1 according to their diabetic and non-diabetic status. In both two groups there was no significant difference when CD163, fractalkine, GFAP levels and MM Test score were compared preoperatively and post-operatively.

There was no statistically significant difference between diabetic and non-diabetic patients in terms of preoperative CD163 (p=0.734), fractalkine (p=0.338), GFAP levels (p=0.833) and MM Test score (p=0.572). Also, there was no statistically significant difference between diabetic and nondiabetic patients in terms of postoperative CD163 (p = 0.236), fractalkine (p = 0.542), GFAP (p=0.775) levels and MM Test score (p=0.447).

Table 1: Preoperative and postoperative fractalkine, GFAP, CD163 levels and minimental test scores of the patients

	Preoperative		Postoperative		p* value
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Non-diabetic patients (n:22)					
CD163 (ng/ml)	16,62±6,97	16,82 (1,44-30,63)	17,87±7,15	17,41 (5,39-33,32)	0,485
Fractalkine (ng/ml)	0,21±0,22	0,16 (-0,005-1,08)	0,17±0,10	0,14 (0,04-0,49)	0,903
GFAP (ng/ml)	1,33±3,08	0,11 (0,03-11,85)	0,34±0,48	0,10 (0,03-1,95)	0,330
MM Test	20,59±5,12	20,50 (12-29)	20,27±6,11	19,50 (11-29)	0,314
Diabetic patients (n:22)					
CD163 (ng/ml)	17,44±5,66	16,93 (5,50-29,71)	20,04±5,48	18,91 (10,05-29,67)	0,158
Fraktalkine (ng/ml)	0,18±0,14	0,14 (0,05-0,73)	0,19±0,09	0,18 (0,08-0,38)	0,140
GFAP (ng/ml)	0,56±0,81	0,17 (0,02-3,48)	0,24±0,35	0,13 (0,04-1,73)	0,074
MM Test skoru	21,23±3,90	22 (14-28)	21,68±3,94	22,5 (15-30)	0,600

*MM: Minimental Test; GFAP: Glial Fibrillar Acidic Protein; CD163: Cluster of differentiation 163; * Wilcoxon test was used.*

In our study, the correlations between preoperative and postoperative CD163, GFAP, Fractalkine levels and MM Test scores in both diabetic and non-diabetic patients were examined. There was a positive correlation between preoperative and postoperative CD163 concentrations in non-diabetic patients (r = 0.426, p = 0.048). Preoperative and postoperative fractalkine levels also showed a positive correlation in non-diabetics (r = 0.436, p = 0.042).

There was a positive correlation between preoperative and postoperative MM Test scores in non-diabetic (r = 0.854, p = 0.000) and diabetic patients (r = 0.555, p = 0.007).

A positive correlation was found between preoperative CD163 concentrations and postoperative MM test scores in non-diabetic patients (r=0.536, p=0.010) (Figure 1).

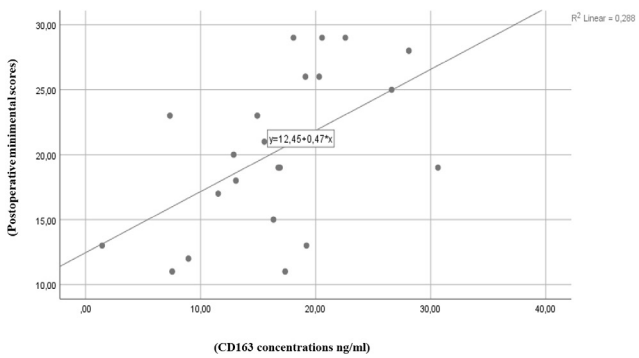


Figure 1: *Correlation between preoperative CD163 concentrations and postoperative Minimental Test Scores in non-diabetic patients (r= 0.536, p=0,010)*

There was also a positive correlation between postoperative CD163 concentrations and postoperative MM Test scores in non-diabetics (r = 0.461, p = 0.031) (Figure 2).

In diabetic patients, a positive correlation was found between preoperative and postoperative GFAP concentrations (r = 0.792, p = 0.000) (Figure 3). There was a positive correlation between preoperative CD163 concentrations and postoperative GFAP concentrations in diabetics (r = 0.440, p = 0.040).

A negative correlation was found between preoperative MM Test scores and postoperative fractalkine concentrations in diabetic patients (r = -0.516, p = 0.014) (Figure 4).

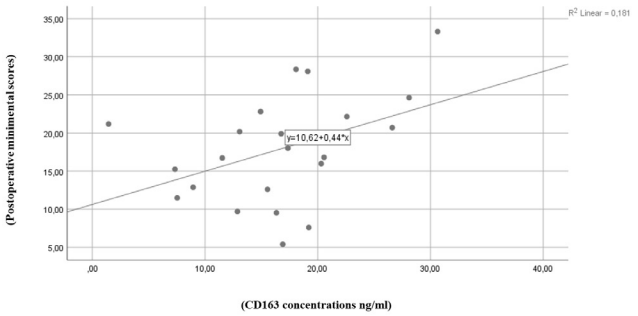


Figure 2: *Correlation between postoperative CD163 concentrations and postoperative Minimental scores in non-diabetic patients (r= 0,461, p=0,031)*

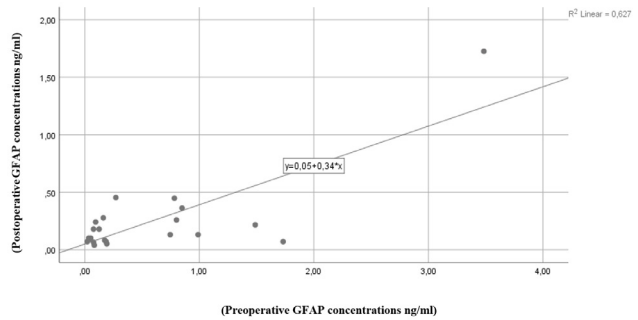


Figure 3: *Correlation between preoperative and postoperative Glial Fibrillar Acidic Protein (GFAP) concentrations in diabetic patients (r = 0.792, p = 0.000)*

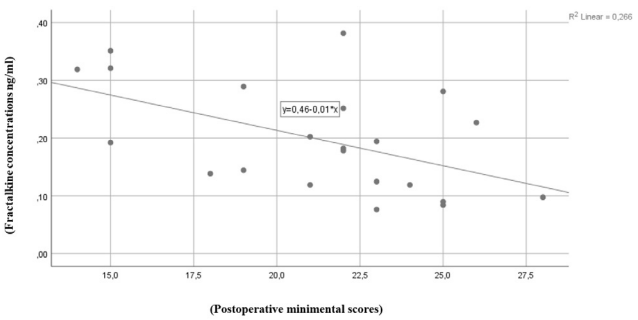


Figure 4: *Correlation between preoperative fractalkine concentrations and postoperative Minimental test scores in diabetic patients (r = -0.516, p = 0.014)*

Variables related to surgery and hospitalization in diabetic and non-diabetic patients were also compared. In the diabetic group, the mean clamp time was 85.95 ± 31.20 minutes, while the CPB time was 133.90 ± 36.69 minutes. The mean clamp time in the non-diabetic group was 100.22 ± 47.82, while the CPB duration was 140.59 ± 51.23 minutes, and there was no significant difference between the two groups (p = 0.445, p = 0.897, respectively).

While the duration of hospitalization was 12.31 ± 4.34 days in the diabetics, it was 12.50 ± 5.71 days in the non-diabetics. The length of stay in the intensive care unit (ICU) was 2.72 ± 1.12 days in the diabetics, 2.90 ± 1.71 days in the non-diabetics, and there was no difference between the two groups in terms of duration of hospitalization and length of stay in the ICU (p = 0.463, p = 0.855, respectively).

When the patients were evaluated in terms of their comorbidities, it was found that all of them had hypertension. Chronic obstructive pulmonary disease was present in 22.7% (n: 5) of diabetic patients, 4.5% (n: 1) of non-diabetics and no statistically significant difference was found between them (p = 0.07).

DISCUSSION

In neuroinflammatory diseases, biomarkers are tried to be developed with blood samples (37,38). Although there are neuroinflammatory mechanisms that may be common with POCD especially in Alzheimer's disease, biomarker studies for POCD are very limited (39-41). CD163 has been suggested to be the specific biomarker of monocyte/macrophage cell populations with a strong anti-inflammatory effect (42,43). Expression of CD163 allows the differentiation of M2 subtype cells of mononuclear phagocytes, which cause the release of anti-inflammatory mediators (44). Although monocyte/macrophage has been shown as the source of serum CD163 levels in the literature, CD163 released from microglia in CNS may also contribute to this (27).

In our study, the positive correlation of CD163 levels with MM test scores in both preoperative and postoperative periods suggests that CD163 may be a biomarker reflecting cognitive functions in non-diabetic patients. This finding is consistent with the activation of the M2 subtype form mentioned above and the microglia and macrophages transformed in the anti-inflammatory process and the accompanying soluble CD163 release. In addition, the positive correlation of CD163 levels with MM Test scores suggests that the release of established microglia originated CD163 in the CNS can also significantly contribute to the level of CD163 in serum. A study examining the relationship between serum CD163 level and POCD has not been found in the literature. Since the mortality rates are also high in patients with high POCD score, biomarkers that can be stabilized from serum are important in terms of predicting both cognitive impairment and mortality risk of patients. Predicting the development of POCD can lead to planning an intervention for it. For example, in a previous study, prophylactic dexamethasone use was reported to reduce the systematic inflammation response and the incidence of POCD in the postoperative period after cardiac surgery compared to the placebo group (13). It may be important to develop a biomarker for these interventions, especially for people who are thought to have risk factors.

In our study, while no correlation was found between pre-op CD163 and pre-op GFAP levels, a significant positive correlation was found between pre-op CD163 levels and post-op GFAP levels. Although CD163 is an anti-inflammatory molecule, GFAP is a molecule that reflects astrocyte activation and the inflammatory process (45,46). This result suggests that the risk of inducing neuroinflammatory processes in the post-op period is higher in patients with diabetic compared to non-diabetic patients. In the meta-analysis in which 2642 patients were evaluated, it was reported that in diabetics, POCD increased 1.26 times compared to non-diabetic patients (32). In our study, although inflammatory processes were thought to be induced in diabetics in the postoperative period, it was found that cognitive functions did not show a significant change compared to both the preoperative period and non-diabetic patients. This situation has been interpreted that other patient-related variables such as metabolic and genetic may be effective in POCD besides neuroinflammation. In addition, accompanying post-op GFAP increase with pre-op CD163 level in diabetic patients can be interpreted as an adaptive mechanism developed against the tendency of neuroinflammation already present in Type 2 DM patients.

Upregulated expression of CD163, a macrophage-specific protein, is one of the major changes in the macrophage switch to alternative activated phenotypes in inflammation. Accordingly, a high CD163 expression in macrophages is a characteristic of tissues responding to inflammation. The scavenging of the oxidative and proinflammatory hemoglobin, leading to stimulation of the heme-oxygenase-1 and production of anti-inflammatory heme metabolites indicates that CD163 thereby indirectly contributes to the anti-inflammatory response (47). Increased

production of AGEs act on various receptors present on microglia and macrophages stimulate production of cytokines and chemo attractant proteins as a result of persistant hyperglycemia (30). Therefore, continuous CD163 activation may lead to increased proinflammatory response in diabetics, and its indirect anti-inflammatory effect may be insufficient compared to non-diabetic patients.

Akerfelt et al. reported that there was a significant and permanent decrease in circulating fractalkine level after orthopedic and coroner bypass surgery (48). Xu et al. reported that fractalkine was involved in the inflammatory and remodeling process and it is negative correlated with myocardial salvage in myocardial infarction patient treated with primary percutaneous coronary intervention (49). Fractalkine level has been shown to decrease in AD, where cognitive impairment is at the forefront, and it has been suggested that this molecule plays a role in the neuroinflammatory processes responsible for the disease (23). Our study showed that serum fractalkine levels decreased in non-diabetic patients, although it was not statistically significant, but this correlation was not correlated with the MM test. On the other hand, statistically significant negative correlation with preoperative MM scores in diabetics suggests that fractalkine can be used as an important parameter in demonstrating a possible deterioration when POCD is evaluated by advanced neuropsychiatric tests.

In a review evaluating anesthetics and POCD, it is stated that a significant proportion of people related to risk factors develop POCD, but it is emphasized that the role of anesthetic selection in the development of cognitive disorder is small (50). Despite this, in our study, standard anesthesia procedure was applied to patients so that the drugs used in anesthesia are not a confounder, and thus, this difference between patients was tried to be eliminated.

There are no standard assessment criteria defined for POCD. The criteria routinely used are a percentage change from baseline in a defined number of neuropsychological tests (usually a decline>20% in two or more tests) (51). In previous studies, it was observed that different neuropsychiatric tests were applied to patients, and as a result, several tests were evaluated and changes in cognitive functions were reported (52,53).

In diabetic and non-diabetic patients, the clamping time, CPB duration, ICU stay and hospitalization times, which can affect cognition and neuroinflammatory markers, do not differ between the two groups, so the groups can be considered homogenized in these respects and this is a strong aspect of this study. In addition, comorbidities are also homogeneous between groups. Conducting studies in which the number of samples is expanded is thought to be important in terms of showing whether this result will be repeated or not.

There are some limitations of our study. Firstly, only the MM test was used to evaluate cognitive functions, which may be the reason for preoperative and postoperative score similarity in the results. The use of the neuropsychiatric test battery, in which cognitive functions are evaluated in more detail, may be a reinforcement in future studies. Secondly, any test before surgery was not used to examine the presence of dementia. It was questioned whether there was a clinical diagnosis for dementia and whether there was a history of treatment, but a detailed neuropsychiatric evaluation could not be made. Finally, although a sample size with a statistically sufficient potency has been reached, a comparison between larger patient groups and groups divided according to comorbidities may be important in evaluating diabetes-specific responses.

CONCLUSION

The underlying mechanisms of POCD are thought to be different in non-diabetic and diabetic patients. Evidence suggesting that preoperative serum CD163 levels may be a candidate for biomarkers directly related to postoperative cognitive performance in non-diabetic patients.

Fractalkine can be used as an important parameter in demonstrating a possible deterioration when POCD is evaluated by advanced neuropsychiatric tests.

Cardiac surgery to be performed in patients with diabetic and non-diabetic should be performed differently, taking into account the factors affecting neuroinflammatory processes. It is thought that this study will make an important contribution to the literature as it is the first clinical study established with the hypothesis that the effect of neuroinflammation on POCD in diabetic patients may be different.

DECLARATIONS

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None.

Disclosure of Interest

The authors declare that they have no competing interest.

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Ethics Committee Approval

Ethical approval was obtained from Ankara Numune Education and Research Hospital on April 25, 2018 (Decision number: 1961/2018). Due to the change of principal investigator change, second approval was required and obtained from Ankara City Hospital No.1 Clinical Research Ethics Committee with the decision taken on June 20, 2019 and numbered E1 / 005/2019.

Data-sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Concept – A.Ozbay., S.B. D.E.; Design – A.O., A.Ozbay., S.I.O.; Supervision – O.G., S.B. D.E.; Resources – A.C.K, H.D.; Materials – A.Ozbay., A.O.; Data Collection and Processing - A.Ozbay., A.O.; Analysis and/or Interpretation – A.C.K, H.D., S.I.O. O.G.; Literature Review – A.C.K., S.B., A.Ozbay, D.E.; Writing – A. Ozbay.,S.B., A.C.K., .; Critical Review – O.G., S.I.O., D.E., S.B.

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