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# The effect of type 2 diabetes mellitus on early postoperative cognitive functions

**Seda Seven [1], İlkay Ceylan [2], Durmuş Kaymak [3], Ali G. Kara [3], Veysel Erden [3]**

[1] Marmara University Medical Faculty, Pendik Training and Research Hospital, Department of Anesthesiology and Reanimation- Intensive Care, Istanbul, Turkey
[2] University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Anesthesiology and Reanimation- Intensive Care, Bursa, Turkey
[3] University of Health Sciences, Istanbul Training and Research Hospital, Department of Anesthesiology and Reanimation, Istanbul, Turkey

**ORCID ID of the author(s)**

SS: 0000-0001-8683-5575
İC: 0000-0003-3306-3107
DK: 0000-0003-2879-4685
AGK: 0000-0002-6558-0208
VE: 0000-0002-0039-114X

**Corresponding Author**
Seda Seven
Marmara University Medical Faculty, Pendik Training and Research Hospital 34899 Pendik / Istanbul, Turkey
E-mail: ssedaseven@gmail.com

**Ethics Committee Approval**
Istanbul Training and Research Hospital's Medical Ethics Board (date and number: 11.03.2016 and 801).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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## Abstract

**Background/Aim:** Postoperative cognitive dysfunction (POCD) is an important problem that is encountered perioperatively and has a complex pathophysiology. Diabetes mellitus (DM) can cause adverse effects on cognitive functions, such as memory dysfunctions, psychomotor retardation, slower information processing, impairment of complex motor functions, deterioration of verbal rationality, and attention deficit. We assume that DM will have a triggering effect on POCD. Mild cognitive dysfunction caused by diabetes mellitus may increase the risk of POCD. For this purpose, we aimed to investigate the effect of type 2 DM on early POCD.
**Methods**: Fifty literate patients who ranked 1-2 on the American Society of Anesthesiologists (ASA) scale were included in our prospective case-control study. They ranged in age from 35 to 70. All were scheduled for elective laparoscopic cholecystectomy at the İstanbul Training and Research Hospital. Patients were divided into two groups: the diabetes mellitus group and the control group. The DM group consisted of 25 patients who had been diagnosed with type 2 DM and had been on regular oral antidiabetic medication or insulin for at least five years. To examine the patients neuropsychologically, the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) Test were conducted one day before the surgery. The MMSE and MoCA were repeated at the $4^{th}$ and $24^{th}$ hours postoperatively. The patients were monitored to record their depth of anesthesia, peak heart rate, mean arterial pressure, oxygen saturation, end-tidal carbon dioxide value, and expiratory sevoflurane concentration prior to perioperative intubation and every five minutes after intubation until the end of the operation. The state of postoperative pain and total analgesic dose used for the patients were also recorded.
**Results**: Demographic data in both groups were similar in terms of age, gender, body mass index, and duration of surgery ($P > 0.05$ for each). Perioperative depth of anesthesia, hemodynamic data, and postoperative pain scores were similar in both groups ($P > 0.05$ for each). While there was initially no significant difference between the groups in terms of preoperative cognitive function, compared with the control group, the DM group had significantly lower values of MMSE and MoCA at the postoperative $4^{th}$ ($P = 0.014$ and $P = 0.014$) and $24^{th}$ hour ($P = 0.026$ and $P = 0.01$) .
**Conclusion**: Our study shows that the early postoperative cognitive functions of diabetic patients are affected more than non-diabetic patients in laparoscopic surgery. MMSE and MoCA tests are appropriate for screening type 2 diabetic patients. Thus, complications can be prevented in diabetic surgical patients by detecting cognitive dysfunction in the early stages, so that appropriate treatment can be initiated.

**Keywords:** Cognitive dysfunction, Postoperative cognitive complications, Diabetes mellitus type 2

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## Introduction

Postoperative cognitive dysfunction (POCD) has become one of the most important problems of the perioperative period, with the increasing population of elderly patients [1, 2]. For the first time in 1955, Bedford et al. [3] drew attention to the development of cognitive dysfunction in the perioperative period. The independent variables that play a role in the etiology and pathogenesis of POCD vary. Clinical studies on this subject have concluded that anesthesia and anesthetic agent selection [4], postoperative pain treatment agents used, postoperative pain [5], sleep disorders in the perioperative period [6], perioperative hypoperfusion, and adverse events, such as stress response and inflammation [7, 8], play multifactorial roles in the etiopathogenesis of POCD. The effect of comorbidities, such as cerebrovascular events, hypertension, and obesity in the development of POCD has not yet been clarified [9].

Diabetes mellitus (DM) is a multisystemic disease [10, 11]. As approaches to prevent and treat the microvascular and macrovascular damage of DM advance, the life expectancy with this disease increases. As a result, new complications such as impaired cognitive functions can be observed. DM can cause adverse effects on cognitive functions such as memory dysfunctions, psychomotor retardation, slower information processing, impairment of complex motor functions, deterioration of verbal rationality, and attention deficit [12].

We assume that DM will have a triggering effect on POCD. For this purpose, we aimed to investigate the effect of type 2 DM on early POCD.

## Materials and methods

This prospective case-control study was conducted in the Istanbul Training and Research Hospital between March 2016 and December 2016.

The study included 50 literate patients with perfect vision and hearing in the age group from 35 to 70 years. All participants had scored 1-2 on the pre-anesthesia assessment of the American Society of Anesthesiologists (ASA). All patients were scheduled for elective laparoscopic cholecystectomy. The DM group included 25 patients who had been diagnosed with type 2 DM and had been on regular oral antidiabetic medication or insulin for at least five years. Preoperative blood glucose control had been achieved in these patients. The control group included 25 randomly selected patients who underwent laparoscopic cholecystectomy without a diagnosis of DM. Those over the age of 70 years, with a score of ASA III and above, who were known to be allergic to anesthetic drugs, had liver or kidney dysfunction, alcohol and/or substance addiction, or psychiatric symptoms and diagnosis were excluded from the study. Also excluded were patients who were on psychiatric drugs, had central nervous system disorders, dementia, permanent deficits caused by cerebrovascular events, or had received general anesthesia in the last three months. Patients with a body mass index (BMI) over 40, those diagnosed with hyperthyroidism or hypothyroidism, or scheduled for emergency surgery did not meet the inclusion criteria. Patients whose operation was started by laparoscopic method and completed using open surgery and who were administered intraoperative blood products, vasopressor drugs, antihypertensive drugs, or glucocorticoids were also excluded from the study.

In the preoperative period, age, gender, ASA score, BMI, and the presence and duration of DM diagnosis were recorded. A funduscopic examination was performed in the DM group, and the presence of diabetic retinopathy was recorded. Premedication was not given to the patients. Anesthesia was induced with 2 mg/kg propofol, 1 mcg/kg fentanyl, and 0.6 mg/kg rocuronium. Sevoflurane was used as a volatile anesthetic for anesthesia maintenance. Necessary adjustments were made in the sevoflurane concentration to maintain the depth of anesthesia in each patient so that the Bispectral Index (BIS) value was between 40 and 60. The BIS, peak heart rate (PHR), mean arterial blood pressure (MAP), peripheral oxygen saturation ($SpO_2$), end-tidal carbon dioxide concentration, and the end-expiratory sevoflurane concentration (EX-SEVO) were recorded before intubation and every five minutes thereafter until the end of the operation. As analgesics, 1 gram of paracetamol was administered peroperatively, and tramadol HCL was started intravenously using a patient-controlled analgesia device. The pain status of the patients was evaluated using the Visual Analog Scale (VAS) score at the postoperative 1$^{st}$, 2$^{nd}$, 4$^{th}$, 8$^{th}$, 12$^{th}$, and 18$^{th}$ hour.

The Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) Test were used one day before surgery to examine the patient's neuropsychology. The tests were repeated at the postoperative 4$^{th}$ and 24$^{th}$ hour. Consisting of 11 questions, the MMSE is a test that examines orientation, memory, attention, calculation, recall, language, motor function, and perception abilities and whose validity and reliability in Turkish was confirmed by Güngen et al. [13, 14]. MoCA is a psychomotor test with a maximum score of 30 that assesses attention, concentration, executive functions, memory, language, visual-spatial skills, abstract thinking, evaluating calculation, and orientation functions and whose validity and reliability in Turkish was confirmed by Selekler et al. [15, 16].

**Power analysis**

Group sample sizes of 25 and 25 achieved 85% power, detecting a difference of -3.0 from the null hypothesis; both group means were 21.0. The alternative hypothesis for the mean of Group 2 was 24.0 with known group standard deviations of 3.6 and 3.2 and with a significance level (alpha) of 0.05000 using a two-sided Mann-Whitney test assuming that the actual distribution is normal.

**Statistical analysis**

In the statistical analysis, the descriptive statistics of the data were presented as mean values (standard deviation), median lowest, median highest, frequency, and ratio values. The distribution of variables was measured with the Kolmogorov–Smirnov test. To analyze quantitative independent data, the Independent Samples t-test and Mann–Whitney U test were used. The Chi-squared test was used for analyzing the qualitative independent data, and SPSS 22.0 program was used for statistical analysis.

## Results

The age, gender distribution, and BMI of the patients in the DM group and the control group did not show any statistically significant difference (*P* > 0.05 for each). The surgical duration of the patients in the DM group and the control group did not differ significantly (*P* > 0.05) (Table 1).

Table 1: Comparison of the DM and control groups by demographic data

| | DM group | Control group | *P*-value |
|---|---|---|---|
| Age | 55.8 (7.2) | 51.7 (9.9) | 0.1 |
| Gender: | | | 0.156 |
| Female | 16 (64) | 11 (44) | |
| Male | 9 (36) | 14 (56) | |
| BMI | 30 ( 3.7) | 30.7 (4.6) | 0.539 |
| ASA I | 0 (0) | 12 (48) | < 0.001 |
| II | 25 (100) | 13 (52) | |
| Surgery time | 48.4 (12.7) | 52.2 (14.7) | 0.383 |

Values are given as mean (standard deviation) and n (%); BMI: body mass index; ASA: American Society of Anesthesiology Physical Status Classification System; DM: diabetes mellitus

Of the 25 patients included in the DM group, 3 were found to have retinopathy in the preoperative funduscopic examination, whereas the mean duration of diabetes was 9.16 (3.7) years.

Measured preoperatively and every five minutes during the peroperative period, the values of BIS, HR, MAP, $SPO_2$, $ETCO_2$, EX-SEVO did not show a statistically significant difference between the two groups, and their pain status in the postoperative period was found to be similar (*P* > 0.05 for each).

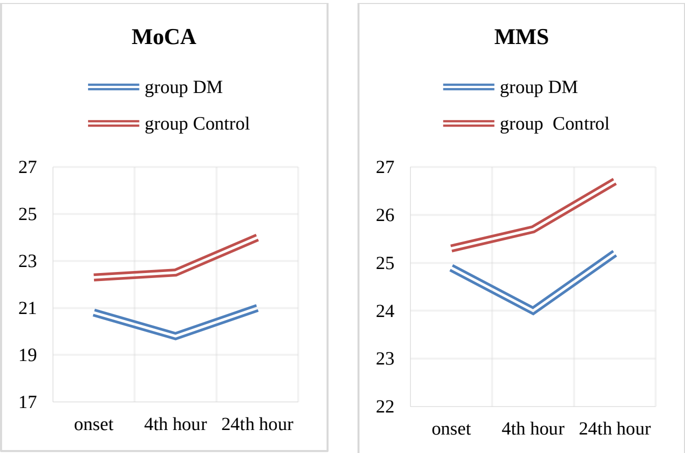
The baseline MoCA score did not differ significantly in both groups. The DM group had significantly lower MoCA scores at the 4th and 24th hours compared with those in the control group (*P* = 0.014 and *P* = 0.010). The baseline MMSE score did not differ significantly in both groups. The DM group had significantly lower MMSE scores at the 4th and 24th hours compared with those in the control group (*P* = 0.014 and *P* = 0.026) (Table 2 and Figure 1).

Table 2: Comparison of the DM and control groups by MoCA and MMSE scores

| | DM group | Control group | *P*-value |
|---|---|---|---|
| Preoperative MoCA | 20.8 (3.1) | 22.3 (3.1) | 0.20 |
| Postoperative 4th hour MoCA | 19.8 (3.6) | 22.5 (3.4) | 0.014 |
| Postoperative 24th hour MoCA | 21.0 (3.6) | 24.0 (3.2) | 0.010 |
| Preoperative MMSE | 24.9 ( 1.7) | 25.3 (2.4) | 0.47 |
| Postoperative 4th hour MMSE | 24.0 (2.1) | 25.7 (2.5) | 0.014 |
| Postoperative 24th hour MMSE | 25.2 (2.1) | 26.7 (2.3) | 0.026 |

Values are given as mean (standard deviation). MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Exam; DM: diabetes mellitus,

Figure 1: a) Comparison of the MoCA Scores in the DM and Control Groups, b) Comparison of the MMS Scores in the DM and Control Groups




## Discussion

In our study, although there was no statistically significant difference between the two groups in terms of preoperative cognitive function, the DM group had significantly lower scores of MMSE and MoCA at the postoperative 4th and 24th hours compared with those in the control group.

Age was the main risk factor in POCD [17]. A study by Monk et al. [18] reports the prevalence of POCD to be 36.6% in the age group of 18–39 years, 30.4% in the age group of 40–59 years, and 41.4% in the age group of over 60 years. These patients were those who had undergone major non-cardiac surgery, and three months later, this rate was found to be 5.7% in the young patient group, 5.6% in the middle-aged group, and 12.7% in the elderly group over the age of 60. In the study by Fodale et al. [19], the increase in amyloid beta peptide level in the elderly brain and its association with Alzheimer's disease should be taken into account, and considering that anesthetics would interact with this substance in cases of long-duration anesthesia administration, it was evaluated as an expected increase in the prevalence of POCD in elderly patients. To reduce age-related cognitive dysfunction, we included individuals aged under 70 herein. In addition, the mean age was 55.8 years in the DM group and 51.7 in the control group, and there were no statistically significant differences between the two groups.

The development of POCD is affected by factors, such as the type of surgery [20, 21], the anesthesia method applied [22, 23], the duration of anesthesia [24], and the depth of anesthesia [25]. The patients included in our study were those who underwent laparoscopic cholecystectomy under general anesthesia and the mean anesthesia duration was less than 75 minutes. The depth of anesthesia in both groups was monitored peroperatively by BIS monitoring to ensure a BIS value between 40 and 60. According to our results, surgical time, BIS follow-ups, and respiratory sevoflurane concentrations were similar in both groups. According to the literature, studies have shown that peroperative hypoxia and hypotension are risk factors for POCD [5, 25]. In our study, $SpO_2$ was not observed to be below 90 in any patient, and the levels of PHR, MAP and $SpO_2$ in both groups were similar in the peroperative follow-up. It has been shown in many studies that postoperative pain is one of the important risk factors in the development of POCD [5, 26]. In our study, no statistically significant difference was observed between the DM and control groups in terms of their VAS values at the postoperative 1st, 2nd, 4th, 8th, 12th, and 18th hour.

Cognitive values can be expected to worsen in the preoperative period in diabetic patients [27-29], and it is known that the risk for postoperative cognitive dysfunction is increased in patients with impaired preoperative cognitive functions [18]; however, no significant difference was found in preoperative cognitive tests between diabetic patients and non-diabetic patients in our study.

Type 2 diabetes has been associated with reduced frontal lobe executive function, psychomotor speed, verbal memory, processing speed, complex motor speed, recall, delayed recall, verbal fluency, visual memory, and attention [12]. The underlying pathophysiology of the development of cognitive dysfunction in DM patients has not been fully elucidated. There are many hypotheses including hypoglycemia, insulin resistance, vascular damage, and amyloid accumulation [30, 31]. In the peroperative period, imbalances in the neurotransmitter system, such as acetylcholine and serotonin, increase in inflammatory mediators, and disruption of the blood–brain barrier due to cytokine release are the primary mechanisms responsible for the development of postoperative cognitive function [7, 8]. Considering these factors, it is expected that diabetic patients will experience a greater decrease in cognitive functions during the peroperative period.

Cognitive dysfunction is more common in cardiac surgery compared with non-cardiac surgery, and extracorporeal circulation-related micro-embolism, non-pulsatile flow, hypotension, and hypoxia contribute to its etiology. In these patients, cerebral perfusion impairment plays a major role in postoperative neuropsychological outcomes [32]. In a prospective study by Nötzold et al. [33], 14 diabetic and 20 non-diabetic patients who underwent coronary artery bypass graft operation were studied. Both groups were operated on by the same surgeon under standard intraoperative and perioperative conditions. Cognitive changes were evaluated daily at a 2–5-day interval postoperatively. Their results demonstrated that all patients had postoperative cognitive deterioration, and compared with the non-diabetic group, this deterioration was found to be significantly higher in the diabetic group. A study by Tang et al. [34] included a total of 131 patients undergoing valve replacement with cardiopulmonary bypass in the study group, along with the control group that included 40 healthy volunteers. Their cognitive functions were measured preoperatively one day before the surgery and on the seventh day postoperatively through neuropsychological testing, and the prevalence of POCD was found to be 43.8% seven days after the surgery.

Insulin resistance was significantly higher in the POCD patients than in the non-POCD patients. Insulin resistance was demonstrated to be correlated with incidence of POCD and increased proinflammatory cytokines. The meta-analysis conducted by Feinkohl et al. [35] in 2017 investigated the relationship between diabetes and POCD, and the risk of POCD after cardiovascular surgery was found to be 1.26 times higher in diabetic patients compared with non-diabetic patients. In the study conducted by Kadoi et al. [36] in 180 patients who underwent elective coronary artery bypass graft surgery, POCD was at 68% in the diabetic group and 55% in the control group on postoperative day 7. Age, presence of hypertension, jugular venous oxygen saturation, presence of atherosclerosis in the ascending aorta, diabetic retinopathy, and insulin treatment have been associated with short-term cognitive dysfunction. In the postoperative sixth month, POCD was detected in 28% of the diabetics and in 11% in the control group. Insulin therapy, diabetic retinopathy, and hemoglobin A1c levels have been associated with long-term cognitive dysfunction.

There are also studies showing a relation between the presence of diabetic retinopathy and cognitive dysfunction in non-cardiac surgery [37]. In our study, three patients had retinopathy, which we think is due to the short duration of diabetes (9.16 (3.7) years). Therefore, we could not make a significant comparison. We also indicated that elevated HbA1c levels and cognitive dysfunction were correlated [38, 39]. Yaffe et al. [40] showed that those with an HbA1c of over 7% have a four times higher risk of developing mild cognitive dysfunction. We did not measure HbA1C levels, because we included patients with close follow-up in our study, whose blood glucose was regulated in the preoperative period, and who received regular oral antidiabetic medication or insulin therapy.

There are only a few studies that have investigated the relation between DM and POCD in non-cardiac surgeries. Three studies including cardiac and non-cardiac surgery were examined in a meta-analysis conducted in 2018. After adjustments on age, gender, type of surgery, randomization, obesity, and hypertension, diabetes was associated with a 1.84-fold increased risk of POCD (OR 1.84; 95% CI 1.14, 2.97; $P$ = 0.01). Obesity, BMI, hypertension and baseline blood pressure were not found to be associated with POCD [9]. Seventy-seven patients aged 65–75 years were included in the study by Zhang et al. [41] in patients who had undergone colorectal surgery, and cognitive dysfunction was demonstrated in 29 patients on postoperative day 7. As a result of multivariate logistic regression analysis, diabetes history (OR = 8.391 [2.208–31.882]; $P$ = 0.012) was shown to be an independent risk factor for early cognitive dysfunction in elderly patients who underwent colorectal surgery. Therefore, the POCD-triggering effect of DM, especially in the elderly, should be considered to result in prolonged duration of hospital stay, decreased functional independence, increased risk of dementia, burden for the caregiver, increased healthcare costs, morbidity, and mortality [42, 43].

**Limitations**

This was a monocentric study and our patients were selected from a specific group. Cognitive dysfunctions that developed in the first 24 hours in both groups were evaluated, and the lack of follow-up of patients in the long term is our main limitation.

**Conclusion**

Today, as in laparoscopic cholecystectomy, outpatient surgeries are preferred more frequently and early postoperative discharge is emphasized. Our study has shown that the early postoperative cognitive functions of diabetic patients are affected more than non-diabetic patients. We believe that patients with DM should be evaluated in terms of POCD especially in the early postoperative period after outpatient surgery before deciding on their discharge.

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