

The effect of type 2 diabetes mellitus on perioperative neurocognitive disorders in patients undergoing elective noncardiac surgery under general anesthesia. A prospective cohort study

Maria P. Ntalouka, Eleni Arnaoutoglou¹, Spyridon Vrakas², Chryssoula Staikou³, Fragkiskos A. Angelis⁴, Georgios Papadopoulos⁵, Petros Tzimas⁶

Department of Anesthesiology and Postoperative Intensive Care, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece; Department of Anesthesiology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, ¹Department of Anesthesiology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, ²Department of Gastroenterology, Tzaneio Hospital, Piraeus, ³Department of Anaesthesiology, Aretaieio Hospital, National and Kapodistrian University of Athens, ⁴Department of Orthopedics Surgery and Musculoskeletal Trauma, Medical School, University of Thessaly, Larissa, ⁵Department of Anesthesiology and Postoperative Intensive Care, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, ⁶Department of Anesthesiology and Postoperative Intensive Care, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

Abstract

Background and Aims: Preliminary evidence suggests a possible relationship between type 2 diabetes mellitus (T2DM) and perioperative neurocognitive disorders (NCD). We sought to investigate whether patients with T2DM, undergoing elective noncardiac surgery under general anesthesia, are at increased risk of perioperative NCD.

Material and Methods: A prospective cohort study was designed. One-hundred and forty-four patients with T2DM and 144 healthy controls were recruited. Controls were matched for sex, age, type of operation, and educational background. Postoperative delirium (POD), delayed neurocognitive recovery and postoperative NCD were evaluated.

Results: Two hundred twenty-eight patients were analyzed. Compared to controls, patients with T2DM were diagnosed with higher rates of NCD preoperatively ($n = 96$ vs. $n = 26$, $P < 0.05$) and higher POD up to 4 days postoperatively ($n = 204$ vs. $n = 68$, $P < 0.05$). Increased rates of delayed neurocognitive recovery and postoperative NCD were recorded in patients with T2DM up to 9 months postoperatively ($n = 473$ vs. $n = 192$, $P < 0.05$). Insulin-dependent patients had higher rates of POD on the second ($n = 38$ vs. $n = 24$, $P < 0.05$) and third day ($n = 27$ vs. $n = 16$, $P < 0.05$) when compared to noninsulin-dependent patients. Logistic multivariable analysis revealed that patients with T2DM are at increased risk for postoperative cognitive disorders.

Conclusion: Patients with type 2 diabetes mellitus appear to be at a higher risk of perioperative NCDs up to 9 months after elective noncardiac surgery under general anesthesia.

Keywords: Anesthesia, diabetes mellitus, elective surgical procedures, general, neurocognitive disorders, postoperative cognitive complications, type 2

Address for correspondence: Dr. Maria P. Ntalouka, Department of Anesthesiology and Postoperative Intensive Care Unit, Faculty of Medicine, School of Health Sciences, University of Ioannina, P.O. BOX 1186, 45111, Ioannina, Greece. E-mail: maria.ntalouka@icloud.com

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Introduction

Cognitive change in otherwise well cognitive patients undergoing surgery has been recognized for many centuries.^[1-8] It is estimated that approximately 10% of elderly undergoing surgery will develop cognitive changes perioperatively, while in some reports the incidence rises up to 80%.^[7,9] Despite the reported high prevalence of perioperative neurocognitive disorders (NCD), their exact etiology is still largely unknown.^[7,10]

Perioperative NCD affects multiple aspects of patients' quality of life and it seems that there is a clear link between NCD, impaired recovery, and prolonged rehabilitation.^[1-3,6-9] Although perioperative NCDs are not considered as direct life-threatening conditions, they are associated with increased morbidity and mortality.^[5,7] Postoperative delirium (POD), delayed neurocognitive recovery, and postoperative NCD, may lead to increased physical frailty, while up to 70% of patients suffering from some form of perioperative NCD may die within 5 years, compared to 35% of patients with intact cognition.^[6,7]

Cognitive dysfunction is a recognized comorbidity of type 2 diabetes mellitus (T2DM).^[11] Patients suffering from T2DM are at 50%–140% increased risk of dementia and at 20%–50% increased risk of cognitive decline, compared to healthy population.^[12] In T2DM chronic hyperglycemia may lead to vascular complications and subsequent transient or permanent cognitive abnormalities.^[13] T2DM is characterized by slowing of neural conduction, increased cortical atrophy, and altered concentrations of brain metabolites.^[13] The aforementioned changes are expressed as mental and motor slowing, along with decrements of similar magnitude on measures of attention and executive function, such as planning attention, working memory, and problem-solving.^[13] However, the underlying mechanism and the risk factors that may lead to the development of severe and prolonged cognitive dysfunction, such as dementia, in patients with T2DM are not well understood.^[14]

Preliminary evidence suggests a possible relationship between pre-existing T2DM and postoperative cognitive disorders.^[5,12] Age, glycemic control, and cardiovascular complications are identified risk factors contributing to perioperative NCD development in patients with T2DM.^[5] However, there are limited data about the long-term cognitive function of patients undergoing noncardiac surgery, as most studies are focused on patients undergoing cardiac surgery.^[5,12] The aim of this study was to investigate whether patients with type II DM are at increased risk of developing POD up to the 4th,

delayed neurocognitive recovery, and postoperative NCD up to 9 months after elective noncardiac surgery under general anesthesia.

Material and Methods

This is a prospective, cohort study and was conducted between January 2016 to August 2018, in accordance with the Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki) and the STROBE Statement.^[15,16] Ethical approval (Ethical Committee N° 679/21-9-2015) was provided on November 8, 2015. All patients were fully informed and provided written informed consent before participation.

Only patients with certain criteria were eligible for inclusion: (1) T2D with <10 years of diagnosis, (2) Hemoglobin A1c (HbA1c) <7.5%, (3) 45–80 years, (4) American Society of Anesthesiologists physical status I to III, (5) elective general, urological, gynecological and orthopedic surgery under general anesthesia, (6) native speakers of the Greek language. Patients were excluded from the study if: (1) refused to participate or sign the informed consent form, (2) had undergone surgery or anesthesia within the last 30 days, (3) had any prior or current history involving an affliction of the central nervous system, (4) were diagnosed with severe cognitive decline based on the 16-item Informant Questionnaire on Cognitive Decline (IQCODE-16), (5) suffered from severe hearing or visual impairment, (6) or any psychiatric disorder, (7) had a score >5 in the Geriatric Depression Scale (GDS-15), (8) or a score in females <4 males <2 in the Lawton-Brody Instrumental Activities of Daily Living Scale (I.A.D.L.), (9) reported alcohol consumption >35 units/week, (10) or drug dependence, (11) had undergone previous neuropsychological testing, (12) suffered from hemodynamical instability (>20% alterations of blood pressure perioperatively), (13) or desaturation (one or more events of SpO₂<80% for more than 2 min) perioperatively, (14) or blood loss of more than one unit. The participants in the control group were matched for sex, age, type of operation, and education. Moreover, for each noninsulin-dependent T2D patient one insulin-dependent T2D patient was matched for the same criteria.^[7,9,17-20]

The same perioperative care protocol was used for all patients. Premedication with benzodiazepines was avoided and preoperative fasting time was limited to the minimum acceptable duration based on current guidelines. Surgery was performed under general anesthesia with standard monitoring setup and adequate pain control with multimodal continuous

analgesia regimen (remifentanyl) at appropriate dose. The anesthesia depth was monitored and maintained within the recommended values with the use of bispectral index (BIS). Induction was performed with fentanyl 3–5 µg/kg and propofol 1.5 mg/kg. Intubation was facilitated with rocuronium 0.6 mg/kg and mechanical ventilation was initiated with a 50% oxygen-air mixture and adjusted tidal volumes of 6–8 mg/kg, respiratory rate of 10–12/min aiming at oxygen saturation via pulse oximetry (SpO₂) values >97% and end-tidal carbon dioxide values of about 35 mmHg. Anesthesia was maintained with desflurane by adjusting end-tidal concentrations aiming to a MAC of 0.8 to 1.1. Postoperatively all patients were treated for postoperative pain to keep Visual Analogue Scale (VAS) score below 44 mm with a multimodal opioid-sparing analgesia.

Our aim was to investigate whether patients with type II DM are at increased risk of developing POD up to the 4th, delayed neurocognitive recovery and postoperative NCD up to 9 months after elective noncardiac surgery under general anesthesia. The secondary outcome was to compare the incidence of POD up to the 4th, delayed neurocognitive recovery and postoperative NCD between the insulin-dependent and the noninsulin-dependent patients.

For the diagnosis of POD the Confusion Assessment Method (CAM) Diagnostic Algorithm was used, while for the evaluation of delayed neurocognitive recovery and postoperative NCD the IQCODE-16 was used, respectively. The test administered for the cognitive evaluation was selected based on the following criteria: (1) short time for administration, (2) simple enough to assure the maximum cooperation, (3) should control for education and culture, (4) should distinguish the delirium from dementia (5) should identify delirium when superimposed by dementia, (6) should classify the cognitive dysfunction (7) should indicate good sensitivity and high test-retest reliability. The IQCODE-16 is a well-accepted measure that meets all the aforementioned criteria.^[17,21-24] The short form, IQCODE-16, indicates a good correlation (0.98) and comparable validity with the full version.^[23] All patients included in the study subjected to the IQCODE-16 preoperatively and postoperatively on the 10th day, 3, 6, and 9 months. The cognitive status was classified as cognitively normal and slight, moderate or severe decline.^[17,22-24] The CAM Diagnostic Algorithm has a high sensitivity and specificity (94%, 89%), high inter-rater reliability ($\kappa = 0.7-1.0$), and an impressive correlation with expert opinion for the diagnosis of POD.^[18,23] Patients were screened for POD on the 1st, 2nd, 3rd, and 4th postoperative day. When the test was positive the patient was considered as delirious.^[17-19] The CAM Diagnostic Algorithm and the IQCODE-16 were carried out in a quiet room and only the patient and the examiner were present.^[20] The examiner

received the appropriate training from a neuropsychiatrist regarding the use of the CAM Diagnostic Algorithm and the IQCODE-16 and he was blinded to both the T2D and the control group.

To minimize the bias due to the based on the potentially increased coronary heart disease risk of T2D group, the <10 years duration of diabetes was selected.^[7,9,17,25] The age group was selected in order to avoid patients with known reduced or increased risk of perioperative NCD.^[17] All biochemical analyses were performed using an Olympus AU600 clinical chemistry analyzer.

Based on the available literature, during the study design, group sample sizes of 133 in the T2D group and 133 in the control group (enrolment ratio 1) achieve 90% power to detect a difference of 15% in the incidence of perioperative NCD between the T2D group and the non-T2D control group (confidence level 5%, confidence interval 95%).^[9] This number was increased to 144 patients for both groups, in order to account for possible dropouts. Baseline patient characteristics were compared using Chi-square and fisher exact tests. The associations between: (i) delirium and T2D and (ii) cognitive decline and T2D were evaluated using a logistic regression model, with T2D being included as dependent variable (T2D group, non-T2D group control group). The associations between: (i) delirium and insulin dependence and (ii) cognitive decline and insulin dependence were evaluated using the logistic regression model, with insulin dependence being the dependent variable. Variables for which to adjust were considered a priori and included Atherosclerotic Cardiovascular Disease Score (ASCVD)-10-year risk, eGFR (estimated glomerular filtration rate), urine micro-albumin and previous exposure to surgery/anesthesia in the diabetes mellitus model and duration of T2D in the insulin dependence model. Statistically significant level was set at $P < 0.050$ throughout the analysis. Statistical analysis of the acquired data was performed with Stata 14.1 software (StataCorp, College Station, Texas).

Results

Data from 288 patients (144 T2D group and 144 control group) were analyzed. Figure 1 illustrates the patients' flow diagram. The demographics and perioperative characteristics of the 288 patients (50% male and 50% females) are described in Tables 1a and 1b. The mean age of the patients was 66.5 years and the mean duration (minutes) of surgery/anesthesia was 164.2 ± 10.2 (T2D group) vs. 162.4 ± 10.6 (control group, $P < 0.05$). Participants with T2D underwent general surgery

with longer duration (168.6 ± 11 vs. 162.5 ± 11.6) and had greater values of ASCVD and micro-albuminuria and lower values of eGFR ($P < 0.050$). In T2D group greater rates of previous exposure to surgery and/or anesthesia were recorded ($P < 0.0001$).

T2D patients were diagnosed with higher rates of POD on the 1st ($P < 0.0001$), 2nd ($P < 0.0001$), 3rd ($P = 0.004$) and 4th ($P < 0.0001$) day [Table 2a] and higher rates of slight ($P < 0.0001$) and moderate ($P < 0.0001$) cognitive decline preoperatively [Table 2b]. Patients in the T2D group had increased slight ($P = 0.001$), moderate ($P < 0.0001$) and severe ($P < 0.0001$) delayed neurocognitive recovery at 10 days and increased slight ($P < 0.0001$), moderate ($P < 0.0001$) and severe ($P < 0.0001$) postoperative NCD 3, 6 and 9 months [Table 2c]. The sub-analysis T2D group revealed greater rates of POD on the 2nd ($P = 0.018$) and 3rd ($P = 0.045$) postoperative day in the insulin-dependent group when compared to noninsulin-dependent [Table 3a]. However, there was no significant difference between the insulin-dependent and the noninsulin-dependent group regarding the pre-operative cognitive status [Table 3b], the delayed neurocognitive recovery at 10 days and the postoperative NCD at 3, 6 and 9 months respectively [Table 3c].

Logistic multivariable regression analysis in T2D and control group revealed that age and sex are not confounding factors

for perioperative NCD [Tables 4a, 4b and 4c]. Adjustment with multivariate analysis for ASCVD-10-year risk, eGFR, micro-albumin and previous exposure to surgery, increased rates of POD on the 1st (OR, 2.82; 95% CI 1.36–5.86; $P = 0.005$) and 4th (OR, 11.8; 95% CI 1.40–99.17; $P = 0.023$) day and of slight (OR, 2.87; 95% CI 1.47–5.61; $P = 0.002$) and moderate (OR, 10.52; 95% CI 2.18–50.6;

Table 1a: Baseline demographics and clinical characteristics of participants

Variable	Subgroups		P
	Control group (n=144)	T2D* group (n=144)	
Age (years)	66.6±7.4	66.4±7.5	0.830
Sex			
Female	50% (n=72)	50% (n=72)	1
Male	50% (n=72)	50% (n=72)	
ASA PS†			
ASA PS 1	34.72% (n=50)	0	Ref.
ASA PS 2	45.83% (n=66)	41.67% (n=60)	0.983
ASA PS 3	19.44% (n=28)	58.33% (n=84)	0.981
Duration of surgery/anesthesia			
General	162.4±10.6	164.2±10.2	0.130
Urological	162.5±11.6	168.6±11	0.029
Gynecological	164±12	165.4±10.8	0.600
Orthopedic	162.7±10.1	164.7±9.2	0.390
	160.4±8.3	158.3±6.5	0.240

*T2D: type II Diabetes Mellitus; †ASA PS: American Society of Anesthesiologists physical status

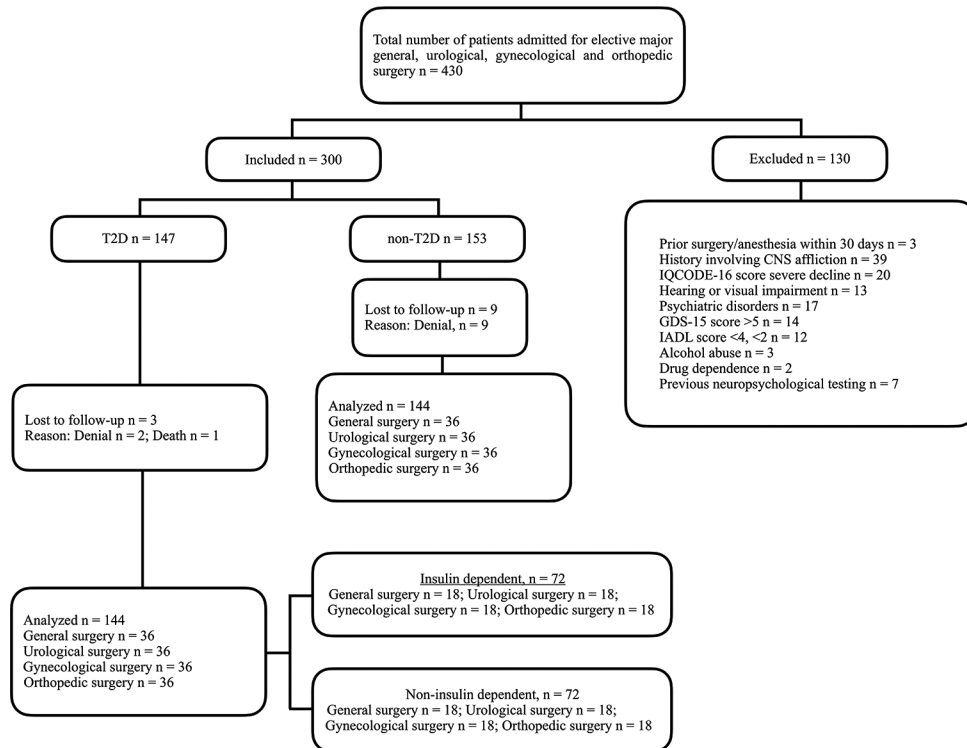


Figure 1: Patients' flow diagram. T2D: type II diabetes mellitus; CNS: central nervous system; IQCODE-16: 16-item Informant Questionnaire on Cognitive Decline; GDS-15: 15-Geriatric Depression Scale; I.A.D.L: Lawton-Brody Instrumental Activities of Daily Living Scale

Table 1b: Baseline demographics and clinical characteristics of participants

Variable	Subgroups		P
	Control group (n=144)	T2D* group (n=144)	
Waist/Height			
< 0.5	68.06% (n=98)	49.31% (n=71)	Ref.
0.5-0.6	19.44% (n=28)	36% (n=25)	0.053
> 0.6	12.5% (n=18)	25.69% (n=37)	0.001
ASCVD 10-year risk*			
Low	30.56% (n=44)	1.39% (n=2)	Ref.
Borderline	18.06% (n=26)	7.64% (n=11)	< 0.006
Intermediate	31.94% (n=46)	36.81% (n=53)	< 0.0001
High	19.44% (n=28)	4.17% (n=78)	< 0.0001
Smoking			
No	55.56% (n=80)	54.17% (n=78)	Ref.
Yes	19.44% (n=28)	21.53% (n=31)	0.670
Quit	25% (n=36)	24.31% (n=35)	0.990
eGFR [†] (ml/min/1.73m ³)			
>90	40.28% (n=58)	9.03% (n=13)	Ref.
60-89	56.94% (n=82)	71.53% (n=103)	< 0.0001
45-59	2.78% (n=4)	19.44% (n=28)	< 0.0001
Micro-albuminuria			
No	94.44% (n=136)	59.03% (n=85)	< 0.0001
Yes	5.56% (n=8)	40.97% (n=59)	
Previous exposure to anaesthesia			
No	93.06% (n=134)	54.86% (n=79)	<0.0001
Yes	6.94% (n=10)	45.14% (n=65)	

*ASCVD 10-year risk: Atherosclerotic Cardiovascular Disease score 10-year risk; [†]eGFR: estimated glomerular filtration rate

Table 2a: Postoperative delirium rates in type II diabetes mellitus and control group, based on Confusion Assessment Method Diagnostic Algorithm

	CAM [†] (postoperatively)	Control group (n=144)	T2D* group (n=144)	P
1 st day	No delirium	88.89% (n=128)	49.31% (n=71)	<0.0001
	Delirium	11.11% (n=16)	50.69% (n=73)	
2 nd day	No delirium	80.56% (n=116)	56.94% (n=82)	<0.0001
	Delirium	19.44% (n=28)	43.06% (n=62)	
3 rd day	No delirium	84.72% (n=122)	70.14% (n=101)	0.004
	Delirium	15.28% (n=22)	29.86% (n=43)	
4 th day	No delirium	98.59% (n=140)	81.69% (n=116)	<0.0001
	Delirium	1.41% (n=2)	18.31% (n=26)	

*T2D: type II Diabetes Mellitus; [†]CAM: Confusion Assessment Method Diagnostic Algorithm

$P = 0.003$) cognitive decline preoperatively were found ($P < 0.05$, Tables 5a and 5b). Severe delayed neurocognitive recovery at 10 days (OR, 7.35; 95% CI 1.87–28.9; $P = 0.004$), moderate (OR, 3.38; 95% CI 1.29–8.83; $P = 0.013$) and severe (OR, 12.5; 95% CI 2.03–77.0; $P = 0.006$) NCD at 3 months, slight (OR, 3.08; 95% CI 1.49–6.33; $P = 0.002$) and moderate (OR, 6.35; 95% CI 1.81–22.1; $P = 0.004$) NCD at 6 months and slight (OR, 2.99; 95% CI 1.48–6.04; $P = 0.002$) and moderate (OR, 15.72; 95% CI 3.28–75.35; $P = 0.001$) NCD at 9 months were revealed respectively ($P < 0.05$, Table 5c). Adjustment

for the duration of DM (insulin dependent vs. noninsulin dependent, tables 6a, 6b, 6c) identified greater rates of POD on the 2nd (OR, 2.32; 95% CI 1.16–4.63; $P = 0.0017$) and 3rd (OR, 2.16; 95% CI 1.02–4.56; $P = 0.043$) day [Table 6a], and of severe NCD at 3 months (OR, 3.36; 95% CI 1.06–10.65; $P = 0.040$) respectively [Table 6c].

Discussion

Our study indicates that T2D patients are affected with higher rates of cognitive decline pre-operatively and they are at a greater risk of POD up to 4 days, delayed neurocognitive recovery at 10 days and postoperative NCD up to 9 months after surgery. Insulin-dependent T2D patients are diagnosed with increased rates of POD on the 2nd and 3rd day and severe postoperative NCD at 3 months, when compared to noninsulin dependent. Overall, it seems that T2D patients are at increased risk for more severe and long-lasting perioperative NCD.

Cognitive decline is a recognized comorbidity and an important complication of T2D. There is an increasing awareness of its multifaceted impact on an individual's overall well-being.^[5,11] Therefore, guidelines recommend yearly screening for early detection of cognitive impairment in adults >65 years of age with T2D, as unrecognized cognitive deterioration may

Table 2b: Preoperative neurocognitive disorders in type II diabetes mellitus and control group, based on 16-item Informant Questionnaire on Cognitive Decline score

IQCODE-16 [†]		Control group (n=144)	T2D* group (n=144)	P
Preoperatively	Cognitive normal	81.94% (n=118)	33.33% (n=48)	Ref.
	Slight decline	16.67% (n=24)	36.81% (n=53)	<0.0001
	Moderate decline	1.39% (n=2)	29.86% (n=43)	<0.0001
	Severe decline	0% (n=0)	0% (n=)	-

*T2D: type II Diabetes Mellitus; [†]IQCODE-16: 16-item Informant Questionnaire on Cognitive Decline

Table 2c: Perioperative neurocognitive disorders in type II diabetes mellitus and control group, based on 16-item Informant Questionnaire on Cognitive Decline score

IQCODE-16 [†]		Control group (n=144)	T2D* group (n=144)	P
10 days postoperatively	Cognitive normal	43.06% (n=62)	7.64% (n=11)	Ref.
	Slight decline	25% (n=36)	17.36% (n=25)	0.001
	Moderate decline	27.78% (n=40)	22.92% (n=33)	< 0.0001
	Severe decline	4.17% (n=6)	52.08% (n=75)	< 0.0001
3 months postoperatively	Cognitive normal	63.89% (n=92)	14.58% (n=21)	Ref.
	Slight decline	22.22% (n=32)	23.61% (n=34)	< 0.0001
	Moderate decline	12.5% (n=18)	33.33% (n=48)	< 0.0001
	Severe decline	1.39% (n=2)	28.47% (n=41)	< 0.0001
6 months postoperatively	Cognitive normal	77.08% (n=111)	20.83% (n=30)	Ref.
	Slight decline	18.75% (n=27)	34.03% (n=49)	< 0.0001
	Moderate decline	4.17% (n=6)	31.25% (n=45)	< 0.0001
	Severe decline	0% (n=0)	13.89% (n=20)	< 0.0001
9 months postoperatively	Cognitive normal	82.64% (n=119)	28.47% (n=41)	Ref.
	Slight decline	15.97% (n=23)	31.25% (n=45)	< 0.0001
	Moderate decline	1.39% (n=2)	34.03% (n=49)	< 0.0001
	Severe decline	0% (n=0)	6.25% (n=9)	< 0.0001

*T2D: type II Diabetes Mellitus; [†]IQCODE-16: 16-item Informant Questionnaire on Cognitive Decline

Table 3a: Postoperative delirium rates in type II diabetes mellitus group, with respect to insulin therapy, based on Confusion Assessment Method Diagnostic Algorithm

	CAM [†] (postoperatively)	T2D* group		P
		Noninsulin dependent (n=72)	Insulin dependent (n=72)	
1 st day	No delirium	52.78% (n=38)	45.83% (n=33)	0.400
	Delirium	47.22% (n=34)	54.17% (n=39)	
2 nd day	No delirium	66.67% (n=48)	47.22% (n=34)	0.018
	Delirium	33.33% (n=24)	52.78% (n=38)	
3 rd day	No delirium	77.78% (n=56)	62.5% (n=45)	0.045
	Delirium	22.22% (n=16)	37.5% (n=27)	
4 th day	No delirium	87.32 (n=62)	76.06% (n=54)	0.080
	Delirium	12.68% (n=9)	23.94% (n=17)	

*T2D: type II Diabetes Mellitus; [†]CAM: Confusion Assessment Method Diagnostic Algorithm

increase morbidity and mortality and affect the patients' independence.^[11] The results from cognitive screening should lead to an individualized T2D management strategy, based on the patient's capabilities, with lenient treatment targets and simplified regimens to improve compliance and reduce treatment-related risks.^[11]

Two meta-analyses have shown that there might be an association between pre-existing T2D and postoperative cognitive disorders.^[5,12] These findings are in line with our study, which indicates that T2D patients, and especially insulin dependent, are at a greater risk of perioperative NCD. Hermanides *et al.*^[5] found that DM and acute peri-operative hyperglycemia may be associated with an increased risk of POD and postoperative NCD and Feinkohl *et al.*^[12] that individuals with DM are more vulnerable to postoperative NCD. However, the interpretation of the literature is hindered by the lack of definition of DM and the variety of the screening methods for perioperative NCD. There are still limited data to enable identification of T2D patients at risk for perioperative NCD and to establish T2D as an independent risk factor for POD, delayed neurocognitive recovery and postoperative NCD respectively.^[5,12]

Experts suggest that cognitive decline in people with T2D should not be considered a unitary construct.^[11,14] T2D patients are facing a greater risk for mild cognitive impairment, diabetes-specific mild to moderate cognitive decrements and dementia.^[11,13,14] Although the mild to moderate degree of cognitive impairment does not have a significant impact on

Table 3b: Preoperative neurocognitive disorders in type II diabetes mellitus group, with respect to insulin therapy, based on 16-item Informant Questionnaire on Cognitive Decline score

IQCODE-16 [†]		T2D* group		P
		Noninsulin dependent (n=72)	Insulin dependent (n=72)	
Preoperatively	Cognitive normal	31.94% (n=23)	34.72% (n=25)	Ref.
	Slight decline	41.67% (n=30)	31.94% (n=23)	0.380
	Moderate decline	26.39% (n=19)	33.33% (n=24)	0.720
	Severe decline	0% (n=0)	0% (n=0)	-

T2D*: type II Diabetes Mellitus; IQCODE-16[†]: 16-item Informant Questionnaire on Cognitive Decline

Table 3c: Perioperative neurocognitive disorders in type II diabetes mellitus group, with respect to insulin therapy, based on 16-item Informant Questionnaire on Cognitive Decline score

IQCODE-16 [†]		T2D* group		P
		Noninsulin dependent (n=72)	Insulin dependent (n=72)	
10 days postoperatively	Cognitive normal	9.27% (n=7)	5.56% (n=4)	Ref.
	Slight decline	20.83% (n=15)	13.89% (n=10)	0.830
	Moderate decline	31.94% (n=23)	13.89% (n=10)	0.700
	Severe decline	37.50% (n=27)	66.67% (n=48)	0.090
3 months postoperatively	Cognitive normal	18.06% (n=13)	11.11% (n=8)	Ref.
	Slight decline	29.17% (n=21)	18.06% (n=13)	0.990
	Moderate decline	31.94% (n=23)	34.72% (n=25)	0.280
	Severe decline	20.83% (n=15)	36.11% (n=26)	0.062
6 months postoperatively	Cognitive normal	20.83% (n=15)	20.83% (n=15)	Ref.
	Slight decline	37.50% (n=27)	30.56% (n=22)	0.650
	Moderate decline	34.72% (n=25)	27.78% (n=20)	0.630
	Severe decline	6.94% (n=5)	20.83% (n=15)	0.082
9 months postoperatively	Cognitive normal	25.0% (n=18)	31.94% (n=23)	Ref.
	Slight decline	38.89% (n=28)	23.61% (n=17)	0.090
	Moderate decline	34.72% (n=25)	33.33% (n=24)	0.500
	Severe decline	1.39% (n=1)	11.11% (n=8)	0.090

T2D*: type II Diabetes Mellitus; IQCODE-16[†]: 16-item Informant Questionnaire on Cognitive Decline

Table 4a: Logistic multivariable regression analysis in type II diabetes mellitus and control group (adjusted for age and sex)

T2D* CAM [†]	Unadjusted		Adjusted	
	Odds ratio (95% C.I.)	P	Odds ratio (95% C.I.)	P
1 st day postoperatively	8.22 (4.45-15.19)	<0.0001	8.42 (4.53-15.62)	<0.0001
2 nd day postoperatively	3.13 (1.84-5.31)	<0.0001	3.22 (1.88-5.49)	<0.0001
3 rd day postoperatively	2.36 (1.32-4.2)	0.004	2.5 (1.38-4.53)	0.002
4 th day postoperatively	15.68 (3.64-67.49)	<0.0001	16.03 (3.71-69.11)	<0.0001

*T2D: type II Diabetes Mellitus; †CAM: Confusion Assessment Method Diagnostic Algorithm

Table 4b: Logistic multivariable regression analysis in type II diabetes mellitus and control group (adjusted for age and sex)

T2D* IQCODE-16 [†]	Unadjusted		Adjusted	
	Odds ratio (95% C.I.)	P	Odds ratio (95% C.I.)	P
Preoperatively				
Slight decline	5.42 (3.01-9.76)	<0.0001	5.65 (3.41-10.25)	<0.0001
Moderate decline	52.85 (12.31-226.88)	<0.0001	57.29 (13.24-247.89)	<0.0001
Severe decline	-	-	-	-

*T2D: type II Diabetes Mellitus; †IQCODE-16: 16-item Informant Questionnaire on Cognitive Decline

everyday activities of most patients, it may cause problems during more stressful situations, such as the perioperative stress.^[14] In our study insulin-dependent individuals were diagnosed with higher levels of POD up to 4 days postoperatively and with slight, moderate, and severe delayed

neurocognitive recovery and postoperative NCD. Of note, during the 9 months of reassessment 9 patients were diagnosed with severe and 49 patients with moderate postoperative NCD respectively. Severe or moderate long-lasting postoperative NCD may lead to serious disability and poor quality of

Table 4c: Logistic multivariable regression analysis in type II diabetes mellitus and control group (adjusted for age and sex)

T2D* IQCODE-16†	Unadjusted		Adjusted	
	Odds ratio (95% C.I.)	P	Odds ratio (95% C.I.)	P
10 days postoperatively				
Slight decline	3.91 (1.72-8.88)	0.001	4.01 (1.74-9.24)	0.001
Moderate decline	4.65 (2.1-10.2)	< 0.0001	5.72 (2.49-13.11)	< 0.0001
Severe decline	70.4 (24.6-201.3)	< 0.0001	98.97 (32.51-301.3)	< 0.0001
3 months postoperatively				
Slight decline	4.65 (2.36-9.15)	< 0.0001	5.32 (2.63-10.76)	< 0.0001
Moderate decline	11.68 (5.68-23.99)	< 0.0001	14.48 (6.74-31.07)	< 0.0001
Severe decline	89.8 (20.1-401)	< 0.0001	129.53 (27.83-602.86)	< 0.0001
6 months postoperatively				
Slight decline	6.71 (3.61-12.47)	< 0.0001	7.92 (4.12-15.22)	< 0.0001
Moderate decline	27.75 (10.8-71.2)	< 0.0001	38.41 (14.14-104.3)	< 0.0001
Severe decline	-	-	-	-
9 months postoperatively				
Slight decline	5.67 (3.06-10.5)	< 0.0001	6.58 (3.46-12.54)	< 0.0001
Moderate decline	71.1 (16.5-305.5)	< 0.0001	84.26 (19.3-367.89)	< 0.0001
Severe decline	-	-	-	-

*T2D: type II Diabetes Mellitus; †IQCODE-16: 16-item Informant Questionnaire on Cognitive Decline

Table 5a: Logistic multivariable regression analysis in type II diabetes mellitus and control group (adjusted for Atherosclerotic Cardiovascular Disease Score - 10 - year risk, estimated Glomerular Filtration Rate, urine micro-albumin and previous exposure to surgery/anesthesia)

T2D* CAM†	Unadjusted		Adjusted	
	Odds ratio (95% C.I.)	P	Odds ratio (95% C.I.)	P
1 st day postoperatively	8.22 (4.45-15.19)	<0.0001	2.82 (1.36-5.86)	0.005
2 nd day postoperatively	3.13 (1.84-5.31)	<0.0001	1.5 (0.77-2.91)	0.220
3 rd day postoperatively	2.36 (1.32-4.2)	0.004	0.59 (0.27-1.29)	0.190
4 th day postoperatively	15.68 (3.64-67.49)	<0.0001	11.8 (1.4-99.17)	0.023

*T2D: type II Diabetes Mellitus; †CAM: Confusion Assessment Method Diagnostic Algorithm

Table 5b: Logistic multivariable regression analysis in type II diabetes mellitus and control group (adjusted for Atherosclerotic Cardiovascular Disease Score - 10 - year risk, estimated Glomerular Filtration Rate, urine micro-albumin and previous exposure to surgery/anesthesia)

T2D* IQCODE-16†	Unadjusted		Adjusted	
	Odds ratio (95% C.I.)	P	Odds ratio (95% C.I.)	P
Preoperatively				
Slight decline	5.42 (3.01-9.76)	<0.0001	2.87 (1.47-5.61)	0.002
Moderate decline	52.85 (12.31-226.88)	<0.0001	10.52 (2.18-50.6)	0.003
Severe decline	-	-	-	-

*T2D: type II Diabetes Mellitus; †IQCODE-16: 16-item Informant Questionnaire on Cognitive Decline

life.^[6] Furthermore, perioperative NCD are a major cause of increased physical frailty and may lead to a 3-fold higher need for health care service provision with the potential complete loss of independence.^[5,6] The median everyday expenses per patient developing some form of perioperative NCD may be up to 2.5 times higher, when compared to the everyday costs of the rest surgical patients.^[6] Thus, it is of vital importance to: (a) follow the updated guidelines regarding perioperative NCD, (b) identify patients at increased risk for perioperative NCD and (c) be engaged in designing integrated actions, aimed to reduce the incidence and duration of perioperative cognitive complication.^[26]

To the best of our knowledge, the present work is the first prospective, cohort study that investigated whether T2D patients are at increased risk of developing perioperative NCD up to 9 months after elective noncardiac surgery under general anesthesia. It is worthy to mention that we recruited patients with a proper diagnosis of well-treated (HbA1c <7.5%) T2D and we included equal number of insulin and noninsulin-dependent patients. One important strength of our study is the homogeneity of the T2D sample. Moreover, the screening tool used for delayed neurocognitive recovery and postoperative NCD diagnosis” (1) is simple enough to assure maximum cooperation, (2) controls for education and

Table 5c: Logistic multivariable regression analysis in type II diabetes mellitus and control group (adjusted for Atherosclerotic Cardiovascular Disease Score - 10 - year risk, estimated Glomerular Filtration Rate, urine micro-albumin and previous exposure to surgery/anesthesia)

T2D* IQCODE-16†	Unadjusted		Adjusted	
	Odds ratio (95% C.I.)	P	Odds ratio (95% C.I.)	P
10 days postoperatively				
Slight decline	3.91 (1.72-8.88)	0.001	1.23 (0.45-3.39)	0.680
Moderate decline	4.65 (2.1-10.2)	<0.0001	0.93 (0.32-2.71)	0.900
Severe decline	70.4 (24.6-201.3)	<0.0001	7.35 (1.87-28.9)	0.004
3 months postoperatively				
Slight decline	4.65 (2.36-9.15)	<0.0001	2.08 (0.92-4.68)	0.075
Moderate decline	11.68 (5.68-23.99)	<0.0001	3.38 (1.29-8.83)	0.013
Severe decline	89.8 (20.1-401)	<0.0001	12.5 (2.03-77)	0.006
6 months postoperatively				
Slight decline	6.71 (3.61-12.47)	<0.0001	3.08 (1.49-6.33)	0.002
Moderate decline	27.75 (10.8-71.2)	<0.0001	6.35 (1.81-22.1)	0.004
Severe decline	-	-	-	-
9 months postoperatively				
Slight decline	5.67 (3.06-10.5)	<0.0001	2.99 (1.48-6.04)	0.002
Moderate decline	71.1 (16.5-305.5)	<0.0001	15.72 (3.28-75.35)	0.001
Severe decline	-	-	-	-

*T2D: type II Diabetes Mellitus; †IQCODE-16: 16-item Informant Questionnaire on Cognitive Decline

Table 6a: Logistic multivariable regression analysis in type II diabetes mellitus patients (adjusted for duration of diabetes mellitus)

T2D* CAM†	Unadjusted		Adjusted	
	Odds ratio (95% C.I.)	P	Odds ratio (95% C.I.)	P
1 st day postoperatively	1.32 (0.68-2.54)	0.400	1.34 (0.68-2.66)	0.388
2 nd day postoperatively	2.23 (1.13-4.38)	0.018	2.32 (1.16-4.63)	0.017
3 rd day postoperatively	2.10 (1.00-4.36)	0.045	2.16 (1.02-4.56)	0.043
4 th day postoperatively	2.16 (0.89-5.26)	0.080	2.23 (0.9-5.53)	0.081

*T2D: type II Diabetes Mellitus; †CAM: Confusion Assessment Method Diagnostic Algorithm

Table 6b: Logistic multivariable regression analysis in type II diabetes mellitus patients (adjusted for duration of diabetes mellitus)

T2D* IQCODE-16†	Unadjusted		Adjusted	
	Odds ratio (95% C.I.)	P	Odds ratio (95% C.I.)	P
Preoperatively				
Slight decline	0.7 (0.32-1.54)	0.380	0.7 (0.32-1.54)	0.380
Moderate decline	1.16 (0.5-2.65)	0.720	1.17 (0.5-2.71)	0.700
Severe decline	-	-	-	-

*T2D: type II Diabetes Mellitus; †IQCODE-16: 16-item Informant Questionnaire on Cognitive Decline

culture, (3) distinguishes the delirium from dementia, (4) identifies delirium when superimposed by dementia and (5) classifies the cognitive dysfunction (cognitively normal and slight, moderate or severe decline).^[17,21-24] Nevertheless, there are a few limitations that should be mentioned. First of all, although the sample size was based on a power analysis, it is a single-center study. Further multi-center studies seem mandatory for more definite conclusions. Also, we included patients undergoing different types of surgery. All procedures were performed under general anesthesia and a standardized anesthetic protocol was applied. Additionally, the compared groups had equal number of participants and the same protocol

of peri-operative care was followed for all patients. Lastly, as the follow-up of our patients was only for 9 months, we do not have any information regarding the cognitive status of our patients beyond this time frame, that is, at 12 and 15 months respectively. Hence, further studies seem mandatory in order to ascertain that.

Conclusion

In conclusion, patients with T2D are at greater risk for developing perioperative NCD up to 9 months after elective noncardiac surgery, under general anesthesia.

Table 6c: Logistic multivariable regression analysis in type II diabetes mellitus patients (adjusted for duration of diabetes mellitus)

T2D* IQCODE-16†	Unadjusted		Adjusted	
	Odds ratio (95% C.I.)	P	Odds ratio (95% C.I.)	P
10 days postoperatively				
Slight decline	1.16 (0.26-5.05)	0.830	1.2 (0.27-5.23)	0.808
Moderate decline	0.76 (0.18-3.19)	0.700	0.87 (0.2-3.76)	0.859
Severe decline	3.11 (0.83-11.59)	0.090	4.04 (1-16.26)	0.050
3 months postoperatively				
Slight decline	1.00 (0.32-3.08)	0.990	1.00 (0.32-3.08)	0.949
Moderate decline	1.76 (0.61-5.03)	0.280	2.05 (0.68-6.16)	0.197
Severe decline	2.81 (0.95-8.34)	0.062	3.36 (1.06-10.65)	0.040
6 months postoperatively				
Slight decline	0.81 (0.32-2.02)	0.650	0.81 (0.32-2.03)	0.660
Moderate decline	0.8 (0.31-2.02)	0.630	0.81 (0.31-2.12)	0.670
Severe decline	3.00 (0.86-10.36)	0.082	3.05 (0.86-10.71)	0.080
9 months postoperatively				
Slight decline	0.478 (0.2-1.12)	0.090	0.47 (0.19-1.12)	0.090
Moderate decline	0.75 (0.32-1.72)	0.500	0.77 (0.33-1.8)	0.550
Severe decline	6.26 (0.71-54.74)	0.090	6.58 (0.74-58.43)	0.090

*T2D: type II Diabetes Mellitus; †IQCODE-16: 16-item Informant Questionnaire on Cognitive Decline

Insulin-dependent patients are facing an increased risk for more severe and long-lasting perioperative NCD, when compared to noninsulin-dependent patients. Further research is needed to elucidate if T2D, with respect to insulin treatment, is a strong and independent risk factor for perioperative NCD.

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Conflicts of interest

There are no conflicts of interest.

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