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Research article

Assessment of fatigue severity and neurocognitive functions in the real setting of Ramadan in patients with type 2 diabetes mellitus

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ABSTRACT

Objectives: Type 2 diabetes mellitus (T2DM) is linked with a risk of dementia and decline in neurocognitive function. The current observational case-control study was conducted to evaluate the effect of fasting during Ramadan on cognitive functions and fatigue severity in T2DM patients using the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Methods: This research was conducted at King Saud University Medical city, on 82 subjects including 43 control and 39 T2DM patients of both genders. The standardized Fatigue Severity Scale (FSS) and tests from CANTAB, including the Motor Screening Task (MOT), Spatial Span (SSP) and Intra-Extra Dimensional Set Shift (IED) were recorded during 3rd week and 2–3 weeks after Ramadan under controlled environmental conditions. Neurocognitive functions were recorded through CANTAB.

Results: IED errors (24.43 vs 50.73, p = 0.007), MOT mean and median latency (1466.32 vs 1120.27, p = 0.002) were significantly higher in T2DM than controls. IED stages completed (7.43 vs 8.69, p = 0.003) and SSP Span length were significantly lower in T2DM than controls (4.13 vs 4.82, p = 0.059). The significant differences between T2DM patients and controls persisted in the post. T2DM patients made more errors and completed less IED stages than did the controls, indicating that a worsened flexibility of attention relative to controls. Moreover, T2DM patients exhibited longer latencies in MOT, indicating poor motor performance. A comparison of performances by T2DM patients on FSS and CANTAB during and after Ramadan showed that fasting substantially increased fatigue scales, motor performance, and working-memory capacity.

Conclusions: Patients with T2DM have impaired cognitive functions including poor motor performance, low flexibility of attention, and poor working memory capacity compared to healthy control subjects during and also in post Ramadan period. However, there is no clear statistical evidence that the cognitive functions (except for SSP SL scores) and fatigue severity of T2DM subjects differ between Ramadan and after Ramadan in both T2DM and controls.

1. Introduction

Diabetes mellitus (DM) is a common metabolic disease which is associated with a state of hyperglycemia as a result of impaired insulin secretion or insulin action or both [1]. The condition impacts the nervous and vascular systems, and the resulting complications account for its being a leading cause of cardiovascular mortality and morbidity. The World Health Organization estimates that the number of diabetes patients has reached 382 million worldwide [2]. The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 with a very high incidence in Saudi Arabia of more than 29% [3, 4]. Moreover, the mortality rate due to DM in the Middle Eastern region and North African region reached 368,000 in 2013 [5].

DM causes, among other neurological and vascular complications, the progressive impairment of mental abilities and cognition, particularly processing speed and verbal memory. In particular, among patients aged >70 years, the DM-induced cognitive decline ultimately leads to

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dementia. Controlling blood glucose levels and exercise seem to play major roles in the protection against cognitive deterioration [6, 7]. Although prior research indicates that diabetes may cause alterations in different aspects of cognition and fatigability regardless of blood sugar levels and disease control [8]. It was concluded that hyperglycemia was reported to be associated with impaired cognition [9]. Furthermore, higher adiposity reportedly exacerbates progression to dementia and a decline in overall mental status [10]. Previous investigations have found that better glycemic control could benefit treatment outcomes for depression patients [11]. Depressive symptom severity has been reported to be related with poor nutrition and adherence to some medications, functional impairment, and more health care budget in primary care diabetic patients [12]. In addition, fatigue and cognitive-function analyses conducted with T2DM patients using CANTAB and the Multidimensional Fatigue-Inventory (MFI) and revealed high scores of fatigue regardless of insulin treatment [13, 14].

Although the aforementioned research has established an association between T2DM and diminished neurocognitive functions as well as a consequent higher risk of dementia, the literature features a dearth of data on how glycemia relates to neurocognitive functions in older adults without DM. Research on this topic has revealed contradictory findings: glucose levels can be both beneficial and deleterious to neurocognition among older adults without diabetes [15]. We have recently reported that T2DM patients have impaired cognitive functions in terms of flexibility of attention, impulse control, and working memory capacity. Moreover, the degree of glycaemia was independently predictive of impulse control in these subjects. We suggested that long-term prospective trials on a much larger scale are needed in order to assess cognitive functions in diabetic patients and to explore the true links between T2DM and brain functions [16].

The assessment of neurocognitive functions and fatigue scoring in patients with T2DM can help to make better therapeutic managements of these patients. Until now, CANTAB and the Fatigue Severity Scale (FSS) have not been used to test cognitive functions among T2DM patients in Saudi Arabia during the hole month of Ramadan. This study aimed to assess the effect of fasting during the holy month of Ramadan on neurocognitive functions using the Cambridge Neuropsychological Test Automated Battery (CANTAB) and severity of fatigue by fatigue severity scoring in patients with T2DM.

2. Methodology

This is an observational case-control study and was carried out at King Khalid University Hospital, Riyadh, Saudi Arabia, recruited 39 cases of T2DM and 43 age and gender matched controls. The mean age of control subjects was 48.6 8.5 (27–69) compared to T2DM patients with mean age of 52.4 8.5 (28–68) [$p = 0.089$]. The study was approved by the Institutional Review Board of the College of Medicine. T2DM participants included men and women aged ≥40 years diagnosed with T2DM as per the recent reported criteria of the American Diabetes Association for at least one year and used oral hypoglycemic agents [1]. Male and female subjects with normal glucose and HbA1c levels, no history of any current uncontrolled acute or chronic illnesses, and who were metabolically stable were selected as controls; we excluded any participant with uncontrolled acute or chronic illnesses, history of cognitive impairment or psychiatric disease (anxiety and depression), liver or renal dysfunction, acute diabetes (Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State), or pregnancy.

All participants signed an informed consent before participation in our study. Each subject spent approximately 15–30 min with a co-investigator, during which their detailed history was recorded on a predesigned proforma including name, age, sex, educational level, job, medication history, and family history of cognitive impairment, any psychiatric illness, body mass index (BMI), and body composition. The proforma also included a detailed evaluation of fatigue using the fatigue severity scale (FSS). Finally, a co-investigator instructed the participants on how to perform a set of selected tests on the CANTAB to assess executive function. The set included Intra-Extra Dimensional Set Shift (IED), Spatial Span (SSP), and Motor screening task (MOT). Both electronic and paper-based questionnaires were used [17].

This study was conducted in the Ramadan month which started from 16th May 2018 to 14th June 2018 which lasted for 30 days. The range of duration for fasting ranged from15-16 h daily. All recordings were made in department of physiology. The temperature of central system remains at 22 °C with a humidity level of 35–40%. The outside temperature ranged at that time from 45-48 C. The recordings were made between 15th to 22nd day of Ramadan. The post Ramadan tests were done 2–3 weeks after Ramadan. All tests were performed after Dhur prayers (afternoon prayers) around 12:30 pm upto 2:30 pm to standardized the tests between all subjects. The duration at that time was approximately 9–10 h of fasting. Sleep and dietry habits were recorded. They used to sleep after Fajar Prayer around 4 am–11 am and secondly they slept after asar prayer from 3:30 pm to 5:30 pm. Dietry habits included a big meal (including all items like dates, pasta, qahwa and fruits) after iftar and then a light snacks before dawn. All individuals were non athletes and were performing normal daily activities. During Ramadan they were not peforming any extra physical activities.

Participation in the study was voluntary, and the study subjected had the right to maintain anonymity and can withdraw from the study or testing at any point in time. The assessment took about 30–40 min: 5–10 min for conducting the Mini-mental State Examination (MMSE) (Vertesi et al. 2001) and 15–30 min for CANTAB test. MMSE is divided into sections including orientation (maximum 10 points), memory (maximum 3 points), attention and calculation (maximum 5 points), recall (maximum 3 points) and language competence (maximum 9 points). The maximum score is 30 points; cognitive impairment begins at < 27 points [18]. FSS assessments were performed using a standardized questionnaire [19]. Fatigue Severity Scale (FSS) is interviewing patients to assess overall fatigue through a standardized designed questionnaire. It contains 9 items with scores 1–7. Cumulative score of more than 36 indicates significant fatigue severity.

CANTAB testing in the current study included three subtests from the computerized battery, and all responses to tasks were recorded using a touch-sensitive screen. The participants received multiple training trials for learning the exact requirements of various tasks. These orientation trials were given to familiarize the subjects with the tests prior to their commencement. The co-investigators were trained for CANTAB testing and worked under the supervision of their senior consultants.

The assessments for CANTAB included SSP to evaluate working memory capacity, IED to assess the shifting of attention and its flexibility in the fronto-striatal areas of the brain, and the MOT to estimate response speed, accuracy, and number of errors.

2.1. Intra/Extradimensional shift (IED)

IED assesses the flexibility of attention and any delay in this test shows cognitive impairment in the fronto-striatal circuit of the subject. This test examined a subject's ability to attend to the special attributes of different visual stimuli, and to shift his attention when required. The test contains two artificial dimensions including color filled shapes and white lines. Simple stimuli were made up of just one of these dimensions, whereas stimuli are made up of both, namely white lines overlying color-filled shapes. The progress is tested by satisfying a definite set criterion of learning at each stage (6 repeated/consecutive correct responses). If at any stage the subject failed to reach this criterion after a maximum of 50 trials, the test would end. Subject took about 7 min to complete the test.

2.2. Spatial span (SSP)

Spatial Span tests the capacity of participant's visuospatial related working memory. Spatial short-term memory is the cognitive system allowing for temporary storage of spatial information. Spatial Span challenges the patient's ability to remember the relationships between objects in space, as opposed to verbally rehearsing items in specific order, which relies on verbal short-term memory.

A grid of boxes appears on the screen. The patient's job is to pay attention when the boxes begin flashing in sequence, then click the boxes in the same sequence. If correct, the next sequence will be one box longer. Performance is indicated by the average number of boxes remembered during the test.

In SSP the subject is shown white squares, which change in color with a variable sequence based on the concept of Corsi block tapping task. The participant must remember the sequence, and then touch the squares in that same order and the number of items recorded. The subject makes selection of the boxes which change color in the same series of sequence that are displayed by the computer screen (forward variant) or may be in the reverse order (backward variant). The range for number of boxes is two to nine and color are varies throughout the test.

There are up to 3 attempts at each sequence length and the test terminates if all three are failed. Outcome measures are length of span (longest sequence successfully recalled), errors made, number of successful right attempts and latency that records the time of speed response. In the real world the "visuospatial sketch pad" that Spatial Planning relies on is also crucial in many everyday tasks, such as driving, following directions, giving directions, searching for a lost item, or learning a new dance. It has been used to assess non-verbal memory deficits; patients with damage to the parieto-occipital parts of their brains show impaired performance on this task.

2.3. Motor screening task (MOT)

MOT is a test to assess motor functions with speed, accuracy and number of errors as parameters recorded. It involves the selection of colored crosses in different locations on the screen as rapidly and accurately by the subject.

2.4. Statistical analyses

Data analysis was performed using SPSS (IBM Corp. Released 2012. IBMSPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Variables were expressed as mean ± standard deviation. We constructed a general linear model and performed 2-way ANOVA with two independent variables (factors) of glycemic condition (2 levels) and fasting state (2 levels) on neurocognitive functions as dependent variables.

Paired comparisons were computed for the diffent variables for the FSS and the neurocognitive functions between control subjects and T2DM patients both during Ramadan and after Ramadan. A p-value of ≤0.05 was considered statistically significant.

Table 1. Demographic data of Study Participants.

	C N = 43	DM N = 39
M/F	24/19	14/25
Age	49.5 ± 4.5	52.7 ± 5.1
BMI	30.83 ± 2.1	33.92 ± 2.9
Medications n (%) Biguanides		26 (66.6)
Sulphonylureas		7 (17.9)
Thiazolidinedione		2 (5.12)
Using other unspecified anti-DM medications		9 (23.07)
Lipid-lowering medicine		27 (69.23)

Values are expressed as Mean ± SD and mentioned otherwise as percentage.
Abbreviations: C, control; DM, diabetes mellitus; M/F, male/female; BMI, body mass index.

3. Results

The demographic characteritics of study participants are presented in Table 1. Comparison of FSS and CANTAB tests between controls and T2DM patients during Ramadan (Table 2) Showed that FSS was significantly higher in control than T2DM patients (28.64 vs 27.18, $p = 0.039$). IED errors (24.43 vs 50.73, $p = 0.007$), MOT mean and median latency (1466.32 vs 1120.27, $p = 0.002$) were significantly higher in T2DM than controls. The difference for MOT Mean errors was non-significant between two groups. IED stages completed were significantly lower (7.43 vs 8.69, $p = 0.003$) and SSP Span length was also lower in T2DM than controls with borderline p value (4.13 vs 4.82, $p = 0.059$) (Table 2). The significant differences in the various neurocognitive functions assessed between the T2DM patients and controls still persisted in the post Ramadan-period (IED errors, 52.62 vs 20.95, $p = 0.003$; IED stages completed, 7.54 vs 8.7, $p = 0.003$; MOT mean latency, 1268.91 vs 1047.41, $p = 0.002$; and SSP SL,4.32 vs 4.71, $p = 0.364$) (Table 3). The effect of glycemia in 2 way ANOVA analysis revealed that IED total errors ($F = 8.27$, $p = 0.001$), IED stages completed ($F = 7.73$, $p = 0.001$), MOT mean latency ($F = 7.94$, $p = 0.001$) and MOT median latency ($F = 6.88$, $p = 0.001$) were significantly different affected in T2DM. While the difference for MOT Mean error ($F = 1.54$, $p = 0.205$) and SSP Span length ($F = 1.61$, $p = 0.189$) was non significant. The effect of fasting was not significant for neurocognitive functions.

The FSS did not differ significantly within control or DM group between fasting and post fasting period. In healthy control subjects all the neurocognitive functions including the performance for motor task, working memory and Flexibility of attention were not affected by fasting since all the differences between fasting states of Ramadan and post Ramadan period were non significant as shown in Table 4.

(Table 4). In DM patients motor performance and working memory was significantly better in the post Ramadan period compared to performance during Ramadan shown by shorter MOT mean latency in post Ramadan period (1292.31 ± 297.70 vs 1466.32 ± 559.29, $p = 0.051$) and longer SSP span length (4.71 ± 1.36 vs 4.32 ± 1.34, 0.025) as shown in Table 5. Other differences werenot significant. In healthy controls motor performance indicated by MOT mean latency did not show any difference during and after Ramadan (Table 4), while in T2DM patients MOT Mean latency was significantly lower in post Ramadan period (control) than during Ramadan (Table 5) indicating an slow motor performance during Ramadan in these patients.

Similarly in healthy control subjects the SSP SL did not show any difference during and after Ramadan (Table 4), while In T2DM patients SSP SL was significantly higher in post Ramadan period (control) than during Ramadan (Table 5) indicating an impaired working memory capacity during Ramadan in these patients.

4. Discussion

It is observed that patients with T2DM are more likely to exhibit cognitive deficits and structural changes in brain tissue. While metabolic control changes and fluctuations in glucose levels are determinants of impaired cognitive performance in diabetes patients, only a few research studies that have reported the effect of pure Ramadan fasting as a live scenario in healthy individuals and fewer have considered diabetes patients [19]. This study therefore sought to address the deficiency of data by evaluating the effects of fasting on cognitive functions during and after the holy month of Ramadan in patients with T2DM compared to controls.

Ramadan fasting significantly affected the fatigue scales and neurocognitive functions in patients with T2DM in terms of motor performance and working memory capacity, which most probably recovers in the post Ramadan period. On the other hand, in healthy individuals, there is no effect of Ramadan fasting on the neurocognitive functions evaluated in this study. Specifically, flexibility of attention, working memory capacity, and motor performance were diminished among T2DM compared to

Table 2. Comparison of FSS and CANTAB tests between diabetes patients and controls during Ramadan.

	Control	T2DM	P-value
FSS score	28.64 ± 2.49	27.18 ± 3.56	0.039
IED Total errors (adjusted)	24.43 ± 14.85	50.73 ± 26.44	0.007
IED Stages completed	8.69 ± 0.71	7.43 ± 2.09	0.003
MOT Mean latency	1120.27 ± 352.06	1466.32 ± 559.29	0.002
MOT Median latency	1056.99 ± 340.03	1287.23 ± 459.79	0.009
MOT Mean errors	7.76 ± 2.83	8.85 ± 3.02	0.107
SSP Span length	4.82 ± 1.59	4.13 ± 1.36	0.059

Values are expressed as Mean ± SD.
Abbreviations: FSS, Fatigue Severity Scale; CANTAB, Cambridge-Neuropsychological-Automated-Battery; IED, intra-extra dimensional shift; MOT, motor screening task; SSP, spatial span; C, control; DM, diabetes mellitus.

Table 3. Comparison of FSS and CANTAB tests Between Diabetes Patients and Controls after Ramadan.

	Control	T2DM	P-value
FSS score	28.98 ± 2.07	26.89 ± 3.71	0.002
IED Total errors (adjusted)	20.95 ± 15.04	52.62 ± 23.69	0.003
IED Stages completed	8.70 ± 0.97	7.54 ± 2.50	0.003
MOT Mean latency	1047.41 ± 369.65	1268.91 ± 297.53	0.002
MOT Median latency	944.73 ± 263.83	1154.04 ± 274.69	0.001
MOT Mean error	8.83 ± 3.73	9.16 ± 3.00	0.666
SSP Span length	4.71 ± 1.47	4.32 ± 1.41	0.364

Values are expressed as Mean ± SD.
Abbreviations: FSS, Fatigue Severity Scale; CANTAB, Cambridge-Neuropsychological-Automated-Battery; IED, intra-extra dimensional shift; MOT, motor screening task; SSP, spatial span; C, control; DM, diabetes mellitus.

Table 4. Comparison of FSS and CANTAB in the control group during and after Ramadan.

	During Ramadan	Post Ramadan	P-value
FSS Score	28.61 ± 2.52	29.00 ± 2.08	0.201
IED Total errors (adjusted)	21.65 ± 14.84	20.79 ± 15.21	0.712
IED Stages completed	8.70 ± 0.70	8.60 ± 0.98	0.592
MOT Mean latency	1123.05 ± 328.55	1035.02 ± 369.65	0.198
MOT Median latency	1030.75 ± 309.72	944.73 ± 263.83	0.126
MOT Mean error	7.89 ± 2.81	8.83 ± 3.73	0.126
SSP Span length	4.89 ± 1.58	4.86 ± 1.48	0.884

Values are expressed as mean ± SD.
Abbreviations: FSS, Fatigue Severity Scale; CANTAB, Cambridge-Neuropsychological-Automated-Battery; IED, intra-extra dimensional shift; MOT, motor screening task; SSP, spatial span.

Table 5. Comparison of FSS and CANTAB in the DM group during and after Ramadan.

	During Ramadan	Post Ramadan	P-value
FSS score	27.03 ± 3.59	26.89 ± 3.71	0.756
IED Total errors (adjusted)	36.95 ± 26.44	36.57 ± 23.88	0.905
IED Stages completed	7.44 ± 2.09	7.31 ± 2.50	0.655
MOT Mean latency	1466.32 ± 559.29	1292.31 ± 297.70	0.051
MOT Median latency	1287.23 ± 459.79	1175.91 ± 276.00	0.097
MOT Mean error	8.85 ± 3.02	9.05 ± 3.05	0.721
SSP Span length	4.32 ± 1.34	4.71 ± 1.36	0.025

Values are expressed as mean ± SD.
Abbreviations: FSS, Fatigue Severity Scale; CANTAB, Cambridge-Neuropsychological-Automated-Battery; IED, intra-extra dimensional shift; MOT, motor screening task; SSP, spatial span; DM, diabetes mellitus.

controls, and the differences remained significant during and after Ramadan. Moreover, our analyses demonstrated that the degree of hyperglycemia in T2DM may be independently predictive of impulse control in these subjects.

Many studies have reported the effects of glycemic and metabolic control on cognition in different populations. In one study the mean amplitude of glycemic increments was found to be significantly associated with worsening of impaired cognitive functions. This effect was even independent of HbA1C, fasting, and post prandial glucose; these results suggest the need for daily monitoring of acute glucose fluctuations [20]. An interesting investigation by our group on normal subjects revealed that Ramadan fasting affects cognitive functions, but the effect was not homogenous; we found a significant improvement of attention switching task (as assessed by the AST test) and congruent condition, along with a decrease in diastolic pressure. Moreover, we observed a positive influence of fasting on psychomotor function/processing speed and attention [21]. However, fluctuations in the cognitive function of athletes evidenced the heterogenous effects of prolonged fasting during the holy month of Ramadan: performances on cognitive evaluations generally declined across the day. Psychomotor functions and vigilance improved at 9th hour of fasting, while verbal learning and memory functions were poorer at 16th hour. A specific time of day related effect was observed for psychomotor related functions, visual perceptions, verbal associated learning and memory retention domains, with significantly poorer cognitive performances at later hours [22].

Moreover, some researches have shown that experimental fasting can affect sleep patterns, cognitive functions and even the patterns of wakefulness. However, these effects observed in experimental fasting study designs cannot be generalized to real fasting during Ramadan due to the unique spiritual characteristics of the latter. Indeed, the effects of real fasting during holy Ramadan has garnered increasing interest, and research has investigated the period's influence on the patterns of sleep, daytime sleepiness, neurocognitive functions, architecture of sleep, and the circadian rhythm patterns. The reasons for the inconsistency of the effects of T2DM and Ramadan fasting on neurocognitive function may be due to change in sleep patterns adopted during Ramadan. More studies with actual Ramadan are needed to confirm this hypothesis [23, 24].

The small sample size and number of neurocognitive function tests selected from the CANTAB battery could limit the generalizability of our study findings. In addition, these tests were not performed before Ramadan and post Ramadan recordings acted as control values for all subjects. Similar studies performed at larger scales with a longer follow-up period and more neurocognitive function tests would help to validate our findings concerning the effect of fasting on fatigue and cognition. Additionally, studies with educational counselling and proper management protocols are required to mitigate the effects of Ramadan on cognitive decline among T2DM patients.

Looking at the importance of cognition in Ramadan recommendations have been reported by Diabetes Canada. These are related to risk stratification, educational counselling, drugs therapy and special monitoring of blood glucose for adults with both type 1 and T2DM who intend to fast during Ramadan. There remain, however, multiple considerations to inform guidelines for patients with T2DM during Ramadan, including data gleaned from neurocognitive assessments. We recommend that, along with glycemic control management during Ramadan, programs targeting the direct improvements of the neurocognitive and psychological functions of patients with T2DM should be made available [25]. The limitations that we observed about our study were its relatively small sample size and secondly we could not record neurocognitive testing before Ramadan period. Moreover, patients with Type 2 diabetes should be screened for cognitive impairment on a regular basis. Further long-term prospective studies are needed, however, to validate and further elucidate the effect of Ramadan fasting on fatigue and neurocognitive functions across all domains.

5. Conclusions

Our study shows that in T2DMhave significantly high fatigue scores and certain domains of neurocognitive functions including poor motor performance, low flexibility of attention, and poor working memory capacity compared to healthy control subjects during and also in post Ramadan period. However, there is no clear statistical evidence that the cognitive functions (except for SSP SL scores) and fatigue severity of T2DM subjects differ between Ramadan and after Ramadan in both T2DM and controls.

Declarations

Author contribution statement

Abdulrahman Alfahadi, Syed Shahid Habib, Shahid Bashir: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Koloud Alharbi, Deema Alturki, Fatimah Alshamrani: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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