IMPULSE CONTROL IMPAIRMENT RELATIONSHIPS WITH VISFATIN AND BODY COMPOSITION INDICES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Objective: Diabetes Mellitus is associated with a higher incidence of neurobehavioral symptoms, inordinate fatigue, and cognitive impairment. The protein known as visfatin which is present in fat cells has been reported to have a direct association with Type 2 diabetes mellitus (T2DM) and neuroinflammation. Therefore, the aim of this study is to ascertain whether or not there is a correlation in terms of cognitive function with visfatin levels in patients with T2DM in relation to body composition indices.

Method: Sixty five participants (31 of whom suffer from T2DM along with 34 control subjects) were recruited from outpatient clinics for the purpose of this observational case-control study. Clinical and demographic characteristics were measured for each participant and these were then matched according to the Fatigue Severity Scale (FSS) and the Visual Analogue Fatigue Scale (VAFS), both of which were used as screening tests before the neurocognitive assessment procedure commenced. s. Cognition was assessed by using the following tests; a Stop Signal Task (SST) test, an Intra-Extra Dimensional Set Shift (IED) test and a Spatial Span (SSP) test using a Cambridge Neuropsychological Automated Battery (CANTAB). Blood samples were then collected in order to measure levels of both visfatin and glycosylated hemoglobin (HbA1c). Body composition was analyzed using a Bio Impedance Analyzer (BIA).

Results: Cognitive impairments in the form of longer reaction times and impaired spatial planning were detected in T2DM study subjects. The SST Stop Signal Reaction Time (SST SSRT) ($p=0.03$), IED errors ($p=0.0412$), as well as the SST Direction Errors during STOP and GO trials ($p=0.0431$) were significantly delayed in T2DM subjects versus control subjects. Moreover, the SSP length was significantly lower in T2DM participants indicating an impaired working memory capacity ($p=0.0209$). By using a general linear model, the degree of hyperglycemia was found to be independently predictive of impulse control. Visceral fat was also found to be significantly correlated with the total proportion of IED errors ($r=0.333$, $p=0.0412$).

Conclusions: The results of this study show that T2DM patients have impaired cognitive functions in terms of flexibility of impulse control, attention span, and working memory capacity. Moreover, the degree of hyperglycemia may be independently predictive of impulse control in these subjects.

Key words: Type 2 Diabetes mellitus, Waist Hip Ratio, CANTAB, Fatigue, Visfatin, MMSE

Declaration of interest: none

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Introduction

Diabetes mellitus Type 2 (T2DM) is a chronic metabolic disorder with increasing prevalence and is associated with high rates of morbidity and mortality. Recent studies have discovered a novel adipokine; known as visfatin (it may also be known as Nicotinamide Phosphoribosyletransferase (NAMPT) or pre-B-cell colony-enhancing factor 1 (PBEF1). The enzyme has been linked to T2DM which binds to insulin receptors thereby inducing glucose utilization according to a study by Chen et al. (2006). It is mostly found in visceral adipocytes which would explain its up-regulation in obesity (see Adeghate's (2008) study). Visfatin has been reported to be high in T2DM subjects and plays a role in the body's immune responses, metabolism, and

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inflammation (Garten 2011). The Tumor Necrosis Factor-Alpha (TNF-α) released from glial cells is triggered by visfatin, which subsequently causes neuroinflammation (Zhao et al. 2013).

Animal studies seem to suggest that intracerebroventricular injections of visfatin induce anorexia, fever, and reduced motor activity via the melanocortin pathway in the brain (Park et al. 2011). A recent study has shown that both BDNF (brain derived neurotrophic factor) and visfatin are involved in cognitive dysfunction in animal models of T2DM (Abdulwahed et al. 2018).

Cognitive impairment is defined as the inability to learn, think, or recall incidents/facts properly (Langa and Levine 2014). One of the complications of diabetes is the progressive decrease in mental abilities and cognition, in particular; an individual's processing speed and verbal memory which may ultimately lead to dementia. However, the onset of this condition may be delayed by the adoption of good glycemic control (Messiet 2005). Previous studies have linked diabetes with alterations in different aspects of cognition and fatigability, regardless of blood sugar levels and disease control (Umegaki et al. 2013, Lasselin et al. 2012).

A recent systematic analysis has shown that hyperglycemia is associated with impaired cognition (Geijselaers et al. 2014). Regarding the relationship between cognition and adiposity levels, Gustafson's (2012) study has pointed out that if the amount of adipose tissue exceeds a certain degree this would consequently facilitate the patient's progression to dementia along with a decline in their overall mental status (see Gustafson 2012). Comparing the cognitive functions between T2DM patients and non-diabetic patients, certain evidence has been obtained which shows impairment in patients' executive function, working memory, attention span, and psychomotor functions that could well affect their daily lives, especially the elderly (Wong et al. 2014).

Patients with T2DM, regardless of their insulin treatment status exhibited higher scores of fatigue and cognitive alterations in the form of longer reaction times and impaired spatial planning (Lasselin et al. 2012). However, in order to determine the independent effect of diabetes on cognitive impairment by controlling the confounding effect of fatigue and mini mental state further studies are required. Considering the association of visfatin with neuroinflammation and T2DM we hypothesized that there are some potential missing links as well as conflicting accounts regarding the relationship between cognitive impairment in T2DM and body composition indices with adipokine visfatin. Therefore, the aim of this study was to establish whether there is a correlation between cognitive functions with visfatin levels in patients with T2DM in relation to body composition indices.

Materials and methods

This observational case control study was conducted in the Department of Physiology, College of Medicine and King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia. The research protocol was approved by the Institutional Review Board, College of Medicine and KKUH. The study was carried out during the time period from October 2014 until April 2015. We recruited a total of 75 individuals by convenience sampling from the, outpatient clinics of KKUH, out of which 65 were finally selected as per our inclusion criteria (31 patients with T2DM and 34 healthy subjects). Patients included had age range between 30 to 70 years and were diagnosed cases of T2DM per recent American Diabetes Association (ADA) criteria (American Diabetes Association, 2010) for at least one-year duration. All patients at the time of recruitment were in a stable metabolic state. Any patient with history of cognitive impairment or psychiatric disorder (Anxiety, depression, obsessive compulsive disorders and schizophrenia etc.) , liver or renal dysfunction, acute diabetic state (Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State), and pregnancy was excluded from the study. Control group included healthy subjects from hospital staff and patients companions without any history of any ongoing acute or chronic illness. They were matched for gender, age, BMI and social status. All were having normal glucose and HbA1c levels. Confidentiality of all subjects was maintained. We used a validated standardized Mini-mental State Examination (MMSE) (Vertesi et al. 2001), Fatigue Severity Scale (FSS) and a Visual Analogue Fatigue Scale (VAFS) as screening tests before neurocognitive assessments (Krupp et al. 1989, Ibn Yacoub et al. 2012). All subjects were matched for FSS & VAFS scores. 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. To exclude any mental or psychiatric disorder we used a Functioning Assessment Short Test (FAST) questionnaire (Rosa et al. 2007).

Measurements of clinical characteristics and body composition analysis

Different parameters such as detailed history-taking, BMI, WHR (waist-hip-ratio), pulse, blood pressure and (BP) were all recorded. Body composition was analysed by means of bioelectrical impedance analysis (BIA) using a commercially available Body Composition Analyzer (Type BC-418 MA, TANITA® Corporation, Japan), (Habib 2012). The bioimpedance analyzer uses eight points of tactile electrodes (which make contact at the hands and feet). The technique uses multiple frequencies to measure total body water, fats, and fat-free mass in total and its segmental distribution in both the trunk and the limbs.

Serum assays

Venous blood samples were collected from all subjects whilst in a fasting state of 10-12 hours. Serum was separated by centrifugation at 1500 and was separated, aliquoted, and stored at -80 °C until required. Blood samples were analyzed for visfatin levels, fasting blood glucose (FBG), and glycosylated hemoglobin (HbA1c).

Serum visfatin concentrations were measured by means of competitive enzyme immunoassay using a Human VF (Visfatin) ELISA kit and by following the manufacturer's instructions (Elabsciences Biotechnology Co., Ltd. China). Briefly pre-coated antibody specific to visfatin in the microtitre plate was reacted with samples and standards for 90 minutes at 37C°. Following incubation, biotinylated visfatin-specific antibody was added and incubated at 37C° for 1 hour. Following washing, Avidin-Horseradish Peroxidase conjugate was used to detect the antigen-antibody complex. An enzyme substrate was added in order to hydrolyse the reaction and the intensity of the reaction was subsequently read at 450nm.

Assessment of cognitive functions

Cognitive functions were evaluated by CANTAB to assess impulse control, attention, and memory span in both groups as follows (http://www.cambridgecognition.com/cantab/cognitive-tests/)

Impulse control task

A Stop Signal Task (SST) assesses impulse control and any delay in this test shows cognitive impairment in the inferior frontal gyrus. The SST is a unique version of a classic approach to measured response inhibition (impulse control). The subject must respond to an arrow stimulus, by touching either of two choices depending on the direction in which the arrow points. If an audio tone is present, the subject must inhibit that response. This test has two parts. In the first part, the participant was introduced to the press pad and told to press the left hand button when s/he saw a left-pointing arrow and the right hand button when they saw a right-pointing arrow. There was an initial set of 16 trials for the participant to practice this skill. In the second part, the participant was told to continue pressing the buttons on the press pad when they saw the arrows (as before) but, if they heard an auditory signal (i.e. a beep), they were required to withhold their response and not press the button at all.

Intra/Extradimensional shift (IED)

This test examined a subject's ability to attend to the specific attributes of stimuli, and to shift their attention when required. Two artificial dimensions were used in the test; color-filled shapes and white lines. Simple stimuli were made up of just one of these dimensions, whereas more complex stimuli are made up of both; namely, white lines overlying color-filled shapes. Subjects progress through the test by satisfying a set criterion of learning at each stage (i.e. 6 consecutive correct responses were required). If at any stage the subject failed to reach this criterion after 50 trials, the test ended automatically. The subject took about seven minutes to complete the test in total. IED assesses the flexibility of attention and any delay in this test shows cognitive impairment in the fronto-striatal circuit of the subject.

Spatial Span (SSP)

Spatial Span (SSP) measures the participants' short-term working memory capacity . In SSP, the participant is presented with white squares which change in color with a variable sequence based on a Corsi block-tapping task. The participant must; firstly, remember the sequence, and then attempt to touch the squares in that same order. The number of items is then recorded. Incidentally, the sequence length increases throughout the test. There are up to 3 attempts at each sequence length and the test terminates if all three attempts fail. .

Statistical analysis

Data was analyzed using the IBM SPSS® statistical package, version 21.0 (SPSS Inc., Armonk, NY, USA) for Windows ®.

The SST measured cover direction errors, the proportion of successful stops, reaction time (RT) on GO trials, stop signal delay (SSD) (50%), and stop signal reaction time (SSRT). We calculated the number of errors, and the number of trials and stages completed in the IED task. The SRM test had three outcome measures, including the number and percentage of correct trials and latency (i.e. the speed of each participant's response).

Categorical data was expressed as absolute numbers and percentages. Numerical data was expressed in terms of mean, median, standard deviation (SD), and range. The student's t-test was used for normally distributed data and the Mann-Whitney U test was used for data which did not follow normal distribution patterns. Spearman's rank order and Pearson correlations were used where needed.

Results

This study was an effort to assess the relationship between visfatin, cognitive functions, fatigue and body composition in patients with T2DM compared with a group of healthy control subjects matched for FSS & VAFS.

Comparison of clinical characteristics between patients with T2DM and healthy subjects showed no significant differences in age, pulse, waist, hip, WHR,

Table 1. *Comparison of clinical characteristics between control and diabetic patients*

Variables	Control	Diabetics	P Value
Age (years)	46.38 ± 13.58	54.84 ± 9.28	0.063
Pulse (bpm)	78.48 ± 12.71	80.93 ±15.21	0.314
Waist (cm)	104.14 ± 16.25	115.80 ± 13.57	0.284
Hip (cm)	117.25 ± 16.69	121.88 ± 13.76	0.828
WHR	0.89 ± 0.07	0.95 ± 0.06	0.447
SBP (mm hg)	118.07 ± 16.43	141.33 ± 20.27	0.545
DBP (mm hg)	78.47 ± 14.75	86.53 ± 8.83	0.042
FBG (mmol/L)	4.95 ± 0.61	9.19 ± 3.06	0.000
HbA1C (%)	5.31 ± 0.45	8.16 ± 1.35	0.009
BMR (kcal)	1508.81 ± 254.98	2001.53 ± 2570.31	0.101
Visfatin	3.93 ± 4.40	8.29 ± 5.60	0.001

WHR (Waist-hip-ratio), SBP (Systolic blood pressure), DBP (Diastolic blood pressure), FBG (Fasting blood glucose), HbA1C (Glycosylated hemoglobin)

Values are compared by Student's t test

Table 2. *Comparison of body composition indices between control and diabetic patients*

Variables	Control	Diabetics	P= Value
Height (cm)	160.48 ± 8.82	158.71 ± 9.01	0.877
Weight (kg)	80.28 ± 17.21	84.34 ± 15.65	0.712
BMI (kg/m^2)	31.29 ± 7.00	33.87 ± 5.81	0.692
Body Fat Percentage (%)	34.93 ± 8.69	39.26± 7.85	0.353
Fat Mass (kg)	30.49 ± 13.18	34.91 ± 11.24	0.566
Fat Free Mass (kg)	49.73 ± 8.66	49.18 ± 11.21	0.499
Visceral Fat (kg)	5.44 ± 4.71	10.03 ± 5.95	0.004
Truncal Fat (kg)	35.18 ± 6.31	38.04 ± 5.70	0.480
Truncal Fat Mass (kg)	14.67 ± 6.41	17.78 ± 5.40	0.428

BMI (Body Mass Index)
Values are compared by Student's t test

Table 3. *Beta coefficients from linear regression models* of associations between the degree of glycemia and cognition test paradigms*

	Beta coefficients	Standard Error	P value
MMSE	-0.148	0.466	.752
Flexibility of attention			
✓ IED Total Errors	5.58	3.34	.103
✓ IED Stages	-0.14	0.158	.350
working memory capacity			
✓ SSP Length	-0.02	0.09	.890
✓ SSRT Half	23.65	12.76	.072
Impulse control			
✓ SST Median	45.39	18.46	.019
✓ SST Directions	1.17	0.47	.018
✓ SST Prop Succ stops	0.002	0.01	.908
✓ SST half	21.74	14.42	.140

*Adjusted for age, BMI, body composition, gender, FSS and VAFS

systolic BP, weight and height (**table 1**). Visfatin levels were significantly (p=0.046) higher in T2DM patients compared to healthy subjects (**table 1**). However, diastolic BP, FBS, and HBA1c were significantly higher in diabetics versus healthy subjects. Body composition indices such as BMI, BMR, fat percentage, fat mass, truncal fat, and truncal fat mass differences were not statistically significant between two groups (**table 2**).

The difference in FSS, and VAFS scores were not significant between the two groups (**figure 1**).

Cognitive impairments, in the form of longer reaction times and impaired spatial planning, were also detected in T2DM patients compared to matched control subjects. **Figure 2** expresses the results obtained from Cambridge Neuropsychological Test Automated Battery (CANTAB) and comparison between control and T2DM subjects. It was observed that (A) Stop Signal Task Stop Signal Reaction Time (SST SSRT) Last half (p=0.03), (B) Stop Signal Task Median Correct Reaction Time on GO trials (p=0.0012), (C) proportion of total IED errors (p=0.0412) and (p=0.02), (D) Stop Signal Task Direction Errors on STOP and GO trials (p=0.04) were significantly delayed in diabetic patients compared to the controls, while the difference for (E) Stop Signal Task proportion of successful stops in the last half (p=0.24) was not significant between the two groups. The SSP length was significantly lower in T2DM compared to control subjects indicating impaired working memory capacity (p=0.02) (**figure 2**).

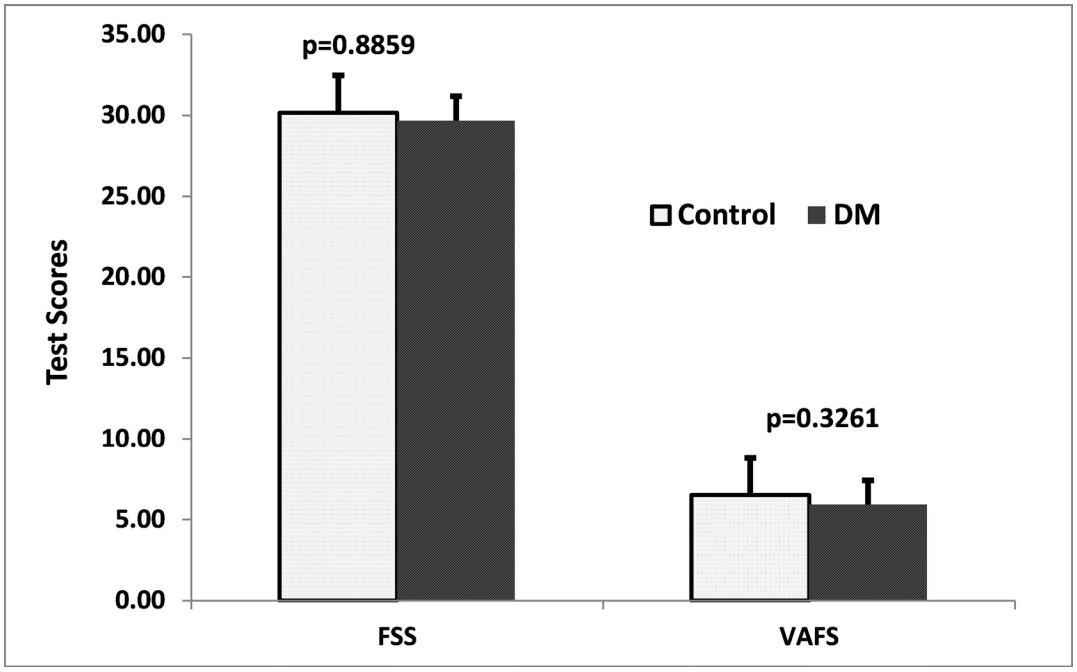
A general linear model was created to find the independent predictors of MMSE, impulse control, working memory and flexibility of attention. **Table 3** shows Beta coefficients from linear regression models of associations between the degree of glycemia and CANTAB cognition tests adjusted for age, BMI, body composition, gender, FSS and VAFS. The degree of glycemia was found to be independently predictive of SST Median latency and SST Directions. Visceral fat was also found to be significantly correlated with proportion of total IED errors (r=0.333, p=0.0412).

Pearson's correlation analysis showed that there was so significant relationship between cognitive function parameters and visfatin levels.

Results

This study was conducted as part of an effort to assess the relationship between visfatin, cognitive functions, and fatigue and body composition in patients with T2DM compared with a group of healthy control

Figure 1. *Comparison of FSS and VAFS between control and T2DM patients*



FSS: Fatigue Severity Scale.

VAFS: Visual Analogue Fatigue Scale.

subjects matched for FSS & VAFS.

A comparison of the clinical characteristics between patients with T2DM and healthy subjects showed no significant differences in age, pulse, waist, hip, WHR, systolic BP as well as weight and height (see **table 1**). Visfatin levels were significantly (p=0.046) higher in T2DM patients compared to healthy subjects (see **table 1**). However, diastolic BP, FBS, and HBA1c were all significantly higher in diabetic subjects versus healthy subjects. Body composition indices such as BMI, BMR, fat percentage, fat mass, truncal fat, and truncal fat mass differences were not statistically significant between the two groups, however (see **table 2**).

The difference in FSS, and VAFS scores were not deemed to be significant between the two groups (see **figure 1**).

Cognitive impairments in the form of longer reaction times and impaired spatial planning were also detected in T2DM patients compared to their matched control subjects. **Figure 2** expresses the results obtained from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and outlines various comparisons between the control subjects and the T2DM subjects. It was observed that: (A) Stop Signal Task Stop Signal Reaction Time (SST SSRT) Last half (p=0.03), (B) Stop Signal Task Median Correct Reaction Time on GO trials (p=0.0012), (C) proportion of total IED errors (p=0.0412) and (p=0.02), (D) Stop Signal Task Direction Errors on STOP and GO trials (p=0.04) were all significantly delayed in diabetic patients compared to the controls, whilst the difference for (E) Stop Signal Task proportion of successful stops in the last half (p=0.24) was not significant between the two groups. The SSP length was significantly lower in T2DM subjects compared to the control subjects indicating impaired working memory capacity (p=0.02) (see **figure 2**).

A general linear model was created in order to find the independent predictors of MMSE, impulse control, working memory, and flexibility of attention. **Table 3** shows Beta coefficients from linear regression models of associations between the degree of glycemia and the various CANTAB cognition tests after they had been adjusted for age, BMI, body composition, gender, FSS and VAFS. The degree of glycemia was found to be independently predictive of SST median latency, and SST directions. Visceral fat was also found to be significantly correlated with the proportion of total IED errors (r=0.333, p=0.0412).

A Pearson's correlation analysis showed that there was no significant relationship between cognitive function parameters and visfatin levels.

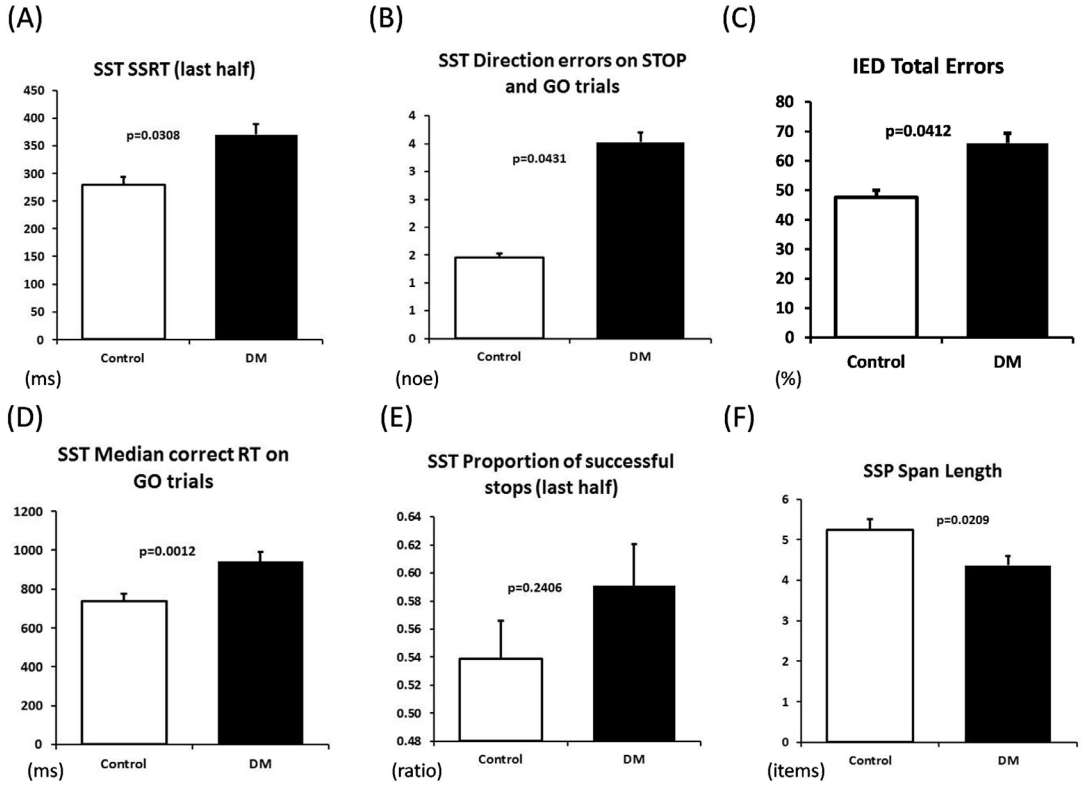
Discussion

This study was conducted as part of an effort to assess the correlation between cognition, visfatin and fatigue in T2DM subjects and to provide us with further insight on visfatin's role as a biomarker for cognitive functions and fatigue severity in Type 2 diabetic patients. Compared to healthy subjects, patients with T2DM demonstrated a significant delay in response time to SST, more IED errors, and a decrease in SSP length times. IED, SST & SSP paradigms assess the flexibility of attention, impulse control, and working memory capacity, respectively. Visceral adiposity was shown to correlate significantly with impairment in cognitive functions including IED & SST tasks whilst no relationship was observed with SSP. However, serum adipokine visfatin levels did not correlate significantly with any neuro-cognitive tests.

We observed that T2DM subjects have higher levels of visfatin compared to the control subjects, despite the fact that subjects in both groups were matched for age, BMI and gender. Similar findings were observed in a study conducted to investigate visfatin levels in newly diagnosed uncontrolled Type 2 diabetic patients, where it was believed that the increase of visfatin levels was caused by hyperinsulinemia due to insulin resistance (Dogru et al. 2007).

We noted that visfatin levels did not correlate

Figure 2. *Comparison of cognitive assessment tests of CANTAB between control and T2DM patients*



(A) Stop Signal Task Stop Signal Reaction Time (SST SSRT) Last half.
(B) Stop Signal Task Median Correct Reaction Time on GO trials.
(C) Proprtion of IED total Errors.
(D) Stop Signal Task (SST) Direction errors on STOP and GO trials.
(E) Stop Signal Task proportion of successful stops.
(F) Special Span (SSP) length.
Note: miliseconds (ms), number of errors (noe) and number of items (Items)

significantly with cognitive functions. However, a study that assessed the cognitive functions in two groups of mice, where one group was lacking NAMPT (visfatin), reported that the lack of visfatin was accompanied with decreased cognitive functions including memory and motor skill dysfunction. The authors hypothesized that this might be due to the role of visfatin in intracellular Nampt-mediated NAD^+ biosynthesis which will improve neuronal function There is also the suggestion that visfatin is crucial for cognitive functions. (Stein et al. 2014). The contradiction discrepancy in this correlation may be due to the small sample size that was used in the current study.

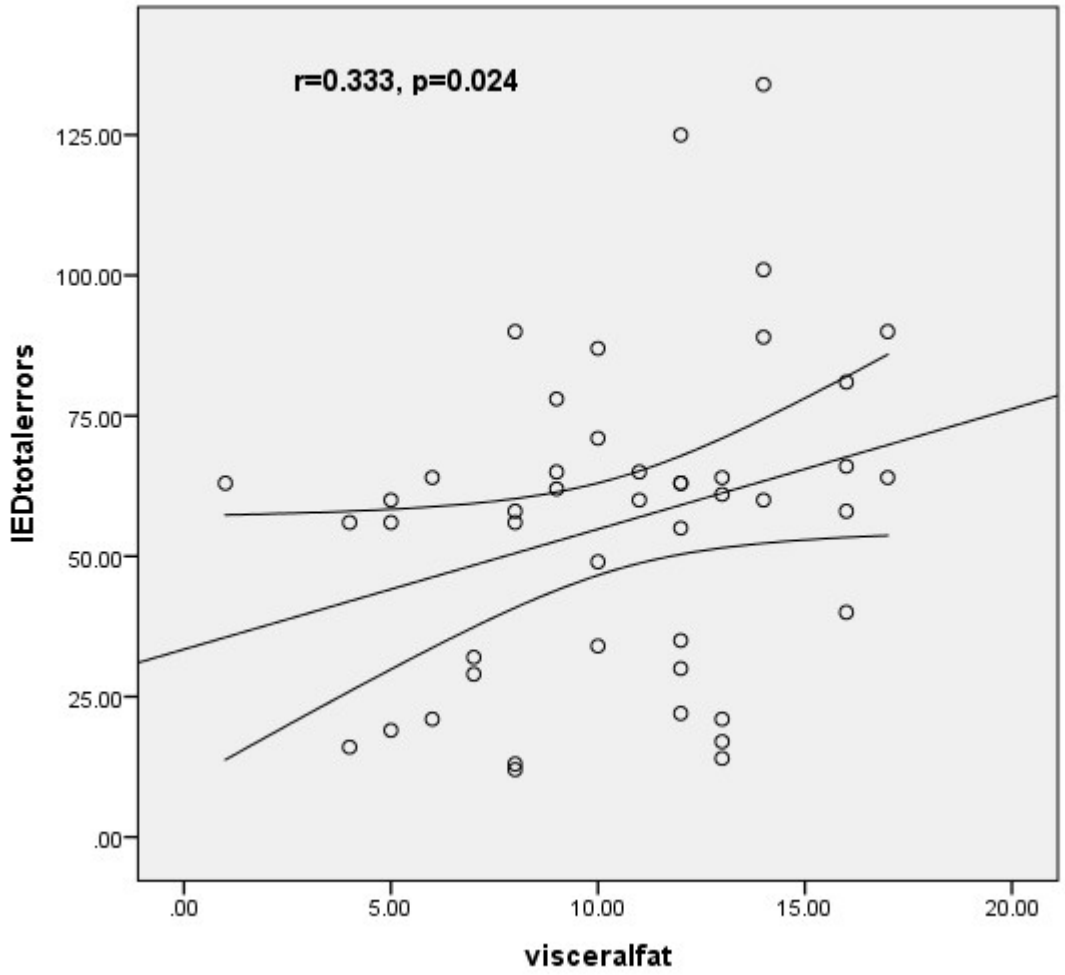
Fatigue levels showed no significant correlation with visfatin levels in both groups in our study. Incidentally, higher than normal levels of fatigue and exercise intolerance have been observed in visfatin transgenic mice according to a (2009) study by Xiong-zhi et al. which indicates that visfatin may play a role in the regulation of such parameters.

Zhang et al. (2015) also reported smaller hippocampal volumes in T2DM patients as well as memory impairment. The findings that were highlighted in the (2015) study by Zhang et al. also seem to support the findings of our study. They observed a positive correlation between HbA1c levels, poorer memory performance, and hippocampal atrophy in Type 2 diabetic patients which was not observed in our study. However, we found that visceral fat was positively correlated with cognitive impairment in our population (Zhang et al. 2015).

However, one of the major findings in our study was the discovery of the positive correlation between a subject's WHR and impaired cognitive functions Cognition was shown to decrease in diabetic subjects for SST SSRT Last half, SST Median Correct RT on GO trials, SST SSD 50% last half, SST Direction errors on stop & go trials and SSP length. Another study assessing the relationship between visceral adiposity and cognitive functions revealed that high visceral fat was associated with poor cognitive functions in an elderly population (Yoon et al. 2012). In the (2012) study conducted by Yoon et al. cognition was assessed using MMSE alone whilst MMSE, FSS and VAFS were used along with CANTAB in the present study. By doing this, we were able to assess executive functions, decision-making, and impulse control, thereby giving a detailed assessment of cognitive functions.

Thereafter, we used tests of Intra-Extra Dimensional Set Shift (IED) which assess the flexibility of attention. Any delay in these tests shows cognitive impairment in the fronto-striatal circuit. SSP measures the participants' working memory capacity and can also be used to assess impulse control. Any delay in reaction time demonstrated during such tests would point to a degree of cognitive impairment in the inferior frontal gyrus.

Figure 3. *Correlations between proportion of total IED errors and visceral fat rating in all subjects*



In a recently published paper by Wang et al. (2015), similar observations were reported (Wang et al. 2015). They observed impairment in the cognitive domains of visuospatial/executive reasoning, attention and language use. These domains were assessed by the use of MoCA (Montreal Cognitive Assessment) tools which can be used to indicate any impairment in the hippocampal area of the brain. In contrast to this, however, we used the CANTAB system for cognitive assessment in our study.

Higher levels of fatigue were observed in Type two diabetic patients compared to non-diabetics. Another comparison between Type 1 and Type 2 diabetics using MFI showed that T2DM subjects demonstrated higher levels of fatigue due to inflammation (Singh and Kluding 2013).

Matching our patients for MMSE and FSS proved to be a point of strength in our study where it would eliminate the confounding factors to obtain accurate results. To the best of our knowledge, then, this is the first study which reports a detailed analysis of cognitive functions being correlated with adipokines and body composition using an integrated approach. This study provides the basis for further research on the topic and should contribute, hopefully, to the development of better disease management plans for diabetic patients.

Compared to healthy subjects patients with T2DM demonstrated a significant delay in response time to SST and a decrease in SSP length time paradigm. IED, SST & SSP paradigms assess the flexibility of attention, impulse control, and working memory capacity, respectively. Visceral adiposity correlated significantly with impairment in cognitive functions including IED & SST tasks, while no relationship was observed with SSP. Although we observed that serum visfatin levels were significantly higher in T2DM subjects than in healthy subjects, there was no significant relationship between cognitive dysfunction and visfatin levels.

This suggests that impaired visfatin levels and cognitive decline serve as independent markers in patients with T2DM.

The limitations of our study could be put down to the relatively small sample size that was used as well as its cross sectional design. Moreover, only three cognitive paradigms were assessed despite the CANTAB battery containing approximately 15 tasks in total.

Conclusion

The results of this study show that diabetic patients have impaired cognitive functions in terms of flexibility of attention, impulse control, and working memory capacity. Moreover, the degree of glycaemia may be independently predictive of impulse control in these subjects. Visceral adiposity may be associated with impairment in cognitive functions. However, although visfatin levels were higher in T2DM subjects, the

levels did not demonstrate a significant correlation with cognitive functions.

Recommendations

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. Moreover, patients with Type 2 diabetes should be screened for cognitive impairment on a regular basis.

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Ethical standards

The authors would like to assert that all of the procedures which contributed to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and are in line with the original Helsinki Declaration as convened by the World Medical Association (1975), as well as its revised version (2008).

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