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THE INCIDENCE OF EXECUTIVE COGNITIVE DYSFUNCTION DETECTED BY A BEDSIDE EXECUTIVE SCREENING TOOL (BEST) IN A COHORT OF TYPE 2 DIABETICS ATTENDING A TERTIARY DIABETIC CLINIC

Dr Hayley Beryl de Wet

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine.

Johannesburg, 2010

DECLARATION

I, Hayley Beryl de Wet declare that this research report is my own work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

.....(signature of candidate)

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22nd April 2010

To: Research Committee
MMed Program – Department of Medicine
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Re: Contribution of Dr Hayley de Wet to article entitled: Executive cognitive impairment detected by simple bedside testing is associated with poor glycaemic control in type 2 diabetes

This article was accepted and published in the South African Medical Journal in November 2007 after peer review. Dr De Wet was the first author. Her contribution to this article included the following:
Obtaining research ethic committee approval, collection of data, primary analysis and interpretation of the data, and writing of the manuscript.

My role was in a supervisory capacity in all phases of the study. Professor Naomi Levitt provided critical revision of the manuscript.

Regards
Brent Tipping



PUBLICATIONS AND PRESENTATIONS

Data from this research project has been presented at the 42nd SEMDSA Endocrinology Congress in Bloemfontein, June 2007 for which I was awarded a prize for the best presentation.

This data has been published as an original research article in the South African Medical Journal, November 2007 Vol. 97, No. 11, pages 1074-1076 *(appendix A)*.

ACKNOWLEDGEMENTS

I would like to acknowledge my mentors Prof Dinky Levitt and Prof Derick Raal. I also need to acknowledge my husband Dr Brent Tipping for pointing out that "patients *can't*, rather than *won't*" and constantly supporting, encouraging me, and sharing his knowledge with regards to cognitive function.

Lastly, but probably most importantly, my diabetic patients for allowing me to gain further insight of their disease and its effects on their daily life.

ARTICLE TITLE:

Executive cognitive impairment detected by simple bedside testing is associated with poor glycaemic control in type 2 diabetes

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ABSTRACT

Aims: To determine whether impairment of the executive functioning domain of cognition could be detected by a battery of simple bedside cognitive tests of executive function associated with inadequate glycaemic control.

Methods: People with type 2 diabetes attending a tertiary referral diabetic clinic who consented to participate in the study underwent a brief battery of cognitive testing (the Bedside Executive Screening Test) designed to detect executive function impairment. Glycaemic control was determined using glycated haemoglobin levels (HbA1c). Inadequate glycaemic control was defined as HbA1c ≥ 7.0%.

Results: Executive function impairment was detected in 51 (52%) of the 98 study participants. The presence of executive function impairment was significantly associated with poor glycaemic control (HbA1c ≥ 7.0%) (odds ratio 4.9, 95% confidence interval 1.3 – 18.8, *p*=0.019). There were no significant differences between patients with and without executive function impairment with regard to age, target organ damage, patient reported adherence, and hypoglycaemic therapy. Patients with a lower level of education were more likely to demonstrate executive impairment when glycaemic control was poor (*p*=0.013).

Conclusion: Executive function impairment is common in a population of people with difficult-to-manage type 2 diabetes. The presence of executive impairment is significantly associated with poor glycaemic control.

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1. INTRODUCTION

1.1 EXECUTIVE FUNCTION

1.1.1 DEFINITION

The Diagnostic and Statistical Manuel of Mental Disorders, 4th edition, defines executive function as one's ability to plan, initiate, sequence, monitor and inhibit complex behaviour [1].

Executive function falls within the domains of cognition. It forms its own separate category alongside other more well known domains, such as language, attention, memory and visuospatial planning [2].

Executive functions comprise a set of skills responsible for orchestrating complex goal directed activities such as finances, medications, transportation, shopping, cooking, housework and using communication devices. These activities constitute the Instrumental Activities of Daily Living (IADLs).

These activities are made possible through successful planning, initiation, sequencing with ongoing monitoring and assessment for possible adjustments of goals or actions[2,3].

Similarly to other cognitive functions, such as language and memory, these are acquired skills. Intact executive functions are thus vital to human autonomy[2].

Anatomically, the pre-frontal cortex and its basal ganglia connections are responsible for executive functioning[2]. It is however difficult to localise specific executive functions to specific areas within the frontal cortex[3]. The frontal cortex is connected to the caudate, putamen, pallidum and thalamus via circuits. These connections are dynamically balanced direct and indirect circuits[2]. The importance of these connections is manifested by the fact

that executive impairment may occur without direct frontal damage i.e. via disruption of these circuits[2].

External sensory information (motivational, emotional, somatosensory) is integrated and translated into goal directed behaviour. This relies on intact frontal lobe higher functions (i.e. insight, judgement and abstraction) along with their connections to the systems they control, allowing for execution of directed actions[2].

Isolated executive impairment falls within the category of "mild cognitive impairment". Mild cognitive impairment being that which does not meet the criteria for dementia and thus by nature a heterogeneous group of disorders[4]. In 1994 executive impairment was added to the definition of dementia by the American Psychiatric Association[5].

1.1.2 MEASURES OF EXECUTIVE FUNCTION

Executive functioning can be assessed using internationally accepted tools. These tools score patients (using standardised norms) on their ability to carry out tasks that utilise the executive domain. However there is no one single gold standard test, and so batteries of tests are rather employed. Batteries often prove to be labour intensive to both the clinician and patient and are often very time consuming[2]. Traditional cognitive screening tools are generally insensitive to executive impairments and deficient in executive components[6]. The mini mental state examination(MMSE) considered a measure of 'global' cognitive ability, and probably the most commonly employed cognitive screening tool, contains no components specifically addressed to executive functioning[3]. Patients with clear executive impairment as detected by other specific executive screens have often been found to score

within the normal range on the MMSE[7]. The MMSE was also found to be significantly affected by socioeconomic status[8].

Some of the well accepted screening tools or measures of executive function include: clock drawing tasks, verbal fluency, the executive interview (EXIT25), Wisconsin card sorting test and Trail making B component of the trail making tests.

Ideal cognitive screening tests should meet the following criteria:

- quick to administer (under two minutes), this helps gain acceptability amongst clinicians
- well tolerated and accepted by patients
- easy to score
- relatively independent of culture, language and education
- good inter-rater reliability
- both high sensitivity and specificity
- concurrent validity(correlate with other screening tools)[6].

CLOCK DRAWING TASKS

Clock drawing tasks meet the above stated criteria. In particular they are quick and easy to administer, easy to score with a good inter-rater reliability as well as having high patient and clinician acceptability. 93% of surveyed physicians said they would use it[6]. Clock drawing tests have been found to be less influenced by socioeconomic status than the MMSE[8]. They also correlate well with other more traditional tests[9]. They were also found to have a sensitivity of 91% and specificity of 95% in predicting future dementia[10], and a sensitivity of 77% and specificity of 87% in detecting moderate cognitive impairment (MMSE specificity

96% but sensitivity only 66%). This is comparable to other well accepted screening tools i.e. mammography for breast cancer[11,12]. Clock drawing tests have an acceptable sensitivity as a first level screening tool, however they are probably not adequate as a stand-alone screening tool owing to the high rate of false positives[11].

Clock drawing tasks utilise many different skills, namely:-

- auditory comprehension
- visual memory
- planning
- abstract thinking
- motor programming and execution
- concentration[6].

These tasks require the patient to plan, initiate a drawing and continue through a sequence of constructional actions (i.e. drawing an outer circle, placement of numbers usually 12, 3, 6, and 9 first and lastly placing the hands). The patient must be able to monitor progress and implement corrections as the need arises[9].

The CLOX1 is the first component of a two part clock drawing task. This first component is specifically designed to detect executive impairment and discriminate it from other non-executive failures such as constructional failure. Whereas the second part (CLOX2) is a copying task much the same as the pentagon illustration used in the MMSE and correlates with posterior cortical defects[9].

CLOX1 is scored out of 15, a score of 10 correlates with 2 standard deviations below the mean[9]. Another attraction of clock drawing is that it offers a visual performance indicator rather than just a numerical score[13].

Table 1. Scoring system for the Executive clock drawing (CLOX) test[9].

RATING			
Organizational Elements	**Point Value**	**CLOX 1**	**CLOX 2**
Does figure resemble a clock?	1		
Outer Circle Present?	1		
Diameter >1 inch?	1		
All numbers inside the circle?	1		
12, 6, 3, & 9 placed first?	1		
Spacing Intact? (Symmetry on either side of the 12-6 axis?) If "yes" skip next.	2		
If spacing errors are present, are there signs of correction or erasure?	1		
Only Arabic numerals?	1		
Only numbers 1 - 12 among the Arabic numerals present?	1		
Sequence 1-12 intact? No omissions or intrusions.	1		
Only two hands present?	1		
All hands represented as arrows?	1		
Hour hand between 1 and 2 o'clock?	1		
Minute hand longer than hour?	1		
None of the following 1) hand pointing to 4 or 5 o' clock?	1		
2) "1:45" present?			
3) intrusions from "hand" or "face" present?			
4) any letters, words or pictures?			
5) any intrusion from circle below?	**TOTAL**		

VERBAL FLUENCY MEASURES

Verbal fluency is a measure of temporal lobe (ability to create word clusters), frontal lobe (ability to shift between clusters) and caudate nucleus function[14].

Two measures commonly clinically employed include:

1. Phonemic verbal fluency, the patient is required to generate as many words as possible within a given time period (one minute) beginning with a specific letter of the alphabet F, then A, and finally S[14].

2. Semantic verbal fluency makes use of categories, patients name as many objects falling within the category, again within a certain time period (usually one minute) i.e. animals, fruits and cities. Animals being the most frequently used category[14].

There are established age and education appropriate norms for the different categories. Age, education and gender influence scores[15]. Final levels of verbal fluency are usually attained by age 12 years[14].

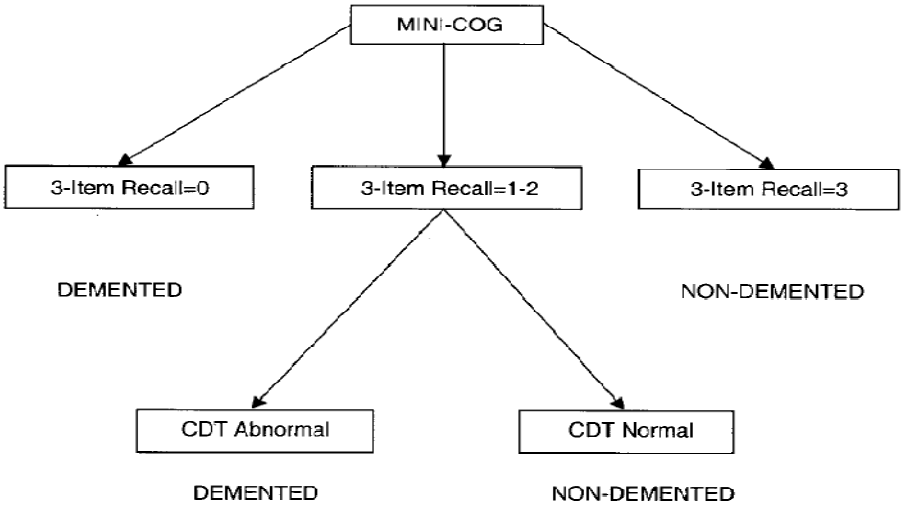
THE EXIT25

This screening tool forms a short battery comprising 25 tasks, all reflecting frontal measures, and takes around 15 minutes to administer. The EXIT25 requires formal training to administer. It has been shown to correlate well with the CLOX1, the Wisconsin card sort test and Trail making part B, two other measures of executive control function[9]. Patients are scored from 0-50, higher scores correlate with worse impairment, with scores above 15 indicating significant impairment, correlating with a CLOX1 score of less than 10. The EXIT25 has been found to correlate well with verbal fluency[16].

THE MINI-COG

This test combines two simple tasks, 3 item word recall testing episodic memory and a clock drawing task. It has been found to be practical and effective as a screening tool for dementia in large populations at risk[17]. It is not influenced by language or education. The time taken to administer the mini-cog is roughly a quarter of that taken to administer the MMSE[13].

Figure 1: Mini-Cog scoring algorithm[13]



1.1.3 IMPACT OF EXECUTIVE IMPAIRMENT ON THE INDIVIDUAL

Executive impairment has been shown to be strongly associated with several chronic medical diseases[1,2,5]. More commonly associated conditions include schizophrenia, major depressive disorders, chronic obstructive airways disease, sleep apnoea, congestive cardiac failure, infection with Human Immunodeficiency Virus, renal failure, lung cancers, hypertension, subcortical ischaemic vascular disease, pituitary tumours and type 2 diabetes mellitus[1,2,5].

During the normal aging process deterioration of executive function correlates with longitudinal decline in functional status, and thus may be considered a predictor of functional status. This was illustrated in the Freedom House Study[5]. In patients with chronic diseases it may be viewed as a predictor of severity and disability[2].

Tests of executive function correlate strongly with instrumental activities of daily living (IADL's) rather than physical activities of daily living. Measures of executive function (i.e.CLOX1 or EXIT25) prove a more reliable predictor of IADL's in both healthy and impaired individuals than measures of other cognitive function domains[1,5,18]. Executive functioning is able to discriminate between independent patients, patients requiring moderate level supervision and those requiring full supervision[1].

Self-management is regarded as a set of skilled behaviours used to manage one's illness. This places a great responsibility on the individual[8].

Executive impairment impacts negatively on a patients' ability to self-manage their disease[19]. It hinders their ability to comply with treatment regimens and implement necessary lifestyle changes[1,19]. These patients have also been found to be more resistant towards care and suffer from impaired medical-decision-making capacity[1]. Patients in retirement communities were less likely to make use of newly introduced prosthetics in the presence of executive impairment, demonstrating an inability to adopt new assistive devices/practices[2].

Dysfunction of the executive domain may be clinically evident if:[2]

1. The patient does not remember what is important
2. The patient cannot get to where they want to go
3. The patient cannot make appropriate decisions
4. The patient cannot complete tasks that he or she starts
5. The patient does not comply with therapy

Patients with executive impairment are less likely to self-report their impairment/difficulty than those with memory impairment, and more frequently may actually report it as memory loss rather than executive dysfunction[1,12]. However impaired executive function may have a more profound effect on ones autonomy than impaired memory[1,2].

1.2 TYPE 2 DIABETES MELLITUS AND COGNITION

1.2.1 DEFINITION

Diabetes mellitus refers to several disorders of abnormal carbohydrate metabolism, all characterized by hyperglycaemia. Type 2 diabetes mellitus is associated with a relative impairment in insulin secretion coupled with varying degrees of peripheral resistance to the action of insulin[20]. Type 2 diabetes may also be considered a syndrome with multiple associated co-morbidities and complications[21]. The associated insulin resistant state of type 2 diabetes is fundamental to the pathogenesis of the metabolic syndrome [19].

1.2.2 PREVALENCE

Type 2 diabetes mellitus accounts for approximately 90% of all cases of diabetes worldwide[22]. There is an overall 4.5% prevalence with an estimated 1,283,400 people 1n 2010 suffering from type 2 diabetes in South Africa as published by the International Diabetes Federation in 2009[23].

Dementia (all causes) has an incidence of 6.5% in those older than 65 years. Of this 4.4% is attributable to Alzheimer's disease, 1.6% vascular dementia and all other forms accounting for the remainder 0.4%[19]. This underestimates the incidence of mild cognitive impairment (MCI) which is generally not defined in epidemiologic studies.

The increasing number of diabetic and dementia patients will be compounded by a generally ageing population worldwide[24].

1.2.3 DIAGNOSIS OF TYPE 2 DIABETES MELLITUS

Table 2: Society for Endocrinology, Metabolism and Diabetes of South Africa: Diagnostic Criteria for Diabetes Mellitus[25]

Criteria for diagnosis of diabetes mellitus	
A. Symptoms [a] of diabetes **PLUS** • Casual/random plasma glucose ≥ 11.1 mmol/l[b] **Or** • Fasting plasma glucose (FPG) ≥ 7.0 mmol/l[c] **Or** • 2 hr plasma glucose (2PG) ≥ 11.1 mmol/l during OGTT[d]	**B. If asymptomatic** The 75 g OGTT is indicated in the following: • In the asymptomatic high-risk individuals • If FPG is ≥ 5.6 – < 7.0 mmol/l (in detection/screening programmes) If random plasma glucose ≥ 5.6 – < 11.1[†] (on screening)
[a] The classic symptoms of diabetes include polyuria, polydipsia and weight loss [b] Casual is defined as any time of day without regard to time of last meal [c] Fasting is defined as no caloric intake for at least 8 hr [d] The test should be performed as described by the World Health Organisation using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in 250 ml water over 5 minutes **Note: Acute metabolic decompensation** In the absence of unequivocal hyperglycaemia accompanied by acute metabolic decompensation a confirmatory laboratory glucose test (a FPG, a casual PG or a 2hPG in a 75-g OGTT) must be done in all cases on another day. Different criteria are used to diagnose gestational diabetes in pregnant women.	[†] or do FPG – WHO 1998/2006 criteria should be used to diagnose diabetes, including the importance of not diagnosing diabetes on the basis of a single laboratory measurement in the absence of symptoms. – Diagnosis should be based on laboratory plasma glucose (preferred) or capillary plasma glucose. – Conversion factor: plasma glucose (mmol/l) = 0.102 + 1.066 x capillary blood glucose.

1.2.4 GLYCATED HEAMOGLOBIN

Glycation occurs throughout the 120 day lifespan of the red blood cell. Of this fifty percent occurs in days 90-120. Glycated haemoglobin (HbA1c) has been established as the monitoring tool of choice when assessing medium term diabetic control[26].

Target HbA1c levels differ between international organisations. However levels below 7% are accepted for type 2 diabetics by the:

- American Diabetes Association
- UK National service framework for diabetes mellitus
- Society for Endocrinology, Metabolism and Diabetes of South Africa[25,26].

HbA1c levels above 7% have been shown to yield a four-fold greater risk for age related mild cognitive impairment. A significant association persisted even when previously diagnosed diabetics were excluded[27]. For every 1% increase in HbA1c there is an associated 40% increase in age-related risk of developing mild cognitive impairment, especially when the HbA1c above 7%[27].

1.2.5 IMPACT OF TYPE 2 DIABETES ON COGNITION

Diabetes mellitus is recognised to be associated with cognitive dysfunction and cognitive abnormalities[28]. Neuropsychological tests have demonstrated deficits in various aspects of cognition in both young and elderly diabetics. Deficits affect global cognition, psychomotor efficiency, episodic memory, semantic memory and working memory[12]. Cognitive decrements may occur at two separate intervals of cognitive vulnerability:

1. Firstly occurring during brain development, ages 5-7 years, typically this would refer to type 1 diabetes.
2. Later on they may develop within the neurodegenerative phase, generally from age 65 years onwards. This would be accounted for in the majority by type 2 diabetes.

Outside of these two periods it would need to occur in the face of both microvascular and macrovascular target organ damage[27].

Diabetes mellitus is a risk factor for neurological conditions of ageing, these include all forms of dementia and cognitive decline[22]. The impact of diabetes mellitus on cognition has been of interest for at least eighty years. It was first explored by Miles and Root who

demonstrated impaired memory, poor mental arithmetic, and slowed psychomotor efficiency in type 1 diabetics exclusively. They hypothesized that the main underlying mechanism might be recurrent hypoglycaemic episodes. However this was disputed when later cognitive impairment was also significantly associated with type 2 diabetics, in whom chronic hyperglycaemia was thought to be responsible[19].

The more typical pattern of cognitive deficits in diabetics is suggestive of frontal sub-cortical dysfunction from a microvascular insult[29]. Structural brain imaging studies in type 2 diabetics between ages 60 to 65 years revealed an increase in both cerebral atrophy and lacunar infarcts (OR 1.3-2.2)[28]. This pattern of microvascular disease of the brain is characteristically associated with cardiovascular risk factors. In particular this frontal sub-cortical syndrome manifests with significant executive impairment, motor slowing and mood symptoms, with minimal memory loss[29]. These deficits impact on the individuals' ability to plan, organize, problem solve, reason and also limits their insight[12].

Longitudinal and population based studies have implicated type 2 diabetes mellitus as a risk factor for age related cognitive decline and dementia[28]. Cognitive impairments have been evidenced in multiple cross-section, longitudinal, and prospective studies[8,19,21,22,24,29,30,31]. The Rotterdam study (cross-sectional study using dementia as a variable) showed a significant association between diabetes mellitus and dementia, with the strongest association for vascular pattern dementia. Importantly this was found to be independent of education, body mass index, atherosclerosis, smoking, blood pressure or the use of anti-hypertensive agents. It was also not explained by cerebral infarcts[19]. The Hisayama Study (seven year follow-up of 828 diabetic residents aged 65 years and over without baseline dementia) demonstrated an increased risk of vascular dementia[19].

In a cross-sectional population based study of home bound individuals diabetics had a worse MMSE score: 24/30 vs 25.7/30. Only 50% of diabetic individuals successfully reproduced the pentagon illustration whereas 68% of non-diabetics were successful. However more sensitive tests of executive function such as the Trail B demonstrated significantly worse scores for diabetics[29]. In a large cohort (10963 patients assessed at two separate occasions six years apart) those with diabetes at baseline had a greater decline in scores on two separate executive measures: digit symbol subset and first-letter word fluency. This persisted after controlling for demographic and vascular risk factors, and was also demonstrated when restricted to a younger age group of 47-57 years[19]. In a literature review by Stewart et al. a strong association between poor verbal fluency scores and type 2 diabetes mellitus was demonstrated[30].

1.2.6 POSSIBLE MECHANISMS OF IMPAIRED COGNITION

Mechanisms responsible for impaired cognition in the diabetic patient include both the direct effects of diabetes mellitus itself as well as the indirect effects of associated co-morbidities, medications used and/or diabetic complications[27]. Each patient is exposed to at least one or more of these variables[28]. Different hypothesis include sub-cortical vascular ischaemia, polypharmacy, hypoglycaemia and concurrent depression[2]. Evidence of structural brain abnormalities has also been identified. Both silent and symptomatic infarcts are seen with increased incidence on magnetic resonance imaging in diabetics. Imaging also reveals a slight degree of cortical and sub-cortical atrophy in a generalised pattern. At autopsy type 2 diabetics have an increased number of macroscopic infarcts[24].

1.2.6.1 DIRECT EFFECTS

There are several biological mechanisms that have been associated with impaired glucose regulation and dementia[27].

HYPOGLYCAEMIA

Hypoglycaemia seems to only be relevant in the acute setting, where it is associated with a poorer cognitive ability, but not with any long term effects[19,30,31]. This would seem true as there has been no association proven with more intensive treatment regimens which often have a higher incidence of hypoglycaemic episodes[19,30].

HYPERGLYCAEMIA

Toxic effects of hyperglycaemia have been thought to slowly cause progressive structural and functional abnormalities in the brain[24]. Cognitive decline has been associated with clinical markers of hyperglycaemia, i.e. use of hypoglycaemics, increased duration of diabetes mellitus and diabetic complications[31]. Non-diabetic patients with hyperglycaemia (patients with poor glucose tolerance or impaired fasting glucose) have been shown to score poorly on cognitive testing[31]. A population based study found an increased rate of errors on the MMSE performed by type 2 diabetic patients with higher fasting glucose levels[30]. Pelmuter et al associated higher HbA1c readings with poorer word memory[30].

States of chronic hyperglycaemia are associated with increased oxidative stress[22]. There is direct neuronal damage from advanced glycation end products (AGES), a process similar to those implicated in peripheral neuropathy[22,27,30]. AGES impairs vascular reactivity and thus predisposes to subtle perfusion abnormalities[19]. Chronic exposure to hyperglycaemia may cause abnormalities in cerebral capillaries i.e. basement membrane thickening and thus lead

to microvascular changes predisposing to insidious ischaemia[24]. Hyperglycaemia may also exacerbate areas of existing sub-clinical ischaemia via increased anaerobic metabolism and acidotoxicity[30].

HYPERINSULINAEMIA

Type 2 diabetes mellitus is initially associated with a state of hyperinsulinaemia. Insulin appears to modulate cognition[28]. There are an abundance of insulin receptors in the brain, insulin is able to actively cross the blood-brain-barrier and is also locally produced within the brain[24]. It has been hypothesized that the increased levels of insulin circulating may be directly responsible, or may serve as a marker of hypofunction of insulin degrading enzyme. This enzyme is also involved in the metabolism of beta-amyloid, which is found in increased amounts in the beta-islet cells of type 2 diabetics[19]. Beta-amyloid is found in patients with Alzheimer's disease at autopsy[24,27,28]. Insulin is believed to have vasoactive properties and perhaps alters cognition through a vascular mechanism[24].

Large population based studies have proven a significant association between MMSE impairment in those with hyperinsulinaemia, this persisted after adjusting for cardiovascular disease and other cardiovascular risk factors[19].

1.2.6.2 INDIRECT EFFECTS

Type 2 diabetes mellitus may be considered a complex with numerous disease related factors rather than just a disease. This complex is associated with multiple co-morbidities (hypertension, dyslipidaemia, obesity), chronic complications and treatment related effects[28]. These may be considered as vascular and non-vascular mediated[30]. Stroke and vascular co-morbidities are established risk factors for dementia in diabetic patients. Type 2 diabetes is itself a known risk factor for stroke, this risk again being both directly due to the diabetes and indirectly secondary to the associated co-morbidities[24]. Several studies of non-diabetic patients with hyperinsulinaemia have reported an increased risk of stroke. The cortical-basal ganglia connections are dopaminergic mediated and very sensitive to hypoperfusion and hypoxia[1].

ATHEROSCLEROSIS

Type 2 diabetes mellitus is associated with hypercholesterolaemia or atherogenic dyslipidaemia. This is a pro-thrombotic state[24]. In the Rotterdam study all indicators of atherosclerosis were associated with dementia, vascular dementia being the most prominent[19]. A large population study demonstrated an association between hypertriglyceridaemia in diabetic patients and worse performance on cognitive testing affecting attention, concentration, psychomotor speed and verbal fluency. These findings were independent of glycaemic control, total cholesterol levels and blood pressure. These effects were felt to be secondary to atherosclerotic disease itself as well as changes in blood viscosity[30].

HYPERTENSION

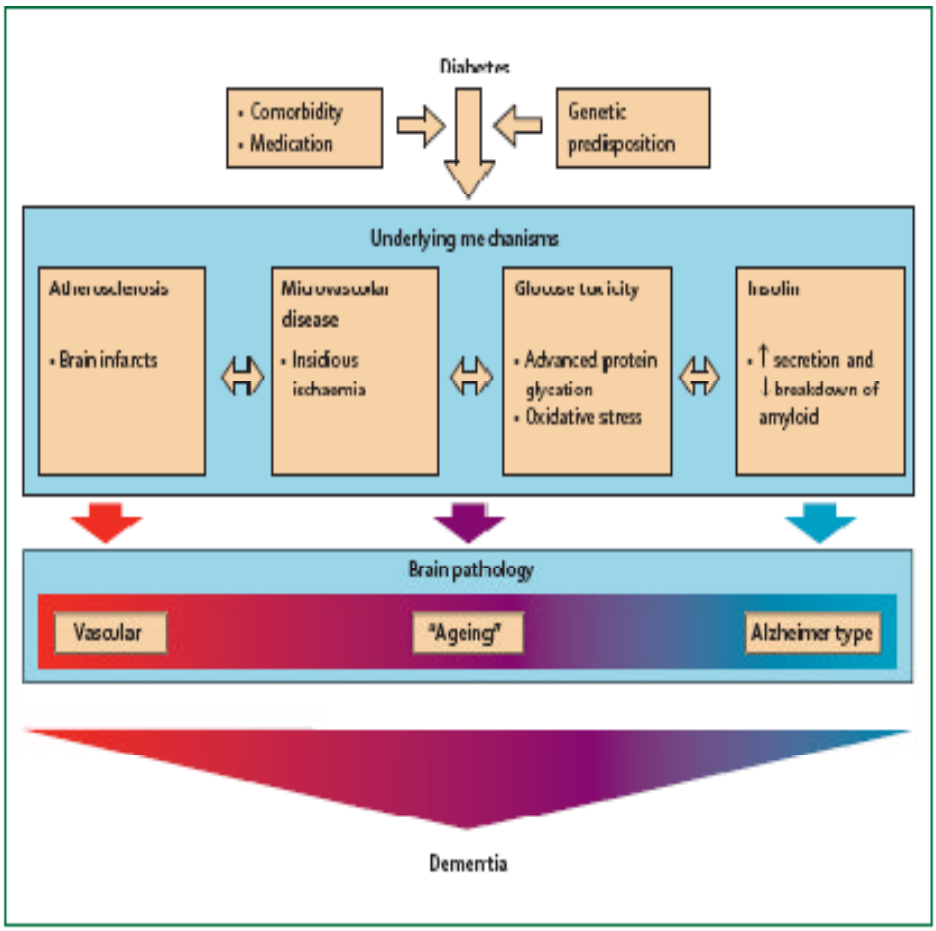
There is a well recognised strong relationship between type 2 diabetes and hypertension. Effects of the hypertension itself are felt to be the cause of poorer cognition rather than medication side-effects. This is demonstrated by the finding that patients on anti-hypertensive treatment show little evidence of cognitive decline. The exception would be treatment induced hypotension in elderly patients[30]. In a study by Kungsholmen hypertension (systolic blood pressure greater than or equal to 180) interacted with diabetes to increase the relative risk of any dementia, particularly vascular dementia[24].

OTHERS

-The Apolipoprotien E (ApoE) allele is a risk factor for dementia[29]. When combined with vascular risk factors such as hyperglycaemia it may interact to increase risks above those associated with the traditional ApoE phenotype. This was shown in the Canadian study of Health and Ageing[19].

- Other associated co-morbid conditions may impact negatively on cognitive function[10,24]. One example is depression, with a higher incidence of depression in diabetic patients this may act as confounder or even exacerbator[31]. Diabetic patients with depression have more cognitive symptoms and poorer diabetic control[19]. Obesity is another important associated condition. Obese individuals are subject to increased risk of stroke. Obesity is also frequently associated with obstructive sleep apnoea which also increases risk of stroke and cognitive decline[1,30].

Figure 1: Pathophysiological mechanisms linking diabetes in the brain and dementia[24]



2. THE STUDY

2.1 RATIONALE FOR STUDY

Adequate cognition particularly executive function is shown to be vital in disease self-management, traditionally upon which diabetes relies heavily. Patients are required to institute lifestyle changes, comply with behavioural and pharmacological interventions aimed at managing their glycaemia, lipid profiles and frequently concomitant hypertension. Patients with Type 2 diabetes are routinely screened for both microvascular and macrovascular complications. This study explores the role of cognitive screening in patients attending a Type 2 Diabetic clinic.

2.2 TOOL SELECTION

There is presently no single gold standard test for executive function[2]. Rather batteries of neuropsychological tests are administered, these are time consuming (may take up to 3 hours) and not available in routine practice. A 7-minute screening battery exists which incorporates four sub-sets testing memory, verbal fluency, orientation to time and clock drawing. This test is however hampered by the need for special equipment and training, and may not be cross-culturally valid. It was also not specifically designed to detect impairment of executive function[32].

To detect executive cognitive impairment in a busy clinical setting such as this one we proposed a 5 minute test battery that is easy to score, can be administered with minimal training and requires no equipment besides a pen and scoring sheet. However the patient is

required to be fluent in English and must have adequate eyesight. We termed this test the **Bedside Executive Screening Tool (BEST)**.

The proposed **BEST** (appendix B) comprises the following 5 different tasks:

Task 1 – Registration/attention

Three word registration affirms that a patient is able to attend (concentrate) on a task. If a patient cannot complete this task, then they will be unable to perform further cognitive testing. This also affords the opportunity to learn the words that will test episodic memory function (task number 4). Episodic memory refers to the laying down and recall of a specific event or details.

Task 2 – Executive clock drawing task (CLOX1)

The CLOX is an executive task based on clock drawing. The patient is presented with a blank piece of paper and given the instruction "draw me a clock that says 1:45. Set the numbers and hands on the face so that a child could read them". The instructions may be repeated if necessary however once they begin the task no further assistance from the examiner is permitted. CLOX is divided into parts 1 and 2 which discriminates the executive control of clock drawing from actual clock drawing itself. For the BEST only part 1 (CLOX1) is used as this part is dedicated to determining executive function. A clock is well recognised by most individuals and is not biased by culture[32]. Clock drawing is also able to overcome language barriers[6]. A score of 10 out of 15 represents the 5th percentile for young adults[9].

Task 3 – Verbal fluency

Verbal fluency tests the patient's ability to manipulate semantic memory (the knowledge of facts and concepts). The patient is requested to name as many animals that walk on four

legs in a 1 minute period. Selection of the category of four-legged animals was made to minimise cultural and educational bias. Normative data for the naming of animals shows that 90% of people with 9 or more years of education will name 13 or more animals, while those with less than 9 years education name 12 or more animals[14].

Task 4 – Three item delayed recall

Recalling the three words named in task 1 is a test of episodic memory functioning. This does not test executive function but has been included in the battery with the goal of adding to the value of the BEST as an evaluating tool of general cognition, and thus affording an opportunity for appropriate dementia referral and management. There is evidence that combining a clock drawing test and a 3 word recall test (the mini-cog) are helpful in bedside screening of dementia[13].

Task 5 – Problem solving

This is a complex problem solving task that tests the ability of the patient to formulate an efficient problem solving strategy. "I have 18 books that need to be packed on 2 shelves. One of the shelves needs to have twice as many books on it as the other shelf. How many books must I put on each shelf?" It is not unreasonable to ask a patient, who may potentially be required to understand and implement a complicated management regimen, to solve this reasonable problem to reaffirm that they understand the complexities of managing their illness. For example if a patient is a diabetic, they may be required to administer therapeutic regimens such as multiple varied insulin dosing as well as the other complicated lifestyle requirements that are required for successful medical management. This task is particularly relevant to patients on a biphasic insulin regimen where doses are divided into two thirds in the morning and one third in the evening.

Executive impairment was diagnosed as present in a patient who demonstrated two or more of the following criteria:

1. CLOX1 score of <10
2. Naming ≤12 animals (or ≤11 if patients had completed fewer than 9 years of education)
3. Inability to solve the problem correctly

2.3 AIMS

- To ascertain the incidence of executive dysfunction in patients attending a tertiary diabetic clinic.
- To correlate executive impairment with glycaemic control, target organ damage, patient report adherence and prescribed medications.

2.4 METHODS

2.4.1 STUDY DESIGN

A prospective clinical study

2.4.2 STUDY POPULATION

People with type 2 diabetes attending the tertiary referral Diabetic Clinic at Groote Schuur Hospital, Cape Town, were invited to participate in the study during their usual clinic visits between 1 March 2006 and 31 June 2006. Groote Schuur Hospital is a university teaching hospital serving an open population of approximately 2.9 million persons. The clinic provides care for people with diabetes from lower socioeconomic income groups (more affluent patients with health insurance tend to seek medical care in the private sector), with poor disease control and/or established target organ damage.

Exclusion criteria: (rationale for exclusion)

1. Patients not fluent in English (These patients would be disadvantaged with regards to the verbal fluency task).
2. Visual impairment to the degree that it precluded the completion of the clock drawing task.
3. Laboratory tested blood glucose recorded on the day of their clinic visit of less than 4 or greater than 15mmol/l (Extremes of glucose may be responsible for transient/reversible cognitive dysfunction and thus bias result interpretation).
4. Prior cerebrovascular accident.
5. Patients known to suffer from depression.

2.4.3 MEASUREMENT TOOLS

1. Completion of the BEST (*appendix B*), administered according to a standardised proforma by either the attending clinician or a research nursing assistant.
2. A copy of the routinely completed diabetic clinic clerking proforma (*appendix C*). Data collected from this source included:
   - Age
   - Patient reported dietary and medication adherence
   - Target organ damage: this comprised microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (ischaemic heart disease, peripheral vascular disease) complications
   - Prescribed medications
3. Glycated haemoglobin and random laboratory glucose measurement on the day of assessment.

2.5 ETHICAL CONSIDERATIONS

- The only non-routine intervention that a study participant underwent was completion of the BEST battery, which takes only 5 minutes to administer. All other data collected was obtained from the diabetic clinic proforma clerking sheet on which patient details are routinely recorded (*appendix C*).
- All patients provided written informed consent which was obtained by the administering physician (*appendix D*).

- No financial compensation was available for either the participant or the physician collecting the data.
- All patient information was kept strictly confidential.
- What were the implications of discovering cognitive impairments in any of the study population?

  Treatment of executive dysfunction where there was preliminary evidence of benefit at the time of the study included:[13]

  1. Consideration of statin use if clinically indicated, as there is evidence that this may improve cognitive function.
  2. The use of low dose aspirin as an antithrombotic medication where clinically indicated.
  3. Exercise.

All of the above measures are current management goals for all patients attending the diabetic clinic.

When behavioural, social, psychiatric problems or other medical problems were discovered that could not be appropriately managed in the diabetic clinic setting the additional resources of the Memory, Geriatric or community Psychiatric services were made use of on a referral basis. These clinics are routine services available to all referred patients.

The study was conducted in accordance with the principles of good clinical practice enunciated in the World Medical Association Declaration of Helsinki 2000 (clarified 2002 and 2004)[33].

2.6 STATISTICAL METHODS

Data was entered into a database, coded, and then analysed. The Student's T-test was used to determine the statistical difference between the means of age, years of education and total number of target organs affected by diabetes. The Chi square test was employed to assess the statistical difference between medication and dietary adherence as well as difference in drug usage between patients with and without executive impairment. Fisher's exact test was used to assess the statistical differences in diabetic control between those with and without executive impairment.

2.7 FUNDING

The only implicated costs of the study were those of copying the data recording sheets and this was born by the affiliated departments and individuals.

2.8 RESULTS

Of the 107 patients recruited, 98 consented to participation in the study.

DEMOGRAPHIC DATA

- Women comprised 61 patients (62%), whilst there were 37 males (38%)
- Mean age was 57.7 years, standard deviation (SD) 10.4 with a range of 31-85 years.
- The mean education level was 8.2 years (SD 2.5) with a range of 3-16.

Figure 3: Distribution of age of screened type 2 diabetic patients

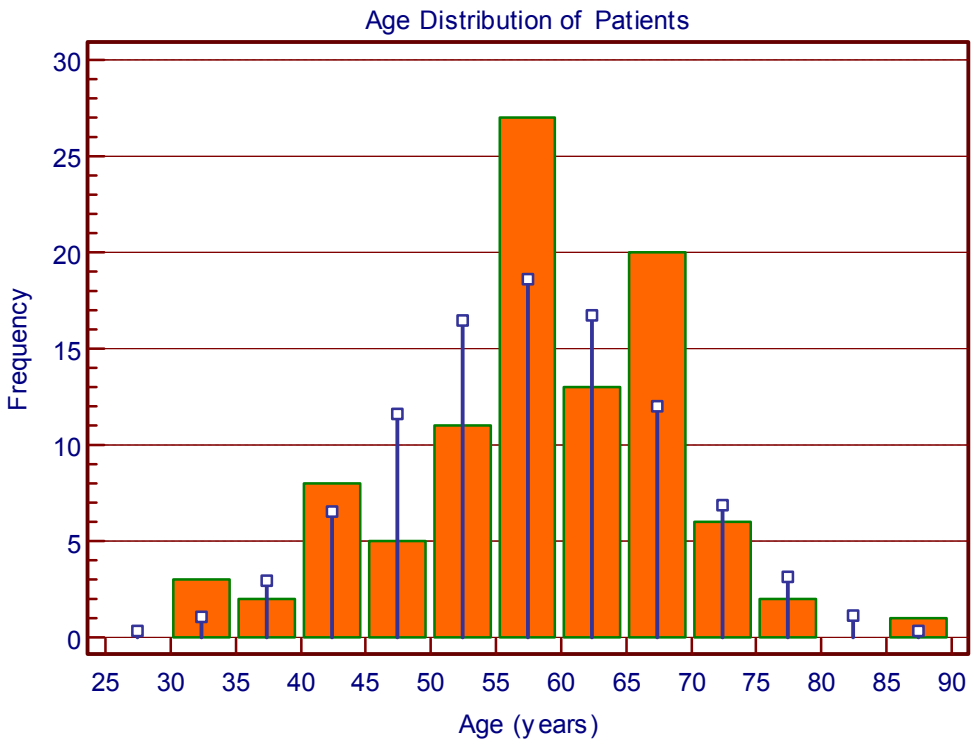
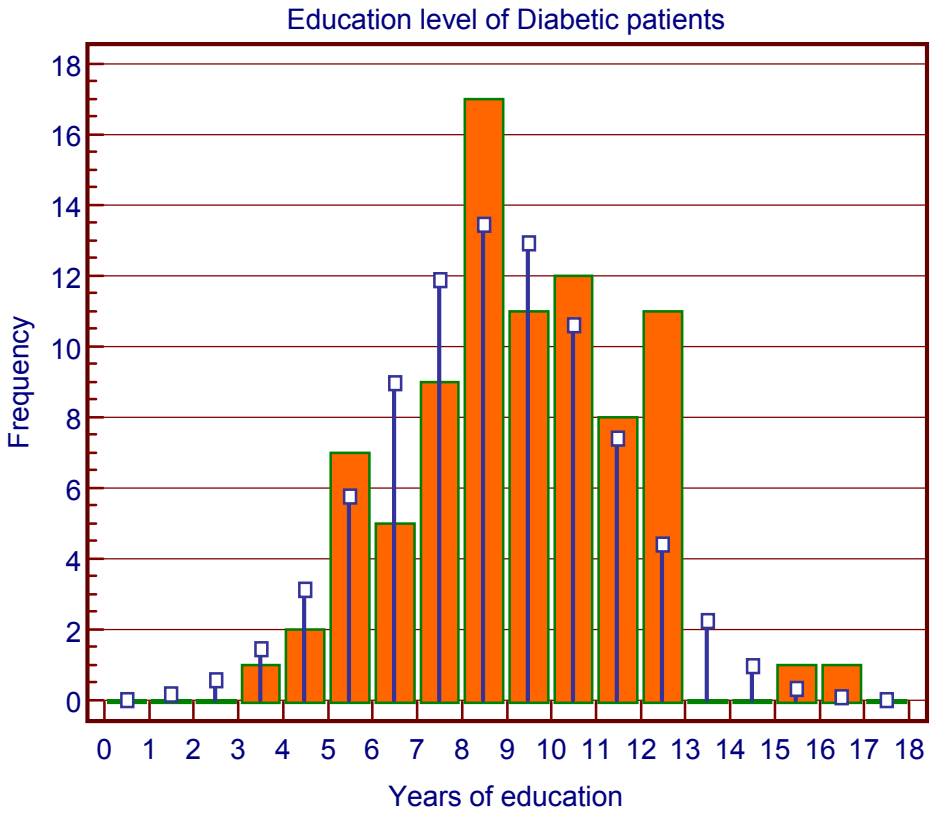


Figure 4: Distribution of years of education in screened type 2 diabetic patients



COGNITIVE TEST RESULTS

1. Three word registration: - Participants scored a mean of 2.95 words (SD 0.2), ranging between 2-3 words with no participant registering less than 2 words.
2. Executive Clock-drawing task part 1(CLOX1): - This task yielded a mean score of 11.0 (SD 3.2) with 15 being the maximum achievable score possible. Scores ranged from 2 to 15. Twenty-two (22%) participants scored less than 10 indicating possible executive impairment.

Figure 5: Examples of poor scoring clocks as drawn by screened type 2 diabetics[34]

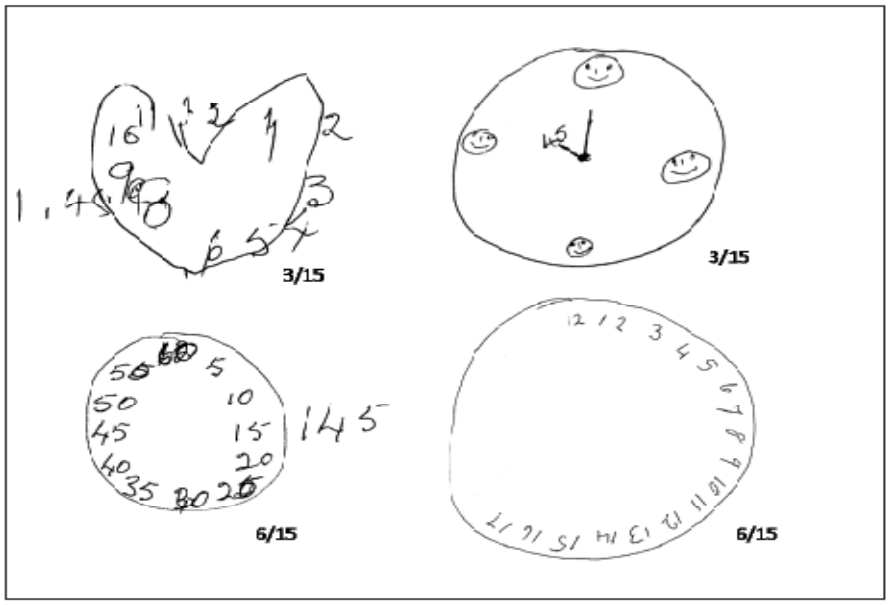
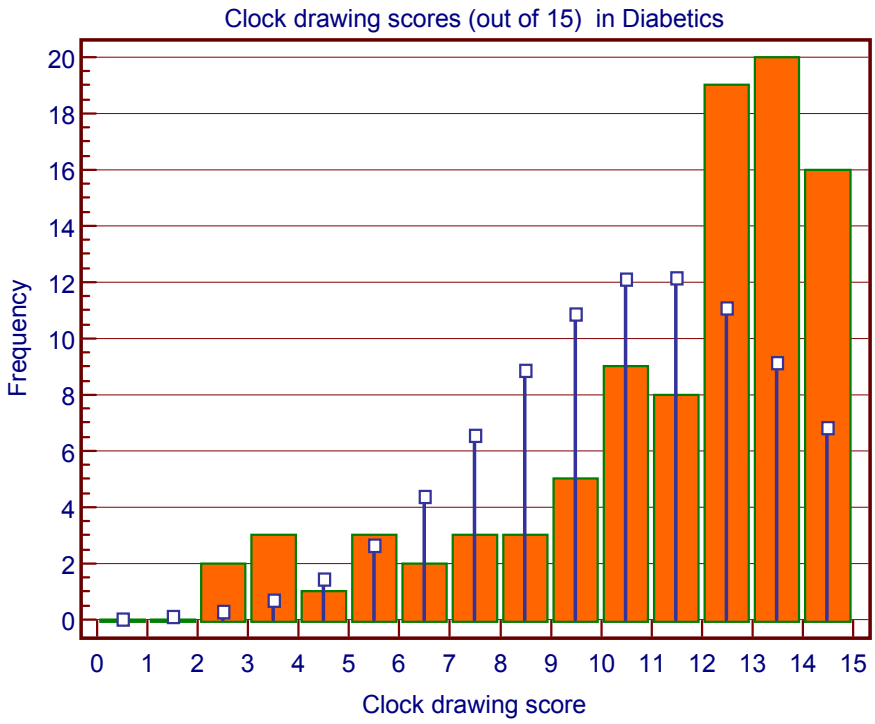
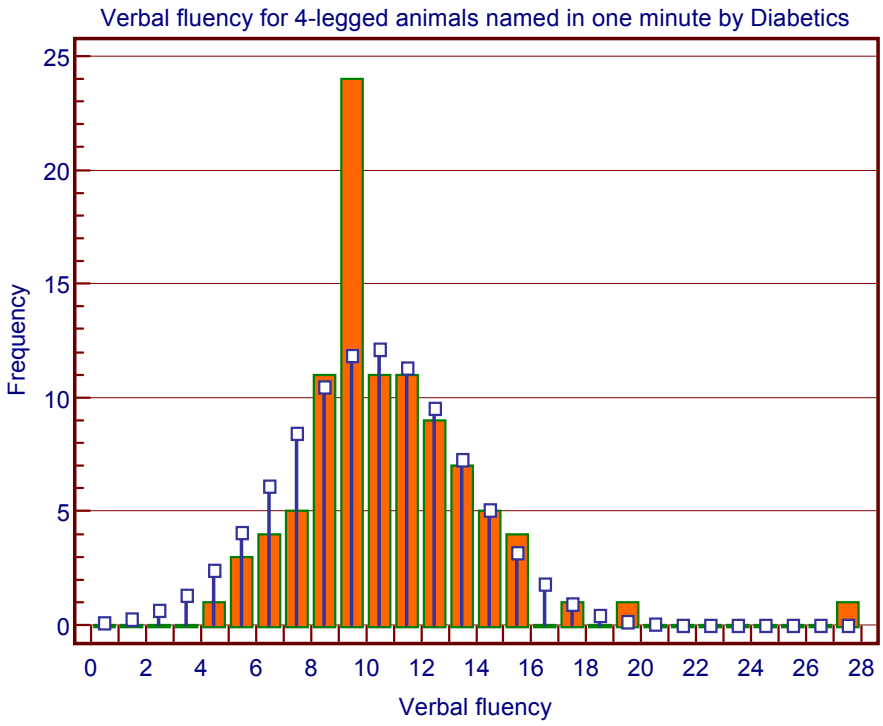


Figure 6: Distribution of clock drawing scores in screened type 2 diabetic patients



3. Verbal fluency: - The mean number of animals named was 10.3 (SD 3.2), the range was wide with between 4 to 27 animals being named. Seventy of the participants (71%) named 12 or less animals.

Figure 7: Distribution of verbal fluency scores for screened type 2 diabetic patients



4. Delayed three word recall: - Mean number of words recalled was 2.3 (SD 0.8), range between 0 to 3 words. Twenty of the participants (20%) recalled less than two words.

5. Book problem solving task: - Only 46 participants (47%) solved this problem correctly, with 28 patients making the similar mistake and giving the answer as “9 and 9”.

6. Executive function impairment : - Fifty one of the 98 participants (52%) failed to complete two or more tasks (task no. 2, 3, and 5) meeting the criteria of executive impairment.

7. Min-cog: - This was abnormal in 15 out of the 51 participants (29%) with executive impairment and only 2 out of the 47 participants (4%) without executive impairment. Executive impairment was strongly associated with an impaired Mini-cog (p=0.001) with an odds ratio of 9.4 (95% confidence interval 2.0-43.7).

GLYCAEMIC CONTROL

- Mean HbA1c was 8.8% (SD 1.6) with values ranging from 6.0% to 14.0%
- Eighty four of the 98 screened participants were found to have inadequate glycaemic control (HbA1c ≥7%) and only 14 had adequate control.
- A total of 51 participants demonstrated executive impairment, 48 of these 51 participants with executive impairment (94%) had inadequate glycaemic control, whilst only 3 participants with executive impairment (6%) had adequate glycaemic control.
- Patients with executive function impairment were more likely to have poor diabetic control (p=0.019). Odds ratio: 4.9 (95% confidence interval 1.3-18.8).

Table 3: Glycaemic control in relation to presence of executive impairment

	EXECUTIVE IMPAIRMENT PRESENT *(n=51)*	**EXECUTIVE IMPAIRMENT ABSENT** *(n=47)*	
HbA1c <7.0%	3 (6%)	11 (23%)	***P=0.019***
HbA1c ≥7.0%	48 (94%)	36 (77%)	*NS*

- Education level and glycaemic control – For participants with adequate glyacemic control (HbA1c <7%) there was no significant difference in years of education between those with and without executive impairment. However, in participants who did not have glycaemic control (HbA1c ≥7%) there was a significant difference in years of education with a mean of 9.5 years (SD 2.9) in those without executive impairment and only 8.0 years (SD 2.1) in those with executive impairment (p=0.013).

Table 4: Years of education in relation to glycaemic control

	EXECUTIVE IMPAIRMENT PRESENT (years of education)	**EXECUTIVE IMPAIRMENT ABSENT** (years of education)	
HbA1c <7.0%	8.7±1.2	9.8±3.3	NS
HbA1c ≥7.0%	8.0±2.1	9.5±2.9	***p=0.013***

- Mini-cog test scores and glycaemic control – there was no significant difference in mini-cog test scores in patients with poor glycaemic control compared to those with good control (p=0.43).

Table 5: Mini-Cog scores in relation to glycaemic control

	NORMAL MINI-COG *(n=81)*	**ABNORMAL MINI-COG** *(n=17)*	
HbA1c <7.0%	9 (11%)	3 (18%)	***p=0.43/***NS
HbA1c ≥7.0%	72 (89%)	14 (82%)	

PATIENT REPORTED ADHERENCE

1. Dietary reported adherence: - 47 participants (49%) reported adherence, of these 20 (43%) were without executive impairment and 27 (53%) fulfilled the criteria for executive impairment. A total of 49 (50%) were self-reported as non-adherence. Of these non-adherence patients, 27 (55%) patients were free of executive impairment whilst 22 (45%) were impaired. In 2 participants dietary adherence was not assessed.

2. Adherence to medication: - 72 (73%) patients reported adherence to medications. Of these patients there was an equal distribution of executive impairment, 36 (50%) participants meeting requirements for executive function impairment and 36 (50%) not being impaired.

Table 6: Patient reported adherence to diet and medication

	EXECUTIVE IMPAIRMENT PRESENT *(n=51)*	**EXECUTIVE IMPAIRMENT ABSENT* *(n=47)***	
DIET			
Adherence	27	20	*NS*
Non-adherence	22	27	***p=0.30***
MEDICATION			*NS*
Adherence	36	36	*NS*
Non-adherence	13	11	***p=0.90***

*In two patients dietary adherence was not known

TARGET ORGAN DAMAGE

Target organ damage included retinopathy, nephropathy, neuropathy, ischaemic heart disease and peripheral vascular complications as recorded on the diabetic clerking proforma with a maximum possible total of five. There was no significant difference between the mean number of target organs damaged 1.7 (SD 1.2) in those participants with executive impairment and 1.4 (SD 1.3) those without (p=0.79).

PRESCRIBED MEDICATIONS

Usage of metformin, sulphonylureas, insulin, aspirin and statins was not significantly different between those participants with and without executive impairment. There was a significant relationship between the use of an angiotensin converting enzyme (ACE) inhibitor and the absence of executive impairment, this class of drug was used by a total of 64 (66%) participants. Usage was 28 out of 51 (55%) participants who had executive impairment and 36 out of 47 (77%) participants who had no executive impairment (p=0.027). Medication data was missing from one patient.

Table 7: Prescribed medications with relation to incidence of executive impairment

Medication prescribed	**Executive impairment present** ***(n=51)***	**Executive impairment absent** ***(n=47)***	
Metformin	32 (63%)	32 (68%)	NS
Sulphonylureas	16 (31%)	18 (38%)	NS
Insulin	39 (76%)	37 (79%)	NS
Aspirin	32 (63%)	36 (77%)	NS
Statin	17 (33%)	18 (38%)	NS
ACE inhibitor	28 (55%)	36 (77%)	***p=0.027***

3. DISCUSSION

Both the chronic diseases of type 2 diabetes mellitus and cognitive impairment are increasing in incidence. This is compounded by a generally ageing population worldwide and warrants a closer look at their association[24]. The diabetic clinician cannot afford to be ignorant to the possibility of executive impairment in his/her patients.

This study population was in keeping with diabetic populations seen at many other type 2 diabetic clinics throughout the world, burdened predominantly by patients with poor glycaemic control and/or target organ damage.

The achievement of individualised glycaemic targets is challenging for people with diabetes. Diabetes requires complex self-management i.e. glucose monitoring, meal planning and complex medication regimen adherence. Patients also need to be able to manage acute conditions, such as hypoglycaemia as well as other more chronic associated conditions e.g. hypertension[12]. Thus impairment of executive functioning jeopardises glycaemic control. Patients with executive dysfunction are at an increased risk of:

- Omission of medications
- Omission of meals
- Incorrect dosing
- Incorrect timing of dosing[12]

Hence the finding in this small study that poor glycaemic control (HbA1c ≥7%) was significantly associated with executive function impairment as detected by simple clinical testing is notable, yet not surprising.

Whether this impairment is another form of target organ damage or rather the cause of poor control, is not clear. Considering the close relationships, both are probably true with an intertwined cause and effect relationship. A vicious circle exists where executive impairment hampers glycaemic control which in turn makes the patient more vulnerable to further cognitive insults etc.

Sinclair et al (after adjusting for age and sex) demonstrated the following in diabetic individuals with poor cognitive scores:-

- Patients were less likely to undertake self-management
- Patients were less likely to attend a specialist diabetic clinic
- Patients were more likely to have been hospitalised in the past year
- Patients were more likely to require help with self-care
- Patients were more likely to be living in an institution
- Patients had impaired scores on tests of activities of daily living (ADL's)[8].

Thus in these individuals the need for informal caregiver input is vital and increases[8]. Indeed impaired executive functioning may have a more profound impact on a patients' autonomy than poor memory[1].

Physicians routinely screen for target organ damage and other cardiovascular risk factors, but not for cognitive dysfunction. Health care providers are generally unaware of the problem[12]. The clinician cannot rely on self-report as patients with executive impairment are less likely to self-report, perhaps due to impaired insight. This study confirms this with no difference in reported adherence between participants with and without executive impairment. This is a particular problem in those patients living alone. The under-

recognition of executive impairment places the patient in danger of receiving inappropriate less aggressive care, whereas such patients warrant more specialist input rather than less[8].

Demonstrating cognitive dysfunction reaffirms current clinical practice which should aim to provide optimal diabetic management, providing the clinician with an understanding of the cognitive limitations a complex therapeutic regimen may pose.

Traditional bedside /clinic cognitive testing has used the MMSE, which does not adequately test for executive function and may lead to further under-recognition[3]. The alternatives are complicated and time consuming batteries of tests which are not practical in busy clinics. The BEST takes less than five minutes to complete, it is easy to score and seems acceptable to both patients and administering clinicians. The BEST proved to be effective in screening for executive impairment as it was able to confirm the suspected increased incidence of executive impairment in type 2 diabetics as demonstrated by other studies. Impairment of the executive components of the BEST correlated with impaired glycaemic control while the delayed recall component plus clock drawing task in the BEST (the mini-cog component) did not. The mini-cog is recognised as an acceptable screening tool at a population level for dementia[35]. The BEST was therefore more associated with impaired glycaemic control than a dementia screening tool in this study.

Not only did the study look at the association between HBA1C and executive function, but also looked for any other possible correlations between executive impairment, target organ damage, adherence and/or medications prescribed. None of these yielded any major significant associations. However, there did appear to be an association of some significance between the absence of executive impairment and the use of ACE inhibitors. ACE inhibitors

appeared to play a possible protective role, perhaps this would be more pronounced in a study with a larger cohort of patients.

Previous studies have shown a positive association between the use of anti-hypertensive agents and cognitive impairment in type 2 diabetes[30]. However these agents most likely serve as a surrogate marker for hypertension, and the effects are probably due to the hypertension and not a side effect of treatment. There is little evidence of cognitive impairment or decline associated with the use of anti-hypertensive agents except for treatment induced hypotension in the elderly[30]. To the contrary this study hints at a possible protective role of these agents, specifically ACE inhibitors. Vascular risk factors in diabetics are diminished by lowering blood pressure[19]. In the Systolic Hypertension in Europe trial (Syst-Eur trial) active treatment of hypertension was shown to decrease the incidence of dementia by 50% after two years of follow-up[36]. ACE inhibitors are known to be protective for other forms of diabetic target organ damage, such as diabetic nephropathy.

This association may also serve to signify the association between hypertension and cognitive impairment, particularly a sub-cortical frontal vascular pattern. A significant association exists between diabetes and hypertension although there is evidence of specific deficits associated with type 2 diabetes independent of hypertension[30].

The lack of a significant association with these co-morbidities strengthens the finding that hyperglycaemia itself is related to executive impairment and is not merely being misrepresented by these confounding co-morbid conditions. A similar finding was reported by Sinclair et al. where eight forms of target organ damage (nephropathy, peripheral neuropathy, history of depression, ischaemic heart disease, hypertension, autonomic neuropathy, diabetic foot and stroke) were considered however only previous stoke and

established autonomic neuropathy were associated with lower MMSE scores[8]. This study excluded patients with known stroke.

Another interesting observation made was that those with executive impairment and inadequate glycaemic control had a lower mean number of years of education as compared to those without impairment with inadequate glycaemic control. Executive functioning comprises a set of acquired complex skills[2]. Education seems to assist in the acquisition of these skills and increases ones cognitive reserve, thus buffering against future possible cognitive decline[14]. Hence this finding illustrates that patients with a lower mean number of years of education are more vulnerable to cognitive insults manifesting in clinically significant executive impairment.

Why screen for executive impairment? As discussed above patients detected early with executive function impairment may benefit from individualized goals, management review, caregiver support, psychosocial interventions and more intense specialist input[8]. These interventions would serve to improve their future glycaemic control. There are still no established specific treatments or measures to prevent or ameliorate executive impairment. However early findings suggest benefit on cognition to be gained through improving glycaemic control and thus preventing a downward spiral of further executive impairment and decreasing medication adherence[30]. Other treatment strategies suggest avoidance and treatment of cardiovascular risk factors[28]. In the PROSPER trial pravastatin decreased dementia rates and improved scores on the MMSE and CLOX[1]. Some have suggested benefit from the appropriate use of anti-cholinesterase drugs such as Donepezil[8]. Physical activity (aerobic fitness) is recommended to improve cognition as well as play a preventative role in

decline. These effects are mediated through improved cerebral perfusion/oxygenation, decreased inflammatory mediators and decreased levels of stress hormones[1].

Weaknesses of this study are largely based on the small number of patients screened and the observational nature of the study. Data gathered was limited due to the time constraints of a busy diabetic clinic and could have included instrumental activities of daily living and additional cognitive testing such as trail making tests and the mini-mental state examination. This weakness is however also a strength since the BEST performed well in a real life clinical setting.

4. CONCLUSION

Executive functioning is vital to the type 2 diabetic patients' ability to self-manage their disease complex and to achieve glycaemic targets. There is an increased incidence of executive function impairment in type 2 diabetics. This small real life clinical study demonstrates a meaningful relationship between poor glycaemic control (HbA1c ≥7.0%) and executive impairment. Poor glycaemic control in these patients may be both the cause and effect of executive impairment.

Diabetic clinicians may largely be unaware of executive impairment in their patients due to a lack of screening. Traditional screening tools are either insensitive (MMSE) or impractical, time consuming batteries. Our tool, the BEST, is easy to both administer and score and takes less than five minutes.

Education plays a protective role against future cognitive decline and this seems to also apply specifically to the executive domain. The use of ACE inhibitors may also prove to be protective against executive impairment, possibly preventing another form of target organ damage.

Executive functioning is important in all type 2 diabetics and regular screening, ideally annually, is recommended, as well as screening for other associated cardiovascular risk factors and target organ damage, especially in those patients with poor or declining glycaemic control.

5. RECOMMENDATIONS

Findings in this study are an impetus to conduct a study with a larger population group. This study could be extended to implementing interventions in those found to have executive impairment, specifically targeting executive function with a view to following HbA1c levels for improvement.

However I feel that already with this small study and the reviewed literature there is enough evidence and motivation for clinicians to start screening for executive impairment in type 2 diabetics.

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Executive cognitive impairment detected by simple bedside testing is associated with poor glycaemic control in type 2 diabetes

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Aims. Cognitive impairment in people with type 2 diabetes is a barrier to successful disease management. We sought to determine whether impaired executive function as detected by a battery of simple bedside cognitive tests of executive function was associated with inadequate glycaemic control.

Methods. People with type 2 diabetes attending a tertiary referral diabetic clinic who consented to participate in the study underwent a brief battery of cognitive testing (the Bedside Executive Screening Test) designed to detect executive function impairment. Glycaemic control was determined using blood glycated haemoglobin levels (HBA_{1c}). Inadequate glycaemic control was defined as HBA_{1c} ≥7%.

Results. Executive function impairment was detected in 51 (52%) of the 98 study participants. The presence of executive function impairment was significantly associated with poor glycaemic control (HBA_{1c} ≥7%) (odds ratio 4.9, 95% confidence interval 1.3 - 18.8, p=0.019). There were no significant differences between patients with and without executive function impairment with regard to age, target organ damage, patient reported adherence, and hypoglycaemic therapy. Patients with a lower level of education were more likely to demonstrate executive impairment when glycaemic control was poor (p=0.013).

Conclusions. Executive function impairment is common in a population of people with difficult-to-manage type 2 diabetes. The presence of executive impairment is significantly associated with poor glycaemic control.

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Conventional management of type 2 diabetes relies heavily on the principles of self-management. This is in essence a series of complex goal-directed behaviours required for lifestyle and behavioural changes as well as adherence to pharmacological interventions aimed at managing glycaemic control, hypertension, lipid profiles, weight and physical activity. Successful disease management is dependent on the patient's ability to execute these interventions and maintain lifelong adherence. Not only do people with type 2 diabetes have a greater rate of decline in cognitive functioning and risk of future dementia than people without diabetes,[1,2] but the cognitive impairment is associated with poor diabetes control.[3,4]

The executive functioning domain of cognition is important in allowing the development of adaptive strategies and the ability of an individual to modify his/her behaviour in response to dynamic task requirements.[5] Impairment of executive function has been clinically linked with functional impairment, poor medication adherence, increased level of care needed and even patient resistance to care.[6-8] Executive impairment divorces ability from implementation.[5] Type 2 diabetes has been shown to be associated with impairment in executive cognitive functioning.[6,9,10] This is attributed to frontal-subcortical dysfunction due to microvascular disease.[5,10]

We sought to determine whether executive impairment as detected by a simple battery of beside executive function tests was associated with inadequate glycaemic control as defined by an HBA_{1c} level ≥7%.

Patients and methods

People with type 2 diabetes attending the tertiary referral Diabetic Clinic at Groote Schuur Hospital, Cape Town, were invited to participate in the study during their usual clinic visits between 1 March 2006 and 31 June 2006. Groote Schuur Hospital is a university teaching hospital serving an open population of approximately 2.9 million persons. The clinic provides care for people with diabetes from lower socio-economic income groups (more affluent patients with health insurance tend to seek medical care in the private sector), with poor disease control and/or established target organ damage. Study exclusion criteria included poor fluency in the English language, visual or hearing impairment, current management with an antidepressant, and/or precognitive evaluation blood glucose <4 mmol/l or >15 mmol/l on the day of assessment.

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Cognitive testing was performed using a battery we termed the Bedside Executive Screening Test (BEST). This comprised five parts:

- three item registration
- three item delayed recall test
- executive clock drawing task part 1 (CLOX1): *'draw me a clock that says 1:45. Put the numbers on the face so that a child could read them'*[11]
- verbal fluency test: *'name as many animals with 4 legs as you can think of in 1 minute'*
- problem solving task: *'I have 18 books that I need to put on 2 shelves. One of the shelves must have twice as many books on it as the other shelf. How many books must I put on each shelf?'*

The latter three cognitive tests draw mainly on the cognitive domain of executive functioning.[6,7] Abnormal tests were defined as:

- CLOX1 score of <10[11]
- naming ≤12 animals (or ≤11 if patients had completed fewer than 9 years of education)[12]
- inability to solve the problem correctly.

An assessment of executive impairment was made if patients had abnormal results for at least two of the three tests of executive functioning. The cognitive tests were administered according to a standardised proforma by either the attending clinician or a research nursing assistant.

Clinical, demographic and laboratory characteristics were recorded at the time of assessment and included gender, age, level of education (in completed years), laboratory blood glucose and glycated haemoglobin level on the day of assessment, the presence or absence of microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (ischaemic heart disease, peripheral vascular disease) complications, patient-reported dietary and medication adherence, and the various medications the patient reported using.

All microvascular and macrovascular complications were defined according to our clinic protocol. A composite score of the three abovementioned microvascular and two abovementioned macrovascular complications was created.

Student's *t*-test was used to determine the statistical difference between the means of age, years of education and total number of target organs damaged. The chi-square test was used to assess the statistical difference between dietary and medication adherence as well as the difference in drug use between patients with and without executive impairment. Fisher's exact test was used to assess the statistical differences in diabetic control between those with and without executive impairment. The institutional Ethics Committee approved the study protocol and all study subjects gave written informed consent.

Results

Of the one hundred and seven patients recruited, 98 consented to participation in the study. Women comprised 61 patients (62%). The mean age was 57.7 years (standard deviation (SD) 10.4) (range 31 - 85 years), and the mean education level was 8.2 years (SD 2.5) (range 3 - 16 years). Executive function impairment was present in 51 (52%) of the participants. For the clock drawing task (CLOX1) the mean score was 11.0 (SD 3.2) (range 2 - 15), with 22 (22%) of patients scoring below 10 (Fig. 1). The mean verbal fluency score was 10.3 (SD 3.2) (range 4 - 27), with 70 patients (71%) naming fewer than 12 animals. Only 46 patients (47%) answered the book problem correctly, with 28 patients giving the answer as '9 and 9'.

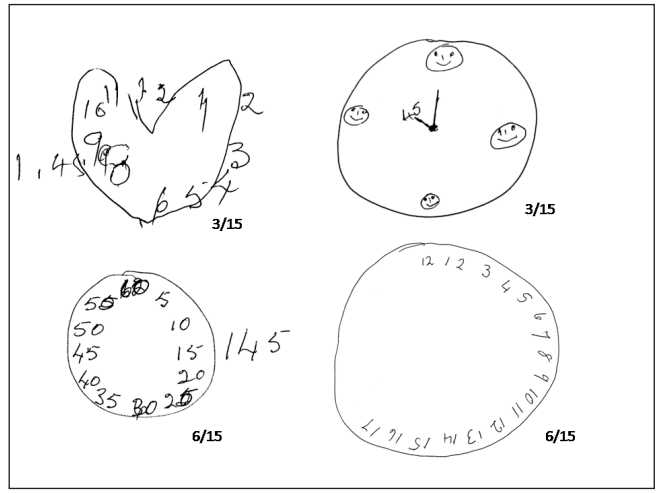


Fig. 1. Examples of abnormal clocks drawn by study participants demonstrating executive cognitive impairment. CLOX score is indicated.

Table I shows the demographic characteristics, diabetic control, reported adherence, target organ damage and drug usage differences between the study patients with and without executive impairment.

Patients with executive impairment were more likely to have poor diabetic control (odds ratio 4.9, 95% confidence interval 1.3 - 18.8).

Discussion

Our study population, in keeping with many other diabetes clinics throughout the world, comprised predominantly people with type 2 diabetes with inadequate glycaemic control and/or target organ damage. Education is shown to affect executive function.[12] In our study patients with lower levels of education appeared more vulnerable to executive impairment when glycaemic control was inadequate.

The achievement of individualised glycaemic targets is challenging for people with diabetes.[13] The observation that the

Table I. Differences in demographic characteristics, diabetic control, reported adherence, target organ damage and drug usage between patients with and without executive impairment

	Executive impairment		
	Absent (*N*=47)	Present (*N*=51)	
Age (mean±SD)	56.2±10.0	59±10.7	NS
Years of education (mean±SD)			
HBA_{1c} <7.0%	9.8±3.3	8.7±1.2	NS
HBA_{1c} ≥7.0%	9.5±2.9	8.0±2.1	*p*=0.013
Diabetic control (*N* (%))			
HBA_{1c} <7.0%	11 (23%)	3 (6%)	*p*=0.019
HBA_{1c} ≥7.0%	36 (77%)	48 (94%)	
Patient reported adherence (*N* (%))			
Dietary	20 (43%)	27 (53%)*	NS
Medication	36 (77%)	36 (71%)	NS
Mean No. of target organs damaged (±SD)	1.4±1.3	1.7±1.2	NS
Drugs used (*N* (%))			
Metformin	32 (68%)	32 (63%)	NS
Sulphonylureas	18 (38%)	16 (31%)	NS
Insulin	37 (79%)	39 (76%)	NS
Aspirin	36 (77%)	32 (63%)	NS
Statin	18 (38%)	17 (33%)	NS
ACE inhibitors	36 (77%)	28 (71%)	*p*=0.041

*In 2 patients dietary adherence was unknown.
NS = not significant.

presence of executive cognitive impairment was significantly associated with poor glycaemic control in this small study was therefore notable and potentially adds another dimension to the already complex interaction between health provider and patient. Indeed, people with executive functioning deficits as detected by cognitive testing may require alternative management strategies to enhance disease control.

Traditional bedside/clinic cognitive testing has used the Mini Mental State Examination, which does not adequately test for executive cognitive impairment, with poor sensitivity, especially in early disease.[14] Formal batteries of neuropsychological tests are time consuming (taking up to 3 hours to administer) and may not be available or practical in routine clinical practice. Even a validated test such as the Executive Interview takes 15 minutes to administer, too long for the busy diabetic clinic.[15] Our bedside battery takes 5 minutes or less to administer and requires minimal training beyond the scoring of the clock drawing task (CLOX1).[11]

Clinicians are largely unaware that executive impairment may occur frequently in a variety of medical conditions, including diabetes.[6] The findings of this study should be repeated in a larger study and may well provide impetus to perform a brief cognitive screening battery routinely – we propose the use of a battery such as ours.

Specific strategies required to improve control in people with type 2 diabetes and executive impairment remain to be determined, but awareness and increased recognition of executive impairment is currently the greatest clinical challenge.

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APPENDIX B

<u>The Bedside Executive Screening Test (BEST)</u>

Age of patient:

Level of education of patient:

Test tasks

1. Three word registration: *"I want you to remember 3 things for* me*: a pen, an apple, and a table" "Please tell me the three items" "Good, remember them I will ask you again later"* Score out of 3*.*
2. Clock drawing test*: "draw me a clock that says 1:45. Put the numbers on the face so that a child could read them"* Score out of 15 as per the CLOX1 scoring method. Do not help patient any further once they start the task. Use back of this sheet for the task.
3. Verbal fluency: 4-legged animals named in one minute: *"name as many animals that walk on 4 legs as you can think of in one minute*." Score one point per animal named correctly.
4. Delayed three word recall: *"please could you tell me the three items I asked you to remember earlier."* Score out of three.
5. Problem solving task*:" I am going to ask you to solve a problem for me: I have 18 books that I need to put on 2 shelves. One of the shelves needs to have twice as many books on it as the other shelf. How many books must I put on each shelf?"* Repeat the clinical problem once. Record the answer given by the patient.

Scoring system:

1. Attention /3
2. Clock drawing (see CLOX1 scoring) /15
3. Verbal fluency one point per animal
4. Delay recall /3
5. Problem solving task solved correctly yes/no answer given=

Executive dysfunction present if two or more of:

- Clock drawing score <10/15
- Scores ≤ 12 animals on verbal fluency test if has ≥ 9 years of education or scores ≤ 11 animals on verbal fluency if has < 9 years education.
- Cannot correctly solve bookshelf packing problem.

Scoring system for CLOX1

	Point value
• Does figure resemble a clock?	1
• Outer circle present?	1
• Diameter >2.5cm	1
• All numbers inside circle	1
• 12,6,3,9 placed first	1
• Spacing intact (symmetry on either side of the	
• 12-6 axis?) If yes, skip next.	2
• IF spacing errors are present, are there signs of	
• Correction or erasure?	1
• Only Arabic numerals?	1
• Only numbers 1-12 amoung the Arabic numerals?	1
• Sequence 1-12 intact? No omission or intrusions?	1
• Only two hands present?	1
• All hands represented as arrows?	1
• Hour hand between 1 and 2 o'clock	1
• Minute hand longer than hour hands	1
• None of the following 1) "hand pointing to 4 or 5"	1
2) "1:45" present	
3) Intrusions from "hand" or "face" present	
4) Any letters, words or pictures	

GSH Diabetic Clinic

Date _____

Glucose _____

HbA1C _____

Weight _____

Urine dipstix _____

PROBLEMS

Type 1 DM ☐ Type 2 DM ☐

Other DM _____

HPT ☐ IHD ☐ PVD ☐

Dyslipidaemia ☐

COPD/Asthma ☐

Other _____

_____

MEDICATION

Actraphane

Actrapid
Protophane

Gliclazide/Glibenclamide
Metformin
Simvastatin

Aspirin
Enalapril

COMPLICATIONS

None

Retinopathy - background ☐
proliferative ☐

Neuropathy - peripheral ☐
autonomic ☐

Nephropathy microalbuminuria ☐
macroalbuminuria ☐
creatinine ☐ _____

Other _____

PRESENT HISTORY

Smoking Y / N **Alcohol** Y / N

Hypoglycaemia Y / N HBGM Y / N _____

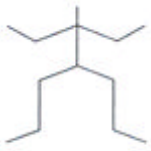
Compliance : Diet Y / N Meds Y / N Chest pain Y / N Calf claudication Y / N

Other : _____

EXAMINATION

Not done

Lipohypertrophy Y / N _____ **BP** ___/___ **Pulses**



Feet : AJs Y / N Sensation Y / N Vibration Y / N Ulcer Y / N

Fundoscopy Not done Retinopathy Y / N

Other :

ASSESSMENT

1) DM control - poor adequate good **2) BP -** poorly-controlled borderline well-controlled

PLAN

Insulin _____ Oral agents _____

Dietary advice **Y / N** Diabetic sister **Y / N** Ophthalmologist **Y / N** Podiatrist **Y / N**

Renal function **Y / N** Lipid profile **Y / N** Microalbumin-creatinine ratio **Y / N** ECG **Y / N**

Referral _____ Other _____ **TCA** x ____ **months**

Repeat CEU/ Microalbumin-creatinine ratio _____ / 20 ____

Annual review _____ / 20 ____

PRINT _____ **SIGN** _____

APPENDIX D

Patient Information and Consent Form

Study: The incidence of executive cognitive dysfunction detected by a Bedside Executive Screening Tool (BEST) in a cohort of type 2 diabetics attending a tertiary diabetic clinic.

Invitation to participate:

You are invited to take part in a study which we hope will enable us to detect changes in the way that diabetic patients are able to plan and approach problem solving tasks.

Why have I been asked?

Patients attending their Diabetic Clinic visits at Groote Schuur Hospital will be asked to participate in this study if they have type 2 diabetes, satisfactory eyesight and can speak English fluently.

What is the purpose of this study?

We hope to determine whether a short questionnaire comprising 5 tasks is able to detect problems with the way diabetic patients are able to plan and solve tasks that require complex thinking. At present we know that diabetes may impact on the functioning of the brain. We do not however know how common this problem may be.

What will happen to me if I take part?

During your routine clinic visit the doctor will ask a series of 5 short tasks aimed at testing your problem solving ability. These tasks should take no longer than 5 minutes to complete.

Are there any risks?

No, you will not be asked to take any additional medicines or to undergo any treatments for this study. Taking part is strictly voluntary and your care in the Diabetic Clinic will not be affected by whether or not you participate in the study.

What are the benefits of taking part?

Although the purpose of this study is to gather information so that we can develop an understanding of how to manage diabetic patient's care better, if any problems are found that cannot be dealt with by the Diabetic doctor, referral to other specialist help is available as needed. This is the usual practice in the Diabetic clinic.

Will my taking part be kept confidential?

Yes. Only the project researchers will know your details. You will never be identified as having taken part as the conclusions will draw on information provided by all the participants in the study.

I confirm that I have understood the above information for the study and that I have had the opportunity to ask questions.

I understand that my participation is voluntary and that I am free to withdraw at any time.I agree to take part in the above study.

Printed patient name	Date of patient signature	Patient sign

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
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03 April 2006

REC REF: 083/2006

Dr HB De Wet
Division of Endocrinology and Geriatric Medicine
Dept of Medicine

Dear Dr. De Wet

THE INCIDENCE OF EXECUTIVE COGNITIVE DYSFUNCTION DETECTED BY A BEDSIDE EXECUTIVE SCREENING TOOL (BEST) IN A COHORT OF TYPE 2 DIABETICS ATTENDING A TERTIARY DIABETIC CLINIC

Thank you for submitting your study to the Research Ethics Committee for review. It is a pleasure to inform you that the Ethics Committee has approved the above mentioned study.

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Please quote the REC. REF in all your correspondence.

Yours sincerely

pp **PROF. T ZABOW**
CHAIRPERSON