Introduction

Diabetes in older adults has become a major public health problem affecting an increasing number of individuals worldwide. Both old age & diabetes are independently associated with an increased risk of cognitive dysfunction; the risk is even greater for older adults with diabetes ***(Ryan 2005)***.

Neuropsychological tests have shown deficits in various aspects of cognitive function in both young and older patients with diabetes. Deficits have been seen in areas of psychomotor efficiency, global cognition, episodic memory, semantic memory, and working memory ***(Arvanitakis et al., 2004)***.

Abnormalities in cognitive functions mediated by frontal lobe (executive functions), including a number of complex behaviors such as problem solving, planning, organization, insight, reasoning, and attention, are noted in patients with diabetes ***(Munshi et al., 2006)***.

Considering the importance of self-management behaviors in diabetes treatment and the high complexity of diabetes management (e.g., blood glucose testing, meal planning and medication compliance), diabetic patients with cognitive dysfunction may experience significant difficulty managing their disease. They may also have difficulty treating acute conditions associated with diabetes treatment such as hypoglycemia ***(Munshi et al., 2006)***.

Cognitive dysfunction, especially executive dysfunction, can affect insight into one's behavior and may, therefore, contribute to the patient minimizing the difficulties that he/she is experiencing. Such patients are unlikely to self-report either cognitive problems or difficulty managing their diabetes. As a result, many healthcare providers may be unaware that their patients have cognitive dysfunction ***(Seltzer et al., 2001)***.

Not only cognitive function, but also psychiatric illness was found to be related to glycemic control. Depression is a risk factor for poor metabolic control, decreased physical activity, higher obesity and potentially more diabetes end-organ complications and impaired function ***(Lin et al., 2004)***.

On the other hand, treatment of depression in diabetics may improve glycemic control and thereby reduce the risk of diabetic complications ***(Sahota et al., 2008)***.

Also, the existing literature suggests that anxiety has been associated with poor glycemic control, regimen adherence, and with accelerated rates of coronary heart disease in diabetic patients ***(Mitsonis , Dimopoulos and Psarra 2009)***.

Aim of the Work

To study the impact of cognitive impairment and psychiatric illness on glycemic control in a sample of Egyptian Elderly diabetics.

Chapter 1
Cognitive Impairment & Diabetes

A recent study predicted that by 2030 a 42% increase in T2DM prevalence can be expected in developed countries, mainly among elderly ***(Whiting et al., 2011)***. These figures may be more in developing countries.

Diabetes mellitus is a complex metabolic disease that has hazardous effects on many body organs. A less addressed and not as well recognized complication of diabetes is cognitive dysfunction and dementia. Patients with type 2 diabetes mellitus (T2DM) have been found to have cognitive deficits that can be attributed to their disease ***(Kodl and Seaquist ., 2008)***.

Screening for individuals at risk of dementia may help in preventive and/or treatment. Currently, there is no specific preventive treatment, although some studies with antihypertensive agents were done ***(Peters et al., 2008).*** Preventive strategies for dementia are likely to be most effective if treatment can be initiated in people in whom the absolute dementia risk is high, at an early stage that offers a potential to modify disease progression ***(Exalto , et al., 2012)***.

Compared to the general population, people with T2DM have a 1.5–2.5 times greater risk of dementia ***(Strachan et al., 2011)*** and currently one in 10–15 cases of dementia can be attributed to T2DM ***(Kloppenborg et al., 2008)***. Due to the

aging of the population an increasing number of people will be affected by T2DM ***(Whiting et al., 2011)*** or dementia ***(Ferri et al., 2005***) and an increasing number of people will have both conditions together***(Exalto , et al., 2012).***

Like diabetes, cognitive dysfunction shows a rising prevalence worldwide, especially among the elderly (***Thomas et al., 2001)***. Cognitive impairment due to diabetes mainly occur at two main periods: during the first 5–7 years of life when brain systems is in development; and the period when the brain undergoes neurodegenerative changes due to aging (older than 65 years) ***(Roriz-Filho , et al. 2009)***.

Cognitive dysfunction in DM

Diabetes is known to affect areas in the brain that involve some cognitive functions as reported by different studies . For instance, a study found that the structural connections between the prefrontal regions (responsible for executive functions) exerting top-down cognitive controls and other regions subserving complex brain functions including language and mnemonic/emotional processing were likely to be less integrated in T1DM patients relative to control ***(Lyoo , et al. 2013)***.Also ***Pell, et al. (2012)*** found prefrontal regional deficits frequently observed in T1DM patients [along with the dorsolateral prefrontal thickness reductions in the T1DM patients in his study.

More over a study found that T2DM-related gray matter loss was distributed mainly in medial temporal, anterior cingulate, and medial frontal lobes, and white matter loss was distributed in frontal and temporal regions. T2DM was associated with poorer visuospatial construction, planning, visual memory, and speed ***(Moran, et al. 2013)***.

Another study found that Concomitant with the memory impairments observed in T2DM, four reports have described hippocampal volume loss in T2DM, suggesting that the hippocampus and associated declarative memory function are particularly vulnerable to the effects of T2DM ***(den Heijer et al., 2003; Gold et al., 2007; Bruehl, et al. 2009; Bruehl et al 2010)***.

Neuropsychological studies consistently report modest cognitive decrements in patients with T2DM, even in people without dementia. In cross-sectional studies, worse performance was noticed on measures of verbal memory, information processing speed and attention and executive functioning ***(Reijmer et al., 2010)***. Cross-sectional studies evaluating cognition in T2DM patients demonstrate that immediate noncontextual, verbal memory, processing speed, and brief cognitive screening measures are much worse in diabetic patients than among controls . Taken together, the results of well-controlled cross-sectional population studies demonstrate that findings across all evaluated neuropsychological measures are inconsistent ***(Awad, et al. 2004).***

Longitudinal studies show that, relative to people without diabetes, cognitive deficits occurs only slowly over time ***(Nooyens et al., 2010; van den Berg et al., 2006)*** . Longitudinal studies, however, almost universally reveal a higher risk of dementia or significant cognitive decline in diabetic populations ***(MacKnight, et al. 2002.)***. Studies with cognitive batteries or comprehensive neuropsychological tests show that the rate of cognitive decline due to aging is increased 15 to 20 folds in individuals with T2DM ***(Cukierman, et al. 2005)*** . On the other hand a study of cognitive function in the oldest old (age at study entry 85 years) did not find any significant association between T2DM and accelerated cognitive decline ***(van den Berg, et al. 2006, Biessels, et al. 2006)***.

This is attributed to the fact that Many elderly above 80 might improve their T2DM control by losing weight ***(van den Berg, et al. 2006)***. The mild-moderate caloric restriction increases insulin sensitivity and decreases the formation of AGEs (advanced glycosilation end products) and ROS,(reactive oxygen species) resulting in less oxidative stress ***(Mair&. Dillin 2008)***.

Pathophysiology:

T2DM is a complex metabolic disorder that is closely associated with other established risk factors for dementia, such as hypertension and atherosclerotic vascular disease. These and other risk factors, such as demographic factors (e.g. age,

education), diabetes-specific factors (e.g. diabetes duration, glycemic control), medication use and genetic factors may be involved in the association between T2DM and dementia ***(Roriz-Filho, et al. 2009).***

Type 2 diabetes and cognitive decline: linking mechanism

I-Clinical factors

The exact pathophysiology of cognitive dysfunction and cerebral lesions in diabetes mellitus is not completely understood ***(Roriz-Filho, et al. 2009).***

Ethnicity: There is no data on the influence of ethnicity on the risk of dementia specifically among those with T2DM, but comparisons of the relative risk of dementia associated with T2DM across different study populations, does not suggest major effects of ethnic background ***(Biessels et al., 2006) (Exalto, et al., 2012)***. Genetic predisposition may **contribute** to the increased dementia risk in T2DM patients. The APOE ε4 allele is the most widely examined genetic risk factor for dementia and is related to cardiovascular disease and late-onset AD in the general population ***(Takeda et al., 2010)***. Several studies have shown interaction effects between T2DM and the APOE ε4 allele, further increasing the diabetes associated risk of dementia ***(Dore et al., 2009; Irie et al., 2008; Peila et al., 2002; Takeda et al., 2010; Xu et al., 2004)***.

Age: Furthermore, also the occurrence of diabetes and dementia is very high in older patients, suggesting a possible link between the two, overall because diabetic patients have a higher chance of developing dementia ***(Frisardi ,et al. 2010).***

Education: There is no data on the influence of education on the risk of dementia among those with T2DM ***(Biessels et al., 2006).***

Gender: However, the risk of dementia among those with T2DM is seldom reported separately for men and women. Only one study found a slightly increased risk in men ***(Leibson et al., 1997)***, whereas others reported no difference ***(Ott et al., 1999).***

Glycemic control: Glycemic control appears to play an important role in preserving cognitive performance among patients with T2DM] ***(Ryan & Geckle 2000)***. In patients with T2DM, studies have demonstrated an inverse relationship between serum HbAlc and working memory ***(Munshi , et al. 2006)***, executive functioning ***(Munshi , et al. 2006)***, learning ***(Reaven, et al. 1990)***, and complex psychomotor performance ***(Sommerfield, et al.2003)***. This finding supports the hypothesis that an inadequate glucose control is associated with worsening cognitive function. The impact of diabetes on cognitive functions seems to be greater in older people with worse glycemic control and long duration of the disease ***(Roriz-Filho , et al. 2009).***

Several studies have shown that hyperglycemia has toxic effects and can lead to slowly progressive functional and structural abnormalities in the brain ***(Arvanitakis, et al. 2004)***. Chronic hyperglycemia could, thus, be one of the determinants of cognitive decline in people with abnormal glucose metabolism ***(Roriz-Filho , et al. 2009).***

Glycemic control, as measured by glycated hemoglobin (HbA1c) is not clearly associated with dementia in T2DM patients ***(Bruce et al., 2008b)***. However, the Kungsholmen study indicated that patients with very high HbA1c levels (≥11.0 mmol/l) were at the highest risk of dementia independent of vascular co-morbidities ***(Xu et al., 2009).***

Poor glycemic control is associated with accelerated cerebral atrophy ***(Roriz-Filho, et al. 2009)***. Some studies demonstrated that patients with IGT may have the same pattern and severity of cognitive deficits as patients with T2DM ***(Vanhanen, et al. 1997).***

Multiple investigations on patients with IGT have shown them to have lower MMSE and long-term memory scores, impaired verbal fluency ***(Kanaya , et al. 2004)***, increased risk for Alzheimer's disease, and increased odds for vascular dementia. However, not all studies found that patients with pre-diabetes perform worse than normoglycemic individuals ***(Fontbonne, et al. 2001, Lindeman.,et al 2001, Kumari. & Marmot ., 2005).***

Duration and severity of T2DM: Another important finding is the association between both the duration and severity of T2DM at one side, and the degree of central (brain) and peripheral nervous system involvement, as demonstrated by decreased cognitive function and peripheral neuropathy, respectively ***(Roriz-Filho, et al. 2009).***

On the other hand, some cross-sectional studies revealed no consistent relationship between disease duration and cognition ***(Brands, et al 2005).***

Insulin-dependent T2DM: Insulin-dependent T2DM subjects had a higher risk of major cognitive decline than those with an adequate metabolic control only with oral hypoglycemiants ***(Roriz-Filho, et al. 2009)***.

The effect of diabetes treatment and glycemic control on dementia risk are less clear. A study in a large cohort of non-insulin users showed that the use of metformin and sulfonylureas decreases the risk of dementia in T2DM patients, as compared to T2DM patients who did not use diabetes medication ***(Hsu et al., 2011)***. Some studies have associated insulin use with dementia ***(Luchsinger et al., 2001; Peila et al., 2002)*** while others did not confirm this relation ***(Bruce et al., 2008a, 2008b)***. Importantly, these observational studies provide no evidence of causality as "confounding by indication" may provide an important source of bias, since patients using insulin tend to have had longer duration of T2DM ***(Exalto, et al., 2012).***

Hypoglycemia episodes: Conversely, repetitive episodes of moderate to severe hypoglycemia have been implicated as one possible etiology for long-term cognitive dysfunction in T2DM ***(Sommerfield, et al. 2003),*** even though the strongest evidence for memory disturbances is for the short period in which the subject is hypoglycemic ***(Biessels, et al.2001, Schmidt, et al. 2004).***

In addition, the occurrence of hypoglycemia in both T1DM and T2DMgroupswas correlated with increased cerebral atrophy in several cerebral regions, more specifically in certain areas of the frontal and temporal lobes, besides the thalamus ***(Wessels, et al. 2006).***

T2DM complications: Some other studies have showed that the presence of peripheral diabetic complications is more associated with lesions of certain specific cerebral area ***(Musen, et al. 2006, Wessels, et al, 2006).***

Macro-vascular complications, such as a history of stroke or the presence of peripheral artery disease substantially increased the risk of dementia in patients with T2DM ***(Bruce et al., 2008b; Luchsinger et al., 2001; Velayudhan et al., 2010)***.Cerebrovascular damage is therefore likely to be a major factor in the association between T2DM and dementia and could explain the increased risk of Vascular dementia. Data from experimental studies also suggest that T2DM associated metabolic disturbances may accelerate the development of AD-type pathologies ***(Craft, 2009 & Echavarri et al., 2012).***

Moreover, particularly in the oldest old, the neuropathology of dementia is most commonly a combination of AD-type and vascular lesions ***(Schneider et al., 2007)***.

Microalbuminuria, a micro-vascular diabetes complication, was related to the development of cognitive impairment in older patients with T2DM ***(Bruce et al., 2008a)***. In the same cohort a trend towards an association with other micro-vascular complications, namely nephropathy and peripheral neuropathy, was seen. No published study has investigated the association between diabetic retinopathy and dementia as an outcome, but diabetic retinopathy has been associated with modest cognitive decrements ***(Crosby-Nwaobi et al., 2011).***

Recent large cohort studies have identified other comorbidities as risk factors for dementia in T2DM patients. In a prospective study of approximately 20,000 T2DM patients, comorbid depression was associated with an approximately 2-fold increased risk of dementia ***(Katon et al., 2012)***. Poor oral health, as Periodontitis may be a risk factor for cognitive decline ***(Stewart, et al. 2013).***

Pre-diabetes and the metabolic syndrome (MetS):

Pre-diabetes: Insulin resistance (IR) is a feature of T2DM. The term ‘pre-diabetes’ is employed when, in the presence of IR, enough insulin is still produced to prevent overt diabetes, but it results in impaired fasting glucose and/or impaired glucose tolerance ***(Cole, et al. 2007, Luchsinger, et al. 2004, Yaffe, et al. 2004).***The complex relationship between

diabetes and cognitive decline can be better understood under the "Metabolic-Cognitive Syndrome" theory ***(Frisardi ,et al. 2010).*** Impaired glucose tolerance (IGT) is a component of MetS. It was found that impaired fasting glucose and abnormal glucose tolerance have also been associated with cognitive impairment ***(Roriz-Filho et al., 2009, Frisardi ,et al. 2010).***

.In pre-diabetes, body tissues are exposed to hyperinsulinemia for extended periods, may be for decades. Hyperinsulinemia seems to be involved in neurodegeneration and cognitive decline ***(Luchsinger, et al. 2004, Yaffe, et al. 2004)***. Impaired glucose tolerance and hyperinsulinemia were associated with reduced Mini Mental State Examination (MMSE) scores ***(Folstein, et al. 1975)*** and linked to increased risk for mild cognitive impairment (MCI). In one study, reduced glucose tolerance was associated with decreased general cognitive performance, memory deficits, and hippocampal atrophy on the MR ***(Convit, et al. (2003)***.

Hypertension: T2DM patients with comorbid hypertension have an increased dementia risk as compared to those without hypertension ***(Johnson et al., 2012)***. Especially, severe hypertension elevates the risk of dementia ***(Xu et al., 2004)***. When hypertension is treated dementia risk can decrease ***(Bruce et al., 2008a &Johnson et al., 2012)*** ranging from 24% for angiotension receptor blockers to 4% for beta-blockers ***(Exalto, et al., 2012)***.

Obesity: the results of studies is not conclusive as Obesity is associated with a significant reduction in insulin sensitivity (insulin sensitivity inversely correlates with BMI) ***(Ferrannini, et al. 1997)***. The occurrence of central obesity in midlife increases the risk of dementia ***(Whitmer, et al. 2008)***. Generalized brain atrophy and regional alterations in gray matter volume occur in obese male subjects, suggesting that subjects with a high BMI are at greater risk for cognitive decline ***(Taki, et al. 2008)***. Higher waist-to-hip ratio (overweight and obesity) is an independent protective factor for dementia. Body Mass Index (BMI) and cholesterol levels have not been associated with dementia in older T2DM patients ***(Bruce et al., 2008a, 2008b)***.

Both high (>29), low (<21), rising and falling BMI have been associated with increased risk of cognitive decline (Panza et al., in press). Weight loss seems to occur during the preclinical phases of dementia, and follow-up studies have suggested that low BMI could actually be an early sign of dementia ***(Stewart et al. 2005)***. Epidemiological studies of increased BMI as a risk factor for dementia have shown conflicting results ***(Fitzpatrick et al. 2009)***. Elevated BMI in middle age may be associated with higher dementia risk ***(Whitmer et al. 2008)***.

II-Biochemical:

General: Both AD and T2DM share common biochemical features, particularly impaired insulin signaling