Editorial

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Diabetes Mellitus and Cognitive Decline – Prevention Should Not Be Delayed!

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The recent addition of the Diabetes and Cognitive Decline section to JPAD marks a milestone in the history of this progressive journal as it recognises the important contribution that Diabetes makes to the aetiology of both vascular and neurodegenerative dementia syndromes (1-3). It has been observed that diabetes in the presence of hypertension leads to a more pronounced cognitive decline (4) and that at an early stage of cognitive decline (mild cognitive impairment (MCI)), diabetes accelerates the progression of MCI to dementia (5).

Research into diabetes and cognitive decline has not been straightforward with many earlier studies being limited in their interpretation of causal relationships between diabetes and the development of dementia because of their cross-sectional nature (6). However, a large number of prospective longitudinal studies have formed a platform to shed light on these intriguing relationships (7-9). These generally confirm that dementia risk in those with diabetes is 2-3 higher than those without diabetes and this applies to both Alzheimer's Disease and vascular dementia. A large pooled analysis of 2.3m people from 14 studies (a large proportion of unpublished data) estimates that those with type 2 diabetes are at approximately 60% greater risk for the development dementia compared with those without diabetes, with the effect being strongest in women for vascular dementia (10).

A recent study of long term study of trajectories of glucose control with cognitive performance in older people with type 2 diabetes demonstrated that instability of glucose regulation over time showed worse cognitive performance and that a trajectory of stable HbA1c levels is associated with better cognitive function (11). Furthermore, a small anatomical MRI study has demonstrated a link between glycaemic variability (measured by continuous glucose monitoring) and grey matter atrophy and cognitive decline (worse learning and memory scores) in type 2 diabetes which was independent of HbA1c level and hypoglycaemia (12). In a 9-year follow up of well-functioning older adults with type 2 diabetes, worse cognitive function and greater decline were exhibited in those with poorer glucose control (13): this should prompt clinicians to aim for stable levels of glucose within an optimal range determined by consideration of multiple factors such as physical functional status, life expectancy, comorbid profile and cognitive status. A risk score for the prediction of the 10-year risk of dementia in subjects with type 2 diabetes has recently been published (14). Out of 45 candidate predictors only 6 (after age and education) were found to be strongly predictive : microvascular, cerebrovascular and cardiovascular disease, depression, diabetic foot, and acute metabolic events.

The situation in type 1 diabetes is less clear (15) and requires greater study into the similarities and differences between the underlying mechanisms seen in type 2 diabetes, what areas of cognitive performance are mainly affected, are these changes clinically relevant, and what preventative aspects are needed? Some studies in individuals with type 1 diabetes show impairments in problem solving skills or visuo-spatial ability, whilst others report changes in learning and memory or psychomotor speed but these findings are not universal (16) but in selected cases the changes seen may be sufficient to affect diabetes self -management abilities. A recent systematic review of type 1 diabetes and dementia discusses the associations in greater detail (17).

Another less investigated area has been the relationship between pre-diabetes states and cognition with some studies indicating that lower MiniMental scores and reduced verbal fluency are more common in those with diabetes and is associated with an increased risk of developing a dementia syndrome (18). Whilst not always a consistent finding, a study in postmenopausal women without diabetes showed a relationship between HbA1c level and the risk of developing MCI or dementia (19) and in the secondary analysis of the Finnish Diabetes Prevention Study (involving middle-aged overweight subjects with impaired glucose tolerance) a lower mean 2-h glucose at an oral glucose test and HbA1c predicted better cognitive performance after 9 years of follow-up post-intervention (20).

The pathophysiological basis remains uncertain but multiple factors are likely to play a part (21)including the hyperglycaemic state itself, hypoglycaemia,

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impaired neuroregulatory aspects of insulin action (leading to dysregulation of Aβ amyloid peptide, inflammation, modulating neurotransmitter release) ,microvascular disease, obesity, and elevated levels of butyrylcholinesterase activity which may predict the development of type 2 diabetes and Alzheimer's Disease (22). A recent review has concluded that tau-related neurofibrillary tangles and not amyloid-beta plaques are likely to be the pathological hallmarks of type 2 diabetes-related dementia (23). MRI imaging has revealed that the diabetic brain (mainly type 2 diabetes) is also likely to have structural abnormalities such as cerebral infarcts, smaller brain parenchyma, and more white matter hyperintensities (WMH), and temporal lobe and hippocampus atrophy compared with those without diabetes (24). Even in patients with mild cognitive impairment and diabetes, functional MRI has revealed impaired neuronal activity in those areas linked to cognition including the amydala, frontal lobe, temporal lobe and hippocampus (25) whilst another study has shown abnormalities of spontaneous brain activity in the cuneus and lingual gyrus of the occipital lobe as well (26). These studies may assist us in understanding how and why changes in the neurophysiology of the brain in diabetes may lead to cognitive decline and dementia.

What does all this mean to policy makers and the clinician involved in everyday direct clinical care? The potential public health and clinical burden of diabetes and dementia is of staggering with high global prevalence rates for both chronic disorders with dementia estimated to affect 35.6 million people worldwide in 2010 (forecast to be 65.7 million in 2030) (27) and in 2014, the number of people with diabetes had risen to 422 million, with the biggest rise seen in middle and low income countries (28). As both conditions often co-exist, it is important to determine ways to enhance detection of the two index conditions and plan care pathways within hospital and primary care settings. A recent best clinical practice statement has provided guidance on how to detect the index conditions (diabetes, dementia) in several clinical settings as case finding is usually poor, as well as providing care pathways and indicating what skills and competencies are required by those involved in direct patient care (29) . Published International Clinical Guidelines have made recommendations of care based on functional category including those with dementia (30) and stress the need for comprehensive evaluation with clinicians being required to identify other important factors that may increase the risk of cognitive decline and/or influence management and outcome such as hypoglycaemia (31), clinical depression (32, 33), and the presence of frailty (34).

As cognitive impairment leads to difficulties in diabetes self-care, it is advisable to screen for cognitive impairment routinely and opportunistically all patients aged 55 years and over with type 1 or type 2 diabetes as part of an individual plan of care. This recommendation is supported by observations from a large case control study in older people aged 65 years and over showing the impact of poor cognition on a wide range of actions, consequences and behaviours: in summary, diabetic subjects with an MMSE score <23 were significantly less likely to be involved in diabetes self-care ($P<0.001$) and diabetes monitoring ($P<0.001$), and a low MMSE score was also significantly associated with higher hospitalisation in the previous year ($P=0.001$), reduced ADL (activities of daily living) ability ($P<0.001$) and increased need for assistance in personal care ($P=0.001$) (35). A recent realist review approach to identifying what key mechanisms within the context of interventions are likely to improve outcomes in diabetes care in subjects with diabetes and dementia (36). The review concluded that the workforce needs to be better aligned with a flexible service model that prioritises quality of life, independence as well as patient and carer needs.

Prevention of cognitive decline in subjects with diabetes is a major challenge that requires well-designed clinical trials that address some of the treatment aspects of the diabetes state (hyperglycaemia ± other metabolic deficits) but also prevents or inhibits the underlying neurocognitive change. The glucagon-like peptide-1 (GLP-1) mimetics are now established glucose-lowering therapy for patients with type 2 diabetes and recently, in experimental rodent models, neuroprotective effects of GLP-1 have been demonstrated raising the possibility that they may be of benefit in neurodegenerative diseases such as Alzheimer's disease (AD) (37). Studies involving another class of anti-hyperglycaemic agents, peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists are showing promising results in Alzheimer's Disease particularly with pioglitazone rather than rosiglitazone (38, 39). TOMMORROW is a Phase III placebo-controlled delay of onset clinical trial to determine whether low doses of pioglitazone, a molecule that induces mitochondrial doubling, delays the onset of MCI-AD in normal subjects and may have great relevance to the treatment of subjects with co-morbid diabetes (40). This new area of investigation is clearly important in the future prevention of cognitive decline in diabetes mellitus.

This Editorial has meant to stimulate researchers to take a greater interest in this emerging area and at the same time encourage submissions of good quality articles to the new section. In this way, we hope that this will bring added value to the journal and our readership.

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