Cognitive Impairment and Dementia in Older Adults with Type II Diabetes Mellitus

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Abstract

The number of older adults in our societies is rapidly increasing. As a consequence of such demographic change there is set to be a large increase in age related illnesses and syndromes. One such age-related illness which attracts a great deal of media and academic attention is dementia. Similarly, in accordance with rising obesity levels, Type 2 Diabetes Mellitus (T2DM) is also rapidly increasing in prevalence. Taken together, and in the context of better medical treatment of T2DM and its complications, older adults with T2DM are living longer with T2DM, which may itself present new issues and complications in the management and treatment of this cohort. At the intersection of ageing and obesity trends, there is a wealth of evidence to suggest that a diagnosis of T2DM places older adults at increased risk of cognitive impairment and dementia. The epidemiological and neuro-pathological evidence for this risk is reviewed in the present essay. The main pathophysiological hypotheses gaining traction in the literature are reviewed and discussed, as are the effects of certain treatments to mitigate the cognitive impairment/dementia seen in older adults with T2DM. The main danger here is of a positive-feedback cycle, where cognitive impairment may result in poor control of T2DM, which may in turn lead to a deterioration in cognitive function in older adults with T2DM. The present essay, by way of literature review, addresses cognitive impairment and all-type dementia as unrecognised complications of T2DM. Such complications are of utmost importance in the context of population ageing and an increase in the number of older adults living with T2DM.
Introduction

In accordance with demographic trends, the proportion of older adults in our societies is rapidly increasing. Globally, it is predicted that at least 2 billion people will be aged 65 or older by 2050 [1]. In the UK, this translates to a doubling in the number of adults aged 65 and older between the present day and 2050 from roughly 10 to 19 million people [2]. On foot of such trends, age-related illnesses and syndromes are also set to increase in prevalence. Another trend, particularly in developed countries, which may result in a consequent increase in illness is the rising obesity “epidemic”. In America for instance, two-thirds of adults are classified as overweight or obese [3]. In the UK just over 60% of adults were classified as such in 2014 [4]. Such demographic changes mean diseases where obesity is a risk factor are set to similarly increase in prevalence.

At the intersection of these two demographic trends, there is set to be an increase in both age and obesity related disease. Prime examples of such illnesses are dementia and Type 2 Diabetes Mellitus (T2DM) respectively. Dementia is defined as an acquired global impairment of intellect, memory and personality and is divided into several types, with Alzheimer’s Dementia (AD), Vascular Dementia (VaD) and mixed AD/VaD accounting for most cases [5]. T2DM is a metabolic disorder characterised by hyperglycaemia (high blood glucose levels) and a plethora of micro and macro-vascular complications [6, 7]. Age is the most significant risk factor for the development of dementia and is an independent risk factor for the development of T2DM, for which obesity represents the most significant risk factor. To further compound projected exponential increases in the incidence of these illnesses, there is a consistent and significant literature to support the fact that T2DM, independent of age alone, increases the risk for the development of dementia. Such a risk may increase the prevalence of dementia even more in the coming years. The present essay discusses the evidence for diabetes as a risk factor for dementia, and by way of literature review, discusses some of the additional risk factors, protective factors and aetiological hypotheses gaining traction in the literature to explain this increased risk.

Type II Diabetes Mellitus (T2DM)

About 2.8% (171 million people) of the population had T2DM at the turn of the Century, which is predicted to increase to 4.4% (366 million people) of the world’s population by 2030 [8]. In addition to obesity, one of the most important risk factors for the development of T2DM is increasing age, with T2DM disproportionately affecting individuals aged 60 and older [9, 10]. Defining the needs, risks and complications of older adults with T2DM is essential in order to provide adequate care and treatment for this potentially vulnerable cohort. To this end, many
specific guidelines have been developed for the management and care of older adults with T2DM [11, 12]. In those whom develop T2DM, the prevention of diabetes related complications by measures such as blood pressure and glycaemic control, means more individuals with T2DM are surviving to an older age. In itself, this may result in the emergence of novel complications and consequences of T2DM. Cognitive impairment and an attendant increase in the prevalence of dementia may be one such complication [13].

**Dementia**

In the UK it is estimated that the prevalence of dementia will more than double over the next 30-40 years [14]. Provision of adequate care and services for this complex and vulnerable population represent a major challenge to our healthcare systems in the coming years. An important strategy in understanding how such an increase in dementia could be prevented is the exploration of risk factors for dementia and cognitive impairment. Like T2DM, age is an extremely important risk factor in the development of dementia. Whilst age increases risk for dementia and diabetes individually, there is now a plethora of evidence in the literature suggesting that the risk of dementia is further increased in those with T2DM, adding to the vulnerability and complexity of older adults with T2DM.

**Type 2 Diabetes Mellitus and Cognitive Impairment**

**Epidemiological Evidence: T2DM as an Independent Risk Factor for Cognitive Impairment and Dementia**

There is a well reported association between diabetes and cognitive impairment in older adults. Chief amongst these are prevalence studies which demonstrate an increased prevalence of all forms of dementia in patients with T2DM. In examining the link between a diagnosis of T2DM and increased risk of dementia, a note on methodology is first prudent. Early studies in the field were mainly cross-sectional in nature. Such methodology, whilst useful in highlighting potential trends, lacks the power to attribute causality. Another caveat of many studies are the potentially loose definitions of cognitive impairment and dementia. Cognitive impairment, whilst easy to quantify as a standard cut-off value on traditional batteries is not a clinical endpoint. Dementia diagnosis is a clinically definable entity and the main consideration in the present essay. Notwithstanding these methodological issues, the literature provides a plethora of high quality evidence to suggest that the risk of all type dementia (AD/VaD/mixed) is further increased in individuals with a diagnosis of T2DM.
Recent meta-analysis have been supportive of a diabetes-dementia link at the epidemiologic level, many of which consider adults with T2DM aged 65 and over [15]. Two of the earliest high quality longitudinal cohort studies demonstrating the increased risk of cognitive impairment in T2DM were the Rochester and Rotterdam studies which considered individuals aged over 45 and 55 respectively [16, 17]. Early at the turn of the Century, findings from longitudinal studies of ageing emerged and lend further support to the T2DM-dementia with findings exclusively pertaining to individuals aged 65 or older [18-20].

Individual estimates of Risk Ratio (RR) for T2DM on the risk of developing cognitive impairment vary between studies (to be expected for studies with different methodologies/designs). A recent meta-analysis of 20 medium and high quality prospective observational studies reports a RR of 1.73 (1.65-1.82) for any type of dementia, 1.56 (1.41-1.73) for Alzheimer’s Dementia and 2.27 (1.94-2.66) for Vascular Dementia [15]. These figures have been replicated across various settings and cultures to support the increased risk of all types of dementia in T2DM [21-23]. Whist many of these studies pertain to adults aged 65 years or older, it appears the predisposition may not be as strong in those aged 85 and older [24], further highlighting the need for early intervention and prevention of cognitive impairment in those with T2DM aged 65 and older.

T2DM is also linked with an increase in risk for Mild Cognitive Impairment (MCI) [25]. Further, T2DM has been shown to accelerate the progression to dementia in those individuals with MCI [26, 27]. In fact, T2DM even predisposes to MCI in middle aged individuals, which may set the stage for further cognitive decline when individuals concerned reach older age [28]. Recognition of those adults with T2DM whom have MCI is important in the prevention of further cognitive decline. Further, in those adults with T2DM and MCI recognition and management of risk factors may prevent further cognitive deterioration.

**Predictors of Cognitive Impairment in T2DM**

A rapidly growing and interesting body of literature has emerged on additional factors in patients with T2DM that may predispose to dementia. Older adults with T2DM represent a large and heterogeneous cohort, and such studies aim to uncover particular factors which may further increase risk of cognitive impairment/dementia in this population. One issue with the interpretation of such studies is the definition of cognitive impairment. Most studies correlate biological and other parameters with scores on standardised tests such as the Montreal Cognitive Assessment (MoCA), Mini Mental State Examination (MMSE) or Clinical Dementia Rating (CDR). Notwithstanding
such heterogeneity, numerous factors have been implicated in the predisposition to cognitive impairment/dementia in older patients with T2DM.

Many studies have examined the relationship between scores on standardised assessments and serological measurements. These include: cholesterol levels [29, 30], Hb1Ac [31-34], NT-proBNP [35], cortisol [36], soluble RAGE [37], Brain-Derived Neurotropic Factor (BDNF) [38] leptin levels [39] and 25-hydroxyvitamin D [40]. Similarly, measurements from urine include urine pentosidine (indicator of RAGE levels) [41], microalbuminaemia [42] and haptoglobin genotype [43]. Perhaps a composite of these tests may increase reliability and specificity in indicating older adults with T2DM whom are at risk of cognitive impairment or dementia.

Additionally, diabetes duration in terms of time since first diagnosis [34, 44-47], and severity in terms of diabetes-related complications [46, 48] are also associated with an increased risk of cognitive impairment in those with T2DM. This further highlights the impact of global demographic trends on the incidence of cognitive impairment and dementia in T2DM. With more adults living longer with diabetes coupled with a rising incidence of T2DM may result in even further increased rates of cognitive impairment or dementia. Interestingly, an association is documented between cognitive impairment and diabetic retinopathy, a clinically accessible indicator of microvascular disease, and a meta-analysis has supported such a link [49]. Further study into the sensitivity and specificity of such a clinical measure is warranted. An interesting report also details an association with olfactory epithelium function [50].

Measures of central adiposity, total fat mass, systolic blood pressure indicative of hypertension and arterial stiffness are predictive of cognitive impairment in those with T2DM [51-54]. In terms of lifestyle factors, it appears smoking may increase risk [55] and exercise use may decrease risk [46]. Use of certain medications are associated with an increase or decrease in risk, however, this is discussed further below. Many of these metabolic and haemodynamic risk factors are obtained routinely in the clinical setting, or would be simple to obtain, and the development of a test or composite of tests to predict those older adults with T2DM at risk of cognitive impairment may emerge in the coming years. Further investigation of the many detailed additional risk factors is warranted in larger populations to further stratify older adults with T2DM by dementia risk.

**Neuroimaging Findings in T2DM**

Both structural and functional neuroimaging studies spanning various modalities have been applied to the study of cognitive impairment in diabetes. There is evidence for cortical and subcortical
atrophy, hippocampal and amygdalar atrophy as well as decreased grey matter volumes in fronto-parietal areas in patients with T2DM [56-59]. Many of these are features which recapitulate imaging alterations seen in Alzheimer’s disease [60]. Some studies have looked specifically at imaging findings in those with comorbid MCI and T2DM in comparison to either factor alone and demonstrated decreased grey matter volume alterations in the medial temporal gyrus [61]. In addition, predictors of grey matter atrophy in those with T2DM have emerged and include Hb1Ac levels [62], perturbation of hypothalamic-pituitary-adrenal (HPA) axis feedback [63] and insulin resistance [64]. Many of these mirror the risk factors detailed above and the prevailing aetiological hypotheses detailed below for cognitive impairment in T2DM.

Diffusion Tensor Imaging (DTI) studies demonstrate reduced fractional anisotropy in fronto-temporal regions in those with T2DM [65]. A recent interesting study by Hsu and colleagues (2012) on cognitively intact patients with T2DM demonstrated a link between disease duration and an increase in mean diffusivity, axial and transverse diffusivity [66]. Thus, DTI studies lend support to the presence of white matter changes consistent with cognitive impairment in patients with T2DM. The finding by Hsu and colleagues (2012) is an important one in demonstrating a link between T2DM and imaging findings consistent with cognitive impairment in cognitively intact individuals. Such evidence for change at the neuropathological level in older adults with T2DM without a diagnosis of dementia or cognitive impairment further emphasises the need for early intervention and prevention in order to prevent further cognitive decline in this population.

Reduced connectivity between fronto-temporal regions and the hippocampus, reduced fronto-temporal blood flow and glucose utilisation all support the role for frontal and temporal cortex abnormalities in those with diabetes [67-69]. Such findings mirror those seen Alzheimer’s Dementia [60]. Alterations in the resting state have also been documented in those with T2DM, with MRI demonstrating altered attentional network activation in patients with T2DM [70]. Further, there are diffuse abnormalities in the amplitude of low frequency fluctuations (ALFF) in a variety of brain areas such as frontal and temporal lobes, hippocampus and the percuneus in patients with both MCI and T2DM ([71] as well as in the lingual gyrus and occipital lobe, middle temporal gyrus and middle occipital gyrus in patients with T2DM [72, 73]. In sum, the rapidly growing neuroimaging literature supports the epidemiological evidence presented above.
Pathophysiological Hypotheses Underlying the Association between Dementia and Type 2 Diabetes Mellitus

Whilst the epidemiological evidence above highlights T2DM as a risk factor for dementia, the exact mechanisms by which T2DM increases risk at the aetiological level has not been elucidated. Many theories have been put forward in the literature and are gaining significant tract, whilst others are in their infancy. A particularly memorable paper even discusses Alzheimer’s Dementia as “Type 3 Diabetes Mellitus” [74]. Both recent and classical evidence supporting the main hypotheses of the T2DM-dementia link are now discussed. Emergent hypotheses include the acute and chronic effects of hyperglycaemia and hypoglycaemia, insulin signalling abnormalities, oxidative stress, neuroinflammation and Hypothalamic-Pituitary Adrenal (HPA) axis perturbations. Whilst a significant body of literature exists to support each hypothesis individually, they are not to be seen as separate, and an integrative approach to their interpretation may better explain the aetiology of cognitive impairment in T2DM.

Glycaemic Control

Elevated blood glucose levels (hyperglycaemia) is central to T2DM both diagnostically and pathologically. Much research into the putative pathological links between T2DM and dementia have focussed on hyperglycaemia. Hyperglycaemia may impair cognition in both acute and chronic scenarios [13]. One of the most commonly cited studies supporting the role of hyperglycaemia in the T2DM-dementia link is that from the Memory in Diabetes sub-study, which found that a 1% higher glycated haemoglobin (HbA1c) was associated with a significant lower test scores in both the Digit Symbol Substitution Test (DSST) and the MMSE [75]. This study adds evidence to the link between glycaemic control and cognitive impairment previously reported in the literature [76, 77].

Interestingly, in a recent longitudinal study over 6 years in individuals with and without T2DM, higher glucose levels were associated with the incidence of all-type dementia, associated with a hazard ratio of 1.4 in over 2,000 patients [78]. In a more acute scenario, a study using a hyperinsulinemic glucose clamp to maintain glucose levels at euglycaemia or hyperglycaemia has shown defects in working memory and attention with acute hyperglycaemia in patients with T2DM [79]. Diet based glycaemic load and elevated blood glucose have also been associated with poorer performance on measures of perceptual speed, visual and spatial, as well as general cognitive ability [80]. This association of hyperglycaemia and cognitive impairment has been replicated across cultures [81, 82]. Hyperglycaemia has also been shown to accelerate the conversion from MCI to
Alzheimer’s Dementia [83], and high glucose levels (even within the normal range) has been shown to decrease frontal grey matter volumes [84].

Hypoglycaemia has been also speculated to have a role to play in the link between T2DM and dementia. This follows findings from cross-sectional studies on Type 1 Diabetes Mellitus (T1DM) which demonstrated a significant link between episodes of hypoglycaemia and cognitive impairment. However, in longitudinal designs such as in the DCCT/EDIC study, no association between hypoglycaemia and subsequent dementia was demonstrated [85]. Another study in the same year demonstrated an increase in the risk of dementia in those who had experienced three or more episodes of hypoglycaemia [86]. Interpretation of these findings is difficult, in that cognitive impairment and dementia are themselves risk factors for hypoglycaemia due to adherence issues with medication [13, 87].

Acute changes hyperglycaemia may alter cerebral blood flow and cause osmotic changes and oxidative stress in cerebral neurones [88]. The maintenance of high blood glucose is associated with the enhanced formation of Advanced Glycation End Products (AGEs). Levels of AGEs are reportedly increased in patients with T2DM and cognitive impairment [88]. Similarly, AGE levels are correlated with accelerated cognitive decline in individuals both with and without T2DM. Interestingly, the soluble receptor for AGEs (esRAGE) has been implicated as a possible protective factor in the development of MCI in patients with T2DM [37]. Interestingly, the AGE/RAGE axis was suppressed by ibuprofen treatment in a mouse model of diabetic encephalopathy, with NSAIDs such as ibuprofen known to have a protective effect on the development of dementia [89].

AGEs have also been shown to act as Damage Associated Molecular Patterns (DAMPs) which activate microglia in the CNS, the brain’s resident immune cells and microglial activation is well documented in Alzheimer’s Dementia [90]. Such activation may lead to the production of Reactive Oxygen Species (ROS) and pro-inflammatory cytokines adding further damage to neurons, potentially via mitochondrial dysfunction. Thus, the effects of hypoglycaemia on neurons may be to induce a cellular and metabolic stress through activation of the brain’s immune cells. Such a putative pathological mechanism, especially when combined with the clinical evidence above, supports the pathogenic role of hyperglycaemia in the cognitive impairment/dementia associated with T2DM [91].
Insulin Resistance

Another hallmark feature of T2DM is the resistance of tissues to the effects of insulin. Insulin is a growth factor and is rapidly transported over the Blood-Brain Barrier. The receptors for insulin are located in areas such as the hippocampus, entorrhinal cortex and frontal areas involved in memory and learning, of note when exploring the putative links between T2DM and dementia [9]. Insulin may also be produced locally within the brain [92]. In accordance with various clinical and biological evidence, Insulin Resistance (IR) is a key aetiological hypothesis in the aetiology T2DM-dementia [93, 94]. Brain IR is increasingly recognised as an independent risk factor for cognitive impairment and has been the subject of recent review [95]. IR as measured by the homeostasis model assessment of insulin resistance (HOMA-IR) has been shown to significantly correlate with cognitive performance in both patients with and without T2DM [96, 97].

Resistance to the effects of insulin is associated with the reduction in the synthesis of many proteins, including Insulin Degrading Enzyme (IDE). IDE is noted to degrade amyloid-beta, and insulin resistance may contribute to decreased IDE leading to the formulation of neuritic plaque [88]. Similarly IR may contribute to tau phosphorylation pathogenesis in AD with evidence from over 30 studies recently reviewed in the literature [98]. Such effects of insulin resistance on the neuropathological correlates of AD add further evidence to its role in linking T2DM and dementia.

Further, there is evidence of suggest that insulin resistance exists in neurons in AD. Insulin signalling in the brains of AD patients is greatly reduced measured as phosphorylation of insulin receptor substrate 1 [88]. Serum measurements of IGF1 and IGFBP3 are also shown to be reduced in patients with AD [99, 100]. Similarly, decreases in signalling pathways such as the insulin-PI3K-Akt pathway in AD patients with diabetes has also been reported [101]. Perhaps the most convincing evidence originates from a longitudinal study of over 2,000 adult men aged 50 in 1970. In this study low insulin response, as assessed by IV glucose tolerance test and HOMA-IR was predictive of AD development during a median follow up of 32 years [97].

Neuroinflammation

From the evidence discussed above, it can be seen that inflammation may have a key role to play in mediating the increased risk of cognitive impairment in older adults with T2DM. With hyperglycaemia and the attendant metabolic stress from AGEs accumulation, activation of the immune system with AGEs functioning as DAMPs may ensue. A resultant increase in pro-inflammatory cytokines and ROS may lead to a pro-inflammatory state in the diabetic brain.
Similarly, insulin resistance discussed above is linked to inflammation, particularly to increased IL-6 and C-reactive protein [102]. Thus, neuroinflammation may have a key role to play in the genesis of cognitive impairment in diabetes, serving as an intermediate in the aetiological relationship between the metabolic derangements which are so characteristic of T2DM and end organ damage to the brain which may account for the increased risk of cognitive impairment/dementia in this population.

In considering the pathology of T2DM alone, pro-inflammatory cytokines such as IL-1B has shown to be elevated in pancreatic beta cells [103]. It is noteworthy that IL-1B increases the release of insulin from pancreatic beta cells and also leads to increased expression of IL-1B driven inflammatory cytokines such as Tumor Necrosis Factor-a (TNFa), Monocyte Chemotactic Protein 1 (MCP-1) and Macrophage Inflammatory Protein 1-Alpha (MIP-1a) [104]. Similarly, pro-inflammatory cytokines such as IL-6 and TNF-a are elevated in patients with diabetes and inflammatory mediators have an important role to play in the pathophysiology of T2DM.

In examining the link between inflammation and cognitive decline, a great deal of research has been produced. Epidemiological study of cognitive decline and dementia consistently implicate circulating inflammatory mediators such as CRP and IL-6 risk factors as risk factors for dementia [14, 105, 106]. Similarly, cytokines such as TNFa are reported as raised in people with dementia and cognitive impairment [107]. For IL-1B, a genetic link has also been established between variants in the gene encoding IL-B converting enzyme and cognitive function in elderly individuals [108].

Thus, in older adults with T2DM, inflammation may be a significant aetiological player in predisposing to cognitive impairment and dementia. An interesting cross sectional study demonstrated that raised plasma levels of IL-6 and CRP were associated with poor cognitive ability in T2DM [109]. Thus, the pro-inflammatory state of T2DM resulting from the metabolic derangements of the disease may predispose to cognitive impairment, with pro-inflammatory cytokines and proteins acting as the mediators between a pro-inflammatory state and end organ damage specifically affecting the brain. The above studies are just a small taste of a much broader literature supporting the role of inflammation in both diseases individually [104, 110]. Further studies are needed to clarify the exact role of such inflammatory states on the aetiology of cognitive impairment in those older adults affected with T2DM.
Glucocorticoid Excess

Evidence has emerged demonstrating that individuals with T2DM have central dysregulation of the hypothalmic-pituitary-adrenal (HPA) axis. Findings such as raised plasma cortisol levels, increased Adrenocorticotrophic hormone (ACTH) levels and impaired dexamethasone depression populate the T2DM literature [111-113]. Such dysregulation of the HPA axis exposes the hippocampus of older adults with T2DM to elevated levels of glucocorticoids, which are well known to have deleterious effects on vulnerable hippocampal neurons [14, 114]. Thus, one attractive hypothesis in the aetiology of cognitive decline in older adults with T2DM may be that the glucocorticoid excess in patients with T2DM and the deleterious effects of such on areas known to be involved in memory formation and cognition.

An impressive animal study using insulin-deficient rats and insulin resistant mice elegantly demonstrated that diabetes impaired hippocampus dependent memory formation and synaptic plasticity, with corticosterone contributing to these effects. Interestingly, these changes were reversed when normal physiological levels of corticosterone were maintained [115]. Exogenous glucocorticoid administration is humans (or raised plasma glucocorticoids e.g in Cushing’s syndrome) is associated with affective, cognitive and psychotic disorders [116]. Similarly, individuals with dementia (specifically of the Alzheimer’s type) have raised plasma cortisol levels and low hippocampal volumes [117, 118]. Further, in individuals not suffering from dementia, alterations in HPA axis activity have been associated with cognitive decline [119]

An important study to discuss when reflecting on the role of glucocorticoid excess in the aetiology of cognitive impairment in T2DM is the Edinburgh Type 2 Diabetes Study (ET2DS). Here, in a cross sectional study of over a thousand individuals aged 60-75 living with T2DM, it was found that high fasting cortisol in the morning was associated with accelerated cognitive decline. Specifically, high cortisol levels were associated with reduced general cognitive ability with reductions in letter number sequencing and the digit symbol test [36]. Taken with the known effects of high glucocorticoid levels on hippocampal function, as well as the evidence above in the discussions on additional risk factors and neuroimaging, it appears HPA dysregulation may have a key role to play in the aetiology of cognitive decline in T2DM.

A Note on Vascular Pathology

Whilst many studies in the literature are devoted to the study of Alzheimer's Dementia or any type dementia, the risk for vascular dementia is the most increased in epidemiological studies of
cognitive impairment in T2DM. T2DM patients have a well-recognised increased risk of developing cerebrovascular disease and T2DM is one of the most consistent predictors for stroke in older adults [120]. A somewhat intuitive link here is seen in linking T2DM and vascular dementia in the well-recognised association between T2DM and micro and macro-vascular disease [114, 121].

Neuroimaging studies demonstrate that cerebral microvascular disease and is increased in patients with T2DM [122]. T2DM patients also show a decreased cerebral blood flow [120]. These effects are particularly pronounced in the older age group [123]. Conditions of ischaemia and hyperglycaemia seen in patients with longstanding T2DM may thus contribute to the cognitive impairment seen in patients with T2DM. In such a context, vascular disease and particularly small vessel disease may lower the threshold for the development of dementia [88]. Such pathology may reflect the common aetiology above, with hyperglycaemia contributing to abnormalities of small blood vessels accelerating vascular pathology as well as Alzheimer-type pathology. Dichotomizing dementia into Alzheimer vs vascular types may appear parsimonious, the reality is more complex, due to the frequent occurrence of the pathologies in older adults with cognitive impairment.

**The Effect of Cognitive Impairment on Diabetes Control**

Whilst the main thrust of the present essay has been the effect of T2DM on cognitive status, cognitive impairment and dementia may have a detrimental impact on T2DM control and treatment adherence in affected individuals. The greatest concern here is that of a positive feedback loop, where cognitive impairment leads to adverse effects of adherence, leading to poorer disease control which may worsen cognitive impairment [124]. Lower MMSE scores have been correlated with more outpatient care in one recent study [124]. In a large cross sectional study, the Health and Retirement Study Diabetes Survey, adults with greater levels of cognitive impairment were less likely to adhere to dietary and exercise measures [125]. Similarly, control of T2DM, as measured by Hb1Ac, was found to be worse in individuals with cognitive impairment in comparison to cognitively normal counterparts [126]. However, such an association may not be true for those in the mild stage of cognitive impairment [127]. Measures to aid older adults with cognitive impairment and T2DM to adhere to treatment plans may show some promise in this regard. A case history of note in the literature reports improvements in patient’s adherence and Hb1Ac levels using a medication reminder device. Such simple measures may act to abrogate the complications arising from impaired cognitive status in older adults with T2DM.

**Treatments Which Mitigate the Risk of Cognitive Impairment in T2DM**
An extensive literature has emerged on medications and interventions that may help mitigate cognitive impairment in those adults with T2DM. Much of this literature is concerned with pre-clinical models such as animal and cellular based research. These are not reviewed here. One promising area in the literature is the study of the effect of medications already used in the treatment of Diabetes on cognitive impairment in older adults with T2DM.

Insulin Resistance may have a key role in the aetiological link between T2DM and cognitive impairment. Intranasal insulin represents a potential treatment in cognitive impairment both with and without diabetes [128]. The advantage of intranasal insulin is that it takes advantage of the nasal epithelium as a transport system to the CNS. Interestingly, intranasal administration of insulin has been shown to improve memory function in both acute and chronic contexts [129, 130]. Similarly, in a clinical trial of insulin in patients with Alzheimer’s Dementia, moderate improvements were seen, and maintained at 2 months. However, the study included 64 patients with MCI and 40 AD patients, and the sample size may have limited the findings of the pilot trial [131]. Subsequent trials have demonstrated improvements in memory tasks, CSF biomarkers and in a fluorodeoxygucose PET study [132]. A subsequent trial has demonstrated that insulin was effective in the treatment of cognitive impairment only in insulin resistant individuals at baseline [133]. Thus, in those with T2DM who are insulin resistant (as part of the pathology of T2DM), intranasal application of insulin may be specifically advantageous. In fact in a recent innovative trial, Zhang and colleagues (2015) have demonstrated beneficial effects of intranasal insulin application on neuroimaging parameters known to be abnormal in those with T2DM [134]. A recent review of 8 published studies on intranasal insulin effects on cognition concludes that the limited clinical experience suggests potential benefit of this approach in bridging T2DM and dementia treatment [135].

Other medications used for T2DM at present have also demonstrated favourable effects on cognition. The thiazolidinediones, acting at the nuclear receptors in insulin sensitive tissues may favourably affect cognition [92]. This effect has been demonstrated in studies examining the efficacy of Pioglitazone in a pilot study on Alzheimer’s Disease and MCI patients with T2DM [136]. A similar effect on cognitive measures was seen for Rosiglitazone in a trial of 97 older patients with T2DM [137]. A review of the available evidence has concluded that thiazolidinediones may confer some benefit in AD patients who are IR, or have/had a diagnosis of T2DM [138]. Similar results are slowly emerging for other classes of T2DM approved medication. A retrospective longitudinal study last year for instance examining Dipeptidyl Peptidase 4 inhibitors
found that administration of these medications (in combination with glycaemic control) protected against a worsening of cognitive function [139]. Such translational observations add weight to the shared aetiology of these conditions, and highlight potential avenues for the treatment of cognitive impairment in those older adults with T2DM.

Metformin deserves special mention here. Initial cellular based reports highlight concern in that metformin was associated with an up-regulation of beta-secretase which may accelerate the production of amyloid beta [140]. Recent literature has reported that this may not be the case with metformin use associated with least risk for cognitive decline in those with T2DM [141], although reports showing increased risk also exist [142]. Interpretation of the evidence around metformin’s impact on cognitive ability of patients T2DM may be difficult, and controversy exists around findings showing an increased risk of cognitive impairment in patients [143, 144]. In the future, high quality longitudinal studies will help define the exact effect of metformin on cognitive status in those older adults with T2DM.

Other clinical and lifestyle measures have shown positive effect on cognitive status in those with T2DM. Such measures include exercise [46] and intensified glycaemic control [145]. However, dietary and exercise measures, which are essential to the control of T2DM may be particularly difficult to implement in older adults with T2DM. In summarizing the available evidence, it essential to acknowledge the effects that well established anti-diabetic medication has on cognitive function in older adults with T2DM. Coupled with prudent management of lifestyle factors such as diet and exercise, better treatment of T2DM may result in the prevention of cognitive decline and dementia as a complication of T2DM. Only long-term studies examining the effects of such measures on cognitive status will afford true insight to the benefit of such approaches in the treatment of cognitive impairment in older adults with T2DM.

Conclusions

In conclusion, there is a rich and broad body of literature demonstrating an increased risk of dementia and cognitive impairment in older adults with T2DM. Many popular hypothesis continue to be explored at the molecular and aetiological level, whilst clinically it appears that many T2DM drugs have the ability, at least based on preliminary evidence, to mitigate the cognitive impairment seen in T2DM to some degree. Cognitive impairment as a complication of T2DM is not routinely screened for in same fashion as other complications such as diabetic retinopathy. As an unrecognised complication of T2DM, cognitive impairment and dementia may have detrimental effects on medication adherence in older adults with T2DM, becoming a positive feedback cycle.
Further recognition and attention in the literature on this often unrecognised complication of T2DM in older adults is thus warranted. In the context of increasing levels of obesity in an ageing population, further attention to the treatment and management of this insidious complication of T2DM is of paramount importance to older adults in our present demography.
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