We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Neurocognitive Dysfunction and Diabetic Foot

Caroline A. Fisher

Abstract

Diabetic foot ulcers are one of the most serious complications associated with diabetes. People with diabetes experience an accelerated rate of age-related cognitive decline, and comorbid complications increase the likelihood of neurocognitive attenuation. The current body of research into neurocognitive functioning in individuals with diabetic foot ulcers is small, but suggests significantly increased rates of neurocognitive dysfunction, and that up to one quarter of this cohort have cognitive functioning consistent with dementia samples. This has implications for utilising disease self-management as the primary treatment model. Neurocognitive deficits mean that understanding, retaining, and adhering to management recommendations are likely to be difficult in this group. Further research is needed in this area to determine the specific neurocognitive profile associated with diabetic foot, including which cognitive domains are the most impacted. The provision of a framework for tailoring management strategies to assist this group with more efficacious disease management is also required.

Keywords: cognition, diabetic, diabetic foot, neurocognitive functioning, neuropsychology, self-management, ulcers

1. Introduction

Diabetes mellitus is a disorder of insulin deficiency and is categorised into two types. The primary mechanism of disease in Type 1 is the loss of pancreatic islet β-cells [1], resulting in an inability to produce insulin. The typical trio of onset of symptoms for Type 1 are excess thirst, increased appetite, and excess urine production, as well as overt hyperglycaemia [2]. The definitive cause of Type 1 diabetes is not known. However, it is believed that it is likely to be related to an immune or auto-immune system disorder in 70–90% of those affected (Type 1A), with remainder of cases considered idiopathic (Type 1B) [2]. Type 1 is most commonly diagnosed in childhood, although onset can occur at any age [2]. Type 1 is estimated to account for 5–15% of all cases of diabetes [1]. There is no cure for the condition and individuals with this disorder require the injection of insulin to survive [3].

Type 2 diabetes is generally triggered by a number of lifestyle factors including being overweight or obese, having a sedentary lifestyle and consuming a diet containing high amounts of processed and red meat, refined grains and drinks that are high in sugar [4]. It shares many of the symptoms of type 1, and also involves progressive pancreatic β-cell failure. The initial phases are characterised by changes in the bodies' response to insulin and can later progress to insufficient insulin being

produced [3]. However, it has been indicated that the mechanisms that trigger β-cell death via cytokine and nutrient changes in Type 2 are different from those that occur in Type 1 [5]. In contrast to Type 1, Type 2 diabetes can be controlled by dietary changes and oral medication, but can require the need for the injection of exogenous insulin with progression and worsening of the disease [3].

Type 1 diabetes is the most common type in children, with Type 2 very rare in those under 30 years of age [3]. The onset of Type 2 diabetes most commonly occurs in adulthood and is the most prevalent type of diabetes. Rates of both types appear to be growing with a global rise in all forms of diabetes noted over the last 40 years with the greatest magnitude of increase thought to be driven by adult Type 2 cases [6, 7]. Thus, the health burden of diabetes is becoming more pronounced, increasing the strain on health systems and resulting in an upturn in diabetes related disease burden across the world.

1.1 Diabetes complications: foot ulcers

Diabetic foot ulcers are one of the most serious complications of the disease as they can lead to amputation [8], significantly increasing disease burden [9]. They are more common in people with peripheral arterial disease, and are generally caused by repeated pressure on an area that has high rates of vertical or sheer stress in people who suffer from peripheral neuropathy [10]. Healing of foot wounds can be slow, particularly if management guidelines are not followed, with 23% of wounds still present, after 12 months [11]. Foot ulcers can occur in people with both Type 1 and Type 2 diabetes. A recent systematic review indicated that the global rate of foot ulcers in people with diabetes is 6.3% [12]. Although variance in regional prevalence rates was found, with North America and Africa having the highest rates and Europe and Oceania the lowest [12]. Individuals who develop diabetic foot ulcers tend to have a longer duration of diabetic exposure, and higher rates of hypertension, diabetic retinopathy and smoking, but lower body mass indexes [12]. Diabetic foot ulcers occur prior to lower extremity amputations in around 84% of cases, and are associated with an increased risk of death by almost two and a half times, compared to people with diabetes without ulcers [13–15]. Research utilising a large Australian sample recently indicated a five-year mortality rate of 24.6% and a 10 year mortality rate of 45.4% in individuals treated at a multi-disciplinary foot clinic for diabetic foot ulcers [16]. Foot ulcers are also consistently shown to be associated with a significant decrease in quality of life, impacting on many lifestyle areas including social functioning, employment, financial security, interpersonal relationships, psychological and physical health [17, 18].

1.2 Diabetes complications: neurological abnormalities

Despite being anatomically located at opposite ends of the body, foot ulcers and changes in brain functioning have a number of similar predisposing factors in individuals with diabetes. Co-occurring hypertension, diabetic retinopathy and current smoking are correlated with higher rates of neurological abnormalities observed through brain imaging in people with diabetes [19–21]. A systematic review of the diabetes brain imaging literature by van Harten et al. in 2006 included 55 studies the majority with predominantly middle age to early elderly cohort [22]. The review indicated that lacunar infarcts and cerebral atrophy are associated with diabetes, but that an association with white-matter lesions was unclear, due to the poor quality of the available studies in detecting subtle abnormalities of this kind. A narrative review from 2014 suggested that Type 1 diabetes was associated with small alterations in brain volume in specific areas, including frontal, temporal and posterior

cortical areas, as well as subcortical grey matter [23]. These changes appear to occur early, with volumetric changes in Type 1 diabetes detectable, relative to controls, in childhood. In Type 2 diabetes volumetric loss is also observed but tends to be most commonly found in cortical and subcortical areas surrounding the ventricles [23]. While smaller hippocampal volumes have been found, this has generally been commensurate with the magnitude of total volume loss, and thus specific atrophy of hippocampal areas (which have relevance to memory) in diabetes is not definitive.

A recent a systematic review of dynamic brain imaging investigated task and resting-state fMRI functional magnetic resonance imaging (fMRI) in diabetes. It concluded that reductions in the default mode network (DMN) connectivity are associated with diabetes [24]. The DMN is the brain network that is engaged when individuals are not actively participating in task-based pursuits (i.e. 'at rest'). Findings of abnormal network activity during task based studies were reported to be less consistent, with some studies reporting reduced brain activation in brain areas related to the task, and others over activation [24]. Neurological changes in diabetes have relevance to neurocognitive functioning and this association will be explored further in Section 2.2.

1.3 Diabetes self-management

The impact of diabetes on health, wellbeing and functioning can be seen, from head to toe, with the effect of non-optimal management of the disease having significant implications for quality of life and morbidity. The importance of diabetes self-management has been promoted within the field as a means to assist individuals with diabetes to manage their condition effectively and minimise complications [25–28]. Best practice self-management support has been identified as including; education about diabetes and treatment options; managing nutrition and exercise as part of on-going lifestyle changes; utilising prescribed medications safety to maximise their therapeutic efficacy; self-monitoring of factors such as blood glucose levels and using effective decision making to interpret the results; employing strategies to manage complications, detecting these when they do arise and treating them early and appropriately; identifying and managing psychosocial issues; and developing strategies to promote health and behaviour change that will be effective for the individual [25]. Many of these self-management strategies require a range of higher level cognitive skills to be implemented and maintained consistently. However, neurocognitive attention is associated with the disease, and neurocognitive difficulties may impact on the capacity of individuals with diabetes to effectively implement disease self-management strategies.

2. Neurocognitive functioning in diabetes

Neurocognitive abilities are localised in the brain and encompass a broad range of thinking skills including attention, concentration, processing speed, new learning and memory, language, planning, organisation, problem solving and visual-perceptual and spatial abilities. In addition to looking at skills in specific neurocognitive domains, overall measures of ability, such as intellectual assessment (IQ) can also be conducted to provide information about general cognitive functioning. Neurocognitive skills impact on daily living and deficits can effect an individual's functional and vocational capacity. Neurocognitive deficits are defining features of a number of neurological cognitions, including dementia and traumatic brain injuries, and the assessment and management of these difficulties falls within the specialty of clinical neuropsychology.

2.1 Theory of neurocognitive functioning across the lifespan in diabetes and complications

There is a relatively large body of literature that has investigated the impact of diabetes on neurocognitive functioning. In 2008, Biessels and colleagues hypothesised a framework for conceptualising the impact of diabetes on neurocognition, across the lifespan [3]. Following a thorough review of the literature available at the time, they proposed two age-related time point vulnerabilities for diabetes to detrimentally impact on neurocognitive functioning, with additional further increased risk observed in individuals with high levels of co-morbid diabetes related complications. Biessels et al. proposed that the first time period for cognitive attenuation vulnerability was during the period of neuronal maturation and brain development in childhood [3]. They suggested that those children who developed Type 1 diabetes at a younger age (i.e. between 5 and 7 years) were at higher risk of showing attenuated cognitive development, compared those who developed Type 1 later in childhood. The second age-related period of increased vulnerability to cognitive attenuation was proposed to occur at the time point were normal age-related cognitive decline begins across several cognitive domains, in middle age. Biessels et al. suggested that individuals with diabetes in middle and older age (predominantly a Type 2 cohort) are likely to show an accelerated rate of cognitive decline, relative to their age matched peers [3]. Diabetes related co-morbidities were proposed as a third variable that increased the risk of cognitive attenuation in diabetes cohorts. The primary conditions posited in this area were microvascular disease, severe hypoglycemic episodes, and hypertension [3].

The hypothesis outlined by Biessels et al. [3], continues to hold merit since it was first proposed, with subsequent findings that have been published in the last 10 years largely supporting this framework. Longitudinal data from Type 1 diabetes research (following individuals with childhood diagnoses through to youth, at 12 years follow-up) has indicated that early onset is associated with poorer sustained attention, divided attention, new learning, and mental efficiency [29]. Longitudinal data from ageing studies has indicated that in middle aged cohorts accelerated cognitive decline is observed in those who had Type 2 diabetes at study baseline, relative to non-diabetes age-matched peers [30]. Additionally, incident diabetes (those who go on to develop diabetes but have not been diagnosed at baseline) showed subtle early decline in information processing speed, which became more pronounced following diagnosis and with increasing duration of illness [30]. The Biessels et al. proposal [3] that higher rates of diabetes complications increases the risk of cognitive decline has also been supported, with several studies showing greater rates of neurocognitive attenuation in people with diabetes who also have hypertension, neuropathy, retinopathy [30–32].

Recent research has also indicated a link between diabetes, neurocognitive decline and dementia, and that the link may be stronger in women [23, 33–35]. The primary dementia syndromes associated with diabetes are Alzheimer's disease and vascular dementia. It has been suggested that the neuropathogenesis in diabetes and Alzheimer's disease may be related, and that the increased burden of small-vessel disease in diabetes can contribute to the development of a vascular based dementia [23, 33]. Dementia, as defined under the Major Neurocognitive Disorder framework within Diagnostic and Statistical Manual of Mental Disorders, is primarily a disorder of neurocognitive dysfunction [36]. As such, it is not surprising that capacity for disease self-management in people with diabetes and co-occurring dementia is diminished [33]. It has been posited that there is a bidirectional impact, whereby poor self-management, due to cognitive impairment from dementia, leads to poorer diabetes control, increasing the likelihood of further cognitive impairment [33].

As such, further investigation is needed into how to specifically target education and management strategies in this group, as they may not be able to utilise these in the same way as those with stronger neurocognitive functioning.

2.2 Neurocognitive profile in diabetes

Not all studies separate Type 1 and Type 2 diabetes cases when investigating neurocognitive functioning in adults. Where the types have been looked at individually, or in studies where the research has demarked the groups discretely, there are both similarities and differences in the profile of cognitive attenuation [37]. A systematic review of the Type 1 literature was conducted in 2005 and included 33 studies [38]. This review indicated that Type 1 diabetes is associated with attenuation in functioning on overall intelligence measures, as well as attention, psychomotor processing speed, cognitive flexibility and visual-perceptual and spatial functioning at the domain level [37, 38]. Notably however, the mean age of participants in studies included in this review most commonly fell in the 30s, with the oldest mean age of 47.6 years. Thus, the review data was mainly comprised of younger adult cohorts, and relatively little is known about the Type 1 neurocognitive profile in middle aged and older adults.

Type 2 diabetes cohorts show some similarities in their neurocognitive profile to Type 1. They exhibit attenuation in their processing speed, attention and executive functioning, but tend show a greater magnitude of decrement in memory functioning compared to Type 1 [30, 37, 39]. There is presently no seminal, overarching systematic review and meta-analysis that has attempted to synthesise the evidence base regarding cognitive functioning in adults with Type 2 diabetes, relative to controls, across all major neurocognitive domains. The most comprehensive attempt to integrate the literature was a meta-analysis published by Palta and colleagues in in 2014. This meta-analysis looked at neurocognitive functioning in six areas, across 24 studies with a total of 3351 patients with diabetes [40]. The included studies were predominantly from western countries, and there was a relatively large age range between the studies with means in the late 50s to early 80s. The results indicated that at a domain level, the largest effect size for diabetes status was seen in the areas of motor function ($d = -0.36$), executive function ($d = -0.33$) and processing speed ($d = -0.33$), followed by verbal memory ($d = -0.28$), visual memory ($d = 0.26$) and attention/concentration ($d = -0.19$). Specific neurocognitive tests were also identified that were most likely to demonstrate diabetes related cognitive attenuation. These included the dominant hand condition on the Grooved Pegboard, immediate recall on the Rey Auditory Verbal Learning Task, trails A and B from The Trail Making Test, delayed recall from the Rey-Osterreith Complex Figure task, and part 1 of the Stroop task. The research team did note, however that they were unable to stratify the results according to age, could not make any comments in regard to gender, and also noted that the results may not be representative across different ethnicity groups.

Task based fMRI studies have indicated that alterations in activation networks may be correlated with performance levels on neuropsychological assessment [24]. There is some evidence that poorer memory performances are seen in individuals with diabetes who have reduced activation in the default mode network [41]. Reduced speed on a complex trail making activity requiring set-shifting (trails B) and complex figure delayed recall has been associated with neural abnormalities in the cuneus and lingual gyrus, areas associated with inhibitory control and visual memory [42]. Thus, there is some evidence linking functional brain activation changes and poorer neuropsychological functioning in this population.

3. Neurocognitive functioning in individuals with diabetic foot ulcers

Relative to the general diabetes literature, fewer research studies have been conducted that have investigated neurocognitive functioning specifically in people with diabetes and foot ulcers [43–46]. The research that is available appears to indicate attenuated functioning, at a group level, and significant impairments in a proportion of patients. This section of the chapter reviews what is known about neurocognitive functioning in people with diabetic foot ulcers and provides suggestions for future research.

3.1 Cognitive screening and diabetic foot

Cognitive screening measures are short, easy to administer assessments that provide an overall measure of basic cognitive functioning. They generally require limited or short-duration training to administer and are utilised by a wide range of clinical disciplines. One of the most commonly administered cognitive screening measures is the Mini Mental State Examination (MMSE) [47]. A study by Marseglia et al. [43] utilised the MMSE to investigate cognitive functioning in a moderately sized cohort (n = 153) of individuals with diabetic foot complications. The sample was predominantly male (75.8%). The mean age of the cohort was 65 years (SD 10.5) and the authors further sub-grouped this cohort into patients aged under 65 years (n = 73) and those aged over 65 years (n = 80). HbA1c levels were reported at a mean of 7.7 (SD 1.4). The medium length of diabetes duration was 20 years, and a high proportion (70.6%) had undergone amputation.

In the Marseglia, et al. study [43] the mean MMSE score was found to be 24.6 (SD = 3.6), with a range of 11–30. The authors used the cut-off score derived by Kivipelto et al. [48], with scores ≤24 defined as being indicative of general cognitive function impairment. Using this criterion, 39% of the total sample demonstrated cognitive impairment. The was a significant difference by age stratification with 25% of the patients below 65 years showing impairment, compared to 53% of those above 65 years. Logistic regression indicated that foot amputation was associated with lower MMSE scores. No information was provided about which items/domains within the MMSE assessment were more commonly impaired. However, a small range of additional cognitive assessment measures were also employed in this study, and these will be reported, by domain, in Section 3.2.

A recently published study by Corbett and colleagues investigated neurocognitive functioning in individuals with diabetic foot ulcers using a newer, and increasingly widely used, cognitive screening measure, the Montreal Cognitive Assessment (MoCA) [45]. The like the MMSE, the MoCA is a quick (5–10 min) assessment tool that provides an overview of cognitive functioning, and is designed to detect cognitive decline. The MoCA provides better coverage of executive functioning, and higher-level language and visuospatial processing, relative to the MMSE, and produces less of a ceiling effect (i.e. is harder overall) [49]. The study by Corbett et al. [45] reported on MoCA and Patient Interpretation of Neuropathy (PIN) data in 30 patients with diabetic foot ulcers admitted to a specialist hospital unit for inpatient management of their foot wounds. The mean age of the study cohort was later middle age (m = 58.37 years, 10.64 SD), and the sample predominantly male (83%). Most of the cohort had type 2 diabetes (93%) of between 1 and 38 years duration (mode 10 years). The mean HBA1C level was 9.27 (SD 2.45), and there were high rates of macrovascular disease (60%) and hypertension (47%), moderate rates of nephropathy (27%) and retinopathy (23%). Thus, the cohort was younger than in the Marseglia et al. [43] study, but with poorer diabetes control, based on HbA1c results.

The education corrected total mean MoCA score in the Corbett et al. [45], study was 22.37 (SD 3.65), and range 12 to 27, with no patients achieving a full score of 30/30. Recommended MoCA cut-off scores to demark mild cognitive impairment vary from study to study [50–53]. Thus, the authors provided the percentages of participants below the full range of suggested cut-of values. A total of 87% of the cohort fell below the stringent cut-off criteria of <27, a further 77% below <26 and 43% below <23. Further, 27% of the sample had a total MoCA score of <20. This indicates that more than one quarter of diabetic foot ulcer patients in this study had a MoCA score consistent with diagnosed dementia cohorts [52, 53]. When separated into individual cognitive areas, patients most commonly made errors on items assessing short-term recall (90%), executive functioning (87%) and language (77%), while in contrast items assessing orientation showed the highest degree of accuracy (90% scoring full marks).

The results of this study also reported on patients' interpretations of their neuropathy on the PIN. Correlation analysis indicated that patients with higher MoCA scores provided more accurate responses on the Acute Foot Ulcer Onset PIN subscale. This subscale measures knowledge about how foot ulcers can develop. Thus, individuals with diabetic foot ulcers and lower cognitive functioning may have reduced understanding of how foot wounds occur.

The Australian MoCA results from the Corbett et al. [45] study can be further compared with existing studies that have used the MoCA for cognitive screening assessment in other diabetes cohorts [31, 54, 55], see **Table 1**. Participants in one of the comparison studies were Japanese inpatients receiving training on diabetes management [31], in another they were Canadian patients at diabetes education clinics [55], and in the third it is not reported where the Turkish subject group were recruited from [54]. In each comparison study foot ulcer status was not commented on, but prevalence could be expected to parallel that of global estimates of foot ulcers in people with diabetes at around 6%, with a range between 2 and 14% consistent with prevalence rates found in each of the study countries [12].

The results displayed in **Table 1** suggest that cognitive attenuation in diabetic foot ulcer individuals exceeds expectation, based on their diabetes status and age. The mean MoCA scores obtained by individuals with diabetic foot ulcers in the Corbett et al. [45] study were higher than those reported by Ozcan et al. [54] However, the mean age of the Ozcan et al. [50] study group was 13 years older. The Corbett et al. [45] MoCA results were similar to the Mori et al. [31] results—a group that had comparable HbA1c scores but a higher mean age, by 9 years. Compared to the cohort with the closest age match, Alagiakrishnan et al. [55] the Corbett et al. [43] MoCA results were notably lower.

Lead author, study year	**Ozcan, 2014**	**Mori, 2015**	**Alagiakrishnan, 2013**	**Corbett, 2019**
Mean age (SD)	71.27 (8.57)	67.3 (9.9)	59.9 (7.1)	58.37 (10.64)
Sample size	15	29	30	30
Mean HbA1c (SD)	N/A	9.6 (1.8)	N/A	9.27 (2.45)
Foot ulcer status	N/A	N/A	N/A	100%
MoCA mean (SD)	15.53 (6.18)	22.87 (3.80)*	26.45 (2.72)*	22.37 (3.65)

**Total cohort Mean and SD calculated from pooled MCI present and MCI absent groups.*

Table 1.
Comparison of MoCA Cognitive Screening scores in Older Diabetes Cohorts.

3.2 Neuropsychological assessment and diabetic foot

Screening measures such as the MoCA and similar measures like the MMSE are useful as quick and easy to administer assessments, providing an overview of cognitive functioning [56]. They are designed to identify patients who may be experiencing cognitive decline but are limited in their capacity to pin-point specific cognitive deficits and the magnitude of neurocognitive attenuation, relative to estimated premorbid cognitive functioning. Neuropsychological assessments are the gold standard for eliciting this type of in-depth information on neurocognitive functioning, and ideally, where access is available, individuals with reduced scoring on cognitive screening measures should be referred for neuropsychological assessment to accurately quantify cognitive deficits and provide information about likely causes of the cognitive dysfunction.

Notably, there are few studies that have used specialised and specific neuropsychological assessment measures in patients with diabetic foot complications. The Marseglia et al. [43] MMSE study described above, utilised a small number of focussed neuropsychological assessment tasks, in addition to cognitive screening, in their predominantly male, diabetic foot cohort. This included the Trail Making Test A & B assessing processing speed and mental flexibility, the Rey Auditory Verbal Learning Test assessing verbal memory and Ravens Coloured Progressive Matrices assessing visual reasoning skills. The overall group means, and their deviation from expected premorbid or average age-matched norms, were not reported. However, age stratified data was provided and indicated that mental flexibility/set shifting, short-term verbal recall, processing speed and visual abstract reasoning were poorer in participants over 65 years of age. Logistic regression of disease factors indicated that HbA1c levels correlated with verbal memory difficulties in all patients, and that concurrent microvascular complications, and prior amputation was associated with verbal memory attenuation in patients over 65 years of age.

A further study by Kloos et al., attempted to determine if there was an association between foot ulcer relapse rate and cognitive impairment in 59 people with diabetes and previous foot ulcers [44]. The authors found no association between cognitive performance and re-ulceration at 1 year follow-up. However, a very limited number of neuropsychology tasks were employed in this study, assessing functioning only in the areas of vocabulary knowledge, perceptual logic and processing speed. There were no tasks assessing attention, memory or executive functioning. The follow-up period was also relatively short at 12 months, and no information was provided about re-ulceration in the three patients who died during the follow-up period.

The most comprehensive study to investigate neurocognitive functioning in diabetic foot patients using a broad assessment battery was undertaken by Natovich and colleagues in 2016 [46]. To date, this is the only published study that has used a wide-range multi-domain neuropsychological assessment battery to investigate neurocognitive functioning specifically in a diabetic foot ulcer cohort. This study investigated neurocognitive functioning in a group of 99 individuals with diabetic foot ulcers, along with a comparison group of 95 people with type 2 diabetes without foot ulcers. The study design incorporated the use of a computerised cognitive testing battery, NeuroTrax, with two more commonly used pencil and paper cognitive assessment tasks (Digit-symbol substitution task from the Wechsler Adult Intelligence Scale, WAIS; and a verbal fluency task).

The two late-middle aged study groups in Natovich et al. [46] were broadly matched on demographic and health related factors. This included gender ratio (predominantly male), smoking status and depressive symptoms. However, the non-foot ulcer group were slightly older, more highly educated, and had better

diabetes control than their foot-ulcer counterparts, including significantly lower HbA1c scores, and lower hypertension, retinopathy, neuropathy, nephropathy and microvascular disease prevalence.

The neurocognitive test results from this study were age and education adjusted, in order to mitigate any impact of the mild cohort imbalances in these demographic factors [46]. The results on the NeuroTrax battery and additional pencil and paper tasks indicated significantly poorer cognitive functioning in participants with foot ulcers, compared to the non-foot ulcer group, across all activities assessing current cognitive functioning. This included scores in domains described as memory, attention and concentration, reaction time, executive functioning (with the description indicating predominantly a task of response inhibition), psychomotor speed, verbal fluency (phonemic and semantic), digit-symbol substitution, and global cognitive score (mean of domains, minus non-verbal intelligence). Post hoc adjustment for multiple comparisons was not reported in the study paper. However, when a Bonferroni correction is applied to the data, these group differences remain significant (i.e. $p < 0.005$). The only task on which a significant difference was not observed, was that estimating premorbid cognitive functioning (i.e. cognitive skills prior to any acquired neurocognitive impairment). It was further reported that global cognitive scores of the foot ulcer group differed significantly, from their estimated premorbid functioning, while the non-foot ulcer group did not. This appears to indicate generalised cognitive attenuation in the foot ulcer group.

A second important factor to consider from the data reported in the Natovich et al. [46], study is the magnitude of the differences between the foot ulcer group scores in each of the cognitive areas, relative to their estimated premorbid baseline. The results were normalised to a standard distribution (i.e. a mean score of 100–50th percentile, and standard deviation of 15–34 percentile ranks). The estimated premorbid cognition score for the foot ulcer group is reported as 96.78, which places at the 42nd percentile. None of the current cognitive functioning scores for the foot ulcer group were close to matching this. The current functioning score means ranged from as low as the 4th percentile (standard score of 72.77) for phonemic verbal fluency, to the 30th percentile (standard score of 91.76) for reaction time, with all but two results falling in the lowest quartile of functioning, for the age group. This contrasted with the non-foot ulcer group where the biggest percentile difference with premorbid cognition was 16 percentile ranks (standard score of 94.16 verses 100.19; 34th verses 50th percentile). With six out of the nine cognitive areas reported scoring within 5 percentile ranks of the premorbid estimate for this group. This indicates that attenuation in cognitive functioning in the foot ulcer group is at magnitudes of clinical significance for all cognitive areas, and likely to represent significant impairment in a number of individuals. The results also show the cognitive attenuation is generalised across areas and occurs relative to estimated premorbid abilities, age-matched normative data, and non-foot ulcer diabetic peers.

This study is a useful addition to the literature, as the first to examine neurocognitive functioning in a relatively comprehensive way, in a medium to large sample of individuals with diabetic foot ulcers. The researchers also attempted to match the sample, as closely as possible, with a non-foot ulcer diabetes comparison group. However, there are several limitations of the Natovich et al. study [46]. The first is the use of a less commonly used computerised measure of cognitive functioning, NeuroTrax. Although this measure has been reported on since 2003 the program appears to have been developed on a small normative sample, and its applicability outside studies of mild cognitive impairment and Parkinson's disease remains unclear [57, 58]. It is also unclear from the Natovich paper [46] exactly how NeuroTrax assesses functioning in each of the cognitive areas reported. For example, it is not clear what form the memory assessment takes (e.g. word list learning,

narrative stories, paired associates), and this limits its comparability to other neuropsychological and diabetes research. It would have also been useful for the authors of this study to have provided information about the percentage individuals with neurocognitive dysfunction pronounced enough to meet the criteria for dementia. An additional limitation is the data in the study are taken from a single cross-sectional time point. The field would significantly benefit from research that takes a longitudinal approach to cognitive functioning in individuals with diabetic foot ulcers to determine if the development of cognitive attenuation precedes the development of foot ulcers, or vice-versa.

3.3 Theoretical framework of neurocognitive dysfunction in diabetic foot

The results from the Natovich et al. [46], study appear to support the earlier hypothesis proposed by Biessels and colleagues [3], of cognitive ageing and diabetes comorbidities acting as correlating or catalytic factors for diabetes related cognitive deterioration. The foot ulcer group in the Natovich et al. [46] study had a mean age of 58.04 years (SD 6.87). Research indicates that normal age related cognitive decline is demonstrated from as early as 45 years onwards, and most prominently occurs in the cognitive areas of visual spatial ability, processing speed, and fine motor skills [59]. Further, the foot-ulcer group had a considerably higher level of diabetes disease burden and comorbidity relative to the non-foot ulcer diabetes comparison group, with higher HbA1c scores, and significantly increased rates of retinopathy (51.5% vs. 9.5%), neuropathy (88.9% vs. 15.8%), nephropathy (33.3% vs. 3.2%) and microvascular disease (88.9% vs. 51.6%). The results of the cognitive screening study by Corbett et al. [45] also support the idea proposed by Biessels et al. [3], with cognitive attenuation seen above expectation for age in a late 50s cohort of diabetes foot ulcer patients, with high rates of comorbidity including hypertension, retinopathy and neuropathy. Thus, diabetic foot wounds could be argued to be an important risk variable for cognitive decline in middle-aged people with diabetes.

In **Figure 1**, a graphical representation has been provided to visually illustrate the impact of diabetes, across the lifespan, for Type 1 diabetes, Type 2 diabetes, and people with diabetic foot complications, relative to normal functioning. The graph provides a representation of generalised cognitive proficiency (summed across cognitive domains) and illustrates what is known about neurocognitive functioning

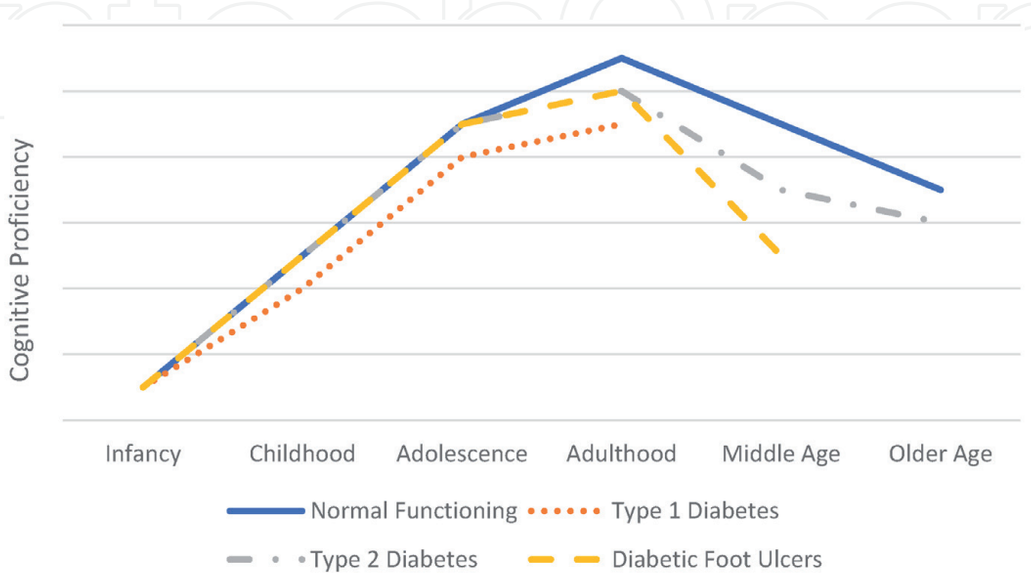

Figure 1.
Neurocognitive functioning across the lifespan.

in each of the groups, based on the currently available literature. Further research is needed to definitively characterise the magnitude of neurocognitive decline in individuals with diabetic foot ulcers, and also to determine if there are any differences in the rates and types of decline in Type 1 versus Type 2 suffers. Additional research would also be beneficial into neurocognitive functioning in Type 1 cohorts into middle and older age, as currently there are few studies that include Type 1 patients in these age groups.

3.4 Self-management

The available neurocognitive functioning results in diabetic foot ulcer samples raise a number of concerns about the capacity of this group to effectively implement self-management practices. Self-management requires the ability to adequately understand, process and recall recommendations, as well as to consistently implement these effectively in daily life. Given the rates of pronounced cognitive decrement that appear to be present in a number of diabetic people with foot wounds, it could be expected that a sizable proportion of this cohort may lack the capacity to do this. Interestingly, in 2017 a second study was published by the Natovich lead study group, that compared adherence to self-care in two diabetes samples, those with and without foot ulcers [60]. Although not specifically stated by the authors, this study appears to have utilised the same cohort of participants and controls to their neurocognitive study, described above [46], as the reported sample numbers and demographic details of participants are the same. This study employed the Summary of Diabetes Self-Care Activity self-report scale as well as two objective measures of diabetes control and adherence (BMI and HbA1C levels). The results indicated that individuals with foot ulcers were more adherent to blood tests, but less adherent to physical activity recommendations and had poor glycaemic control (HbA1c). The authors speculated that this may be due to difficulty in linking problematic glycaemic test results to changes in actual behaviour, as a result of cognitive impairment. They also suggested that the reduced physical activity in the foot-ulcer group may make glycaemic levels more difficult to control. The cognitive screening study by Corbett and colleagues [45] indicated that individuals with foot ulcers and lower cognitive functioning had reduced understanding of how foot wounds occur, relative to cognitively higher functioning participants. It would be interesting for this to be investigated further to determine if these individuals are at higher likelihood of experiencing poorer wound healing and re-ulceration in the future.

4. Conclusion

The available evidence indicates that neurocognitive dysfunction in individuals with diabetic foot ulcers is more pronounced than expected, for both their age and diabetes status. Thus, diabetic foot complications appear to be associated with cognitive impairment. The mechanistic causes of this dysfunction is likely to be related to the overall poorer diabetes control in this group, including higher HbA1c scores, and higher rates of hypertension, retinopathy, neuropathy, nephropathy and microvascular disease, relative to diabetes peers without foot ulcers. Many of these complications have been found to contribute to an increase in the prevalence of vascular dementia and Alzheimer's disease in people with diabetes. Thus, cognitive impairment in this group may represent disease burden caused by a combination of glycaemic and vascular factors, leading to accelerated neuronal death. Cognitive impairment may contribute to a 'vicious cycle' reducing the capacity of people

to effectively self-manage their diabetes and foot health, which in turn results in poorer diabetes control and an increase in complications, leading to further attenuation in cognitive functioning.

More research is needed to provide further information about the cognitive profile of individuals with diabetic foot ulcers, using a large battery of commonly utilised clinical neuropsychology assessment measures. The four existing studies have provided some useful initial information. However, additional work clearly outlining the specific domains of cognitive impairment, and the magnitude of this impairment, using commonly utilised neuropsychological tests, is required. Longitudinal research to determine whether cognitive decline increases over time in this group would be useful. Combining cognitive functioning measures with neuroimaging in the same cohort would also help to determine if cognitive impairment is associated with observable neurological abnormalities. Including psychological factors, such as the high frequency mental health conditions of depression and anxiety, as well as diabetes distress ratings, would provide information about whether psychological factors also impact on cognitive functioning, and potentially treatment adherence in this group.

Routine cognitive screening is likely to be beneficial in individuals with diabetic foot ulcers, as the available evidence indicates a high proportion will have cognitive dysfunction. Where available, individuals showing moderate to significant difficulties on screening measures should be referred for clinical neuropsychological assessment, to quantify the magnitude and specific nature of their cognitive difficulties. Neuropsychologists can also provide an individualised plan for cognitive remediation and management strategies to assist with cognitive difficulties in daily life. This may assist in improving effective self-management compliance and improve over outcomes in his group.

Conflict of interest

The authors declare no conflict of interest.

Author details

Caroline A. Fisher[1,2]

1 Allied Health – Psychology, Royal Melbourne Hospital, Melbourne, Victoria, Australia

2 The Melbourne Clinic, Melbourne, Victoria, Australia

*Address all correspondence to: caroline.fisher2@mh.org.au

References

[1] Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 diabetes mellitus. Nature Reviews. Disease Primers. 2017;**3**:1-18

[2] Atkinson M, Eisenbarth G, Michels A. Type 1 diabetes. Lancet. 2014;**383**(9911):69-82

[3] Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: A lifespan perspective. Lancet Neurology. 2008;**7**(2):184-190

[4] Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature Reviews Endocrinology. 2018;**14**:88-98

[5] Cnop M, Welsh N, Jonas J-C, Jorns A, Lenzen S, Eizirik DL. Mechanisms of pancreatic β-cell death in Type 1 and Type 2 diabetes: Many differences, few similarities. Diabetes. 2005;**54**:S97-S107

[6] Dabelea D, Mayer-Davis E, Saydah S, Imperatore G, Linder B, Divers J, et al. Prevalence of Type 1 and Type 2 diabetes among children and adolescents from 2001 to 2009 Dana. JAMA: The Journal of the American Medical Association. 2014;**311**(17):1778-1786

[7] NCD Risk Factor Collaboration. Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;**387**(10027):1513-1530

[8] Jeffcoate WJ, Harding KG. Diabetic foot ulcers. Lancet. 2003;**361**(May 3): 1545-1551

[9] Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005;**366**(9498):1719-1724

[10] Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. The New England Journal of Medicine. 2017;**376**(24):2367-2375

[11] Prompers L, Schaper N, Apelqvist J, Edmonds MJ, Ude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: Focus on the differences between individuals with and without peripheral arterial disease: The EURODIALE Study. Diabetologia. 2008;**51**:747-755

[12] Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: A systematic review and meta-analysis. Annals of Medicine. 2017;**49**(2):106-116

[13] Lepäntalo M, Apelqvist J, Setacci C, Ricco J, De Donato G, Becker F, et al. Chapter V: Diabetic foot. European Journal of Vascular and Endovascular Surgery. 2011;**42**(Dec 1):S60-S74

[14] Walsh J, Hoffstad O, Sullivan M, Margolis DJ. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. Diabetic Medicine. 2016;**33**:1493-1498

[15] Boyko E, Ahroni J, Smith D, Davignon D. Increased mortality associated with diabetic foot ulcer. Diabetic Medicine. 1996;**13**:967-972

[16] Jeyaraman K, Berhane T, Hamilton M, Chandra AP, Falhammar H. Mortality in patients with diabetic foot ulcer: A retrospective study of 513 cases from a single Centre in the Northern Territory of Australia. BMC Endocrine Disorders. 2019;**19**(1):1-7

[17] Goodridge D, Trepman E, Embil JM. Health-related quality of life in diabetic patients with foot ulcers: Literature review. Journal of Wound, Ostomy, and Continence Nursing. 2005;**32**(6):368-377

[18] Meusel LC, Kansal N, Tchistiakova E, Yuen W. A systematic review of type 2 diabetes mellitus and hypertension in imaging studies of cognitive aging: Time to establish new norms. Frontiers in Aging Neuroscience. 2014;**6**(July):1-17

[19] Schmidt R, Launer L, Nilsson L-G, Pajak A, Sans S, Berger K, et al. Magnetic resonance imaging of the brain in diabetes. 2004;**53**:687-692

[20] Hankey GJ, Anderson NE, Ting RD, Veillard AS, Romo M, Wosik M, et al. Rates and predictors of risk of stroke and its subtypes in diabetes: A prospective observational study. Journal of Neurology, Neurosurgery, and Psychiatry. 2013;**84**(3):281-287

[21] Geijselaers SLC. Cognitive Dysfunction: At the Crossroads of Glucose Metabolism and Vascular Function. Maastricht: Maastricht University; 2016

[22] Van Harten B, De Leeuw FE, Weinstein HC, Scheltens P, Biessels GJ. Brain imaging in patients with diabetes: A systematic review. Diabetes Care. 2006;**29**(11):2539-2548

[23] Biessels GJ, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: What can we learn from MRI? Diabetes. 2014;**63**(7):2244-2252

[24] Macpherson H, Formica M, Harris E, Daly RM. Brain functional alterations in Type 2 diabetes—A systematic review of fMRI studies. Frontiers in Neuroendocrinology. 2017;**47**(June 2017):34-46

[25] Funnell MM, Brown TL, Childs BP, Haas LB, Hosey GM, Jensen B, et al. National standards for diabetes self-management education. Diabetes Care. 2008;**31**:S97-S104

[26] Kisokanth G, Prathapan S, Indrakumar J, Joseph J. Factors influencing self-management of diabetes mellitus: A review article. Journal of Diabetology. 2013;**3**(1):1-7

[27] Funnell MM, Anderson RM. Empowerment and self-management of diabetes. Clinical Diabetes. 2004;**22**(3):123-127

[28] Haas L, Maryniuk M, Beck J, Cox CE, Duker P, Edwards L, et al. National standards for diabetes self-management education and support. Diabetes Care. 2012;**35**:2393-2401

[29] Lin A, Northam EA, Rankins D, Werther GA, Cameron FJ. Neuro-psychological profiles of young people with type 1 diabetes 12 yr after disease onset. Pediatric Diabetes. 2010;**11**(4):235-243

[30] Spauwen PJJ, Köhler S, Verhey FRJ, Stehouwer CDA, Van Boxtel MPJ. Effects of type 2 diabetes on 12-year cognitive change: Results from the Maastricht Aging Study. Diabetes Care. 2013;**36**(6):1554-1561

[31] Mori Y, Futamura A, Murakami H, Kohashi K, Hirano T, Kawamura M. Increased detection of mild cognitive impairment with type 2 diabetes mellitus using the Japanese version of the Montreal Cognitive Assessment: A pilot study. Neurology and Clinical Neuroscience. 2015;**3**(3):89-93

[32] Ogurel T, Oıurel R, Özer M, Türkel Y, Daı E, Örnek K. Mini-mental state exam versus Montreal Cognitive Assessment in patients with diabetic retinopathy. Nigerian Journal of Clinical Practice. 2015;**18**(6):786-789

[33] Ojo O, Brooke J. Evaluating the association between diabetes, cognitive decline and dementia. International Journal of Environmental Research and Public Health. 2015;**12**:8281-8294

[34] Chatterjee S, Peters SAE, Woodward M, Arango SM, Batty GD,

Beckett N, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: A pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes Care. 2016;**39**(2):300-307

[35] Ahtiluoto S, Polvikoski T, Peltonen M, Solomon A, Tuomilehto J, Winblad B, et al. Diabetes, Alzheimer disease, and vascular dementia. Neurology. 2010;**75**(13):1195-1202

[36] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). USA: American Psychiatric Pub; 2013

[37] McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. Lancet. 2012;**379**(9833):2291-2299

[38] Brands AM, Biessels GJ, De Haan EH, Kappelle LJ, Kessels RP. The effects of type 1 diabetes on cognitive performance. Diabetes Care. 2005;**28**(2005):726-733

[39] Ruis C, Biessels GJ, Gorter KJ, Van Den Donk M, Kappelle LJ, Rutten GEHM. Cognition in the early stage of type 2 diabetes. Diabetes Care. 2009;**32**(7):1261-1265

[40] Palta P, Schneider ALC, Biessels GJ, Touradji P, Hill-Briggs F. Magnitude of cognitive dysfunction in adults with type 2 diabetes: A meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. Journal of the International Neuropsychological Society. 2014;**20**(3):278-291

[41] Chen Y, Liu Z, Wang A, Zhang J, Zhang S, Qi D, et al. Dysfunctional organization of default mode network before memory impairments in type 2 diabetes. Psychoneuroendocrinology. 2016;**74**(2016):141-148

[42] Cui Y, Jiao Y, Chen YC, Wang K, Gao B, Wen S, et al. Altered spontaneous brain activity in type 2 diabetes: A resting-state functional MRI study. Diabetes. 2014;**63**(2):749-760

[43] Marseglia A, Xu W, Rizzuto D, Ferrari C, Whisstock C, Brocco E, et al. Cognitive functioning among patients with diabetic foot. Journal of Diabetes and its Complications. 2014;**28**(6):863-868

[44] Kloos C, Hagen F, Lindloh C, Braun A, Leppert K, Muller N, et al. Recurrent foot ulcers in patients with diabetes and neuropathy. Diabetes Care. 2009;**32**(5):894-896

[45] Corbett C, Jolley J, Barson E, Wraight P, Perrin B, Fisher C. Cognition and understanding of neuropathy of inpatients admitted to a specialized tertiary diabetic foot unit with diabetes-related foot ulcers. The International Journal of Lower Extremity Wounds. 2019;**18**(3):294-300

[46] Natovich R, Kushnir T, Harman-Boehm I, Margalit D, Siev-Ner I, Tsalichin D, et al. Cognitive dysfunction: Part and parcel of the diabetic foot. Diabetes Care. 2016;**39**(7):1202-1207

[47] Folstein M, Folstein S, McHugh P. Mini-mental state: A practical method of grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975;**12**:189-198

[48] Kivipelto M, Helkala EL, Hänninen T, Laakso MP, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology. 2001;**56**(12):1683-1689

[49] Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Relationship between the Montreal cognitive assessment and mini-mental state examination for assessment of mild cognitive impairment in older adults. BMC Geriatrics. 2015;**15**(1):1-9

[50] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005;**53**(2):695-699

[51] Carson N, Leach L, Murphy KJ. A re-examination of Montreal Cognitive Assessment (MoCA) cutoff scores. International Journal of Geriatric Psychiatry. 2018;**33**(2):379-388

[52] Smith T, Gildeh N, Holmes C. Validity and utility in a memory clinic setting. Revue. 2007;**52**(5):329-332

[53] Costa AS, Reich A, Fimm B, Ketteler ST, Schulz JB, Reetz K. Evidence of the sensitivity of the MoCA alternate forms in monitoring cognitive change in early Alzheimer's disease. Dementia and Geriatric Cognitive Disorders. 2014;**37**(1-2):95-103

[54] Özcan T, Demir EY. Investigation the cognitive impairment in diabetes mellitus type 2 with moca test. African Journal of Psychiatry (South Africa). 2014;**17**(6):13-15

[55] Alagiakrishnan K, Zhao N, Mereu L, Senior P, Senthilselvan A. Montreal cognitive assessment is superior to standardized mini-mental status exam in detecting mild cognitive impairment in the middle-aged and elderly patients with type 2 diabetes mellitus. BioMed Research International. 2013;**2013**:1-5

[56] Karan SN. Assessment of the cognitive status in diabetes mellitus. Journal of Clinical and Diagnostic Research. 2012;**6**(10):1658-1662

[57] Dwolatzky T, Whitehead V, Doniger GM, Simon ES, Schweiger A, Jaffe D, et al. Validity of a novel computerized cognitive battery for mild cognitive impairment. BMC Geriatrics. 1 Dec 2003;**3**(1):4

[58] Schweiger A, Doniger GM, Dwolatzky T, Jaffe D, Simon E. Reliability of a novel computerized neuropsychological battery for mild cognitive impairment. Acta Neuropsychologica. 2003;**1**:407-413

[59] Hoogendam YY, Hofman A, Van Der Geest JN, Van Der Lugt A, Ikram MA. Patterns of cognitive function in aging: The Rotterdam Study. European Journal of Epidemiology. 2014;**29**(2):133-140

[60] Natovich R, Harman-boehm I, Margalit D, Cukierman T. Adherence to self-care among individuals with diabetes with and without diabetic foot complications: Objective and self-report measures. Diabetes Management. 2017;**7**:234-239