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Review

Diabetes mellitus in the young and the old: Effects on cognitive functioning across the life span

van Duinkerken Eelco[a,b,c,*], Christopher M. Ryan[d]

[a] Epilepsy Center, Instituto Estadual do Cérebro Paulo Niemeyer, Rio de Janeiro, RJ, Brazil
[b] Department of Medical Psychology, Amsterdam University Medical Centers, Free University, Amsterdam, the Netherlands
[c] Amsterdam Diabetes Center, Department of Internal Medicine, Amsterdam University Medical Centers, Free University, Amsterdam, the Netherlands
[d] Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

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ABSTRACT

Mild to moderate cognitive decrements are a well-known phenomenon associated with diabetes mellitus. In this review, we provide an overview of the cognitive consequences of type 1 and type 2 diabetes based on hallmark studies that follow patients over an extended period of time. In patients with type 1 diabetes, cognitive dysfunction appears soon after diagnosis and can be found in individuals of any age. The magnitude of these effects is generally modest, although their severity is especially pronounced in those with early onset type 1 diabetes (diagnosis before 7 years of age) or those who have developed microvascular disease, such as proliferative retinopathy. Rates of type 2 diabetes have increased dramatically over the past 20 years, in part driven by the world-wide epidemic of obesity, and this form of diabetes is appearing at a progressively younger age. Again, cognition may be disrupted, particularly in those who are in poorer glycemic control, and there is some evidence to suggest that with increasing diabetes duration, the rate of cognitive decline is accelerated and the risk of dementia is increased significantly.

1. Introduction

Brain function and structure are disrupted in individuals with diabetes mellitus. The nature and extent of these effects are now known to be influenced by a variety of factors, including type of diabetes (type 1; type 2), age at onset of diabetes, disease duration, degree of glycemic control, presence or absence of comorbid conditions like hypertension and obesity, occurrence of micro- and macrovascular complications (McCrimmon et al., 2012; Ryan et al., 2016b). Because diabetes is a chronic metabolic disease that can affect children and adults over an extended period of time, one might expect to see dramatic changes in the appearance and severity of neurocognitive dysfunction across the lifespan. Our goal is to examine the development of these changes, track them over time, and identify biomedical variables that are believed to influence the risk of decline as individuals grow older. This is a highly selective review that focuses on longitudinal research that measures cognition in the same individuals over time, or examines cross-sectional data at different ages in similar, well-defined cohorts. Because the two major forms of diabetes (type 1 [T1D] and type 2 [T2D]) have different origins, manifestations, and long-term outcomes, we describe their neurocognitive consequences and temporal course separately.

2. Type 1 diabetes

2.1. Disease characteristics

Type 1 diabetes makes up somewhat < 10% of all cases of diabetes, with an estimated prevalence in the United States of 1.3 million in 2017 (Bullard et al., 2018). This metabolic disorder most often develops during childhood and adolescence in otherwise healthy individuals and is characterized by a relatively sudden clinical onset that is secondary to an autoimmune reaction that leads to destruction of insulin-producing pancreatic beta cells. In the absence of endogenous insulin, blood glucose levels increase abnormally and may eventuate in an acute metabolic crisis (diabetic ketoacidosis; DKA). On the other hand, too much insulin, or a failure to balance insulin dose with exercise and carbohydrate intake, can trigger an episode of severe hypoglycemia, when blood glucose values fall below 54 mg/dl (3.0 mmol/ml) (American Diabetes Association, 2017). The goal of modern treatment is to keep blood glucose levels as close to the normal range as possible with multiple daily insulin injections. A patient's success is indicated by their

* Corresponding author at: Epilepsy Center, Instituto Estadual do Cérebro Paulo Niemeyer, Rua do Rezende 156, Centro, Rio de Janeiro, RJ CEP 20230-024, Brazil.
E-mail address: e.vanduinkerken@amsterdamumc.nl (E. van Duinkerken).

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glycosylated hemoglobin A1c value (HbA1c): the lower the value, the better the degree of glycemic control and the lower the risk of developing vascular complications that affect the retina, kidney, heart and brain.

Treatment regimens have evolved dramatically over the past 30 years, from one or two insulin shots taken about the same time daily, to a far more intensive management strategy that requires monitoring blood glucose values frequently and using that information to correspondingly adjust the dose and timing of multiple daily insulin injections or a continuous infusion insulin pump. These treatment changes are associated with a reduced incidence of clinically significant micro- and macrovascular complications, as well as with increased longevity (DCCT/EDIC Research Group, 2009). However, for the researcher studying the natural history of cognitive change over time, these changes also make it more difficult to draw conclusions about how diabetes per se affects cognition across the lifespan. Individuals diagnosed before the 1990s, prior to the widespread use of self-blood-glucose monitors and the introduction of intensive insulin therapy, were more likely to experience prolonged episodes of very high blood glucose levels, more episodes of recurrent severe hypoglycemia, and more dramatic fluctuations in blood glucose during their lifetime. They were also more likely to develop microvascular complications at a somewhat earlier age. Because all of those factors have been found to adversely affect brain function and structure to some extent, it is possible that those individuals recruited into research studies 20 or 30 years ago may show somewhat different neurocognitive trajectories compared to those studied within the past 5 to 10 years.

2.2. Neurocognitive phenotypes

Results from several meta-analyses of > 15 cross-sectional pediatric studies suggest that there are 2 distinct phenotypes that are associated with diabetes age at onset (Gaudieri et al., 2008; Tonoli et al., 2014). As a group, those diagnosed within the first 4 to 6 years of life (the early onset phenotype) show small to medium standardized effect sizes (Cohen's d) when compared to healthy peers without diabetes in virtually all cognitive domains, including learning and memory ($d = -0.5$), attention and executive functions ($d = -0.4$), psychomotor speed ($d = -0.37$), and verbal intelligence ($d = -0.35$). Differences of this magnitude may be clinically significant and may have an impact on performance in the classroom and workplace (Biessels et al., 2008; Gaudieri et al., 2008). On the other hand, those diagnosed after the age of 6 years (later onset phenotype), show much smaller differences on a more limited set of cognitive domains, when compared to their healthy peers ($d < 0.2$) For these individuals, verbal intelligence and psychomotor speed are most consistently affected, while executive functions are only sometimes affected, and learning and memory are usually intact.

In contrast, T1D adults show somewhat larger effect sizes, particularly on measures of verbal intelligence ($d = -0.8$), psychomotor efficiency ($d = -0.6$), attention ($d = -0.35$), and cognitive flexibility / executive functioning ($d = -0.5$), with learning and memory skills generally unaffected (Brands et al., 2005). Although this meta-analysis of T1D adults was unable to ascertain the differential influence of early age at onset on cognition, it did note that the higher rates of clinically significant micro- and macrovascular complications in adults contributed to the larger effect sizes, whereas episodes of recurrent hypoglycemia did not.

From our perspective of having studied cognitive functioning in both children and adults over the past 40 years, the “core” or fundamental diabetes-associated cognitive dysfunction – regardless of age at onset – appears to be slowed information processing. This mental slowing appears early in the course of the disease – certainly within the first 2 year after diagnosis (Northam et al., 1998; Schwartz et al., 2014), and because of the way neuropsychological tests are designed, may affect results from a broad array of cognitive tests because so many include components that depend on mental flexibility and the rapid integration of information. This is particularly true of neuropsychological tests assessing attention, executive functioning, problem-solving, and intelligence.

2.3. Cognitive changes over time

2.3.1. School-aged children and adolescents

If the metabolic and biomedical changes associated with T1D trigger detectable cognitive dysfunction within the first 2 or 3 years of life, one would predict that with increasing disease duration, children with T1D would show a gradual decline in cognition as they grow older and continue to experience dramatic fluctuations in blood glucose levels, incur episodes of severe hypoglycemia, and begin to develop microvascular damage secondary to prolonged hyperglycemia. Surprisingly, results from several longitudinal studies do not support that prediction. Despite the recruitment of somewhat different cohorts of children and adolescents, and the use of different cognitive measures and highly variable follow-up times, multiple research groups have succeeded in demonstrating only modest cognitive decline over time, and then, only on a limited set of cognitive domains. At least in those individuals first studied during childhood or adolescence, there is no evidence that 10 or even 25 years of diabetes is associated with widespread, inexorable, and profound cognitive deterioration.

Evidence for that conclusion comes from a number of studies, foremost of which is the Melbourne Longitudinal Study. This group recruited 124 children, 3 to 14 years of age, newly diagnosed with T1D and seen at the Royal Children's Hospital between September 1990 and December 1992. A representative sample of 129 “well’ children, similar in age (mean = 8.9 yrs), was also recruited. Subjects completed a battery of cognitive tests 3 months after disease onset, and again at 2, 6, and 12 years, using developmentally-appropriate measures at each assessment. No between-group differences were evident at study entry (Northam et al., 1995), but by 2 years, subjects with diabetes – particularly those diagnosed before 5 years of age, showed smaller age-related improvements in performance than control subjects and earned significantly lower scores on tests of vocabulary knowledge, non-verbal problem-solving, speed of processing, and learning (Northam et al., 1998). Six years after disease onset, small (Cohen's $d = \sim 0.3$) between group differences were evident on a number of cognitive domains (Northam et al., 2001) including attention, processing speed, and executive skills, but again, these effects were most pronounced in those with an earlier onset of diabetes. At year 12 (mean age = 21 yrs), when assessed with a different but comprehensive battery of neuropsychological tests, both the breadth and magnitude of between-group differences was more limited, with only working memory skills affected (Lin et al., 2010). Over the course of the study, a similar decline in full scale IQ was seen in both groups (-6.1 for T1D vs. -5.6 for controls). However, within the T1D group, when age at onset was examined, those with an earlier onset showed a larger, clinically significant decline (-11.4 points); similarly, those with a history of hypoglycemic seizures showed a somewhat larger decline (-7.1) vs no seizure (-5.4) (Lin et al., 2015). What is particularly instructive about these findings is that certain factors, like onset age or history of seizure, appear to be more strongly associated with decline than duration of disease, although subjects in very poor glycemic control (lifetime HbA1c ≥ 9.0% for ≥33% of lifetime glycemic measurements) were more likely to show poorer performance on certain tasks.

The brain substrate underlying these findings remains poorly understood, but magnetic resonance imaging (MRI) and magnetic resonance spectroscopy at year 12 identified differences in brain development. Those in the T1D group had relatively lower gray matter volume in multiple brain regions, and lower *N*-acetylaspartate and higher myoinositol and choline in frontal lobes and basal ganglia that are indicative of reduced neuronal number, gliosis, and demyelination.

Cognitive changes over time in adolescents with T1D have also been

assessed in the Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes and Its Complications (EDIC) (Musen et al., 2008). Between 1983 and 1989, 175 adolescents, 13 to 19 years of age (mean = 16 yrs), were recruited and followed for an average of 18 years. All completed an extensive 4-h neuropsychological assessment that covered 8 cognitive domains: problem-solving, learning, immediate memory, delayed recall, spatial information-processing, attention, psychomotor speed and mental efficiency, and simple motor speed. Over time, performance was either essentially unchanged (i.e., showed a decline < 0.2 Z score units) or improved somewhat. Neither treatment group (intensive vs. conventional insulin therapy) nor cumulative number of severe hypoglycemic events were associated with change in any cognitive domain, but degree of glycemic control predicted psychomotor and mental efficiency. Subjects in the highest HbA1c tertile (> 9.5%) showed a small but statistically significant decline (Z change = −0.28), relative to subjects in average (Z change = 0.18) or better (Z change = 0.33) glycemic control.

Heretofore unpublished data from a 25-year follow-up of participants in the Children's Hospital of Pittsburgh Diabetes Study also shows modest changes in cognition over time, with effects being largest in those with an early onset of diabetes and/or a history of microvascular disease (retinopathy). The original study recruited 125 older children and adolescents in 1980 and 1981 with T1D (mean age = 14.5 yrs) and a comparable group of 83 siblings and friends without diabetes, and found that those with an early onset of diabetes (diagnosis before age 6) showed evidence of mild cognitive impairment on virtually all cognitive domains (Ryan et al., 1985). Twenty-five years later, 66 subjects with T1D and 32 healthy controls were located and re-evaluated (Ryan, unpublished data). Those assessed at year 25 were 38 years old, on average, and had similar baseline verbal IQ scores (110) and age at diagnosis (6.2 yrs) as those not evaluated. Early onset subjects had higher rates of retinopathy than those with a later onset of diabetes, and also had somewhat higher glycosylated hemoglobin values (8.26% vs. 7.79%), but did not differ on measures of depression. Cognitive testing revealed that both the early and later onset subjects were significantly slower than control subjects on measures of psychomotor speed and mental flexibility, and the early onset subjects (but not the later onset subjects) performed more poorly on measures of visual information processing. No differences were evident on measures of learning and memory or on measures of executive functioning. Fig. 1 illustrates the

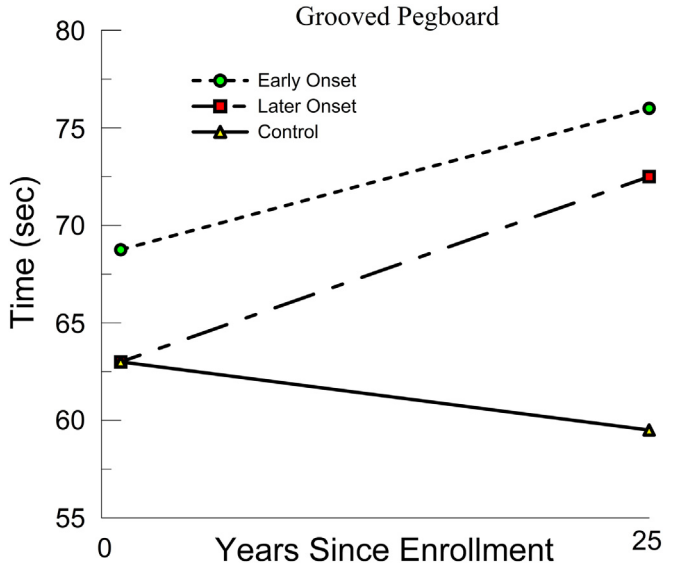

Fig. 1. Change in time to complete Grooved Pegboard with the dominant hand over a 25-year follow-up period in early-onset and later-onset subjects with T1D, and in healthy control subjects participating in the Children's Hospital of Pittsburgh Diabetes Study (Ryan, unpublished manuscript).

25-year change on the Grooved Pegboard, a psychomotor task found to be especially sensitive to diabetes-related changes. Regardless of onset age, individuals with T1D show a consistent slowing over time (~10%), as compared to control subjects who remain essentially unchanged, or performed somewhat faster.

Because there is now evidence to suggest that cognitive dysfunction in people with diabetes may be correlated with the degree of retinopathy (Ding et al., 2008; Ryan et al., 2003), analyses examined the relationship between performance on the Grooved Pegboard test, demographic variables and microvascular complications. While baseline verbal IQ predicted 7% of the variance (R^2 change = 0.07), and systolic blood pressure predicted 7% of the variance, retinopathy predicted 24% of the variance ($p < .001$). Age at onset (early vs. late) was not a predictor after systolic blood pressure and retinopathy was included in the analyses.

Taken together, this work indicates that > 25 years after diagnosis, adults with a childhood-onset of T1D subjects tend to show, at most, relatively modest cognitive decline over time, with comorbid medical conditions, particularly microvascular disease, contributing significantly to the risk of decline. Furthermore, when decline occurs, it tends to be limited to one or two cognitive domains; not all cognitive skills are adversely affected. The strong relationship between retinopathy and cognitive decline over time suggests that structural and functional alterations in the cerebral microvasculature may contribute to these cognitive changes. This is a very plausible possibility because both the retinal and cerebral microcirculation are homologous in terms of their embryologic origin, anatomical features and physiological characteristics, and a growing body of research has demonstrated that digital retinal image analysis can noninvasively evaluate the integrity of the cerebral microvasculature in individuals with cerebrovascular disease (Patton et al., 2005). Indeed, a direct link between proliferative retinopathy and cerebral microvascular damage has been established in middle-aged patients with T1D (Woerdeman et al., 2014).

Changes in cognitive functioning from childhood through adulthood have also been examined in a relatively small study that focused on children and adolescents with a history of severe hypoglycemia and/or an early onset of diabetes. The Trondheim University Hospital Study recruited 28 children with diabetes (mean age = 13 in 1992–1993), approximately half of whom had experienced at least 1 episode of severe hypoglycemia (SH); an equal number of demographically similar children without diabetes were also evaluated (Åsvold et al., 2010). At study entry, those with a history of SH performed more poorly than control subjects (overall mean = −0.7 SD units), and these effects were most pronounced in subjects who experienced their first SH episode before age 6; subjects without SH showed minimal effects relative to controls (−0.3 SD units). When evaluated 16 years later, a similar pattern of results was noted with the SH group performing worse than controls (−1.0 SD units), whereas those without SH showed no overall difference (−0.1 SD units). Analyses of cognitive changes from childhood to adulthood showed minimal additional decline (relative to controls) in either the SH group (−0.3 SD units) or the no-SH group (−0.2 SD units); the only cognitive domain that showed a statistically significant decline was problem-solving; all others were non-significant. However, whether these changes are actually caused by hypoglycemia is difficult to determine in this study, since those subjects with SH were younger at diabetes onset than those without SH and may have experienced early and prolonged periods of hyperglycemia.

All of the studies described above examined the trajectory of change over many years as children transition to adulthood. To evaluate whether meaningful cognitive changes appear earlier in the lifespan, during the transition from early- to later-childhood, or from later-childhood to adolescence, a very recent study from Washington University in St. Louis assessed 61 children with T1D, 4 to 16 years of age (mean = 11.6 yrs), and 28 nondiabetic siblings 3 times over a 5.5 year period (Kirchhoff et al., 2017). All participants with diabetes had received insulin therapy for at least 2 years prior to the first

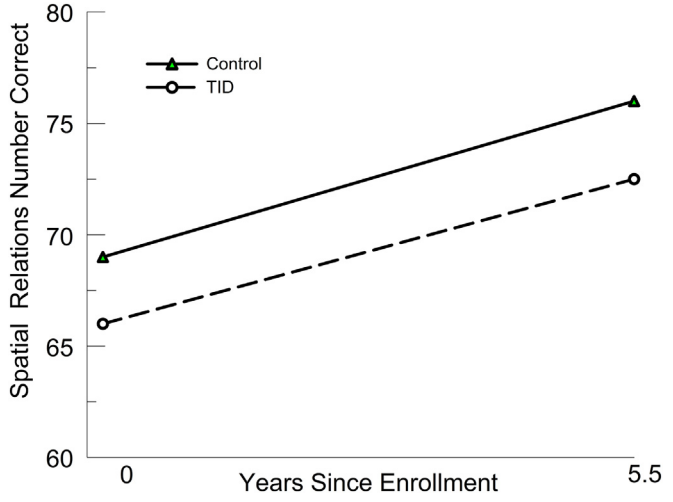

Fig. 2. Group differences in visual-spatial cognitive performance. Individuals with T1D scored lower on the Spatial Relations task than sibling controls through the duration of this study.
From Kirchhoff et al., 2017, used with permission.

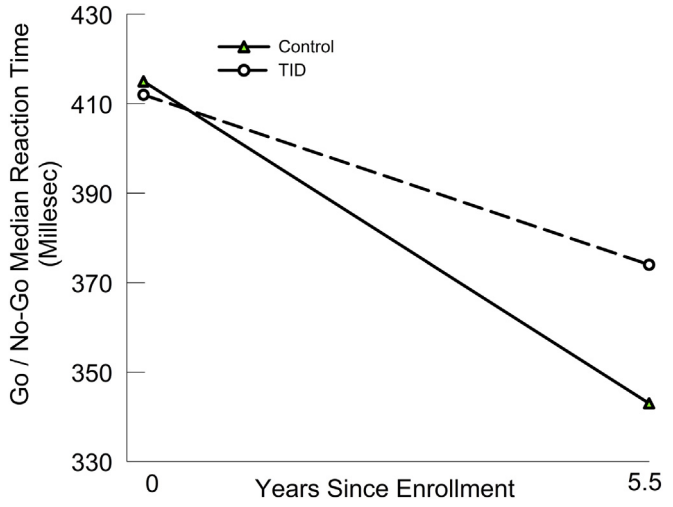

Fig. 3. Group differences in within-person changes in Go / No-Go task median reaction times. The median reaction times of individuals with T1D did not improve as much over time as their siblings.
From Kirchhoff et al., 2017, used with permission.

cognitive assessment, and none had been diagnosed with retinopathy, nephropathy or neuropathy. Two somewhat different patterns were observed. First, compared to subjects without diabetes, those with T1D were consistently poorer on visuospatial and delayed memory tasks at both study entry and 5.5-year follow-up, but both showed similar improvements over time. This is illustrated in Fig. 2 and is consistent with the hypothesis that events around the time of diabetes onset serve as the initial, and perhaps primary, insult that alters brain morphology and development, leading to a permanent, relatively mild, dysfunction in certain cognitive domains, that do not worsen appreciably over time (Ryan, 2008). Second, on other measures like a speeded decision-making go/no-go task, a group x time interaction was observed, with the 2 groups performing comparably at time 1, but by time 2, the T1D group showed relatively less improvement over time (Fig. 3), suggesting that normal developmental processes underlying this executive functioning task are delayed somewhat. Similar patterns have been noted in the long-term follow-up studies from the Melbourne and Pittsburgh research groups. Because different cognitive skills mature at different rates, it is not surprising to find varying patterns of change over time, even within the same study.

There is now no doubt that T1D may alter brain development relatively soon after diagnosis, but these brain changes may have only negligible effects on measures of cognitive functioning early on. This is ably demonstrated by a series of studies conducted by the DirecNet (Diabetes Research in Children Network) group, which studied 144 younger children (mean age = 6.9 years) diagnosed with diabetes early in life (mean age at onset = 4.1 yrs.; 67% diagnosed before 5 years of age) and 72 similar children without diabetes. Participants were followed over an 18-month period and assessed with detailed age-appropriate cognitive testing and high-resolution neuroimaging (Aye et al., 2019; Cato et al., 2016; Mauras et al., 2015). Initial analyses showed no between-group differences over time on measures of cognition, including executive function, but children with T1D showed slower total gray and white matter growth than healthy comparison subjects. Within the T1D sample, slower neurodevelopment was associated with higher cumulative hyperglycemia and glucose variability, but not hypoglycemia (Mauras et al., 2015). Subsequent analyses of the cognitive data indicated that a history of DKA was associated with lower verbal IQ, and greater total hyperglycemia exposure was associated with poorer performance on measures of executive function for subjects with T1D (Cato et al., 2016).

Taken together, the multiple studies that have followed children and adolescents over many years with diverse measures of cognition ultimately reach the same conclusion: significant cognitive deterioration is uncommon, but when modest cognitive changes are seen, they are most likely to be found in those with an early onset of diabetes and a history of chronic hyperglycemia and/or microvascular complications. Most, but not all studies, have failed to find strong evidence that severe hypoglycemia per se is associated with poorer cognitive outcomes, but that may be because severe hypoglycemia and chronic hyperglycemia are often confounded. Following an episode of severe iatrogenic hypoglycemia, many patients (or their parents) attempt to avoid future episodes by keeping blood glucose levels higher than average.

2.3.2. Young adulthood and middle-age

Surprisingly few studies have assessed cognition in T1D adults over an extended time period. The largest study, with the longest follow-up, remains the DCCT. In addition to following 175 adolescents over approximately 18.5 years, the DCCT measured cognitive changes in 969 adults, 19 to 39 years of age at study entry, over that same period (DCCT/EDIC Research Group, 2007). Modest changes were evident for the combined sample of 1144 subjects on only 3 domains: delayed recall (−0.25 Z units), visuospatial (−0.28 Z units), and psychomotor efficiency (−0.25 Z units). Because healthy comparison subjects were not followed over the same period, it is not possible to compare these changes with normal age-related changes. Subsequent analyses showed that chronic hyperglycemia, retinal and renal microangiopathy, and borderline subclinical macrovascular disease were associated with slower performance on psychomotor efficiency tasks; recurrent episodes of severe hypoglycemia had no impact on any measure (Jacobson et al., 2011).

Modest changes in adults with a childhood onset of T1D have also been demonstrated in a case-control study that included 103 young- and middle-aged adults (mean age = 40) participating in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study and 57 demographically similar adults who were followed over a 7-year period with tests from the DCCT cognition battery (Ryan et al., 2003). Analyses showed that that only a single cognitive domain – psychomotor efficiency, differentiated between groups. Compared to control subjects, those with T1D performed more poorly at both baseline and follow-up, and showed a significant decline in performance over time (−0.3 Z units), whereas control subjects showed no change over time. No between-group differences were evident on measures of learning and memory, and on spatial and problem-solving skills. The strongest predictors of psychomotor slowing over time was the presence of

microvascular complications at time 1, incident micro- and macrovascular complications, systolic blood pressure at time 2, and diabetes duration.

A smaller, more recent study, measured cognition and brain structure in 25 T1D adults with proliferative retinopathy (mean age = 46) and 25 demographically similar healthy control subjects without T1D at two time points (van Duinkerken et al., 2018). At baseline, patients earned lower scores on several domains, including processing speed and psychomotor efficiency. Performance remained unchanged approximately 3.5 years later, with the exception of executive functioning, which showed a moderately large decline (Cohen's d = −0.74), which was accompanied by loss of frontal cortical tissue. Higher HbA1c values at follow-up were associated with both decline in executive function and structural cortical changes – an observation consistent with the view that chronic hyperglycemia may adversely affect brain integrity in T1D patients independent of the development of microvascular complications.

2.3.3. Older adulthood

To date, few formal studies have systematically assessed cognition serially, over an extended period of time, in adults with T1D who are older than 50. We suspect this group was largely ignored by researchers because life expectancy was historically lower for patients with T1D than for the general population. However, drastic improvements in diabetes management have led to appreciable increases in longevity. For example, the life expectancy for individuals diagnosed between 1965 and 1980 has been found to be ~ 15 years greater than those diagnosed between 1950 and 1964 (Miller et al., 2012). As more people with T1D reach an age when they are prone to Alzheimer's disease and vascular dementia, one might expect to find that the presence of even modest cognitive dysfunction noted during childhood or midlife could increase the risk of dementia or mild cognitive impairment, or otherwise accelerate the process of brain aging in this older group.

The first study to evaluate patients over 50 years of age (mean = 61 yrs) recruited 40 subjects with T1D, a majority (70%) of whom had evidence of microangiopathy and 1 or more episodes of severe hypoglycemia (75%) (Brands et al., 2006). As a group, subjects with T1D scored slightly poorer across the spectrum of cognitive functions, but only processing speed was statistically significantly lower compared with matched peers (d = −0.34). Interestingly, visual ratings of cerebral small vessel disease (e.g. white matter lesions, infarcts and lacunes) did not differ between groups (Brands et al., 2006). After a 4-year re-assessment that included 36 of the 40 patients and 29 of the 40 control subjects, essentially no changes on any measures were observed (van Duinkerken et al., 2011). That is, the T1D group showed no evidence of accelerated cognitive decline. However, within that group, those who had a cardiovascular event during follow-up showed a steeper decline in overall cognitive functioning and in processing speed; similarly, those with one or more severe hypoglycemic events during follow-up showed an accelerated decline in processing speed (van Duinkerken et al., 2011). That severe hypoglycemic events were related to declining processing speed over a relatively short follow-up period suggests that the brain of older patients, of whom a majority have microangiopathy, may be vulnerable to the effects of hypoglycemia. Two studies of older adults (Ryan et al., 2016a; Weinstock et al., 2016) have similarly demonstrated that a recent episode of severe hypoglycemia may contribute to cognitive decline, particularly in those with microvascular disease. On the other hand, studies of younger adults (e.g., DCCT; (DCCT/EDIC Research Group, 2007)) failed to find any meaningful effects of severe hypoglycemia on cognition.

Despite the absence of other large longitudinal studies, results from two recently published cross-sectional studies provide intriguing information on the differential rates of clinically significant cognitive dysfunction in older adults (mean age = 68 yrs.; mean age at onset = 29 yrs) recruited from the T1D Exchange Study (Chaytor et al., 2019) and in middle-aged adults (mean age = 49 yrs.; mean age at onset = 8 yrs) recruited from the Pittsburgh EDC Study (Nunley et al., 2015). Cognitive impairment in both studies was operationalized as performance ≥1.5 standard deviations below normative data on 2 or more tests. Within the older sample, 48% met criteria for cognitive impairment. After controlling for age, sex, education and disease duration, 5 predictors were associated with an increased odds of impairment: hypoglycemia unawareness, recent severe hypoglycemic events, any microvascular complication, higher HbA1c, and average nocturnal glucose values. Within the middle-aged sample, 28% were found to be impaired (as compared to only 5% without T1D), and the odds of impairment were associated with a 14-year average HbA1c > 7.5%, and the presence of microvascular complications. By comparison, only 12.8% of the Children's Hospital of Pittsburgh pediatric sample (mean age = 14.9; mean age at onset = 6 yrs) with T1D met criteria for clinically significant impairment (using those same criteria), as did < 6% of those without diabetes (Ryan et al., 1985). These studies differ in terms of participants' age at test and their age at diagnosis, as well as in the cognitive measures used; nevertheless, the pattern of results is very intriguing and emphasizes the importance of obtaining serial measurements of cognition in people with T1D as they transition into later adulthood. Whether these older individuals will necessarily develop dementia has not yet been established. However, it is noteworthy that of those with clinically significant cognitive impairment, 12% had impairments in memory alone, 44% only had processing speed impairments, while the remaining 44% had cognitive impairments in both domains (Chaytor et al., 2019). Studies of the general population indicate that purely amnestic clinically significant cognitive impairment, or mild cognitive impairment, is most prevalent (Knopman et al., 2009), and also has the highest conversion rate to Alzheimer's disease in comparison with non-amnestic and multiple domain mild cognitive impairment (Espinosa et al., 2013; Maioli et al., 2007). It is thus reassuring that the percentage of older T1D patients identified with purely amnestic mild cognitive impairment (12%) in the T1D Exchange Study was relatively low (van Duinkerken and Snoek, 2019).

2.4. Risk of dementia

With the increasing life expectancy of T1D patients, studies focusing on cognitive dysfunction and dementia in older adults are becoming increasingly important. One recent study examined English National Hospital Episode Statistics on 10,786 patients with any dementia to identify links between T1D status and any dementia, as well as to Alzheimer's Disease (AD) and to vascular dementia (VaD) (Smolina et al., 2015). Across all ages, the relative risk was 1.65 (95% confidence interval [CI]: 1.61–1.68), indicating an increased risk of any type of dementia in this population. This elevated risk seems to be driven by the risk of VaD, which was 2.21 (95% CI: 2.13–2.28; 3885 patients); the relative risk of AD was only slightly elevated (1.10; 95% CI: 1.05–1.15; 2113 patients). Furthermore, the relative risk of AD decreased from 1.52 for people 60 to 69 years of age, to 1.08 for those 70 to 79, and to 0.84 for those 80 years or older. This indicates that during older adulthood, when the risk of AD normally increases in the general population, that risk seems to decrease in this T1D population. Moreover, those aged 80 years or older had a lower risk of developing AD than non-diabetes controls. On the other hand, while the relative risk of VaD also declined with increasing age (60–69: 3.76; 70–79: 2.09; ≥80: 1.34), it remained significantly elevated when compared to AD.

This study leads us to 2 important conclusions. First, the risk of AD in older T1D patients is not much higher in comparison with non-diabetes controls. This should be most reassuring for patients who may worry that decades of exposure to glycemic extremes might elevate their risk of developing AD. Second, the risk of both AD and VaD appears to decline with increasing age, and that patients in the oldest age category may have an even lower risk of AD (Smolina et al., 2015). At first glance these are salutary findings, although it is possible that it actually reflects a selective survival bias. That is, due to long diabetes

duration and a shorter life expectancy than non-diabetes controls, patients at risk of dementia might have died at an earlier age. In other words, those who are older can be characterized as survivors and hence there will be fewer cases of dementia among them compared to younger patients. This is an issue that clearly requires additional study.

A major shortcoming of that medical record review study was that no cumulative data on glycemic control was available. A very recent study has rectified this and has demonstrated that the risk of any type of dementia is increased in individuals with consistently higher HbA1c values, and is decreased when HbA1c values are consistently lower (Lacy et al., 2018). Using the Kaiser Permanente Diabetes Registry (KPDR), researchers followed 3433 members of a health care system who were diagnosed with T1D and who were > 50 years of age between 1996 and 2015. Over a mean of 6.5 years, 155 were diagnosed with dementia. Patients with > 50% of their HbA1c readings between 8 and 8.9% had a 65% greater risk of dementia; for those with HbA1c values ≥9.0%, the risk increased to 79%, as compared to those with < 50% of their HbA1c values that high. Furthermore, patients with HbA1c values consistently lower than 6–6.9% or between 7 and 7.9% had a risk of dementia that was 45% lower. To our knowledge, this is the first report to provide strong support for a link between consistently elevated blood glucose values and the risk of dementia. Since high HbA1c values are also strongly associated with the presence of microvascular complications like diabetic proliferative retinopathy (Diabetes Control and Complications Trial Research Group, 1995) as well as with macrovascular disease, it is likely that the resulting vascular changes may contribute to the development of dementia. Support for that possibility has come from a number of studies demonstrating that retinopathy is associated with cognitive dysfunction in middle-aged adults with T1D (Ryan et al., 2003) and with dementia in older adults with T2D (Exalto et al., 2014). This is not surprising, given the well-established structural and functional homologies between the retinal and cerebral microvasculature (for review, see (Ding et al., 2008; Patton et al., 2005)). However, a subsequent analysis of data from the previously mentioned T1D KPDR cohort failed to find any significant relationship between the occurrence of dementia and the presence of diabetic retinopathy (Rodill et al., 2018). At this time, the pathophysiological mechanisms underlying the association between a long history of poor metabolic control and dementia remain unclear in older adults with T1D.

2.5. Putative mechanisms underlying cognitive change across the lifespan

Any explanatory model must explain the following. First, cognitive decline appears soon after diagnosis. Second, it is greatest in those with an early onset of diabetes – diagnosed within the first 5 to 7 years of life. Third, the rate of further cognitive decline is quite slow – at least during the first 10 to 15 years after diagnosis. Fourth, in adults with a pediatric onset of diabetes, chronic hyperglycemia and/or the development of microvascular complications increases the risk of cognitive decline to some extent. Fifth, recurrent episodes of hypoglycemia seem to increase the risk of poorer cognition in older (age > 50 years) adults; whether hypoglycemia influences cognition in younger people with T1D remains unsettled.

One possible mechanistic explanation is offered by the 'diathesis' hypothesis, which posits that the metabolic and biomedical events occurring at around the time of diagnosis alter the normal process of brain development (Ryan, 2006; Ryan, 2008). We now know that blood glucose values increase significantly even before the clinical diagnosis of diabetes (Sosenko et al., 2010), and at the time of diagnosis, blood glucose may rise to dangerously high levels that may alter the integrity of the blood brain barrier (BBB) – permitting larger molecules and other potentially neurotoxic substances to enter the CNS (Hawkins et al., 2007), as well as triggering a metabolic crisis like DKA, which also disrupts BBB integrity (Vavilala et al., 2010) and can induce changes in brain structure within a very brief time period (Cameron et al., 2014; Glaser et al., 2017; Siller et al., 2017). If these events occur during the first several years of life – a particularly crucial period for normal brain development (Caviness et al., 1997), the resulting alterations in brain organization may induce a vulnerability, or diathesis, that increases the individual's sensitivity to subsequent brain insults at any time thereafter. On the other hand, if diabetes onset occurs after that crucial period, the risk of neurodevelopmental anomalies (and cognitive dysfunction) is less likely to occur.

Although the original diathesis hypothesis focused on early childhood as the period when the brain is particularly plastic and susceptible to diabetes-related toxicity, later adulthood (60 years of age or older) may be a second crucial period, insofar as this is the time when the brain begins to undergo significant neurodegenerative changes as part of the normal aging process (Biessels et al., 2008). Thus, it is not surprising to find that for older adults with T1D of long duration, a recent episode of severe hypoglycemia may increase the risk of cognitive dysfunction. Other disease-related variables, including microvascular disease and elevated blood pressure, are also likely to independently affect brain function and structure to a limited extent. That said, it is important to keep in mind that mid- or later-life cognitive dysfunction is not mediated solely by the presence or development of microangiopathy. This has been demonstrated by a recent study that assessed 104 middle-aged adults with T1D, half of whom had no clinically manifest microvascular disease while the remainder had proliferative retinopathy and other microvascular complications (van Duinkerken et al., 2012). Compared to matched controls without diabetes, those with proliferative retinopathy showed lower processing speed and attentional performance; their processing speed was also slower than their counterparts with uncomplicated T1D (van Duinkerken et al., 2016; van Duinkerken et al., 2012). On the other hand, subjects with uncomplicated T1D also had processing speed decrements relative to those without T1D, albeit with a smaller effect size (van Duinkerken et al., 2012). These decrements cannot be attributed solely to the presence of microangiopathy, but may reflect the influence of other factors, including chronically elevated blood glucose levels, subclinical macroangiopathy (van Duinkerken et al., 2014), and depressive symptoms (van Duinkerken et al., 2016).

3. Type 2 diabetes

3.1. Disease characteristics

Type 2 diabetes (T2D) most often appears in middle or later adulthood, often in individuals who have a variety of health conditions, including elevated blood pressure, obesity, and inactivity. About 90% of all people with diabetes have the type 2 form; in the US, this disease affects > 21 million people (Bullard et al., 2018). Given the world-wide epidemic of obesity, it not surprising that there has been a recent increased incidence of T2D in adolescents and younger adults. Indeed, between 2002 and 2012, the incidence of T2D in youth 10 to 19 year of age increased by 7% annually, from 9 cases per 100,000 youths per year in 2002–2003 to 12.5 cases per 100,000 in 2011–2012 (Mayer-Davis et al., 2017). This disease tends to develop insidiously as muscle and liver cells lose sensitivity to the glucose-lowering effects of endogenous insulin. The resulting insulin resistance is accompanied by increased blood glucose levels and ultimately, by progressive beta cell impairment.

Depending on disease severity and other patient characteristics, treatments may range from dietary management and increased exercise regimens to the use of one of many anti-diabetic medications, to insulin injections. As is the case with T1D, the goal of treatment is to optimize blood glucose control, and maintain HbA1c values as close to the normal range as possible. Whether an individual has T1D or T2D, a long history of chronically elevated blood glucose levels can trigger microvascular and macrovascular changes in multiple organ systems, including the brain. One of the challenges of studying the relationship

between the development and manifestations of cognitive dysfunction and T2D is that most people with this disorder have several comorbid disorders and life-style characteristics that may also affect cognition to some extent. These include elevated blood pressure, dyslipidemia, cardiovascular disease, obesity, physical inactivity, depression, and iatrogenic hypoglycemia (Feinkohl et al., 2015). Also, because T2D usually develops over a period of years, it is not possible to accurately estimate the duration or extent of glycemic excursions prior to a formal diagnosis. As a consequence, researchers have found it more difficult to draw strong conclusions about the biomedical and psychosocial predictors of cognitive dysfunction in T2D, as compared to T1D.

3.2. Neurocognitive phenotypes

A very large literature has provided compelling evidence that adults with T2D have an increased risk of neurocognitive dysfunction (Reijmer et al., 2010). Many studies have attempted to identify a characteristic profile of cognitive dysfunction associated with T2D. One early review reported that processing speed and verbal memory were most strongly affected, while visuospatial skills, attention, and language were preserved (Awad et al., 2004). A more recent systematic review and meta-analysis that included 3351 T2D adults participating in 24 different studies identified a pattern of generalized cognitive dysfunction that affected verbal and visual memory, processing speed, motor functions, executive functions, and attention and concentration (Palta et al., 2014). For virtually all cognitive domains, effect sizes were moderate (i.e., Cohen's $d = \sim -0.3$), with the exception of attention and concentration (Cohen's $d = -0.2$). Of the specific cognitive tests administered, the largest effect size ($d = -0.6$) was on the Grooved Pegboard, a measure of psychomotor speed, followed by the Rey Auditory Verbal Learning Test ($d = -0.4$) and a measure of mental flexibility and planning: Trail Making Part B ($d = -0.4$).

In reviewing the literature, we have been struck by how inconsistent the results are across studies. For example, 63% of the studies included in one systematic review showed processing speed dysfunction, with attentional dysfunction present in 50% of the studies, and memory affected in 44% of the studies (Van den Berg et al., 2009). It is likely that these variable results reflect the heterogeneity of this patient population. Furthermore, whether or not a given study is able to characterize the presence and nature of cognitive dysfunction depends on a variety of factors, including the sample size, the demographic and health characteristics of the sample (e.g., age; duration of disorder; comorbid medical conditions), and the sensitivity and appropriateness of the cognitive measures used. Nevertheless, like adults with T1D (Brands et al., 2005), older adults with T2D most often show evidence of significantly slowed information processing and poorer executive functions, but in addition, they typically show evidence of verbal and visual memory dysfunction – an impairment rarely associated with T1D.

It is important to keep in mind that neurocognitive sequelae are not limited to older adults with T2D. Preliminary evidence of serious widespread cognitive dysfunction has been reported in a study comparing 18 obese adolescents with T2D and 18 demographically similar obese adolescents without T2D (Yau et al., 2010). As a group, adolescents with T2D performed consistently worse than controls in all cognitive domains, with differences reaching statistical significance on measures of estimated intellectual functioning, verbal memory, and psychomotor efficiency. These findings cannot be attributed to psychosocial factors insofar as neuroimaging showed whole brain and frontal white matter volume reductions and diffuse white matter microstructural abnormalities. Larger studies of this highly vulnerable patient population are clearly needed.

3.2.1. Prediabetes and cognition

Our review has focused on individuals who have been formally diagnosed with, or otherwise meet diagnostic criteria, for T2D. However, development of T2D is a process that may take several years and patients usually pass through several stages before receiving the diagnosis and beginning treatment. The 'prediabetes' stage commonly starts with impaired glucose regulation that is usually manifested by elevated fasting plasma glucose levels or impaired glucose tolerance test results. It is also often closely associated with abdominal obesity, high blood pressure, low levels of HDL (high-density-lipoprotein) cholesterol, and hypertriglyceridemia. Collectively, these factors have been labeled as the metabolic syndrome (MetS) (Alberti et al., 2009), and individuals with this syndrome are at increased risk for T2D and cardiovascular disease.

A growing, albeit controversial, literature has suggested that MetS may increase the risk of cognitive dysfunction in domains such as memory, processing speed, executive functions and visuospatial abilities. Two thoughtful reviews of this literature – one focusing primarily on normal nonelderly adults (Yates et al., 2012), and other focusing on elderly persons (Assuncao et al., 2018), make the point that although there may be some evidence supporting a link between MetS and neurocognitive outcomes, there is actually little consensus across studies – with one exception. Disturbances of glucose metabolism are more likely to be associated with poorer cognition than other components of the metabolic syndrome. Both of those reviews also make the point that the absence of consistent findings largely reflects the high degree of methodological heterogeneity across these studies. Future research on this topic needs to include multiple high-quality measures of cognition, a comprehensive health assessment, use of a standard definition of MetS, and a healthy comparison group comprised of individuals without MetS.

3.3. Cognitive changes over time

Because the appearance of cognitive dysfunction in people with T2D is associated with factors such as chronic hyperglycemia, vascular risk factors and complications, and severe hypoglycemia, it seems reasonable to expect that over time, T2D and its comorbid conditions could accelerate the process of brain aging appreciably and greatly increase the risk of mild cognitive impairment and dementia (Feinkohl et al., 2015; Geijselaers et al., 2015; Reijmer et al., 2010). Unfortunately, the relatively small literature on this is not entirely conclusive. For example, a case-control study conducted by the Utrecht Diabetic Encephalopathy Study Group followed 68 older adults (mean age = 65 yrs) with T2D over a 4-year period and contrasted their performance on a comprehensive test battery to 38 matched peers without T2D (Van den Berg et al., 2010). Compared to control subjects, those with T2D performed worse on measures of information-processing speed (Z difference = −0.37) and attention and executive functioning (Z difference = −0.25) at both baseline and follow-up. At follow-up, both groups showed a similar decline in abstract reasoning and executive functioning (Z difference = −0.16 and −0.29 respectively) – consistent with normal age-related declines. However, there was no evidence of a significant group by time interaction that would be expected if T2D actually accelerated the rate of cognitive decline over time. Older adults with T2D who were recruited as part of the Leiden 85+ study also showed no evidence of accelerated cognitive decline (van den Berg et al., 2006). Over a 5-year period, both subjects with and without T2D completed cognitive assessments annually and showed the same rate of decline over time, even though those with T2D performed consistently poorer than controls on two speeded tasks at both study entry and follow-up.

On the other hand, several other studies have provided evidence that supports the view that T2D can accelerate the rate of cognitive decline. In the Whitehall II study, 5653 middle-aged British civil servants (median age = 54 yrs) were followed over a 20 year period (Tuligenga et al., 2014). For the 187 participants with known T2D, performance on memory measures declined 45% faster as compared to normoglycemic participants, with a faster rate of decline being associated significantly with poorer glycemic control. Both reasoning skills

and global cognitive functioning also declined (29% and 24% faster, respectively). These changes correspond to an aging effect of 3.3 years for memory, 2.9 years for reasoning, and 2.2 years for the global cognition score. On the other hand, those participants with prediabetes or newly diagnosed diabetes showed rates of decline that were similar to the normoglycemic participants.

A similar pattern of results has been reported in three other studies. The Doetinchem Prospective Cohort Study followed 2613 subjects 43 to 70 years of age over a 4 year period and found that global cognitive function declined 2.6 times faster in the 61 subjects with T2D at study entry, as compared to the 2460 subjects without diabetes (Nooyens et al., 2010). Cognitive flexibility declined 3.6 times faster, but this was limited to subjects over the age of 60 at study entry. Of note was their finding that participants over the age of 60 who developed T2D during the study (incident diabetes; $N = 78$) also declined (2.5 times faster). The Maastricht Aging Study followed 1290 adults 40 years of age or older over a 12-year period; 68 with T2D at baseline and 54 and 57 had incident diabetes at the 6- and 12-year follow-up assessments (Spauwen et al., 2013). Subjects with T2D at study entry showed a decline in information-processing speed that was 3 times larger than normoglycemic subjects at 12-years, and showed a decline in rapid executive functioning that was 4 times larger; a smaller (14%) decline was seen in delayed memory. In contrast, there was no significant effect of incident diabetes on cognitive decline, although a trend was seen on information-processing measures.

The Health, Aging, and Body Composition Study measured cognition repeatedly in 3069 elderly adults (mean age 74.2 yrs) over a 10-year period (Yaffe et al., 2012). At baseline, 717 participants had prevalent diabetes and an additional 159 developed diabetes during the study. Those with prevalent diabetes had lower scores at baseline on the Mini Mental State Exam and the Digit Symbol Substitution Test (DSST), compared to those without T2D, and showed significantly steeper declines in performance over time than those without diabetes. These declines were quite modest. For example, on the DSST, a measure of mental and motor speed, participants with prevalent diabetes showed a 7.8-point decline (24%), whereas those without diabetes showed a 5.8-point decline (15.7%). Among those with prevalent diabetes, poorer performance was associated with higher HbA1c values. Participants who developed diabetes during the study were also followed but did not show evidence of accelerated decline.

Taken together, this series of longitudinal studies indicates that there is, as yet, not complete agreement as to whether T2D accelerates cognitive aging. Nevertheless, we find it intriguing (and consistent with results from many cross-sectional studies) that chronically elevated blood glucose values or a history of poor glycemic control increases the risk of poorer performance on cognitive tests and may trigger a faster decline. Given results from several of the large, population-based studies, this is certainly a research topic that deserves more study, particularly as more people develop T2D at an earlier age, and hence experience longer exposure to chronically elevated blood glucose values and vascular disease.

3.4. Risk of dementia

Many have speculated that because T2D appears to accelerate the rate of cognitive decline in older adults, it may also be associated with a greatly increased risk of dementia (Biessels et al., 2014). One meta-analysis examined 19 studies that included 6184 subjects with T2D and 38,530 non-diabetic controls and calculated the relative risk of 4 conditions: mild cognitive impairment, any dementia, VaD, and AD (Cheng et al., 2012; Exalto et al., 2012). The relative risk that patients with T2D would meet criteria for mild cognitive impairment was quite small (RR = 1.21; 95% CI: 1.02–1.45). The risk of any dementia was 1.51 (95% CI: 1.31–1.74), but this figure was driven primarily by the risk of vascular dementia (2.48; 95% CI: 2.08–2.96); the risk of AD was only slightly elevated (1.46, 95% CI: 1.20–1.77). In many ways it is not surprising to find that T2D is associated with an increased risk of vascular dementia, given the very high rates of vascular risk factors (like hypertension) as well as the presence of micro- and macrovascular disease in this patient population (Strachan et al., 2008). Similar results have been reported in an analysis of the English National Hospital Episode Statistics that focused specifically on the association between T2D (1,855,141 cases) and both AD and VaD (Smolina et al., 2015). They included 12,743 cases of AD and 20,427 cases of VaD. Again, for VaD there was a clear elevated risk of 1.80 (95% CI: 1.77–1.83), with the relative risk decreasing as age increased from 30 to 39 years to 80 and over. For AD, however, no elevated risk was observed for the entire cohort (0.99, 95% confidence interval: 0.97–1.01).

It is clear from these, and other, epidemiologic studies, that T2D doubles the risk of VaD, but appears to have a minimal impact on the risk of AD. Results from 2 large brain autopsy studies also support the view that when dementia is associated with T2D, cerebrovascular pathology is more common than is AD-type pathology. For example, an analysis of post-mortem brain tissue from 50 adults with T2D and 89 adults without diabetes (mean age: 85 and 88 yrs., respectively) who were studied at the University of Kentucky Alzheimer's Disease Center demonstrated that those with T2D had a significantly higher prevalence of infarcts, and a significantly lower prevalence of AD-type neurofibrillary tangles and neuritic plaques (Nelson et al., 2009). A similar pattern of results were reported by the Vantaa 85+ study group, which followed 553 residents aged ≥85 yrs. on April 1, 1991 for up to 10 years (Ahtiluoto et al., 2010). Not only did a diagnosis of diabetes at study entry double the incidence of dementia during the study, but at autopsy, cerebral infarcts were significantly more common in individuals with T2D, whereas the presence of amyloid and neurofibrillary tangles was significantly less common.

3.5. Risk factors and putative mechanisms

3.5.1. Predicting cognitive dysfunction

We know that T2D is a multifactorial disease that has been linked with insulin resistance, chronic hyperglycemia, obesity, hypertension, dyslipidemia, micro- and macrovascular disease, hypoglycemia, depression, and sedentary activity – all of which may independently affect cognition to some extent (Feinkohl et al., 2014; Van den Berg et al., 2009). Unfortunately, because of this biomedical and psychosocial heterogeneity, it remains quite difficult to ascertain which of these factors contribute to the cognitive dysfunction, accelerated decline and dementia that is often identified in this patient population. As discussed earlier, we know that individuals in poorer glycemic control, especially those with a long history of elevated HbA1c levels, have a greatly elevated risk of developing cognitive sequelae, and it is likely, but not entirely certain, that these changes are also mediated, at least to some extent, by the development of both micro- and macrovascular pathology that may directly and indirectly affect brain function and structure (Feinkohl et al., 2015).

Another factor that may predict the severity of cognitive dysfunction later in life is age at diagnosis. In one large population-based study, older adults (72–83 yrs. old) with T2D were stratified into subgroups based on whether diabetes onset occurred in mid-life (< 65 yrs. old; mean age at onset = 56 yrs) or later life (65+; mean age at onset = 72 yrs) (Roberts et al., 2014). Compared to subjects without diabetes, mid-life onset was associated with a lower global cognitive score, poorer executive function, and a higher risk of meeting diagnostic criteria for mild cognitive impairment. Mid-life onset was also associated with ischemic (increased risk of subcortical infarctions) and atrophic changes (reduced hippocampal and whole brain volumes). Results from a qualitative mediational analysis suggested that loss of brain volume may mediate the association between T2D and cognitive impairment in older adults with a mid-life onset. Interestingly, late-life onset was unrelated to any cognitive outcome measure.

	Points		Points		Points
60 - 64 years	0	Acute Metabolic Event	2	Up to high-school education	0
65 - 69 years	3	Microvascular Disease	1	(< 12 years)	
70 - 74 years	5	Diabetic Foot	1	College or higher education	-1
75 - 79 years	7	Cerebrovascular Disease	2	(> 12 years)	
80 - 84 years	8	Cardiovascular Disease	1		
> 85 years	1	Depression	2		
	0				

Fig. 4. Assignment of dementia risk points based on age, health, and education. Values are derived from the 29,961 patients with T2D from the Kaiser Permanente Northern California Diabetes Registry. From Exalto et al., 2013, used with permission.

3.5.2. Predicting dementia

One empirically-based effort to identify potential risk factors for all-cause dementia has used data from 29,961 patients (aged ≥60 yrs) enrolled in the Kaiser Permanente Northern California Diabetes Registry to calculate a score to predict 10-year dementia risk in older adults with T2D (Exalto et al., 2013). Points are assigned based on age, diabetes-related variables captured in the medical record, and education (see Fig. 4). Scores range from −1 to 19, with the predicted risk of dementia ranging from < 10% (score ≤ 1) to 25% (score = 5) to 50% (score = 8) to 73% (score = 12–19). When this algorithm was subsequently applied to an external validation cohort of 2413 patients, predictive accuracy for dementia was found to be similar to that from the larger development cohort. By identifying key clinical predictors of dementia and cognitive decline, this work, as well as that of other studies (for review, see (Biessels et al., 2014)) points to potential opportunities for interventions, particularly those that can reduce the risk and/or severity of vascular disorders.

4. Conclusion

More than 40 years of research have demonstrated that individuals with diabetes have an increased risk of cognitive complications. We know that these cognitive complications affect only a subset of people with diabetes, tend to appear relatively early in the course of the disease, seem to be of modest severity, and show relatively little worsening over a 10 to 15-year period – particularly in individuals with T1D. However, for either form of diabetes, a long history of poorer glycemic control, particularly one that is accompanied by the development of micro- and macrovascular complications, seems to increase the risk of cognitive decline. The presence of multiple comorbid conditions like hypertension, central obesity, physical inactivity and depression may further contribute to cognitive decline over time, in individuals with T2D. Rates of vascular dementia are elevated in individuals with either form of diabetes, but most studies have concluded that the risk of Alzheimer's disease is not elevated.

Why are some individuals at greater risk than others? We and others have speculated that at least for individuals with T1D, events occurring around the time of diagnosis, like elevated blood glucose levels and metabolic crises like DKA, may alter the integrity of the blood-brain-barrier so that toxic agents are able to enter the CNS and thereby affect normal neurodevelopmental processes. Such events are particularly devastating if they occur within the first several years of life, during a period of especially active brain development. Limited animal and clinical studies have generated data that are consistent with that view. Nevertheless, far more work is needed to determine how – and to what extent – brain development is adversely affected not only by the glycemic excursions and elevated exogenous insulin levels that occur around the time of diagnosis, but by the osmotic and metabolic changes associated with DKA.

The origin of cognitive dysfunction in individuals with T2D is less well understood, largely because there are so many vascular, metabolic, and psychosocial factors that can influence cognition. Chronic hyperglycemia may be the strongest risk factor, but cerebral microvascular disease and other vascular factors like hypertension, may also be major contributors.

We are sanguine that more definitive answers will emerge within the next 3 to 5 years from several large studies that include long follow-up periods. For example, the Edinburgh Type 2 Diabetes Study began in 2006 and is continuing to follow a very large cohort of older adults over a 10 to 15-year period with extensive measures of cognition as well as with a thorough assessment of biomedical and psychosocial risk factors. Similarly, the large cohort of T1D patients who were recruited into the DCCT/EDIC study between 1983 and 1989 are now undergoing additional cognitive assessments that will continue between 2018 and 2022, and will be supplemented by neuroimaging studies. These studies, as well as others that target older adults with diabetes, are likely to help us determine to what extent, and by what means, diabetes and its comorbid conditions interact with the normal aging process to accelerate cognitive decline. This ongoing research will also help us identify effective intervention strategies that may prevent or ameliorate diabetes-associated cognitive sequelae.

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