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Cognitive Dysfunction in Diabetic Patients

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Diabetes is a disease which existed from the beginning of human civilization.It is associated with a number of complications among which cognitive dysfunction is a disabling one. Cognition is the study of how people perceive, remember, think, speak, and solve problems,[1] in fact every psychological phenomenon is a cognitive phenomenon.[2]

Introduction

In our study done in IPGME&R Kolkata by Mukherjee *et al.*[67] 50 diabetic patients were examined clinically for evidence of cognitive dysfunction by Kolkata Cognitive Screening Battery. It was found that cognitive dysfunction is associated with diabetes with recognition, fluency and immediate memory being most commonly affected. Calculation was least affected but few patients had problems in mini-mental state examination (MMSE), praxis and naming. There was strong association of cognitive decline with history of smoking, poor controlleddiabetes, nephropathy and retinopathy; the age of onset of diabetes and its duration did not have a strong positive correlation with cognitive decline. The cognitive decline appeared to be reversible as improvement of some mental faculties like immediate recall, recognition, praxis and fluency were apparent after strict control of diabetes.

Discussion

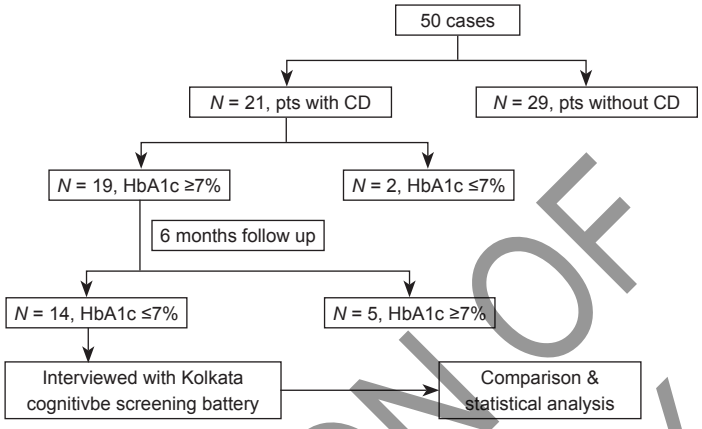
The mind has various faculties—attention, language, verbal fluency, comprehension, naming and word finding, memory, new learning ability, immediate recall, recent memory, remote memory, constructional ability, calculation, proverb interpretation, similarities, insight and judgment are to name a few.

Diabetes has long been thought to affect cognition, as well as emotion, but it was not until the development of clinical neuropsychology that researchers were able to demonstrate unequivocally that mental efficiency can be disrupted by diabetes, its complications and its management, and that this neuropsychologic dysfunction reflects changes occurring in the central nervous system (CNS). The magnitude of these effects is relatively modest in most individuals, and few patients with diabetes manifest cognitive changes that would be characterized as being "clinically significant" – unless they developed diabetes early in life. Until very recently, when cognitive dysfunction was found in patients with diabetes it was invariably attributed to the adverse effects of severe and/or recurrent hypoglycemia on the CNS. New research suggests that chronic hyperglycemia, and the metabolic and vascular complications that are associated with it, underlie the development of most structural and functional changes to the CNS, particularly in adults. Although hypoglycemia can never be considered to be entirely benign, it may have a relatively small role in the etiology of neurocognitive changes in patients with diabetes.[3,4]

The nature and extent of cognitive dysfunction in children and adolescents differs depending on the age of diagnosis. Those diagnosed in the first 5–7 years of life appear to have an elevated risk of manifesting a moderately severe cognitive impairment which is evident across a broad range of cognitive domains, including measures of attention, mental flexibility, psychomotor efficiency, learning, memory, problem-solving ability and overall

intelligence.[5–11] In contrast, those diagnosed after that early "critical period" show very mild cognitive dysfunction which is limited primarily to measures of overall intelligence and to performance on speed-relatedtasks, particularly those having a visuoperceptual component.[11] Learning, memory and problem-solving skills are largely intact in this "later onset" patient population, or are only very minimally[12] and inconsistently affected.[13,14] Regardless of age at diagnosis, children with diabetes also tend to achieve lower scores than their peers without diabetes on measures of academic achievement,[12–15] and have somewhat poorer grades in school,[16] with these latter effects especially pronounced in children with a very early onset of diabetes.[17] The magnitude of the cognitive dysfunction seen in children with diabetes tends to be quite modest, as demonstrated by a formal meta-analysis of 19 pediatric studies encompassing 1393 children with diabetes and 731 healthy comparison subjects. In one large study, it was found that 24% of children with an early onset of diabetes met the criteria for clinically significant impairment, as compared with only 6% of children with a later onset of diabetes, and 6% of a comparison group without diabetes.[9]

This 'age at onset' phenomenon has also been reported in adults diagnosed with diabetes early in life. Young adults who developed diabetes before 7 years of age performed more poorly on measures of information-processing speed, and earned lower performance IQ scores than their peers with diabetes diagnosed at or after age 7.[18] Abnormalities in brain structure were also evident and magnetic resonance imaging (MRI) scans showed higher rates of mild to moderate ventricular atrophy (61% vs. 20%), as well as somewhat higher rates of small punctate white matter lesions within the hippocampus (14% vs. 2%). Smaller brain volumes also correlated with poorer cognitive test performance, supporting the view that cognition dysfunction is necessarily linked to changes in the CNS.[19] Children with an early age at onset were particularly affected, and performed significantly worse on measures of attention and executive function than those with a somewhat later onset of diabetes.[7] Hypoglycemia has long been considered to be the cause of these neuropsychologic deficits, particularly in children with an early onset of diabetes. Although that view seems quite plausible, recent large well-designed cross-sectional[18–20] and longitudinal[21,22] studies completely failed to find any relationship between recurrent episodes of hypoglycemia and cognitive impairment, whereas others have reported only very weak and inconsistent findings.[14] Learning and memory skills, which are generally considered to be sensitive to early brain damage,[23] were well preserved in patients, despite an average of 20 or more years of T1DM. Moreover, with only one exception ("crystallized intelligence"), virtually all of the cognitive tasks on which patients with diabetes perform more poorly were those that also required rapid responding i.e. mental slowing appears



Flow chart 1. 50 cases were followed up in the following way.
Note: CD cognitive dysfunction.

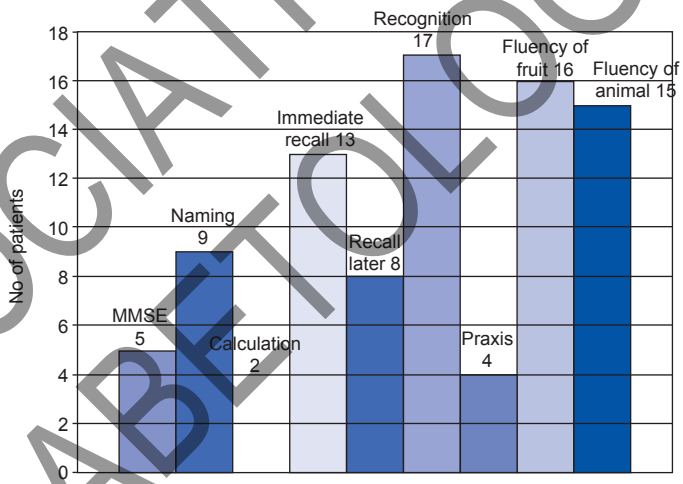


Figure 1. Impaired mental faculty.

to be the fundamental deficit associated with T1DM in adulthood.[24] A similar pattern of results has been found in adults with T1DM who are over the age of 60.[25] Remarkably, the magnitude of the cognitive differences found in these older adults was similar to that reported in their younger counterparts, despite their longer duration of diabetes.

As noted in studies of children with diabetes, adults with diabetes also manifest slowed neural processing on measures of brainstem auditory evoked potentials,[26,27] visual evoked potentials[28] and EEG recordings.[29] In one large study, 85% of middle-aged adults with diabetes showed hypoperfusion in one or more region of interest compared to 10% of controls; similarly, 58% of subjects with diabetes showed hyperperfusion, compared to 20% of controls.[30] Again, these effects were greatest in subjects with microvascular complications.

Older adults with T2DM also show evidence of psychomotor slowing[31–33] and, in that way, are somewhat similar to young and middle-aged adults with poorly controlled T1DM. In addition, elderly adults with T2DM consistently learn new verbal and non-verbal information

Table 1 | Composite table showing correlation of different variables with cognitive dysfunction

Parameter studied	Correlation with	P value	Remarks
Age of onset of diabetes	Cognitive dysfunction	>0.05	Not significant
Duration of diabetes	Cognitive dysfunction	>0.05	Not significant
Sex of diabetic patient	Cognitive dysfunction	>0.05	Not significant
Literacy level	Cognitive dysfunction	>0.05	Not significant
Hypertension	Cognitive dysfunction	>0.05	Not significant
Dyslipidemia	Cognitive dysfunction	>0.05	Not significant
BMI	Cognitive dysfunction	>0.05	Not significant
High HbA1c (>7%)	Cognitive dysfunction	**<0.001**	**Significant**
Regularity of diabetic treatment	Cognitive dysfunction	**<0.001**	**Significant**
Smoking habit	Cognitive dysfunction	**>0.05**	**Significant**
Nephropathy	Cognitive dysfunction	**>0.05**	**Significant**
Retinopathy	Cognitive dysfunction	**>0.05**	**Significant**
Neuropathy	Cognitive dysfunction	>0.05	Not significant
Coronary artery disease	Cognitive dysfunction	>0.05	Not significant
Peripheral arterial disease	Cognitive dysfunction	>0.05	Not significant

more slowly, and remember less of it over a brief delay, compared with subjects without diabetes.[34–36] Interestingly, this phenomenon appears to be limited to individuals over 60 years of age; younger adults with T2DM rarely show memory impairments.[37] Other cognitive skills, particularly problem-solving ability, may also be affected in older adults with T2DM[36] but those skills have been assessed less frequently.[34,38,39] The cognitive effects associated with T2DM are similar in magnitude to those reported in younger adults with T1DM. The strongest predictor of poorer cognitive function has been noted as poor metabolic control; neither duration of diabetes nor severity of peripheral neuropathy were related to any cognitive outcome variable.[40]

Despite their often brief duration of diabetes, patients with T2DM also manifest evidence of neural slowing, overall reductions in cerebral blood flow[41,42] and significant changes in brain structure, including smaller gray matter volumes (approximately 22 ml reduction), greater subcortical atrophy (approximately 7 ml increase in lateral ventricle volume) and larger white matter lesion volume (approximately 57% increase).[43] Structural changes appeared to be more prominent in women and were associated with higher HbA1C values and older age, but were unrelated to diabetes duration, hypertension or hyperlipidemia. Compared with patients with T1DM, those with T2DM showed significantly greater cortical atrophy and deep white-matter lesions, with effect sizes ranging between 0.50 and 0.66[44] even though the patients with T2DM had diabetes for a shorter period of time (7 vs. 34 years) and had lower rates of clinically significant microvascular complications (laser-treated retinopathy: 8% vs. 38%).

The higher rates of macrovascular disease and atherosclerotic risk factors may underlie the development of the CNS changes seen in the T2DM cohort, although there is evidence to suggest that impairments in glucose and/or insulin regulation may be contributory.[45,46] The hippocampus, which has only infrequently been evaluated in most modern neuroimaging studies, was also found to be reduced in a group of relatively healthy adults with T2DM compared to healthy controls (5.4 vs. 6.2 cm^3 ; d=1.4).[46] This could explain, at least in part, the poor memory function seen in many older adults with T2DM. The best predictor of hippocampal atrophy was HbA1C values. Much attention has recently been focused on rates of dementia in older patients with T2DM and it has been argued that diabetes is a significant risk factor for the subsequent development of Alzheimer's disease or vascular dementia. Several recent studies and review articles have noted an increased risk of dementia that ranges from 1.2–2.3 for Alzheimer's disease and 2.2–3.4 for vascular dementia.[44–46] Type 2 diabetes mellitus also has a significant negative impact on activities of daily living, with rates of functional disability doubled (e.g. ability to do housework efficiently and without assistance or walk 2–3 blocks.[47]

The degree of chronic hyperglycemia, as indexed by HbA1C levels, is the best (albeit imperfect) predictor of impairment in the older patient with diabetes, although a growing body of research has identified other diabetes-related conditions, including hyperinsulinemia,[48,49] hypertension and hypercholesterolemia.[50]

Prevalence of Cognitive Dysfunction in Diabetes

Mild cognitive impairment (MCI) is an entity which has been variously labeled as benign senescent forgetfulness, late life forgetfulness, age associated memory impairment, questionable dementia and aging-associated cognitive decline. However, most of the research workers agree that MCI individuals have subjective and objective impairment in memory. In Europe, the MCI is considered among individuals who show impairment on tests of complex function. Our community based study has shown a prevalence of MCI based on Peterson criteria[53] ranging from 3.13 to 6.73% of the non demented population in different age bands from 50 to 80 years and above. Overall prevalence rate was 6.04%. This correlated well with the study from USA[53] and Finland.[54] The prevalence rates fluctuate in earlier age group (60–64 and 65–69 years) than advanced age groups (≥70 years). This may be confounding as the age statement of the participating subjects depended on memory bias since the birth registration was not compulsory when the elderly persons were born. However age related prevalence showed very mild but steady increase in prevalence from 70 years onward. In spite of similar prevalence of MCI in western countries and in the present study the lower rate of prevalence of dementia in our country as compared to developed countries may be related to age related factors and other environmental factors such as diet which may confer a protective influence.[55] This needs to be probed further. There are divergent views that MCI may progress either to Alzheimer's disease or vascular dementia.[57]

There are not too many data of prevalence of cognitive dysfunction in diabetic patients.[58] Prevalence of mild cognitive dysfunction (pre-dementia) in elderly persons aged more than 65 years is 19% and 29% in elderly persons aged more than 85 years. Diabetes is associated with premature mortality and is a risk factor for mild cognitive dysfunction and both Alzheimer's disease[59,63–65] and vascular dementia.[59–62] Indeed individuals with diabetes are 1.5 times more likely to experience cognitive dysfunction than individuals without diabetes.[66]

Implications to Clinical Practice

Control of diabetes may help improve cognition and help in better management of diabetes as cognitive impairment disrupts the individual's usual life style, interferes with self care activities and hampers diabetes control as well.

Another implication is that older patients with diabetes may often have concomitant cognitive dysfunction resulting in suboptimal adherence to complicated diabetes treatment regimes. Preventive measures such as abstinence from smoking might improve the cognitive outcome of such patients.

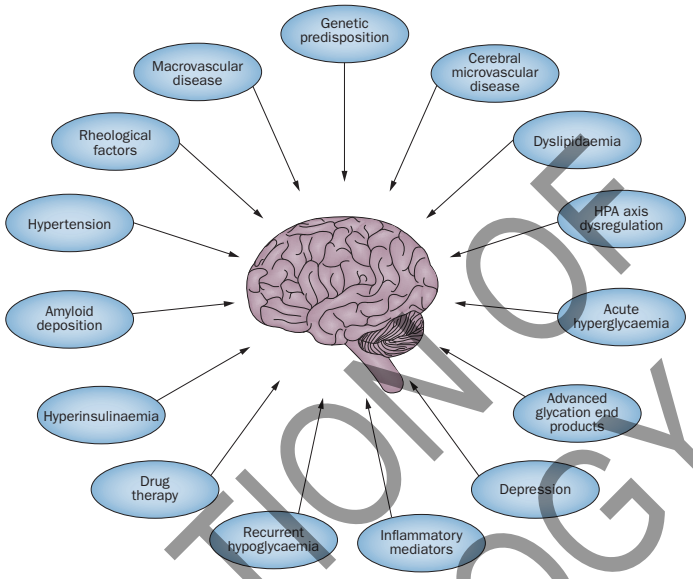


Figure 2 | Potential mediators of cognitive impairment in patients with type 2 diabetes mellitus.

Summary

Extensive research is being conducted across the globe to show the positive effect of good glycemic control over cognition in diabetic patients. Cognitive decline is becoming a serious issue as the longevity of life due to control of various other complications is increasing in diabetics. People are gathering the concept of "adding life to years and not just years to life". Cognitive decline might make living unbearable. Thus physicians need to get more and more aware regarding this issue and simple measure of assessing by clinical questionnaires and OPD based questions requiring very less time to identify the cognitive domains impaired and making caregivers aware of the same might really add life to years of diabetic patients.

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