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Research Paper

Cognitive Impairment in Diabetes Mellitus – A Review

Medical Science

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ABSTRACT

With Diabetes Mellitus spreading as a tsunami,we need to focus on the disease as well as its complications and theirmanagement. Effect of diabetes on central nervous system is relatively unexplored .Even modest effect on cognition can have significant impact on quality of life and tremendous public health implications. This article aims to explore more about this potential complication of diabetes with special emphasis on possible mechanisms, existing literature and studies and potential scope for future.

INTRODUCTION:

Diabetes Mellitus(DM) refers to a group of common metabolic disorders that share phenotype ofhyperglycaemia. Diabetes mellitus has been considered "a special kind of accelerated aging"because it increases an individual's susceptibility to degenerative disease. It has been associated with several macro and microvascular complications. [1] Therole of complications in management of diabetes remains crucial.

The prevalence of Diabetes Mellitus is rapidly rising all over the globe at an alarming rate.The Diabetes Atlas 5th edition shows that in 2011 there are 366 million people with diabetes inthe world with India having the largest burden in the world.[2, 3]India is witnessing a statewhere diabetes has reached a pandemic proportion. The national prevalence of diabetes in Indiais estimated 7.1%, although there are significant differences across geographic areas andsocioeconomic classes.[3]With rapidly escalating rates of diabetes we have also witnessed newtrends like Asian Indians develop diabetes at a younger age, at least 10-15 years earlier thanCaucasian population. [4]The shift in age of onset is alarming as this would leave us withchallenging issues like more disease burden and more chances of complications arising due todisease. Although the role of complications affecting peripheral nervous system associated withthe disease is well known, its effect on central nervous system is relatively unexplored arena.Recently, evidence has accumulated to suggest that diabetes has a role in cognitiveimpairment. This article aims to explore more about this potentially alarming complication in diabetes because even a modest effect on cognitive function hassignificant public health implications. Cognitive dysfunction is associated with poorer ability in diabetes self-care,decreased adherence to anti-diabetic treatment and general poor quality of life.

Cognitive impairment in DM

Basic survival and living is meaningful with the back ground of effective functioning of cognitive abilities. Cognitive functions or the higher mental functions are at the core of what defines competent and independent individuals. The review of various literature from various perspective of understanding the pathology,physiology, neuropsychology ,neurobiology have paved way to understand cognition and itsimplications in greater depth. Understanding of cognitive deficits in various chronic medicalconditions has been relatively unexplored but is gaining significance.

Several studies have found that Diabetes is related to dementia and lower levels of cognitive function.[5-12] Further, some studies found that Diabetes was associatedwith lower scores on some individual cognitive tests, but not on others suggesting that Diabetesmay differentially affect cognition.[6-8]Several evidence also implicate role of Type 2 DM as a risk of developing dementia, as inAlzheimer's Disease.[5,13-15.]

We hereby make an attempt toexplore the realms of cognition and its association with widely prevalent medical condition – Diabetes.

Mild cognitive impairment

Mild cognitive impairment (MCI) iswidely used in studies as an intermediate stage between cognitive normalcy and dementia. [16]Concept of mild cognitive impairment (MCI) criteria include the following: (i) the person is neithernormal nor demented; (ii) there is evidence of cognitive deterioration shown by eitherobjectively measured decline over time and/or subjective report of decline by self and/orinformant in conjunction with objective cognitive deficits; and (iii) activities of daily living arepreserved and complex instrumental functions are either intact or minimally impaired. [17]

MCInow appears, however, to be a heterogeneous clinical entity.Due to heterogeneity indefinitionsnew clinical criteria have thus been proposed for use in research and in clinical practice:1) cognitive complaint from the patient, family, or both, 2) report by the subject or reporter of adecline in cognitive or functional performance, relative to previous abilities,3) cognitive disorders evidenced by clinical evaluation: impairment in memory oranother cognitive domain, 4) cognitive impairment without any repercussions on daily life, evenif the subject reports difficulties concerning complex daily activities, and 5) no dementia. [18]

It can be perceived as a subtle sign before full frank dementia develops could be an alarm. Can this be addressed and prevented? Early studies are showing a ray of hope and if widerprospective studies can translate it into reality, it would probably be the most revolutionizingdiscovery to improve the quality of life of millions of people worldwide.

Structural correlation (anatomical and physiological) basisto cognitive functions

Neuroimaging, experimental neurosurgical procedures, electrophysiology, animal studies on rats and primates have widened our understanding ofbrain functions and paved way in understanding some aspects of the complex neurobiology ofdementia. Dementia syndrome result from the disruption of neuronal networks, location andseverity of synaptic and neuronal loss trans-

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late to produce specific clinical feature.Recent research has confirmed a role for dorsolateral prefrontal cortex (PFC) in the manipulationand updating of information in working memory and cortical striatal pathways produce specific effects on beha vior.[1,19]Diseasespredominantly affecting frontal and subcortical regions are more likely to have difficulties withjudgment, mood and behavior.[1]Neurobiological studies have revealed the difference in various neurotransmitters deficit profilessuch as cholinergic signaling is found to be vital in attention and memory. This can be thepharmaceutical target in management of dementia.[20]

Cognitive impairment in Diabetics:

Possible mechanisms through which diabetes could increase risk of dementia

The pathophysiology and mechanism by which diabetes could cause cognitive impairment is intriguing and is probably multifactorial. More research in understanding the mechanism of this mystifying combination will not only help us know more of the disease process but also possibly open new vistas in our knowledge of basis of physiology and pathology of cognition Also the possible link of increased Alzheimer's disease in diabetics may possibly help us in increasing our knowledge about the possible mechanisms of cognition.[13-15]

The role of insulin resistance as well as vascular pathology has been proposed. Experimental studies found that hippocampal long-term potentiation (LTP) impairment in diabetics manifested by impairment of spatial memory, but it'srelation to hyperglycemia, the duration of diabetes, learning and memory has always beendifferently reported by different researches. Insulin resistance theory makes an effort to join the missing links between Alzheimer's anddiabetes and link mechanism for cognitive dysfunction in both.Recent work has shown insulinsensitiveglucose transporters are localized to the same regions supporting memory and thatinsulin plays a role in memory functions.21-24

Hyperinsulinemiais possible mechanism for aggregation of amyloid products Insulysin- the degrading enzyme forboth insulin and neurotoxic amyloid proteolysis is much more selective for insulin than for Abeta, brain hyperinsulinism may deprive Abeta proteins of its main clearance mechanismthereby accelerating cognitive decline.[21-25]

Studies to show the therapeutic effect of insulin sensitizers on cognition has been encouraging.[24] Also the encouraging role of intranasal insulin for improving memory function have been studied.[26]

Other mechanisms postulated that chronic hyperglycaemia primarily stimulates the formation of Advanced Glucose End products (AGEs), which leads to an overproduction of Reactive Oxygen Species (ROS). Protein glycation and increased oxidative stress are the two main mechanisms involved in biological aging, both being also probably related to the etiopathogenesis of cognitive dysfunction in diabetes. [25]

Other suggested theories of pathophysiology include inflammatory cytokines[27]studies have emphasized that macro and microangiopathy combine to reducecerebral blood flow and reactivity and resulting conditions of hypoxia and ischemia canlead to cell death [28-30]or the development of lesions in the white matter [31].

Previous studies

Many studies have shown how DM can affect different aspects of cognition.

In study of more than 1400 older community-dwelling black and white persons without dementia, enrolled from Memory and Aging Project, epidemiologic, community-based cohort studies ,it was found that diabetes was associated withimpaired semantic memory, but not with other cognitive domains or global cognition.[6]

In a prospective cohort study of 8,442 non-diabetic and 516 diabetic participants i.e.Atherosclerosis Risk in Communities (ARIC) study, it was concluded that diabetes itself wasassociated with decline in one cognitive domain (executive function and processing speed) buthigher values of baseline HbA1cwere not independently associated with cognitive decline over a6 year period in persons either with or without diabetes.[7]

Elias et al in Framingham studyconcluded that duration of NIDDM was associated with increased risk for poor performance ontests of verbal memory and concept formation.[8]Okereke et al in there prospective study showed diabetes and its duration affecting cognitivescoring and verbal memory.[9]

In cognitive analysis of community dwelling elderly women with and without diabetes it was seen after multivariate adjustment, women with type 2 diabetes scored lower on cognitive tests than women without diabetes. On the general test of cognition (TICS), the mean difference in score between women with and without diabetes was -0.60 which is significant.[10]

Hassing et al in there longitudinal population based study points [11]and Prospective cohort study by Yaffe et al [12]concluded that type 2diabetes is associated with accelerated cognitive decline in old age and poor glucose control are associated withworse cognitive function and greater decline.

A number of studies evaluating specific cognitive domains prospectively have demonstrated performance declines in important domains that might impact on independent diabetes self-care, specifically memory [8-11] executive function [7, 9,10,32,33 53,55], language [9, 10] information processing speed[9,11,33,3452,55], verbal memory[35], and abstract reasoning.[8]

In RanchoBernardo cohort there was no relation between Type 2 DM and cognitive function at baseline.The possible proposed explanation could be most of the female participants had duration ofdiabetes of less than 3 years. [36]Vandenberg et al in there study interpretation concluded that in non-demented patients with type2 diabetes, cognitive decline over 4 years is largely within the range of what can be viewed innormal ageing.[37]

On the whole earlier studies have substantial variations in cohort size, selection biases, and the rigor of diabetes ascertainment and, as for dementia, possibly under represent the full impact of diabetes on cognition. Individual aspect of cognition in diabetics had inconsistent results and there wasvariability in decline of different cognitive parameters. This inconsistency can probably beexplained due to inhomogeneity in population, lack of consideration of confounding factors,variability of tests used, subjectivity in analysis and administration of certain tests that were usedor may be regional, genetic, environmental influences in the determination of development ofthis complication Another significant limitation is the frequent lack ofconsideration of important covariates. For example, only selected studies adjusted forhypertension[8,9,10,34]education[8,9,10,11,34] lipids[9],vascular disease[8,34], and mood[37] and no publishedstudy has included all these important covariates into the analyses thus far.

An Indian scenario

Studies to find the correlation between diabetes and cognitive function done in Indian settings are few and mostly cross sectional. Study conducted by Dubey et al at Jaipur assessed a sample of 50 diabetics and30 control subjects for their cognitive functions and hyperglycaemia wassignificantly and negatively correlated with immediate memory and attention, verbal memory,psychomotor functioning (DSST), and visuo-spatial memory.[38]

Small cross sectional study conducted by Shubha et al in Coimbatore concluded that diabetics have lower cognitive levels compared to non-diabetics.[39] However the study sample was too small and included only thirty males and females above the age of 50 years, with and without diabetes. In their study the diabetics showed significant decreased MMSE and 3MS scores. The correlation of age, sex, the duration of diabetes and HbA1C among the diabetics with cognition status was not significant.[39]In yet other study from South India in elderly

type2 diabetics concluded there is correlation between depression and global cognitive score.Depression seems to be associated with duration of diabetes and its control.[40]G.R. Sridhar concluded in his study that Subjects with Type 1 Diabetes can have cognitivedysfunction, eating disorders and developmental disturbances.[41]In triad of diabetes, cognitive dysfunction and psychiatric disorder each may worsen one other. In another study on younger diabetics conducted at AIIMS concluded minimal cognitive impairment is seen in relatively younger diabetics as well. [42] Although the sample size in all of these studies was small and design was mostly cross sectional, more prospective studies and randomized studies are required to find the relation ofcognitive dysfunction and diabetes mellitus in a more refined way.

The data of cognitive profile in Diabetes in Indian Subcontinent is scarce and inadequate to drawconclusive results. However it shows a possible link between poor cognition, diabetes andcognitive complications.

Conclusion

If diabetes increases risk of cognitive impairments and dementia even mildly, the public health implications could beenormous. Possibly if we can alter the progression of disease by identifying factors which arerisk factors for dementia or if good control of diabetes could possibly prevent dementia it will add quality years to lifeof many people who unfortunately suffer from triple D-Diabetes and Dementia and Disablinglife.The past decade has shown tremendous interest in area of cognition, brain physiology,unravelling the mysteries of memory, learning, exploring the molecular level of brain and itscomplex actions identifying the risks which may alter the much valued functions of brain butstill lot more remains to be unraveled. Also such an association will not only have social implications but will also open gates for moreresearch on the delicate balance for prevention and control of the two disabling duo…i.e.diabetes and dementia.Health professionals caring for people with diabetes must be trained to recognize and manage co-morbidcognitive dysfunction conditions that commonly occur. More study in this potentially important aspect in management of diabetes is the need of thehour. More longitudinal studies with large sample size and more detailed cognitive assessmentscan throw more insight into the current problem.

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