

Diabetes Mellitus Type 2 as a Major Risk Factor of Developing Alzheimer Disease in Pakistani Population

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ABSTRACT

Background: Diabetes mellitus type-2 (DMT2) could increase the risk of Alzheimers disease (AD) specifically related dementia, through several biological pathways, but the relationship between DM and the development of AD remains uncertain.

Objectives: The aim of the present study was to explore the status of diabetes as one of the major risk factors of cognitive decline and dementia in AD and to compare the risk of developing AD among subjects with and without DM.

Methods: The baseline examination was conducted from January 2008 to October 2010 on 611 subjects of both sexes who were above 50 years of age, to detect the prevalent cases of dementia. The Mini-Mental State Examination (MMSE) was done on all of these subjects. At each follow-up, random blood glucose levels were determined; all participants underwent a comprehensive clinical examination

Results: The study shows that risk of “dementia” increases with age, duration of diabetes and relevant conditions e.g. obesity. The risk of “Dementia increases with duration of diabetes and the chi-square tests verify the claim. The calculated chi-square test statistics value was found to be 130.26 with degrees of freedom 9, corresponding p-value is (<0.005). It was also found that obese diabetics had higher risk of developing AD, as well as those having borderline diabetes were also at the higher risk.

Conclusion: The present study revealed that DMT2 is one of the major risk factors that would increase the risk of AD; but along with other factors like obesity, lifestyle and aging, it can lead to AD and related pathological conditions in individuals markedly characterized by dementia and cognitive decline.

Key words: Diabetes mellitus type-2 (DMT2), alzheimer’s disease (AD), dementia, cognitive decline, obesity.

INTRODUCTION

Incidence rates for AD have been studied extensively throughout the world.¹⁻⁴ Studies from various populations although have consistently shown an association between diabetes and cognitive deficits or dementia,^{4,5} but the precise relationship remains unclear. Insulin resistance is present in most diabetic patients and is associated with compensatory hyperinsulinemia, which is one of the suggested mechanisms to explain the increased risk of Alzheimer’s disease in diabetic patients.⁶⁻⁸ Now-a-days Type-2 DM is common in old age^{5,9} that can be a risk factor for dementia and cognitive decline.^{10,11} Few evidences also support the

association of borderline diabetes and risk of dementia and Alzheimer’s disease.¹² Besides adding many complications in body, diabetes can contribute to poor memory and lessen cerebral intellectual functions in an assortment of ways. The complications related to it and its pathophysiology as obesity, daily stress, aging and unhealthy lifestyles may worsen the hyperglycemia that is reported to be among a few reasons that put our population at higher risk of memory and thinking problems as we grow older.¹³ The findings are of great concern, as prevalence of diabetes is alarmingly increasing in Pakistan²⁷ and hence may contribute to the growing number of Alzheimer’s cases in coming years.

OBJECTIVES

To explore the status of diabetes as one of the major risk factors of cognitive decline and dementia in AD.

To compare the risk of developing AD among subjects with and without DM.

METHODOLOGY

a Males and females of 50 years and above.

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- b Complaints of memory loss reflected in everyday problems such as difficulty in remembering names of the individuals following introduction, misplacing objects, difficulty remembering multiple items to be purchased or multiple tasks to be performed, problems remembering telephone numbers or zip codes, and difficulty recalling information quickly or following distraction. Onset of memory loss should be described as a gradual phenomenon, without sudden worsening in recent months.
- c Presence of dementia with and without diabetes.

This study included 611 subjects who were above 50 years of age, to detect the prevalence of dementia. The Mini-Mental State Examination (MMSE) was done on all of these subjects. We considered the range from zero to 30, in which 27-30 was normal cognition, 21-26 was mild dementia while 10-20 was considered as moderate dementia and patient of severe dementia scored < 10. Non-diabetic older patients (n=324) and diabetics (n=287) were selected (Age >50Yrs) for this study. All preliminary diagnosed AD participants underwent a comprehensive clinical examination and cognitive tests,¹⁴ as detected previously. The diagnosis of AD was similar to that of international criteria¹⁵ and required gradual onset, progressive deterioration, and lack of any other specific causes of dementia. The Mini-Mental State Examination (MMSE) was done on all of these subjects, while our criterion for identifying Alzheimer’s disease was similar to those used by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA). At each follow-up random blood glucose level was determined, the virtually pain free method was used by using ACCU-CHEK-Active. Patients were monitored for degrees of cognitive impairment and dementia. Statistical analysis was based on incident tables to evaluate the association between the presence or absence of dementia with or without diabetes and was determined by chi-square test for independence between variables.

RESULTS

The risk of “Dementia” increases with duration of diabetes and the chi-square tests verify the claim. The calculated chi-square test statistics value was found to be 130.26 with degrees of freedom 9, corresponding p-value is (<0.005).

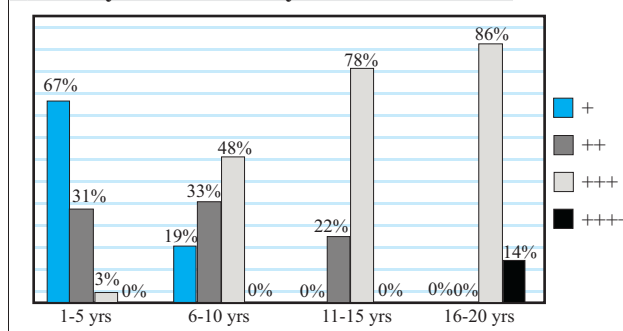
DISCUSSION

In Pakistan, diabetes is reported as a common metabolic disorder, along with other risk factors like obesity and cardiovascular problems.¹⁶ However in older individuals

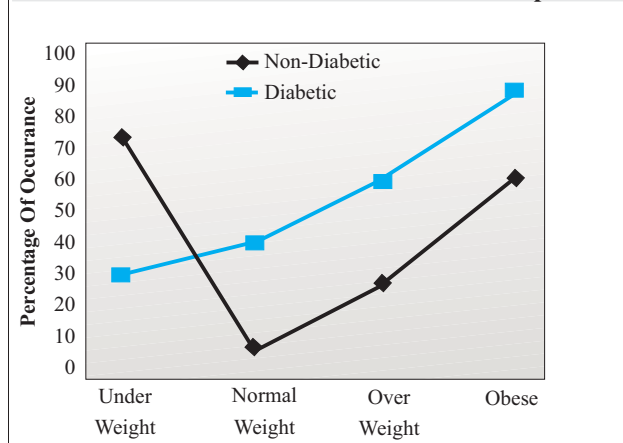
Dementia vs. Diabetes duration

Dementia	Diabetes Duration			
	1-5 yrs	6-10 yrs	11-15 yrs	16-20 yrs
+	67%	19%	0%	0%
++	31%	33%	22%	0%
+++	3%	48%	78%	86%
++++	0%	0%	0%	14%

Tendency of Dementia by Diabetic Duration



Showing relationship of BMI and occurrence of Dementia in both Diabetic & Non-Diabetic Population



dementia is a cognitive problem when observed neuro psychologically in diabetic patients with AD.¹⁷⁻¹⁸ It was hypothesized earlier that perhaps the changes in the insulin receptors in diabetes, obesity, and related insulin resistance may contribute to decreased sensitivity to insulin that can reduce synaptic plasticity in aging. These effects appear to be due to raised brain insulin level as observed in aging, obesity and diabetes which decreases the clearance of A B amyloid thus increasing amyloid toxicity.¹⁹ But there is a continuous lack of knowledge about mechanisms that can lead to impaired cognitive function in hyperglycemic patients.^{8,20}

According to the recent studies, the association between diabetes and dementia is unlikely to be due to the potential confusing effects of demographic variables such as age or sex, educational level or socioeconomic status (Shafqat, 2008). Moreover the kind of usual

neuropsychological routines observed in these patients may be the result of various interrelated pathological processes developed with the duration of disease,¹² such as damaging effects of hyperglycemia on the brain can be linked with complications of cerebrovascular disease²¹⁻²² which is known to be the major cause of the decline in processing, perception & reaction time.^{7,11} It has been suggested that duration of diabetes is responsible for changes in insulin signaling that may be a major cause of hyperglycemic brain cells leading to damaging effects like damaged blood vessels, nerve cell death or the acquisition of amyloid deposits.²⁴ Our data revealed that the older population with diabetes having obesity reported memory problems mostly when compared with non-diabetic and non-obese individuals. In our population though the actual number of diabetic patients is higher but patients who developed dementia are less and this has limited the statistical analysis for the identification of such risk factors for dementia in this subgroup. In the present study, we found that clinical cognitive decline was also becoming a common occurrence in a sample of older individuals with base line diabetes and was predicted by decline in cognitive functions.²⁵ These findings are of potential clinical importance and further confirmatory studies are needed in both diabetic and non-diabetic populations. However, the control over increasing trend of obesity and diabetes or hyperglycemia can help our population minimize the detrimental effects on brain and its functions.

CONCLUSION

Our study revealed that “Type-2 Diabetes” is a major factor (disease) that will increase the risk of AD in Pakistan; along with other factors like obesity, lifestyle and aging. Prolonged duration of diabetes can lead to AD and related pathological conditions in individuals markedly characterized by dementia and cognitive decline. Several limitations of our study warrant further discussion. Our epidemiological observations, coupled with emerging experimental evidence, support a possible role of diabetes in the pathogenesis of AD. Our data also raise the possibility that obesity and related factors like gender, age and lifestyles might provide a link and could be useful for early detection of risk and prevention of AD and its related dementia.²⁶

REFERENCES

- 1 Bachman DL, Wolf PA, Linn R. Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. *Neurology* 1992; 42:115-9.
- 2 Bachman DL, Wolf PA, Linn RT. Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. *Neurology* 1993; 43:515-9.
- 3 Breteler MM, Claus JJ, Van Duijn CM, Launer LJ, Hofman A. Epidemiology of Alzheimer's disease. *Epidemiol Rev* 1992; 14:59-82.
- 4 Fratiglioni L, De Ronchi D, Aguero-Torres H. Worldwide prevalence and incidence of dementia. *Drugs Aging* 1999; 15:365-75.
- 5 Ott A, Breteler MM, Van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. *Am J Epidemiol* 1998; 147:574-80.
- 6 Cook DG, Leverenz JB, McMillan PJ. Reduced Hippocampal Insulin-Degrading Enzyme in Late-Onset Alzheimer's Disease Is Associated with the Apolipoprotein E-4 Allele. *Am J Pathol* 2003; 162:313-9.
- 7 MacKnight C, Rockwood K, Awalt E, McDowell I. Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian Study of Health and Aging. *Dement Geriatr Cogn Disord* 2002; 14:77- 83.
- 8 Ott A, Stolk RP, Van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam Study. *Neurology* 1999; 3:1937-42.
- 9 Zhang M, Katzman R, Yu E, Liu W, Xiao SF, Yan H. A preliminary analysis of incidence of dementia in Shanghai, China. *Psychiatry Clin Neurosci* 1998; 52:291-4.
- 10 De la Monte SM, Wands JR. Alzheimer's Disease is Type 3 Diabetes—Evidence Reviewed. *J Diabetes Sci Technol* 2008; 2:1101-13.
- 11 Hassing LB, Johansson B, Nilsson SE, Berg S, Pedersen NL, Gatz M, et al. Diabetes mellitus is a risk factor for vascular dementia, but not for Alzheimer's disease: a population-based study of the oldest old. *IntPsychogeriatr* 2002; 14:239-48.
- 12 Xu WL, Qiu CX, Wahlin A, Winblad B, Fratiglioni L. Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology* 2004; 63:11816.
- 13 Launer LJ, Andersen K, Dewey ME. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups European Studies of Dementia. *Neurology* 1999; 52:78-84.
- 14 Folstein M, Folstein SE, McHugh PR. Mini-Mental State, a Practical Method for Grading the Cognitive State of Patients for the Clinician. *Journal of Psychiatric Research* 1975; 12:189-98.

- 15 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; 34:939-44.
- 16 Clark G, Zaman H, Chaudry AG. Pakistan Aging Study, Preliminary Report on Six Sites in Punjab: Testing Traditional Assumptions about Family Support. Islamabad: Government of Pakistan, Ministry of Women Development, Social welfare and Special Education. National Council of Social Welfare (NCSW).
- 17 Ali SM, Kiani MF. Ageing and Poverty in Pakistan. Islamabad: Pakistan Institute of Development Economics. MIMAP Technical Paper Series No. 18. 2003.
- 18 Afzal M. Study on the Situation of Elderly People in Pakistan. New York: United Nations 1999
- 19 Messier, C. and Teutenberg, K. The Role of Insulin, Insulin Growth Factor, and Insulin-Degrading Enzyme in Brain Aging and Alzheimer's Disease. *Neural Plast* 2005; 12:311-28.
- 20 Wahlin A, Nilsson E, Fastbom J: Cognitive performance in very old diabetic persons: the impact of semantic structure, preclinical dementia, and impending death. *Neuropsychology* 2002; 16:208-16.
- 21 Cole AR, Astell A, Green C, Sutherland C. Molecular connections between dementia and diabetes. *Neurosci Biobehav Rev* 2007; 31:1046-63.
- 22 Luchsinger JA. Insulin Resistance, Type 2 Diabetes, and AD: Cerebrovascular Disease or Neurodegeneration. *Neurology* 2010; 75:758-9.
- 23 Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer's disease. *Neurology* 2005; 65:545-51.
- 24 Matsuzaki K, Sasaki Y, Tanizaki. Insulin Resistance is Associated with the Pathology of Alzheimer Disease: The Hisayama Study. *Neurology* 2010; 75:764-70.
- 25 Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function 2004; 61:661-6.
- 26 De la Monte SM, Longato L, Tong M, Wands JR. Insulin resistance and neurodegeneration: roles of obesity, type 2 diabetes mellitus and non-alcoholics steatohepatitis. *Curr Opin Investig Drugs* 2009; 10:1049-60.
- 27 Shafqat S. Alzheimer disease therapeutics: Perspectives from developing world. *J Alzheimers Dis* 2008; 15:285-7.

