



DEMENTIA IN DIABETES: A REVIEW

Dr. Faraz Farishta*¹, Dr. Mohammed Salman Hadi², Dr. Mohammed Mudassir³

¹Consultant Endocrinologist. Medicity Hospital, Hyderabad, India.

²Registrar, Department Of General Internal Medicine Medicity Hospital.

³registrar, Department Of General Internal Medicine, Medicity Hospital.

Article Received on 14/06/2015

Article Revised on 05/07/2015

Article Accepted on 26/07/2015

*Correspondence for

Author

Dr. Faraz Farishta,

Consultant

Endocrinologist. Medicity

Hospital, Hyderabad, India.

INTRODUCTION

The world health organization definition of diabetes is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either^[1]: Fasting plasma glucose $>$, 7.0 mmol/l (126 mg / dl) on with a glucose tolerance test, two hours after the oral dose a plasma glucose $>>$ 11.1 mmol/l (200 mg / dl). A Glycated

Hemoglobin of greater than 6.5% is another method of diagnosing diabetes^[2] as is random blood sugar of greater than 11.1 mmol/l (200 mg / dl) in association with typical symptoms.^[3] Globally as of 2010 it is estimated that there are 258 million people diabetes with type 2 making up about 90% of the cases. The term " Dementia " refers to the clinical syndrome of impairment in multiple domains of cognitive function, which must include memory in a patient who remains alert with normal arousal.^[4] A recent survey done by Harvard university School of public Health and the Alzheimer's Europe consortium revealed that the second leading health concern (after cancer) among adults is Dementia.^[5] We will explore the complex relationship between Dementia and Diabetes in this review.

DIABETES AND DEMENTIA TYPES-RELATIONSHIP.

Compared to people without diabetes, people with diabetes have a greater rate of decline in cognitive function and a greater risk of cognitive decline.^[6] Geert Jan Biessels et al, identified 14 eligible longitudinal population based studies if variable methodological quality to understand relationship between diabetes and major types of dementia's. The finding of mechanistic studies suggest that vascular disease and alternations in glucose, insulin, and amyloid metabolism underlie the pathophysiology but which of these mechanisms are clinically relevant in unclear.^[7] Multiple interactions, some of which are yet to be elucidated

may underlie the relationship.

PATHOGENESIS.

Molecular defects associated with the development of diabetes also contribute to increased risk of all – types of dementia, including Alzheimer’s disease, Vascular dementia and picks disease^[8] Rita pilla et-al evaluated the association of diabetes alone combined with the Apolipoprotein E (APOE) gene with incident Dementia and Neuropathological outcomes in a population based cohort of 2574 Japanese – American men enrolled in the Honolulu’s – Asia Aging study including 216 subjects who underwent autopsy, type 2 diabetes was associated with total dementia, Alzheimer’s disease and Vascular dementia. Individuals with both type 2 diabetes and the APOE E4 allele had RR of 5.5 for AD compared with those with neither risk factor. Participants with type 2 diabetes and E4 allele had a higher number of hippocampal neurotic plaques and neurofibrillary tangles in the cortex and hippocampus and they had a higher risk of cerebral amyloid angiopathy. The association between diabetes and AD is particularly strong among carriers of APOE E4 allele. The Neuropathological data are consistent with the clinical results.^[9]

F. Pasquier et.al. also found evidence for an elevated risk of both Vascular Dementia, Alzheimer’s disease in Patient with Diabetes Mellitus type 2, albeit with strong interaction of other factors such as Hypertension, Dyslipidemia, APOE genotype diabetes is an independent predictor of post stroke dementia. Diabetes Mellitus being an atherogenic risk factor, it may increase risk of dementia through association with stroke, causing Vascular dementia and also stable perfusion abnormalities through glycosylated products may exacerbates Alzheimer’s disease through direct interaction between the two pathological process or through cognitive impairment secondary to Cerebrovascular disease unmasking Alzheimer’s disease at an earlier stage than it would otherwise be apparent. Increased risk of AD may also be mediated by the exacerbation of B- amyloid Neurotoxicity by advanced glycosylation end products identified in the matrix of Neurofibrillary tangles and amyloid plaques in AS brains or association with insulin function decreased cholinergic transport across blood brain barrier observed in diabetic animals may exacerbate cognitive impairment in AD.^[10]

PATHOPHYSIOLOGY

Population based studies have shown that those with type 2 diabetes mellitus have an increased risk of cognitive impairment, dementia and Neurodegeneration. There are many

mechanisms through which diabetes could increased risk of dementia, including glycemia, insulin resistance, oxidative stress, advanced glycation end products, inflammatory cytokines and micro vascular disease^[11] Krabbe et al found that low levels of BDNF accompany impaired glucose metabolism, decreased BDNF may be pathogenic factor involved not only in dementia and depression, but also in type 2 diabetes, potentially explaining clustering of there condition in Epidemiological studies.^[12]

Chin cheng Hsu et al found that incidence of dementia is increased in diabetes mellitus type 2 and reduced by the use of sulfonylurea and metformin.^[13] Studies by A.Ott et-al suggested that Alzheimer's disease may be more frequent in elderly diabetic patients treated with insulin.^[14]

Welll Xu et-al concluded that borderline diabetes is associated with increased risk of dementia and Alzheimer's disease, the risk effect is independent of the future development of diabetes borderline diabetes may interact with severe systolic Hypertension to multiply the risk of Alzheimer's disease^[15] W.L. Xu et al found that diabetes mellitus increased the risk of dementia and vascular dementia is especially very high when diabetes mellitus occur together with severe systolic hypertension or heart disease^[16], Rachel A. whitemer et al found that among older patients with type 2 diabetes, a history of severe hypoglycemia episodes was associated with greater risk of dementia whether minor hypoglycemia episode increase risk of dementia is unknown^[17] J.D. curb et al found no association between AD and diabetes, present either 25 or 15 years previously, was found after adjustment for age and education in a multiple regression model. A significant association was found between impaired glucose tolerance at baseline and Vascular dementia.^[18]

DEMENTIA AND OTHER VASCULAR RISK FACTORS.

Kloppenburg et al conducted longitudinal population based studies that assessed the incidence of dementia in relation to Diabetes Mellitus, Hypertension, Dyslipidaemia or obesity was included. All 4 risk factors were associated with increased risk of dementia, but results of studies on diabetes and obesity were most consistent. At midlife, the population attributable risk of dementia was highest for Hypertension up to 3% of cases of late life dementia later in life diabetes appear to convey the highest risk of dementia^[19] whitemer et al found that presence of multiple Cardio vascular risk factors at mid life substantially increased risk of later use dementia in a done dependent manner.^[20]

CONCLUSION

There is substantial evidence that acute hypo and Hypoglycemia have disruptive effects on CNS, although relatively less is known about the slowly developing end - organ damage to CNS that may represent of cognitive by electrophysiological and structures changes and impairment of cognitive functioning.^[21] Furthermore it has been shown that insulin affects several brain functioning including cognition and memory and reveals clinical studies have established links between insulin, resistance, Diabetes Mellitus and AD (Gasparine et.al 2002) recent evidence indicates that insulin regulates the metabolism of AB and tau proteins, which are involved in the formation of two hallmark of Alzheimer's disease, AB deposits and Neurofibrillary tangles, respectively (mandelkow et al 1992, Solano et al 2000, Gasparise et al 2001).^[21] Although AD and Diabetes Mellitus possess several overlapping features, mitochondrial dysfunction is one of the most relevant suggesting that mitochondria is a bridge between both disease.^[21]

CHALLENGES AHEAD.

Though significant amount of work has been done to elucidate the relationship between Diabetes Mellitus and different types of dementia, Lot need to be done to understand complex associations which are directly or indirectly helpful in preventing cognitive decline in diabetic patients.

REFERENCES

1. World Health Organization "Definition, diagnosis and classification of diabetes mellitus and its complications: Report of WHO consultation part 1. Diagnosis and classification of diabetes Mellitus – Retrieved 29/05/2007.
2. Williams textbook of Endocrinology (12th ed) Philadelphia: Elsevier / Saunders PP 1371-1435 ISBN 978-1437703425.
3. Vijan. S (2010 -03-02) "Type 2 diabetes " Annals of internal medicine 152 (5) ITC 31-15 quiz ITC 316 doi: 10, 1059 / 0003 – 4819 – 152 – 5-201003020-01003. PMID 20194231.
4. Rossor, M; NeuroPsychological disorder, dementia and behavioral Neurology; Donaghy, M Brains Disease of the Nervous System, O.U.P. ISBN 0192626183
5. Swaminathan, N. How to save your brain, Psychology today, 2012 February; 45: 74-79.
6. Cukierman, T; Gerstein H.C, Williamson. J.D. COGNITIVE DECLINE AND DEMENTIA IN DIABETES – SYSTEMATIC OVERVIEW OF PROSPECTIVE

- OBSERVATIONAL STUDIES – DIABETOLOGIA, 48(12): 2460 – 2469, DOI: 10, 1007/s00125 – 005 – 0023-4.
7. Geert Jan, Salka Staekenhora, Eric Braneer, Carol Brayne, Philip schelters – Risk of dementia in diabetes mellitus : a systematic review. *The lancet Neurology*, 5(1): 64-74.
 8. Adam R Cole, Arlene Astell, Charlotte green, calum Sutherland – MOLECULAR CONNEXIONS BETWEEN DIABETES – Neurosciences, and Bio behavioral reviews, 31(7): 1046-1063.
 9. Rita Pella, Beatriz – L. Rodriguez, Lenore J. Lauren type 2 diabetes APOE gene and the risk for dementia and related Pathologies. *The Honolulu’s – Asia Aging study Diabetes April 2002*; 51(4): 1256 – 1262.
 10. 10)F. Pasquier, A. Boulogne, D leys, P Fountains – Diabetes Mellitus and Dementia DIABETES AND METABOLISM, November 2006; 32(5): 403-414.
 11. Rachel.A. whitmer type 2 diabetes and risk of cognitive impairment and dementia. *CURRENT NEUROLOGY AND NEUROSCINECE REPORTS*, 7(5): 373 – 380 DOI: 10, 1007/S 11910 – 007 – 0058 – 7.
 12. K.S. Crabbe et. Al brain derived neurotrophic factor (BDNF) and Type 2 diabetes – *Diabetologia*, 50(2): 431 – 438 DOI: 10, 1007/500125 – 006 – 0537 – 4.
 13. Chin- cheng Hsu, Mark L. Wahl quist, Meei – shyuan lee, Hsin – Ni – Tsai – INCIDENCE OF DEMENTIA IS INCREASED IN TYPE 2 DIABETES AND REDUCED BY THE USE OF SULFONYLUREAS AND METAFORMIN *JOURNAL OF ALZHEIMENS DISEASE*, 2011; 24(3): 458 – 493.
 14. A. ott, R.P stolk, A. Hofman, F-van, Hauk amp, D.E. Grobbee and M.M.B. breteler association of diabetes mellitus and dementia: The Rotterdam study: *Diabetologia* 39(11): 1392 – 1397, DOI: 10.1007/S 001250050588.
 15. Well X4, chengxuan qlu, bengt winblad, Laura fratiglioni – the effect of borderline Diabetes on the risk of dementia and Alzheimer’s disease. *Diabetes January 2007*; 50 (1): DOI: 10, 2337 / d6060 – 0879.
 16. W.L X4, C.X GIU, A wahim, B. Winblad, L. Flatiglioni Diabetes Mellitus, and risk of dementia in the Kungsholmein project – A 6 year follow up study. *Neurology October 12, 2004*; 60(7): 1181 DOI 10.1212 / 01 WNZ 0000140291. 86406. D.
 17. Rachel: A Whiteman, Andrew J. Karter, Kristine yaffe, Charles P, Quesen berry, Joseph V Selby – Hypoglycemia episode and risk of dementia in older patients with type 2 Diabetes Mellitus *JAMA* 2009; 301(15): 1565 – 1572, DOI: 10.1001 / JAMA 2009.460.
 18. J.D. Curb et.al; Longitudinal association of vascular and Alzheimer’s Dementia, *Diabetes*

- and glucose tolerance. *Neurology* march1, 1999; 52: 5971.
19. Kloppenburg R.P Esther van den Berg, L. Jape Kappells, Geert jan Beissels, Diabetes and other Vascular risk factor for dementia which factor matters most? A systematic review *European Journal of Pharmacology*, 6 may 2008; 858(1): 97-108.
 20. R.A white men, S.S Sidney, S. Selby, S. Claiborne Johnston, K. Yaffe midlife Cardiovascular risk factors and risk of dementia in late Left – *NEUROLOGY* – January 25, 2005; 64(2): 277 – 281.
 21. *TRENDS IN ALZHEIMERS DISEASE RESEARCH* – EileeIn M. Welsh. Nora science Publishers, Inc. ISBN 1-59454 – 938 – 9.