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Original Research Paper

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ASSOCIATION BETWEEN INFLAMMATORY MARKER AND COGNITIVE IMPAIRMENT IN DIAGNOSED TYPE 2 DIABETES MELLITUS: A CASE CONTROL STUDY.

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a common metabolic disease, especially in older people, with global prevalence estimates ranging from 2.8% in 2000 to a projected 4.4% in 2030 (Wild S et al.2004).

Objectives: The present study was undertaken to assess association between inflammatory marker& Cognitive impairement in people with type 2 diabetes mellitus.

Methods: The present study was conducted in Rajeev Gandhi Centre for Diabetes and Endocrinology and Department of Physiology on patients of Type 2 Diabetes Mellitus attending Diabetes clinic in Jawaharlal Nehru Medical college hospital, Aligarh Muslim University during year 2012-2013 after approval from the ethical committee of J. N. Medical College. Design of the study was case control.A detailed history and physical examination was carried out for every subject who entered the study as per pre-designed proforma.

Results: For cognitive impairment, Type 2 DM subjects showed significantly decrease total MMSE score with decrease in orientation, registration, attention and calculation, recall and language in comparison to controls.

Conclusion: The association between Type 2 DM and cognitive changes is becoming increasingly clear, rendering it necessary for physicians in charge of diabetic patients to have the means to assess cognitive performance as cognitive impairment among the older adults with Type 2 DM may worsen the health outcomes through negative impact on compliance with medical self care recommendations.

KEYWORDS : case-control study, diabetes mellitus, cognitive MMSC score, inflammatory marker,

Introduction:

Type 2 diabetes mellitus (T2DM) is a common metabolic disease, especially in older people, with global prevalence estimates ranging from 2.8% in 2000 to a projected 4.4% in 2030 (Wild S et al.2004) . Although type 2 diabetes is associated with several other vascular risk factors of dementia, diabetes itself has been implicated as an independent risk factor for cognitive impairment and dementia (Allen et.al,2004; Ryan CM,2005). Numerous studies have reported associations of diabetes with vascular brain damage (Biessels et.al,2002), degenerative nerve disease (Korf et.al,2006), cognitive decline and dementia or (MCI) mild cognitive illness (Velayudhan et.al,2010). The cause of cognitive impairment in type 2 diabetes is unknown, but it is most likely multifactorial. The key mechanism of neurodegeneration in diabetics may be insulin dysregulation (Craft S, Watson SG 2004). Levels of circulating inflammatory markers are elevated in people with type 2 diabetes compared with an equivalent non diabetic population (Schmidt et.al,1999) Inflammatory mediators may therefore have a role in the accelerated development of cognitive impairment in people with diabetes either by a direct effect on the brain or through an influence on the development of vascular disease. Evidence of chronic inflammation has been observed in the brains of people with dementia (Rogers et.al,2007). Among the vast array of serologic markers of systemic inflammation, the most frequently investigated are C-reactive protein (CRP), IL-3, IL-12 , interferon-alpha (IFN-α), interferon-gamma (IFN-γ) , TGF-beta1, and TNF-alpha and IL-6 , which may be appropriate markers of systemic inflammation (Teunissen et.al,2003; Schram et.al,2007). Several studies suggest that raised levels of inflammatory markers are associated with cognitive deficit and dementia. Objectives of the present study was undertaken to assess Cognitive changes in people with type 2 diabetes mellitus.

Materials and methods :

The present study was conducted in Rajeev Gandhi Centre for Diabetes and Endocrinology and Department of Physiology on patients of Type 2 Diabetes Mellitus attending Diabetes clinic in Jawaharlal Nehru Medical college hospital, Aligarh Muslim University during year 2012-2013 after approval from the ethical committee of J. N. Medical College. Design of the study was case control.

A detailed history and physical examination was carried out for every subject who entered the study as per pre-designed proforma

Total 50 patients with T2DM aged between 60 to 75 years were found with cognitive impairment on the basis of MMSE score and were asked to report endocrinology laboratory after an overnight fasting of 10-12 hours in fasting state. Clinical data were obtained of all patients included in study and Glycosylated Haemoglobin (HbA1C) and other biochemical tests were done after giving the Valid consent in written, explaining the procedure prior to entering for further investigations.The findings were compared with age, sex and BMI matched Non diabetic patients without cognitive impairment (control n=30). All type 2 diabetic patients with cognitive impairment were divided in two groups based on duration of T2DM.

Group I (n=25) with less than 15 years

Group II (n= 25) with more than 15 years.

INCLUSION CRITERIA:

Controls

- Subjects aged 60-75 years willing for study after informed consent.
- Age, sex and BMI matched Non Diabetic subjects without cognitive impairment.

Cases

- Only T2DM patients aged 60-75 years.
- The diagnosis of diabetes were made on the basis of revised American Diabetic Association Criteria i.e. fasting plasma glucose >126 mg/dl (>6.1 mmol/1) and 2 hours postprandial plasma glucose >200 mg/dl (>1 1.1 mmol/1).
- Consent were taken for detailed clinical examination,cognitive impairment and blood sample.

Exclusion criteria:

- Any systemic condition other than T2DM related to neuropathy (malnutrition, alcoholic neuropathy, renal failure).
- Any known case of chronic depression and psychiatric illness.
- Neuropathies associated with exogenous toxic agents, metals or drugs.
- Pregnancy, Post menopausal women with HRT.

Specimen Collection

Selected patients were asked to report endocrinology laboratory after an overnight fasting of 10-12 hours in fasting state. Blood samples were collected in EDTA-Na vials for estimation of HbA1C, Fluoride vials for plasma glucose, in plain vials for TNF-α.

ROUTINE INVESTIGATIONS

Plasma Glucose: Fasting and P.P.- Glucose oxidase peroxidase
Estimation of Glycosylated Haemoglobin (HbA1C): Cation exchange resin method, reagent supplied by Pointe Scientific Inc. Michigan, USA.

SPECIAL INVESTIGATIONS: (all subjects were investigated for estimation of TNF- and HbA1c)

STATISTICAL ANALYSIS: Analysis was performed using SPSS version 17.0 statistical package for windows (SPSS, Chicago, IL). Continuous variables were expressed as mean +/- S.D. or range, and qualitative data was expressed in percentages. Unpaired t tests for independent samples were used in comparing continuous data between two groups. The association between continuous variables was tested by linear correlation using Pearson's coefficient. All tests were two tailed, confidence intervals were calculated at 95% level and a P-value of < 0.05 was considered significant.

Results :

As shown in Table-1,type 2 diabetic patients show statistically significant elevation of blood sugar (fasting & post prandial),TNF-α and HbA1c levels in Comparison with controls.

Table 1 Comparison of biochemical tests between controls and type 2 diabetes mellitus subjects

	Control (n=30)	T2DM (n=50)
Blood sugar (fasting) (mg/100ml)	90.82±12.93	152.85±24.31*
Blood sugar (pp) (mg/100ml)	125.52±15.35	223.46±34.75*
TNF-α (pg/ml)	23.67±10.82	60.95±23.58*
HbA1c (%)	4.33±1.05	7.87±1.77*

*-significant at p<0.001

As shown in Table-2,type 2 diabetic patients show statistically significant decrease in Total MMSE score in Comparison with controls.

Table-2 Comparison of Cognitive impairment test (MMSE score: max-30, ≤23=cognitive impairment) between controls and Diabetic patients

MMSE	maximum	Control	T2DM
Orientation	10	9 (8.66±1.29)	8 (8.36±1.12)
Registration	3	3 (2.9±0.30)	2 (2±0.35)
Attention & Calculation	5	4 (4±0.45)	3 (3±0.01)
Recall	3	2 (2.06±0.25)	1 (1±0.03)
Language	9	8 (8±0.37)	7 (7±0.01)
Total score	30	26 (25.63±1.56)	21*(21.34±1.12)

*-significant at p<0.001
[Mean values rounded off to nearest whole number]

As shown in Table-3,all the biochemical test parameters in type 2 diabetes mellitus patients having more than 15 years of disease show increased level in Comparison with type 2 diabetes mellitus patients having less than 15 years of disease duration. However, there is statistically significant increase in TNF-α level in type 2 diabetes mellitus patients having more than 15 years of disease in Comparison with patients having less than 15 years of disease.

Table –3 Comparison of Biochemical tests in 2 groups of Type 2 Diabetes Mellitus patients

	Duration(<15 yrs) Group 1 (N=25)	Duration(>15 yrs) Group 2 (N=25)
Blood sugar (fasting) (mg/100ml)	148.31±25.19	157.39±23.00
Blood sugar (pp) (mg/100ml)	216.89±35.73	230.03±33.15
TNF-α (pg/ml)	53.51±20.31	68.38±24.65*
HbA1c (%)	7.39±1.90	8.35±1.52

*-significant at p<0.05
As shown in fig.1, Pearson product-moment correlation coefficient was computed to assess the relationship between the MMSE score and TNF-α level in Type 2 Diabetes patients. There was a negative insignificant correlation between the two variables, r = -0.256, n = 50, p = 0.073.

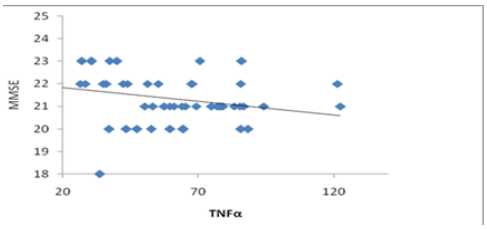

Fig.1Scatter plot showing relationship between MMSE score and TNF-α level in Type 2 Diabetes patients (all cases) Mellitus patients

DISCUSSION

Elderly patients with type 2 diabetes have an increased risk of developing cognitive impairment. Our study is to evaluate Associations between inflammatory marker and Cognitive Impairment in Diagnosed Type 2 Diabetes Mellitus and to correlate it with biomarker TNF- and glycated hemoglobin (HbA1c). Table-1of this study shows Comparison of blood glucose level (fasting & postprandial),TNF- and glycated hemoglobin (HbA1c) between all type 2 diabetes patients (n=50) and controls (30).All the parameters were significantly raised in type 2 diabetes patients in Comparison with controls. Tumour necrosis factor alpha (TNF-) which is an inflammatory marker is raised significantly in type 2 diabetes patients as compared to controls, as shown in Table-1.These findings are consistent with earlier studies done by Jatla Jyothi Swaroop et al.(2012) in their study suggested the possible role of TNF- in the pathogenesis of type-2 diabetes mellitus and the importance of reducing obesity to prevent elevated levels of the cytokine and related complications.Riccardo E. Marioni et al.(2010) studied that people with type 2 diabetes have elevated circulating levels of inflammatory markers and were associated with poorer cognitive ability. Gunel R Huseynova et al.(2009) suggested that increased level of TNF- in the stage of decompensation may show presence of deep inflammation processes in type 2 diabetes patients. Safa Refaat Abd El-moniem et al.(2009) in their study revealed a progressive elevation of serum TNF- in type 2 diabetic patients according to the progression of retinopathy and that the serum levels of TNF- were signifi-cantly correlated with the grade of retinopathy which was also significantly correlated with age and duration of diabetes but not with sex. Esposito K et al.(2002) in their study found,an increased level of circulating TNF- in type 2 diabetes mellitus patients. Shanmugam N et al.(2003) in their study concluded that Hyperglycemia stimulates TNF- secretion from monocytes and endothelial cells. Schmidt MI et al.(1999) in their study found that Levels of circulating inflammatory markers are elevated in people with type 2 diabetes compared with an equivalent non diabetic population. In the present study, Tumour necrosis factor alpha (TNF-) is significantly raised in type 2 diabetes patients in Comparison to controls because TNF- is an adipocytokine involved in systemic inflammation and stimulates the acute phase reaction (Moller DE.2000). TNF- is primarily secreted by macrophages, and also by a broad variety of other cells including adipocytes (Beutler B, Cerami A.1989; Giemeno RE, Klaman LD.2005). TNF- inhibits insulin transduction, and has an effect on glucose metabolism (Zou C, Shao J.2008; Aguirre V et al.2000). Disturbances in the TNF- metabolism have been implicated in metabolic disorders, such as obesity and insulin resistance (Groop LC et al.1991), indicating that perturbations of TNF- metabolism may affect the onset of type 2 diabetes mellitus and the progression of the disease.

Mini mental state examination (MMSE) is most widely used cognitive impairment test. It is a questionnaire based examination having five domains of cognition, which are orientation, registration, attention & calculation, recall and language. Maximum MMSE score is thirty (30) and score below or equal to twenty three

(23) is indicative of cognitive impairment. Table-2 of this study shows Comparison of cognitive impairment test between all type 2 diabetes mellitus patients (n=50) and controls (n=30).There was statistically significant decrease in total MMSE score in type 2 diabetes mellitus patients in Comparison to controls. These decrement in MMSE score in our study are in accordance with previous studies done by various worker ZHONG Yuan et al.(2012) in their study suggested that Glucose excursion is related to cognitive function in aged T2DM patients. Elevated glucose excursion decreased the MMSE score, which reflects general cognitive function. Thus, therapy aimed at controlling glucose excursion may be beneficial for maintaining cognitive function in aged T2DM patients. Priyam Mukherjee et al (2012) in their study concluded 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 problem in MMSE, praxis and naming. MARIA ROSARIA RIZZO et al. (2010) in their study reported that MAGE during a daily period was associated with an impairment of cognitive functioning independent of A1C, FPG, and PPG. The present data suggest that interventional trials in older patients with type 2 diabetes should target not only A1C, PPG, and FPG but also daily acute glucose swings. Ramit Ravona-Springer et al.(2010) in their study concluded that in individuals with questionable dementia (CDR = 0.5), diabetes is associated with a faster rate of cognitive decline as measured by the MMSE, but not in non demented (CDR = 0) or frankly demented (CDR ≥ 1) individuals. Mark W. J. Strachan et al.(2008) in their study reported that the prevalence of type 2 diabetes and dementia will rise substantially in the immediate future. It is clear that cognitive impairment and dementia occur more frequently in people with type 2 diabetes than in the general population. Table-3of this study shows Comparison of blood glucose level (fasting & post prandial),TNF-α and glycated hemoglobin (HbA1c) between the two groups of type 2 diabetes mellitus patients. All the parameters were raised in type 2 diabetes patients of group 2 in Comparison with type 2 diabetes patients of group 1.However there is significantly raised TNF-α level in type 2 diabetes patients of group 2 in Comparison to type 2 diabetes patients of group 1.

Tumour necrosis factor alpha (TNF-) which is an inflammatory marker is raised significantly in type 2 diabetes patients of group 2 as compared to type 2 diabetes patients of group 1, as shown in Table-5.These findings are consistent with earlier studies done by:

Nadeem A et al.(2013) in their study reported that, there is augmented inflammation in T2DM in Pakistani patients which plays role in higher in¬sulin resistance in these patients. TNF- levels increases with longer duration of the disease.

Hany A. Refaat et al.(2010) intheir study concluded that there was significant positive correlation between serum and urine TNF-α and duration of diabetes, as well as between serum TNF-α and glycemic control.

Gunel R Huseynova et al.(2009) suggested that increased level of TNF- in the stage of decompensation may show presence of deep inflammation processes in type 2 diabetes patients.

SAFA REFAAT ABD EL-MONIEM et al.(2009) in their study revealed a progressive elevation of serum TNF-α in type 2 diabetic patients according to the progression of retinopathy and that the serum levels of TNF-α were significantly correlated with the grade of retinopathy whichwas also significantly correlated with age and duration of diabetes but not with sex. Lechleitner M et al.(2002) in their study summarised that in elderly patients with Type 2 diabetes TNF-α plasma levels revealed a continuous increase during an observation period of 2 years. This increase in TNF-alpha plasma levels might add another aspect to the worsening of glycaemic control in the progression of Type 2 diabetes.They have given the result as TNF-α plasma levels increased significantly from 16.2 +/- 9.6 pg/ml at baseline to 28.0 +/- 13.8 pg/ml after 2 years (P = 0.028). HbA1c values also increased from 6.4 +/- 1.2% to 7.7 +/- 1.6% (P = 0.046).

Zinman, B. et al. 1999; Gonzalez, F. *et al*. 1999 suggested that circulating TNF-a concentrations are increased in subjects with obesity and impaired glucose tolerance.Fig.1of this study shows correlation between total MMSE score and TNF-α level in all type 2 diabetes patients. There was a negative insignificant correlation between the two variables, which was supported by Riccardo E Marioni et al.(2010) and concluded that Higher IL-6 and TNF-α levels were associated with poorer age- and sex-adjusted scores on the majority of the individual cognitive tests, and with g with standardised regression coefficients -0.074 to -0.173 ($p<0.05$).

Conclusion:

Thus in this study, Type 2 DM subjects have raised levels of TNF-α and HbA1c which increases as the disease progresses. These raised biomarkers may be implicated as the causative factors in the pathogenesis of Type 2 DM.

Recommendation:

The association between Type 2 DM and cognitive changes is becoming increasingly clear, rendering it necessary for physicians in charge of diabetic patients to have the means to assess cognitive performance as cognitive impairment among the older adults with Type 2 DM may worsen the health outcomes through negative impact on compliance with medical self care recommendations. So for the proper care of patients there must be means to assess cognitive changes by simple tests that can be applied during routine consultations which may be useful for monitoring cognitive functions during the course of diabetes.

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