Indian J Physiol Pharmacol 2018; 62(1) : 74–79

Original Article

Association Between Neutrophil Lymphocyte Ratio and Cognitive Function in Type II Diabetes Mellitus

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Abstract

Introduction: Systemic (cerebral) inflammation has been attributed in the pathogenesis of cognitive impairment in patients with Diabetes Mellitus. Neutrophil Lymphocyte Ratio (NLR) is a reliable marker for inflammation in various diseases. Hence this study was designed to explore the role of systemic inflammation in the pathogenesis of cognitive decline in diabetes by using Neutrophil Lymphocyte ratio as an inflammatory marker.

Materials and methods: 60 Type II Diabetes Mellitus (T2DM) patients in the age group of 30-60 years were recruited. Their cognitive function was assessed using Modified Mini Mental State Examination (3MS test). HbA1c levels were determined and NLR was calculated as ratio between counts of Neutrophil and Lymphocyte.

Results: The overall prevalence of cognitive impairment among patients with T2DM was 30%. The mean age of the patients with cognitive impairment was 50.8 years. No significant correlation was observed between NLR and cognitive function scores (r = 0.078) in T2DM patients.

Conclusion: No significant association was observed between NLR and Cognitive function in Diabetic patients.

Introduction

Diabetes Mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia (1). It is a complex metabolic disease that affects multiple organs in the body. It is recognised as an important cause of premature death and disability. As per 2014 WHO estimate, globally 422 million adults aged over 18years were living with Diabetes. The global prevalence of Diabetes has grown from 4.7% in 1980 to 8.5% in 2014 (2). India had over 69.2 million diabetics (8.7%) as per the 2015 data (3). Diabetes can lead to many systemic complications among which, a less addressed and not as well recognised complication is cognitive dysfunction (2). Both Type 1 and Type 2 diabetes mellitus have been associated with cognitive dysfunction (4). In healthy adults, age related cognitive impairment is mostly reported after the age of 60 yrs (5). When compared with those without diabetes, people with diabetes have 1.5 and 1.6-fold greater risk of developing cognitive decline and

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(Received on August 1, 2017)

dementia in future respectively (6). Many factors such as hyperglycemia, hypoglycemia, insulin resistance and genetic factors have been implicated in the pathogenesis of cognitive dysfunction in diabetes. Recently, systemic or cerebral inflammation has been suggested to play a role in the pathogenesis of cognitive decline in diabetes (7, 8). Diabetes care focuses on independent self care by the patients to achieve glycemic targets and minimize vascular complications. The intactness of important functional domains of cognition like executive function, information processing and memory are required to direct diabetes self care (7). Thus, cognitive dysfunction has an important impact on the quality of life in patients with diabetes. If left undiagnosed, it may progress to dementia.

Although many researchers have examined cognitive dysfunction in diabetes, still more studies are needed to understand the mechanisms of this complication in order to develop strategies for prevention and management. Many studies have focussed on finding the association between duration of diabetes, glycemic control and cognitive dysfunction. Only few studies have reported the role of inflammation in the pathogenesis of cognitive decline in diabetes. Diabetes is associated with chronic low grade inflammation (7, 9). Systemic inflammation can be measured by a variety of haematological markers. Among which, Neutrophil Lymphocyte Ratio (NLR) is a reliable marker for inflammation in various diseases which is cheap and readily available. NLR may be used as a prognostic marker for micro and macrovascular complications in diabetes (10, 11, 12). Considering the above factors, this study was designed to explore the role of systemic inflammation in the pathogenesis of cognitive decline in diabetes by using Neutrophil Lymphocyte ratio as an inflammatory marker. By understanding the relationship between NLR and cognition, NLR may be used as an index of cognitive impairment at its early stages of onset which will facilitate early diagnosis and appropriate management of cognitive dysfunction in diabetic patients.

Aim

To find out the association between Neutrophil Lymphocyte Ratio and cognitive function in type II Diabetes Mellitus patients.

Objectives

1. To assess cognition in Type 2 Diabetes Mellitus (T2DM) patients by using 3MS (Modified Mini Mental State Examination) test.

2. To determine NLR and HbA1c levels.

3. To find the association between NLR, HbA1c levels, duration of diabetes and 3MS scores in diabetic patients.

Methods

This is a cross sectional study. 60 patients with T2DM diagnosed according to WHO criteria were recruited from the Department of Diabetology, Government Stanley Medical College and Hospital, Chennai-1. Inclusion criteria were T2DM patients of age 30–60 yrs of both genders with minimum educational qualification of 8th STD and duration of diabetes of not less than 1 year. Exclusion criteria included patients with established diagnosis of dementia, co-morbid conditions that affect cognitive function such as neurological disorders, psychiatric disorders, history of acute / other chronic illness, patients on any other medications (Steroids, Chemotherapy, Antibiotics, Immunomodulators, Neuropsychotropic drugs or any other drugs for chronic diseases).

The study was approved by Institutional Ethical Committee. The purpose, risks and benefits of the study were explained to all the participants and Informed consent was obtained from each of them. A brief history of their education, duration of disease, current treatment and co-morbid conditions were obtained. Cognitive function was assessed using Modified Mini Mental State Examination (3MS). 3MS test is an extension of Mini Mental State Examination. When compared with MMSE, it assesses a broader variety of cognitive domains and covers a wider range of difficulty levels. It offers a brief assessment of the person's attention,

concentration, orientation to time and place, long-term and short-term memory, language ability, constructional praxis, abstract thinking, and list-generating fluency. 3MS score ranges between 0–100 (13).

Venous blood samples (about 3ml) were collected in Ethylenediaminetetraacetic acid (EDTA) tubes for determining HbA1c levels and NLR. Blood samples were analysed in the Department of Biochemistry, Govt. Stanley Medical College within 2 hours after collection. HbA1c levels were determined by high-performance liquid chromatography method using Bio-rad D-10 Hemoglobin Analyzer. Complete blood counts were determined using Sysmex Hematology Analyzer which works on the principle of Fluorescence Flow cytometry method. NLR was calculated as ratio between counts of Neutrophil and Lymphocytes.

Statistical analysis

Data were analysed using IBM SPSS, version 24. An Independent student's t-test was used to compare the means of variables. Pearson's correlation was used to find out the correlation between the variables. p value < 0.05 was considered significant.

Results

A total of 60 patients with T2DM participated in the study. 3MS test was used to assess their cognition. 3 MS score ≤ 77 was defined as cognitive impairment (14, 15, 16). HbA1c levels and NLR were determined. Patients were divided into 2 groups based on 3MS scores into those with normal cognitive function (group 1) and those with cognitive impairment (group 2). Correlations of age, duration of diabetes, HbA1c levels, NLR with 3MS scores were done in the whole group as well as in the group of patients with cognitive impairment. Data are represented as mean±standard deviation (SD).

Baseline characteristics

Baseline characteristics of diabetics and comparison of variables between patients with normal cognitive function and those with cognitive impairment are given in Table I & II respectively.

All patients were in the age group of 30–60 years. Table I shows that the mean age of the patients with cognitive impairment was 50.8 years which was higher than those with normal cognition (47.9 years) but it was not statistically significant (p = 0.5). Males represented a little more than half (54.8%) of the patients with normal cognition and females represented majority (61.1%) of patients with cognitive impairment. The mean years of education was 9.4 years in the patients with cognitive impairment which was lower when compared with those with normal cognition though it was not statistically significant (p = 0.1). No significant difference was found in the mean levels of duration of diabetes among the two groups.

Table II shows that no significant difference was found in the mean levels of HbA1c and NLR among the two groups.

Table III shows the comparison of variables between

TABLE I: Baseline characteristics of Type 2 Diabetes Mellitus patients.

S. No.	*Variable*	*All T2DM patients (n=60)*	*Group 1 - T2DM patients with normal cognitive function (n = 42)*	*Group 2 - T2DM patients with cognitive impairment (n=18)*	*p value (comparison of Group 1 and Group 2)*
1	Age (Years) mean±SD	48.6±7.8	47.9±8.3	50.8±6.3	0.5
2	Gender Males, n (%) Females, n (%)	 30, (50) 30	 23, (54.8) 19, (45.2)	 7, (38.9) 11, (61.1)	
3	Education (Years) mean±SD	10.1±2.0	10.3±2.0	9.4±2.0	0.1
4	Duration of T2DM (Years) mean±SD	5.4±4.3	5.5±4.4	5.4±4.3	0.8

TABLE II : Comparison of variables between diabetic patients with normal cognitive function and those with cognitive impairment.

S. No.	Variable	All T2DM patients (n=60)	Group 1 - T2DM patients with normal cognitive function (n = 42)	Group 2 - T2DM patients with cognitive impairment (n=18)	p value (comparison of Group 1 and Group 2)
1	3 MS score, mean±SD	80.9±9.9	86.0±4.6	68.9±8.4	0.00*
2	HbA1c levels %, mean±SD	9.1±2.2	9.0±2.3	9.2±2.2	0.8
3	NLR, mean±SD	1.7±0.6	1.7±0.6	1.6±0.5	0.6

*p value < 0.01 – highly significant, HbA1c – Glycosylated Hemoglobin, NLR – Neutrophil Lymphocyte Ratio.

males and females. No significant difference was observed in the mean levels of 3MS scores, HbA1c and NLR between males and females, though the mean value of 3MS score was slightly higher in males when compared to females. As shown in Table I, females represented majority (61.1%) of patients with cognitive impairment.

TABLE III : Comparison of variables between males and females with T2DM.

S. No.	Variable	Males (n = 50)	Females (n = 50)	p value
1	3 MS score, mean±SD	82.2±7.5	79.5±11.7	0.29
2	HbA1c levels %, mean±SD	8.7±1.9	9.5±2.5	0.16
3	NLR, mean±SD	1.8±0.6	1.6±0.6	0.14

Association between age, duration of diabetes, glycemic control, NLR and cognitive function

Age and cognitive function

Overall, no significant relationship (r = –0.031) was observed between age and 3MS test scores, though a weak negative correlation (r = –0.255) was found between age and 3MS test scores in patients with cognitive impairment.

Duration of diabetes, glycemic control and cognitive function

There was no significant relationship between duration of diabetes (r = 0.017), HbA1c levels (r = –0.140) and 3 MS test scores. Similarly, in the cognitive impairment group we observed no significant relationship between duration of diabetes (r = –0.011), HbA1c levels (r = –0.039) and 3 MS test scores. Though the correlations were in the expected direction i.e. negative correlation. Overall, poor glycemic control (HbA1c ≥ 7%) was observed in 49 patients (81.7%), among which 32.7% of the patients had cognitive impairment. Among the patients with good glycemic control (HbA1c < 7%) (n = 11), 18.2% had cognitive impairment.

Neutrophil Lymphocyte Ratio (NLR) and cognitive function

No significant correlation was observed between NLR and cognitive function scores in the cognitive impairment group (r = 0.162) as well in the whole sample of T2DM patients (r = 0.078). Overall, 23.3% (n = 14) of the patients had abnormal NLR (>2). Cognitive impairment was observed in 21.4% of patients with abnormal NLR and in 32.6% of patients with normal NLR (≤2) (n = 46).

Discussion

The main aim of this study was to find out the relationship between systemic inflammation for which NLR was used as an index and cognitive function in T2DM patients.

The following observations were demonstrated by our study. The overall prevalence of cognitive impairment among patients with T2DM was 30%, no significant correlations were observed between duration of diabetes, HbA1c levels, NLR and 3MS test scores in the whole group as well as in the cognitive impairment group, weak negative correlation between age and 3MS test scores in patients with impairment.

The mean age of the patients with cognitive impairment was 50.8 years in our study and we observed a weak negative relationship between age and cognitive function scores in T2DM patients with cognitive impairment. This shows the early onset of cognitive impairment in patients with T2DM. Few studies have demonstrated the cognitive impairment in middle-aged adults with diabetes and in early stages of diabetes (17, 18). Diabetes has been associated with 1.5 fold increase in the development of mild cognitive impairment and hence they are at a greater risk of developing dementia in the future (6).

Majority of the studies have demonstrated a strong negative relationship between duration of diabetes, glycemic control and cognitive function in diabetic patients which are different from our observations (19, 20, 21, 22). The possible reason for the difference could be the following; the mean age of T2DM patients was 48.6±7.8 years in our study, whereas the mean ages of the patients in most of the other studies were nearly or above 60 years eg. Tali Cukierman-Yaffe, 2009 and 62.5 years, Andreea M. Rawlings, 2015 and 57 years, Kristine Yaffe, 2013 and 74.2 years, Paul K. Crane, 2013 and 76 years. Age-related cognitive decline is mostly reported after 60 years of age (23). Thus, majority of the studies included older patients, and hence age-related cognitive decline could have contributed to the increased prevalence of cognitive impairment and strong negative relationship between duration of diabetes, glycemic control and cognition in those studies. Our study results were almost consistent with the results obtained by Satyajeet Roy et al (5); in their study the mean age of T2DM patients was 50 years and they observed weak negative and moderate negative relationship between HbA1c levels, duration of diabetes and cognitive function respectively.

We observed no significant correlation between NLR and 3MS test scores in diabetic patients. Overall, only 23.3% of T2DM patients had increased NLR in our study. Neutrophil Lymphocyte Ratio (NLR) is a new indicator of subclinical inflammation and recent research works have shown that raised NLR may be considered as a reliable predictor of the progression of various diseases (24, 25). NLR reflects the balance between innate neutrophilic and adaptive lymphocytic immune responses. Diabetes is associated with a low-grade chronic systemic inflammation (7). Inflammatory mediators have been found to be increased in patients with T2DM (8, 26). Many studies have showed that, NLR was increased in patients with diabetes and it has been linked to poor glycemic control, insulin resistance and cardiovascular events (10, 12, 25, 27). No study has been reported in the literature, investigating the relationship between NLR and cognitive function in diabetics. However, Riccardo et al, 2010 (8) observed significant association between elevated levels of plasma CRP, IL-6, TNF-α and poorer cognitive ability in patients with T2DM. Inflammation may have a role in the development of cognitive impairment in T2DM either by a direct effect on the brain as suggested by increased inflammation in the brain in dementia or through an influence on the development of vascular disease (7, 8).

Absence of relationship between NLR and cognitive function in patients with T2DM observed in our study could be again due to the same reason mentioned above such as, relatively young adults (mean age = 48.6 years) were included in our study and the duration of diabetes was less (mean = 5.4 years) in T2DM patients. Most of the studies that observed relationship between inflammatory mediators, cognitive function, NLR in diabetes included elderly patients (8, 12, 27). Moreover, only few patients had abnormal values of NLR (>2) in our study.

Since our main aim was to find out if NLR can be used as an index of cognitive impairment in the early stages of its onset in diabetic patients, we included relatively younger patients. Their duration of disease was less and hence only few patients had abnormal NLR. So we could not find a significant association between NLR and cognitive function in diabetic patients. In future, this study can be continued by including patients with wider age group and increasing the sample size for better understanding of the relationship between NLR and cognitive function in patients with diabetes. Further prospective studies are also required to find out the association between inflammatory markers and cognition in diabetes.

Conclusion

We observed cognitive impairment in 30% of T2DM patients suggesting its early onset and no significant correlation was observed between duration of diabetes, HbA1c levels, NLR and 3MS test scores in diabetic patients. Regular screening for cognitive decline and good glycemic control, will enable early intervention and proper management to postpone or prevent the risk of dementia in diabetic individuals.

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