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RESEARCH ARTICLE

Could neutrophil-lymphocyte ratio be an adjuvant marker for cognitive impairment in patients with Type 2 diabetes mellitus?

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ABSTRACT

Background: Diabetes mellitus is a global health concern as many people are getting diagnosed in the early stages of its development. The advancements in the treatment of diabetes have increased life span and prevented complications. However, early detection of cognitive impairment and vascular dementia still poses a great challenge as these conditions are conventionally not addressed as regularly as nephropathy, peripheral neuropathy, and retinopathy. As indicators of various degrees of systemic inflammation, the neutrophil-lymphocyte ratio (NLR) has been found to be closely related to cardiovascular diseases and diabetic microvascular concurrent diseases. **Aims and Objectives:** The objectives of this study were as follows: (1) To assess the prevalence of cognitive impairment in patients with type 2 diabetes mellitus (T2DM) at a tertiary care center and (2) to study the association between NLR and cognitive impairment in T2DM. **Materials and Methods:** A case–control design was used in the study. Thirty cases and 30 controls satisfying the inclusion and exclusion criteria were recruited after obtaining informed written consent. Semi-structured, pretested questionnaires consisting of sociodemographic details of the study population, questions based on health profile and treatment were administered. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) questionnaire. The NLRs were analyzed from blood investigations. Data were analyzed using MS Excel, SPSS version 17. The study was undertaken after obtaining clearance from the Institutional Ethical Committee. **Results:** Majority of the cases (15) were in the age group of 56–70 years and controls (15) were in the age group of 40–55 years. Majority of the cases (18) were in the age group of 40–55 years when diagnosed with T2DM. Most of the cases (29) were diagnosed with T2DM for the duration of 10–20 years. The NLR was <3.5 in 24 cases and 27 controls and >3.5 in six cases and three controls. About 30% (9) of cases showed mild cognitive impairment (MCI) and 23% (7) showed severe cognitive impairment. NLR was 2.79 ± 1.5 (mean ± standard deviation [SD]) and 1.85 ± 0.8 (mean ± SD) in cases and controls, respectively. NLR was significantly increased among diabetics ($P = 0.004$). There was no statistically significant association between NLR and cognitive impairment in diabetics ($P > 0.05$). **Conclusion:** The present study showed 30% prevalence of MCI as per MMSE scores in the first 20 years of diagnosis with T2DM. NLR was significantly elevated in T2DM patients. There was no statistically significant association between NLR and cognitive impairment in T2DM.

KEY WORDS: Cognitive Impairment; Neutrophil-Lymphocyte Ratio; Type 2 Diabetes Mellitus

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INTRODUCTION

The increasing prevalence of type 2 diabetes mellitus (T2DM) is a global health concern considering diabetes can affect various organ systems. The risks of vascular dementia and Alzheimer's disease have been found to be 2-fold in patients

with T2DM.[1] Furthermore, mild cognitive impairment (MCI) which precedes dementia and affects more people (6% of the population[2]) often goes underdiagnosed. MCI is defined as an objective cognitive impairment relative to the person's age, considering the cognitive symptoms, in a person with mainly normal functional activities who does not have dementia.[3] Diabetes has been identified as a key risk factor for dementia and MCI.[4,5] It is, therefore, important to understand the association between cognitive impairment and diabetes and the risk factors that might predict progression to dementia in diabetic patients to mitigate these risks.[6]

Studies in the past have shown the role and importance of inflammatory molecules (e.g., adipokines, chemokines, and cytokines) and endothelial dysfunction in the development of T2DM and its complications.[7,8] The total leukocyte count and the differential leukocyte count are among the easily available and inexpensive classic inflammatory markers.[9] However, establishing a diagnosis by taking individual white blood cells into account has its own biases, unlike the neutrophil-lymphocyte ratio (NLR), which is a dynamic parameter that has a higher prognostic value.[10] The role of neutrophils and lymphocytes has been established in many studies as independent markers of many diseases, especially complications of T2DM such as diabetic nephropathy.[11,12]

NLR is a newly established marker of chronic inflammation that exhibits a balance of two complementary components of the immune system; neutrophils (that are the active non-specific inflammatory mediators) and form the first line of defense, whereas lymphocytes are the regulatory or protective component of inflammation.[13] NLR has been associated with severity of metabolic syndrome.[14] As indicators of various degrees of inflammation, the NLR have been found to be closely related to cardiovascular diseases and diabetic microvascular complications.[15-17] The studies focusing on the association between NLR and cognitive impairment in T2DM are limited. Our study was undertaken to explore the role of NLR as an adjuvant marker of cognitive impairment in patients with T2DM.

Aims and Objectives

The objectives of this study were as follows:
- To assess the prevalence of cognitive impairment in patients with T2DM at a tertiary care center
- To study the association between NLR and cognitive impairment in T2DM.

MATERIALS AND METHODS

Study Design and Study Setting

This was a case–control study design at a tertiary care teaching hospital in a rural set-up.

Study Population

Patients >40 years of age diagnosed with T2DM visiting the hospital and their age-matched controls.

Study Tools

Semi-structured, pretested questionnaires were developed and administered to the study groups after obtaining informed consent. The questionnaire consisted of sociodemographic details of the study population, questions based on health profile and treatment. Cognitive status was assessed using the Mini-Mental State Examination (MMSE) questionnaire.[18] NLRs were estimated from blood investigations obtained from consenting cases and controls.

Inclusion Criteria

The following criteria were included in the study:
- Patients diagnosed with T2DM consenting to be a part of the study
- Age group: > 40 years
- Duration of T2DM: >10 years.

Age-matched healthy controls consenting to be a part of the study.

Exclusion Criteria

The following criteria were excluded from the study:
- Non-consenting individuals
- Non-diabetic
- Pregnant women
- Patients presenting with acute infections
- Patients with a history of neurological conditions, psychiatric disorders, and drug abuse
- Patients with a history of thyroid abnormalities.

Study Duration

The study duration was from July 2019 to August 2019, 2 months.

Sample Size

Based on the previous studies and the present study being a time-bound one, the sample size was calculated as n=30 (cases) and n=30 (controls).

Statistical Analysis

Data were entered into MS Excel, analyzed using SPSS version 17. The data were expressed in frequencies and Pearson's Chi-square test and t-test were used to test statistical association.

Ethical Clearance

The study was undertaken after obtaining clearance from the Institutional Ethical Committee.

RESULTS

Majority of the cases (15) were in the age group of 56–70 years and controls (15) were in the age group of 40–55 years. There were 22 males and 8 females among the cases and 30 males among controls. Majority of the cases were educated up to primary school. Majority of the study population belonged to rural set-up (54) [Table 1].

Majority of the cases (18) were in the age group of 40–50 years when diagnosed with T2DM. Most of the cases (29) were diagnosed with T2DM for the duration of 10–20 years. Among the cases and controls, 9 and 12 subjects had a family history of T2DM. Very few (1 and 6) had a family history of dementia, respectively. Seventeen of cases and 24 of controls followed a mixed diet. Twenty-one of cases and 30 of controls reported adequate sleep (7–8 h a day). Very few subjects were sedentary. Fifteen of cases and 15 of controls reported regular exercise (20 min of brisk walk at least 3 times a week). Eighteen of cases were on insulin and the remaining 12 on oral hypoglycemic drugs. Majority of the cases and controls were non-smokers and non-alcoholics. NLR was <3.5 in 24 cases and 27 controls and >3.5 in six (20%) cases and 3 (10%) controls, respectively. About 30% (9) of cases showed MCI and 23% (7) showed severe cognitive impairment, whereas 40% (12) and 13% (4) of controls showed mild and severe cognitive impairment, respectively [Table 2].

Table 1: Sociodemographic characteristics of the study population

Variables	Group with T2DM (*n*=30)	Group without T2DM (*n*=30)	Total
Age (years)			
40–55	12	15	27
56–70	15	6	21
>70	3	9	12
Gender			
Male	22	30	52
Female	8	0	8
Education			
Primary (up to 7th grade)	12	3	15
Secondary (up to 10th grade)	5	12	17
PUC	4	6	10
College	9	9	18
Marital status			
Single	30	30	60
Married	30	30	60
Residence			
Urban	6	0	6
Rural	24	30	54

T2DM: Type 2 diabetes mellitus

NLR was 2.79 ± 1.54 (mean±SD) and 1.85 ± 0.82 (mean±SD) in cases and controls, respectively. Student's *t*-test showed a statistically significant difference between cases and controls in NLR ($P = 0.004$). There was MCI in both the groups as shown by the MMSE scores, 22.03 ± 4.8 (mean ± SD) and 22.2 ± 4.3 (mean ± SD) in cases and controls, respectively, but no statistically significant difference was found between the two [Table 2].

There was no statistically significant association between neutrophil-lymphocyte ratios and cognitive function in both cases and controls ($P > 0.05$) [Table 3].

DISCUSSION

The present study was aimed at exploring the association between NLR and cognitive impairment in patients with T2DM. The prevalence of MCI was 30% and severe cognitive impairment was 23% among patients with T2DM. Majority of the diabetics in our study were between 56 and 70 years of age. In certain other studies, the mean age of the diabetic patients was almost 60 years.[19,20] Therefore, an age-related cognitive decline which is reported to start after 60 years of age might have contributed to the increased prevalence of cognitive impairment in patients with T2DM in our study.

The NLR varied from 1.25 to 4.33. Among diabetics, 20% (6) showed an increase in NLR (>3.5). There was also a significant increase in NLR among diabetics (cases) when compared with non-diabetics (controls). This finding is consistent with many studies which have shown that NLR was increased in patients with diabetes and it has been linked to poor glycemic control, insulin resistance, and cardiovascular events.[21-23] In our study, we did not find any statistical association between NLR and cognitive impairment. This finding is similar to that conducted by Sasirekha *et al*.,[24] in which no significant correlation was observed between NLR and cognitive dysfunction in T2DM patients. However, a study conducted by Halazun *et al*.[25] concluded that NLR >5 and diabetes mellitus were significantly associated with increased odds of cognitive dysfunction. A similar finding was observed in a study conducted by Shiny *et al*., in which they concluded that NLR can be used as an adjuvant prognostic marker for macro- and microvascular complications in patients with glucose intolerance.[26] Mazza *et al*., in their meta-analysis, supported the hypothesis that an inflammatory activation, as reflected by elevated NLR, occurs in non-affective psychosis. In another study, NLR has been shown to be significantly elevated in patients with increased albuminuria, indicating a relationship between inflammation and endothelial dysfunction in diabetics

Table 2: Study parameters between cases and controls

Study parameters	Group with T2DM (*n*=30)	Group without T2DM (*n*=30)	Total	*P*-value
Age at diagnosis of DM (in years)				
40–50	18	NA*	18	
50–60	6	NA*	6	
>60	6	NA*	6	
Duration of DM (years)				
10–20	29	NA*	29	
21–30	1	NA*	1	
Family history of DM				
Yes	9	12	21	
No	21	18	39	
Family history of dementia				
Yes	1	6	7	
No	29	24	53	
Diet				
Veg	9	0	9	
Non-veg	4	6	10	
Mixed	17	24	41	
Sleep				
Poor	7	0	7	
Adequate	21	30	51	
Excessive	2	0	2	
Physical activity				
Sedentary	0	3	3	
Regular exercise	15	15	30	
Irregular exercise	15	12	27	
Anti-DM medication				
Insulin	18	NA*	18	
Oral hypoglycemic drugs	12	NA*	12	
Smoking				
Current	1	9	10	
Former	13	9	22	
Never	16	12	28	
Alcohol consumption				
Current	2	6	8	
Former	9	12	21	
Never	19	12	31	
N:L ratio				
<3.5	24	27	51	
>3.5	6	3	9	
N:L (mean±SD)	2.79±1.54	1.85±0.82		0.004#
Cognitive status				
No cognitive impairment	14	14	28	
MCI	9	12	21	
Severe cognitive impairment	7	4	11	
MMSE score (mean±SD)	22.03±4.80	22.2±4.35		0.8

*NA: Not applicable, #*P*<0.05 statistically significant. SD: Standard deviation, MMSE: Mini-Mental State Examination, T2DM: Type 2 diabetes mellitus, MCI: Mild cognitive impairment

Table 3: Association between NLR and cognitive impairment

N:L ratio	No cognitive impairment	MCI	Severe cognitive impairment	*P*-value
Cases (with T2DM)				
<3.5	12	11	4	0.39
>3.5	2	1	0	
Controls (without T2DM)				
<3.5	12	8	4	0.18
>3.5	2	1	3	

Pearson's Chi-square test, *$P \leq 0.05$=SignificantT2DM: Type 2 diabetes mellitus, NLR: Neutrophil-lymphocyte ratio, T2DM: Type 2 diabetes mellitus, MCI: Mild cognitive impairment

with nephropathy.[27] The present study included type 2 diabetic patients who were on medication (mainly insulin) and were regular to the hospital for follow-up and revision of medications to prevent complications. They were also advised on lifestyle modification and around 50% of the cases reported regular physical activity. These factors might have contributed to the non-significant association between NLR and cognitive impairment.

The duration of diabetes mellitus was lesser, i.e., 10–20 years in the present study compared with other studies of cognitive decline, wherein the duration of diabetes mellitus was more than 20 years.[28] The present study with patients of relatively lesser duration of T2DM has tried to explore the role of NLR as an early adjuvant marker of cognitive impairment.

In future, prospective studies can be undertaken by including patients in different strata of age distribution, the newly diagnosed and chronic diabetics, and patients with and without good glycemic control for a better understanding of the relationship between NLR and cognitive impairment in T2DM.

CONCLUSION

The present study showed30% prevalence of MCI as per MMSE scores in the first 20 years of diagnosis with T2DM. NLR was significantly elevated in T2DM patients. There was no statistically significant association between NLR and cognitive impairment in T2DM. Nevertheless, the potential of NLR as an adjuvant marker of cognitive impairment in T2DM cannot be ruled out. Early diagnosis, regular follow-up, and lifestyle modification can go a long way in preventing cognitive impairment due to T2DM.

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