COGNITIVE CHANGES ASSOCIATED WITH HYPERCHOLESTEROLEMIA IN TYPE 2 DIABETES MELLITUS

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ABSTRACT Background: Type 2 Diabetes Mellitus (T2DM) contributes to cognitive dysfunction and is also associated with many chronic complications. However, the contribution of hyperlipidemia to cognitive decline in patients with T2DM is not clearly known as the evidence available are inconclusive and variable. This study aims to find the effects of lipid fractions on cognition in patients suffering from T2DM.

Materials and Methods: A cross-sectional study was conducted among 70 patients suffering from T2DM and who visited the outpatient department of a tertiary care hospital in 2019. All patients were tested for lipid profile, i.e. total cholesterol (TCL), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TGL). Out of 70 patients, 35 patients were selected with normal cholesterol levels (<200 mg/dl), and 35 patients were selected with high cholesterol levels (≥200 mg/dl). They were then subjected to Cognition scoring by Montreal Cognitive Assessment (MoCA). Finally, the cognitive score data were analyzed, and results were evaluated.

Result: The mean MoCA score in the present study was 27.2 ± 1.98. No statistically significant difference was observed, when MoCA score was compared with high and normal level of TCL (27.26 ± 2.19 and 27.41 ± 1.77; p=0.460), HDL (26.67 ± 2.08 and 27.22 ± 1.98; p=0.527), LDL (27.21 ± 2.15 and 27.18 ± 1.72; p=0.653), and TGL (27.14 ± 2.04 and 27.27 ± 1.92; p=0.770). Mild correlation, but not a statistically significant one, was seen between MoCA and TCL (r=0.12); MoCA and HDL (rs=0.12); and MoCA and LDL (r=0.18). No statistically significant difference was seen for the cognitive domains between high and normal TCL (p>0.05).

Conclusion: Any significant direct association of cognitive function in T2DM patients with total cholesterol and individual lipid fractions was not found in this study population.

KEYWORDS Cholesterol, Cognitive impairment, MoCA, type 2 Diabetes Mellitus

Introduction

The burden of diabetes is increasing day by day in India, with the majority of the people living with both type 1 and type 2 diabetes. More than 80% of the people living with type 2 diabetes are from low and middle-income countries (LMIC) like India. Prevalence of diabetes and prediabetes were high when compared to previous studies, as reported by India DIABetes (ICMR-INDIAB). This study was conducted in four different zones of rural and urban India by the Indian Council of Medical Research (ICMR) [1]. In 2017, International Diabetes Federation estimated that the prevalence of diabetes among Indian adults
was 72.9 million [2]. In a report by ‘National framework for joint TB-Diabetes collaborative activities’ in population aged above 15 years, 11% of the urban and 3% of the rural population have diabetes [3]. A study conducted in Tamil Nadu states that self-reported diabetes and new diabetes cases have increased in urban and rural areas. In the same study, the prevalence of diabetes was 21.9% in the city, 20.3% in town, and 13.4% in the periurban village area [2].

Diabetes mellitus (DM) is a metabolic disease affecting various body systems. It causes complications that significantly lower the quality of life and has a negative impact on life [4, 5]. Strong evidence from literature reveals that DM increases the risk of cognitive impairment and dementia [5]. Literature shows that cognitive dysfunction is present in type 1 and type 2 diabetic patients and remains less addressed [6]. The prevalence of cognitive impairment was high among T2DM patients in India (35.8%) [7] which, is almost half the prevalence of a study conducted in Saudi Arabia (80.3%) among diabetes patients [8]. In patients with diabetes, multiple changes in brain metabolites and brain structures have been reported, indicating that cognitive decline is closely linked to diabetes and its progression [9]. However, many studies revealed that the patients with type 2 diabetes who have higher levels of plasma triglycerides and elevated cholesterol usually tend to report significantly poorer cognitive function [10].

Findings from literature clearly show that co-morbid conditions such as hypertension, hyperlipidemia, and obesity directly correlate with diabetes-associated cognitive impairments and increased incidence of its complications [11]. Several studies conducted in the past have shown a relation between plasma lipid/lipoprotein levels and dementia. In these studies, higher plasma cholesterol or higher low-density lipoprotein (LDL) was primarily found in elderly people with dementia or cognitive deficits. Other studies also fail to find similar correlations, and these discrepancies in the findings indicate that further investigations of lipid parameters are required [12].

Using a study population of patients with type 2 diabetes, the present study aims to establish the effect exerted cognition by diabetes and high lipid levels (diabetic dyslipidemia) rather than focusing on a single risk factor. Several conflicting results were found from different studies about how different lipid fractions exerted on cognition. Thus, this study highlights evidence about the combined and individual effects of lipid fractions on cognition. There were two objectives of the present study. The first objective was to compare the cognitive levels between T2DM patients with normal cholesterol levels and high cholesterol levels, and the second objective was to find out the effect of individual lipid fractions on cognition in patients with T2DM.

Materials and Methods

A cross-sectional study was conducted among T2DM patients who visited the outpatient department of our tertiary care hospital in 2019. A total of 70 patients in the age group 25 to 60 years having type 2 diabetes were included in the study. Out of 70 patients, 35 patients were selected with normal cholesterol levels (<200 mg/dl) and the other 35 with high cholesterol levels (>200 mg/dl). Based on the criteria for the diagnosis of diabetes according to the American Diabetes Association, the participants of the study were selected [13]. In addition, the diagnosed type 2 Diabetic Mellitus patients were divided based on the cholesterol target levels in Diabetes Mellitus as per the guidelines of the International Classification of Lipoins as recommended by World Health Organization (WHO) and National Cholesterol Education Program (NCEP) [14].

After selection, participants were cross-verified to fulfil the inclusion and exclusion criteria. Both male and female patients who were hypertensive, asthmatics, were on medications other than that for diabetes, thyroid disorders, and cardiac problems were excluded from the study. Apart from this, pregnant patients were also excluded from the study.

Ethics approval (Project No. 19/063) was obtained from our Institutional Human Ethics Committee prior to the commencement of the study. Informed written consent was taken from all the participants before data collection. Adequate measures were taken to ensure patient’s confidentiality. The selected participants were subjected to the ‘Cognition scoring by Montreal Cognitive Assessment (MoCA)’ [15]. Freitas et al. validated psychometric properties and diagnostic accuracy of MoCA, stating that it is a better option for a brief assessment of cognitive impairments in patients with behaviour-variant frontotemporal dementia [16].

The Montreal Cognitive Assessment (MoCA) test is a 30-point scoring test available on one page and can be easily administered. A test score of 26 or above is considered normal. The test was administered by the primary and co-investigators, both in English and in the local language, based on the patient’s preference.

A MoCA test validation study by Nasreddine et al. in 2005 [15] has shown that the sensitivity (90%) and specificity (87%) of this test are much superior comparatively when it comes to detection of cognitive impairment. With the help of MoCA, various cognitive domains like short-term memory recall, visuospatial ability, executive function, attention, concentration, working memory, language and orientation to time and place were assessed. Each domain carried a separate score which, when added up, yielded a collective score of 30. All participants were tested for normal and high individual lipid fractions, i.e. total cholesterol (TCL), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TGL). The collective scores of each participant were collected as data.

The collected data were analyzed using statistical software R 4.0.3. Continuous variables are represented by mean ± SD form and categorical variables by a frequency table. Independent sample t-test / Mann Whitney U test compared two groups. Spearman/ Pearson correlation was used to see the relationship between two continuous variables. The p-value, less than or equal to 0.05, indicates the significance.

Results

Seventy T2DM patients participated in this cross-sectional study. For the normal cholesterol level (<200 mg/dl) group, 35 patients were selected, and the remaining 35 patients were selected from the high cholesterol level (≥200 mg/dl) group. The mean age of the participants in the present study was 45.27±4.0.3. Continuous variables are represented by mean ± SD form and categorical variables by a frequency table. Independent sample t-test / Mann Whitney U test compared two groups. Spearman/ Pearson correlation was used to see the relationship between two continuous variables. The p-value, less than or equal to 0.05, indicates the significance.

Table 2 compares MoCA scores between high and normal lipid fraction levels. When MoCA score was compared with high and normal levels of Total cholesterol (TCL), High-density lipoprotein (HDL), Low-density lipoprotein (LDL), and Triglycerides (TGL), statistically no significant difference was observed
Table 1. Demographic, clinical and cognitive characteristics of Type 2 Diabetes patients

| Characteristics          | Frequency (n) | Percentage (%) |
|--------------------------|---------------|----------------|
| Sex                      |               |                |
| Male                     | 26            | 37.1           |
| Female                   | 44            | 62.9           |
| High density lipoprotein (HDL) (mg/dl) |       |                |
| ≥60                      | 3             | 4.3            |
| <60                      | 67            | 95.7           |
| Low density lipoprotein (LDL) (mg/dl) |       |                |
| ≥130                     | 42            | 60             |
| <130                     | 28            | 40             |
| Triglycerides (TGL) (mg/dl) |            |                |
| ≥150                     | 37            | 52.9           |
| <150                     | 33            | 47.1           |

Table 2. Comparison of MOCA scores between high and normal Lipid fraction levels

| Lipid Fractions          | Lipid Levels (mg/dl) | n  | Mean ± SD | Median (IQR) | p-Value |
|--------------------------|----------------------|----|-----------|--------------|---------|
| Total Cholesterol (TCL)  | ≥200                 | 35 | 27.26 ± 2.19 | 28 (26, 29) | 0.460   |
|                          | <200                 | 35 | 27.41 ± 1.77 | 27 (26, 28.5)|         |
| High density lipoprotein (HDL) |   |    |            |              |         |
|                          | ≥60                  | 3  | 26.67 ± 2.08 | 26 (25.5, 27.5)| 0.527   |
|                          | <60                  | 67 | 27.22 ± 1.98 | 27 (26, 29) |         |
| Low density lipoprotein (LDL) |            |    |            |              |         |
|                          | ≥130                 | 42 | 27.21 ± 2.15 | 27.5 (26, 29)| 0.653   |
|                          | <130                 | 28 | 27.18 ± 1.72 | 27 (26, 28.25)|         |
| Triglycerides (TGL)      | ≥150                 | 37 | 27.14 ± 2.04 | 27 (26, 29) | 0.770   |
|                          | <150                 | 33 | 27.27 ± 1.92 | 28 (26, 28) |         |

Table 3. Correlation of MOCA scores with lipid fractions

| Variables    | MOCA Correlation Coefficient | p-Value |
|--------------|------------------------------|---------|
| TCL          | 0.12                         | 0.334^2 |
| HDL          | 0.12                         | 0.309_{10} |
| LDL          | 0.18                         | 0.14^2 |
| TGL          | -0.05                        | 0.663_{10} |

(p>0.05).

Table 3 shows the correlation of MOCA scores with lipid fractions. A mild correlation was seen between MoCA and TCL, MoCA and HDL, and MoCA and LDL. However, the correlation was not statistically significant (p>0.05). When checked for a correlation between MoCA and TGL, a mild negative correlation was observed, not statistically significant (p>0.05).

Table 4 shows a comparison of individual MOCA scores between high and normal Total Cholesterol (TCL). Statistically, no significant difference was observed for the variables when checked for high and normal total cholesterol (TCL) (p>0.05).

Table 5 shows a comparison of individual MOCA scores between high and normal Triglycerides (TGL). Statistically, no significant difference was observed for the variables when checked for high and normal Triglycerides (TGL) (p>0.05).

Table 6 compares individual MOCA scores between high and normal Low-density lipoprotein (LDL). Statistically, no significant difference was observed for the variables when checked for high and normal Low-density lipoprotein (LDL) (p>0.05).

Discussion

Cognitive dysfunctions are relatively less addressed complications of Diabetes Mellitus [6]. With the increasing age, the likelihood of cognitive impairment and dementia increases in patients having T2DM along with dyslipidemia when compared with people without T2DM or with T2DM alone [17]. In the present study, we compared cognitive changes associated with Hypercholesterolemia in patients with T2DM. This study highlights evidence about the combined and individual effects of lipid fractions on cognition. The study uses the Montreal Cognitive Assessment (MoCA) test, with the help of various cognitive domains like short-term memory recall, visuospatial ability, executive function, attention, concentration, working memory, language and orientation to time place were assessed.

In the present study, the mean age of the participants was 45.27±6.95 years, which is similar to the mean age (55.06±7.28) of participants in a study by Chen et al. [18]. The mean Body Mass Index (BMI) of our study participants was found to be...
Table 4 Comparison of Individual MOCA scores between high and normal Total Cholesterol (TCL)

| Variables   | TCL ≥ 200 (n=35) | TCL <200 (n=35) | p- Value |
|-------------|------------------|-----------------|----------|
|             | Mean±SD          | Median (IQR)    | Mean±SD  | Median (IQR) |
| Visuospatial| 4.40±0.74        | 5 (4, 5)        | 4.43±0.88| 5 (4, 5)      | 0.541    |
| Naming      | 2.97±0.17        | 3 (3, 3)        | 3.00±0.0 | 3 (3, 3)      | 0.331    |
| Attention   | 5.60±0.69        | 6 (5, 6)        | 5.71±0.46| 6 (5, 6)      | 0.691    |
| Language    | 2.40±0.85        | 3 (2, 3)        | 2.17±0.79| 2 (2, 3)      | 0.155    |
| Abstraction | 1.80±0.47        | 2 (2, 2)        | 1.80±0.41| 2 (2, 2)      | 0.814    |
| Delayed recall| 3.91±1.25 | 5 (3, 5)        | 3.89±0.99| 4 (3, 5)      | 0.662    |
| Orientation | 5.86±0.36        | 6 (6, 6)        | 5.91±0.28| 6 (6, 6)      | 0.462    |

Test: Mann Whitney U test

Table 5 Comparison of Individual MOCA scores between high and normal Triglycerides (TGL)

| Variables   | TGL ≥ 150 (n=37) | TGL <150 (n=33) | p- Value |
|-------------|------------------|-----------------|----------|
|             | Mean±SD          | Median (IQR)    | Mean±SD  | Median (IQR) |
| Visuospatial| 4.41±0.86        | 5 (4, 5)        | 4.42±0.75| 5 (4, 5)      | 0.852    |
| Naming      | 3.00±0.0         | 3 (3, 3)        | 2.97±0.17| 3 (3, 3)      | 0.303    |
| Attention   | 5.65±0.63        | 6 (5, 6)        | 5.67±0.54| 6 (5, 6)      | 0.965    |
| Language    | 2.41±0.83        | 3 (2, 3)        | 2.15±0.80| 3 (2, 3)      | 0.130    |
| Abstraction | 1.78±0.42        | 2 (2, 2)        | 1.82±0.46| 2 (2, 2)      | 0.542    |
| Delayed recall| 3.81±1.20 | 4 (3, 5)        | 4±1.03 | 4 (3, 5)      | 0.574    |
| Orientation | 5.84±0.37        | 6 (6, 6)        | 5.94±0.24| 6 (6, 6)      | 0.189    |

Test: Mann Whitney U test

Table 6 Comparison of Individual MOCA scores between high and normal Low density lipoprotein (LDL)

| Variables   | LDL ≥ 130 (n=42) | LDL <130 (n=28) | p- Value |
|-------------|------------------|-----------------|----------|
|             | Mean±SD          | Median (IQR)    | Mean±SD  | Median (IQR) |
| Visuospatial| 4.36±0.73        | 4 (4, 5)        | 4.50±0.92| 5 (4, 5)      | 0.138    |
| Naming      | 2.98±0.15        | 3 (3, 3)        | 3.00±0.0 | 3 (3, 3)      | 0.431    |
| Attention   | 5.57±0.67        | 6 (5, 6)        | 5.79±0.42| 6 (6, 6)      | 0.179    |
| Language    | 2.38±0.82        | 3 (2, 3)        | 2.14±0.80| 2 (1.75, 3)   | 0.172    |
| Abstraction | 1.79±0.47        | 2 (2, 2)        | 1.82±0.39| 2 (2, 2)      | 0.873    |
| Delayed recall| 3.88±1.21 | 4 (3, 5)        | 3.93±0.98| 4 (3.75, 5)   | 0.925    |
| Orientation | 5.88±0.33        | 6 (6, 6)        | 5.90±0.31| 6 (6, 6)      | 0.888    |

Test: Mann Whitney U test

26.8 kg/m², which is similar to a study by He et al. (27.41±5.41) [12]. The mean MoCA score in the present study was recorded as 27.2±1.98. In a study by Nasreddine ZS et al. [15], MoCA administered by the French version showed a score of 23.6±6.4, and MoCA administered by the English version showed a score of 23.7±4.1, indicating impairment. When MoCA scores of the present study were compared with high and normal levels of TCL, HDL, LDL and TGL, statistically no significant difference was observed (p>0.05). A similar finding was reported in a study done by Chen et al. where no significant difference was found in TCL, HDL, LDL and TGL. The study was done by Chen et al. also reported that the cognitive function was not associated with levels of TCL, HDL, LDL and TGL [18].

In the present study, a mild correlation was seen between MoCA and TCL; and MoCA and LDL. However, the correlation was not statistically significant (p>0.05). A similar finding was seen in a study by Zhang et al. [19], which failed to find any correlation between TCL (or LDL-C) and MoCA by Pearson association. For further exploration of the relationship between cholesterol and cognition decline, linear and U-shaped curves were also compared in the study by Zhang et al. However, no significant linear association or U-shaped association was detected between TCL and MoCA (all P>0.05). In a study conducted by Chen et al. [20], MoCA scores were negatively correlated with total cholesterol levels (TCL). However, the correlation was not statistically significant (p>0.05).

In the present study, when checked for high and normal total cholesterol (TCL), Low-density lipoprotein (LDL), and Triglycerides levels (TGL), no statistically significant difference was observed for the variables of the cognitive domain (p>0.05). Unlike other studies, the present study did not find any direct correlation of cognitive function in T2DM patients with individual lipid fractions. The speculated cause for such finding in this present study can be the different age ranges of the patient, which may be with different levels of cognition function.

No similar studies were found in the literature, which compared MoCA scores between high and normal Lipid fraction levels based on various cognitive domains. The limitation of the
The present study can be the self-reported history of the co-morbid conditions during data collection. Furthermore, the sample in the present study was not large enough to represent all diabetic patients.

Conclusion

The findings from the present study show that there was no significant direct association of cognitive function in T2DM patients with total cholesterol and individual lipid fractions. However, a periodical follow-up and assessment of this same group of patients may reveal more on this aspect. Thus, further investigations are suggested as associations are not the proof of a causal relation and sometimes, selection of participants most at risk of cognitive decline in their later stage of life is an important aspect.

Ethics approval and informed consent

Ethics approval (Project No. 19/063) was obtained from our Institutional Human Ethics Committee prior to the commencement of the study. Informed written consent was taken from all the participants before data collection.

Consent for publication

Written informed consent was obtained from all the subjects who signed informed consent regarding publishing their data and photographs.

Data availability

All the data and materials relevant to the current study have been included in the manuscript.

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Competing interests

The authors declare no competing interests.

Authors’ contributions

Vijayabaskaran Shanmugavaradharajan - Conceptualization, Methodology, Writing- Original draft preparation, Review & Editing.
Dhanashree Balaji - Investigation, Software, Data curation
Damodaran Vasu - Formal analysis

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