Association between altered serum lipids levels on cognitive impairment in the pre-elderly and elderly population of South India

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ABSTRACT

Altered serum lipid levels are linked with varying degrees of cognitive impairment due to various mechanisms. The prevalence of cognitive impairment in relation to altered serum lipid levels on cognitive impairment in the pre-elderly and elderly population is of great importance. Therefore, it is important to characterize the features of mild cognitive impairment with respect to altered lipid profile. This study investigated the association between altered serum lipid levels on cognitive impairment in the pre-elderly and elderly population. The present cross-sectional study was done in 406 pre-elderly and elderly patients. The participants were subjected to demographic data collection followed by Mini-Mental State Examination (MMSE). Participants were classified into two groups: cognitively-normal (n=289) and mild cognitive impairment (117). Fasting serum lipids of the participants was estimated using venous blood samples by standard biochemical techniques. Differences in the lipid concentrations between the two groups were then compared using the Mann-Whitney U test. Significant differences were found in MMSE scores between the cognitively-normal and MCI groups (p<0.05). MCI patients had a significantly lower level of high-density lipoprotein when compared to cognitively-normal participants (p<0.05). In addition, the two groups showed differences in education levels attained. The cognitively-normal group had a greater number of educational years when compared to the MCI group. The study found significant differences in serum lipid concentrations between the cognitively-normal individuals and the mild cognitive impairment group.

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INTRODUCTION

Cognitive impairment interferes with an individual's ability to carry out his or her daily life activities. Petersen and colleagues (2005) have described mild cognitive impairment as the beginning stage of cognitive impairment in the elderly population (Petersen and Morris, 2005). Individuals with mild cognitive impairment retain functional abilities. Every year, about 10-12% of the people with MCI convert to dementia (Petersen *et al.*, 1999; Shim *et al.*, 2016). Estimates of the prevalence of MCI vary between 11% and 20% (Petersen *et al.*, 2010; Rao

et al., 2018).

Previous studies have associated imbalances in cholesterol levels to risk of mild cognitive impairment (Zambón *et al.*, 2010). Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein exert different effects on the incidence of MCI (Yasuno *et al.*, 2012). Moreover, cholesterol is essential for the degradation of amyloid precursor protein in the brain (Burns and Duff, 2002). Research also links the accumulation of Aβ in the brain to the onset of Alzheimer's disease (Simons *et al.*, 1998). Elevated cholesterol levels in midlife have also been associated with risk of dementia (Yin *et al.*, 2012).

HDL-C is essential for the removal of excess cholesterol from the brain (Zuliani *et al.*, 2001). It helps maintain cerebrovascular integrity by mediating inflammation and oxidative stress within the central nervous system (Stukas *et al.*, 2014). Previous research also found impaired cognitive function in individuals with low HDL-C levels (Reitz *et al.*, 2010), while other studies have failed to find the association between HDL-C and cognitive impairment (Moroney, 1999; Reitz *et al.*, 2008). These discrepancies suggest that further research on effects exerted lipid parameters is required, particularly in the context they are cheap and easy to use.

In India and worldwide, the ageing population is expected to increase significantly over the next decade (United Nations, 2019). Factors contributing to longevity could be attributed to increased life expectancy. However, elderly people are at increased risk of dementia and other associated neurological complications apart from the risk of other non-communicable diseases. Dyslipidemia, a potential modifiable risk factor, is associated with cognitive decline in previous reports (Reed *et al.*, 2014; Power *et al.*, 2018). Therefore, we wanted to observe the cognitive status with respect to lipid profile and other demographic variables in the local population of the Nilgiris District. We also sought to estimate the prevalence of mild cognitive impairment in the population.

MATERIALS AND METHODS

Standard Protocol Approval

This study was approved by the Institutional Review Board in JSS College of Pharmacy, Ooty. All participants were provided with written, informed consent. IRB no. JSSCP/DPP/IRB/02(PhD)2015-16.

Study design and participants

The present observational, cross-sectional study conducted between January 2017 and July 2018.

The participants were randomly recruited from individuals who attended an outpatient clinic for regular check-up or health problems. A total of 406 patients were recruited into the study.

Inclusion and Exclusion criteria

Participants aged 55 years and above. Participants are willing to provide socio-demographic details and other relevant information. Participants with the ability to communicate in basic English, with good working history and without a diagnosed history of mental retardation were recruited. Participants with severe mental illness or mood disorders, head trauma with loss of consciousness, brain tumours, epilepsy, dementia, psychiatric problems, cardiac failure, other neurodegenerative diseases, stroke, use of medication likely to impair cognitive function, and excessive alcohol abuse were excluded from the study. Participants with severe hearing impairment or impaired eyesight were also excluded from the study.

Study Procedure

Participants meeting the inclusion and exclusion criteria were enrolled into the study after obtaining their informed consent. Socio-demographic details of the patients were collected by the use of a semi-structured data collection form. Clinical characteristics and medication history were collected from the patient medical records. Each participant provided information regarding the level of education completed. Diabetes was ascertained by self-report or from the patient's use of oral hypoglycemic drugs or insulin. Hypertension was ascertained by the history of use of antihypertensive medication or history of systolic blood pressure (SBP) of more than 140 mmHg and diastolic pressure (DBP) of more than 90 mmHg. Self-reported use of alcohol, cigarette smoking, tobacco, and pan products was also recorded. All the participants were subjected to the Mini-Mental State Examination. Lipid profiles of the patients were assessed by freshly drawn venous blood samples within the laboratory attached to the clinic or use of the lipid levels estimated within a month of recruiting the participants.

Mini-Mental State Examination

Global cognitive function of the participants was measured using the English version of Mini-Mental State Examination Standard Version 2.0 developed by (Folstein *et al.*, 1975). The MMSE scores range from 0 to 30. Higher scores indicate better cognitive function. Cognitively normal participants were randomly selected from participants who had MMSE scores between 24-30. Mild cognitive impairment is considered to be a score between 18-23.

Table 1: Demographic characteristics of the participants

Variable	Cognitively-normal (n=289) Mean ± SD	MCI (n=117) Mean ± SD
Age (years)	65.20±6.31	64.25±6.08
MMSE	26.97±1.79	20.87±1.67
Height (cm)	158.83±10.82	156.24±7.81
Weight (kg)	68.03±11.83	64.72±11.12
SBP (mmHg)	136.85±21.17	137.50±19.99
DBP (mmHg)	83.35±13.72	83.63±11.95
Diagnosis	Frequency (%)	
No disease	91 (31.5)	44 (37.6)
Dyslipidemia	18 (6.2)	1 (9)
Dyslipidemia+Diabetes	28 (9.7)	12 (10.3)
Dyslipidemia+Hypertension	5 (1.7)	1 (9)
Dyslipidemia+Diabetes+Hypertension	42 (14.5)	9 (7.7)
Diabetes	57 (19.7)	33 (28.2)
Diabetes+Hypertension	40 (13.8)	16 (13.7)
Hypertension	8 (2.8)	1 (9)
Education		
Primary	24 (8.3)	50 (42.7)
High School	118 (40.8)	63 (53.8)
Graduates	147 (50.9)	4 (3.4)

Abbreviations: MCI, mild cognitive impairment; MMSE, mini-mentalstate examination; n, number of participants; SD, standard deviation

Table 2: Sex-based variations in MMSE scores

Gender	COGN (289)		MCI (117)		P value
	n	Mean ± SD	n	Mean ± SD	
Male	126	26.81±1.81	49	20.84±1.69	<0.05
Female	163	27.09±1.77	68	20.90±1.67	<0.05

Abbreviations: COGN, cognitively-normal; MCI, mild cognitive impairment; MMSE; mini-mental state examination; n, number of participants; SD, standard deviation. *p<0.05represents a statistical difference.

Table 3: Age-based variations in lipid levels

Age group		HDL-C Mean ± SD	TG Mean ± SD	LDL-C Mean ± SD	TC Mean ± SD
50-59 years	COGN (69)	43.40±7.94	187.30±115.16	110.89±48.02	175.68±4.74
	MCI (31)	43.89±10.23	88.47±20.00	101.38±29.00	160.73±36.95
60-69 years	COGN (138)	42.02±9.49	189.46±83.83	112.78±36.94	195.30±45.76
	MCI (57)	45.37±10.96	92.60±21.21	94.89±29.08	156.90±31.39
70+ years	COGN (82)	42.54±8.64	175.71±68.93	104.80±32.26	183.11±38.56
	MCI (29)	42.12±10.81	87.93±18.08	86.39±24.42	146.15±27.02

Abbreviations: CHL, total cholesterol; COGN, cognitively-normal;HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MCI, mild cognitive impairment; SD, standard deviation

Table 4: Mean values of lipid profiles of the participants

Variable	COGN (289) Mean $\pm$ SD	MCI (117) Mean $\pm$ SD	P-value
HDL-C	45.50$\pm$8.89	44.17$\pm$10.73	<0.05
LDL-C	109.92$\pm$38.70	94.50$\pm$28.26	0.936
TC	189.24$\pm$43.76	155.25$\pm$32.17	0.157
TG	185.04$\pm$88.58	90.35$\pm$20.11	0.279

Abbreviations: CHL, total cholesterol; COGN, cognitively-normal;HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MCI, mild cognitive impairment; SD, standard deviation; TG,triglycerides; P<0.05 represents statistical significance

Estimation of plasma lipids

Blood was drawn from each participant by venipuncture after an overnight fast (12 hours), centrifuged at 3000 rpm and stored at -80 degrees Celsius awaiting analysis. Plasma total cholesterol (CHL) and triglycerides (TG) concentrations were estimated by Automatic Biochemistry Analyzer (Hitachi 7180, Japan) using diagnostic kits sourced commercially (Sigma-Aldrich, USA). High-density lipoprotein cholesterol was measured using Hitachi 911 autoanalyzer. Low-density lipoprotein cholesterol (LDL-C) was estimated by the Friedewald equation (Friedewald *et al.*, 1972). All laboratory tests were conducted in Bio-Tech Lab, Kothagiri, Tamilnadu, India.

Statistical Analysis

The collected data were entered into MS Excel, double-checked to eliminate any data entry errors. Mean and standard error means were used to estimate age, MMSE scores, height, weight, waist circumference, blood pressure, and lipid profiles. In order to compare the differences among various lipid parameters between normal and mild cognitive impairment, we planned to use the Independent samples t-test. However, when the data was subjected to normality tests using Shapiro-Wilk's test, the p-values exceeded 0.05 showing the data is not normally distributed. Hence, we applied nonparametric tests which is an equivalent of the Independent samples t-test. All statistical analyses were performed using the student's version of the statistical package SPSS 25 for windows.

RESULTS AND DISCUSSION

Demographic data analysis

A total of 406 participants, above 50 years old, were recruited into this study. In order to find the differences in characteristics between normal individuals and MCI, participants were grouped into two categories: those with MCI (scored 18-23) and cognitively-normal (scored >23). The prevalence of mild cognitive impairment was 28.8%. Out of these, 175 (43.1%) were male participants. The demographic details are given in Table 1.

The participants' social history included those who drank alcohol (n=63), smoked (n=29) and used pan (n=14). However, most of the participants were teetotalers and none of the women ever smoked. Majority of the participants were in the age group of 60-69 years (n=195) that represents midlife age, followed by 70 or more years (n=111). Figure 1 displays the participants according to the family type.

Majority of the participants (79%) conversed in more than one language. The cognitively-normal participants were better educated than the MCI group. More than 90% of the cognitively-normal participants had at least high school education (n=265). The MCI group had less than 4% of participants who attained university education when compared to more than half (50.9%) of the participants in the cognitively-normal group.

The present study revealed a significant difference in the MMSE scores between the cognitively-normal and MCI groups (p<0.05). Male participants with MCI had a mean score of 20.84$\pm$1.96. The current study also revealed that female participants with MCI had similar MMSE scores to their male counterparts. Notably, MCI was more prevalent in female participants than male participants, with 58% of them scoring below the cutoff score (<24). See Table 2.

HDL-C levels were highest between 50-59 years but declined with increasing age with the oldest MCI participants older than 70 years having the least values See Table 3.

In this study, MCI participants had lower levels of HDL-C and triglycerides than the cognitively-normal participants. They also had higher levels of LDL-C and total cholesterol compared to the cognitively-normal group. A Mann-Whitney U test indicated, on average, that the HDL-C levels of cognitively-normal participants significantly exceeded those of
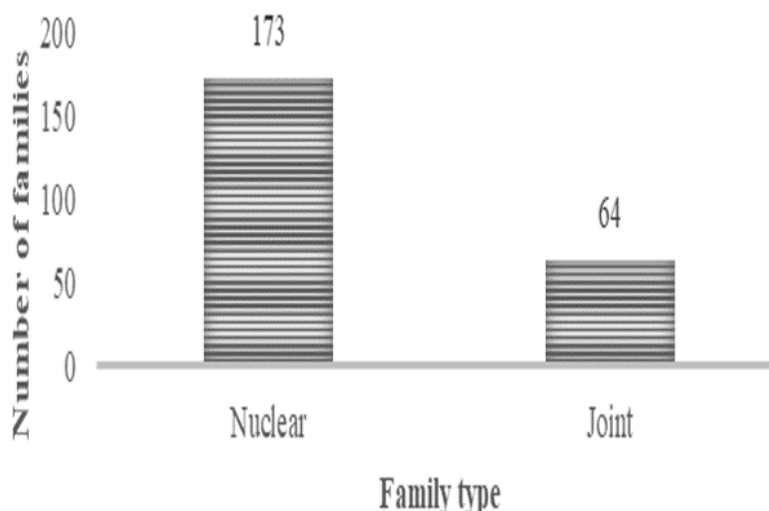
Figure 1: Distribution of participants according to family type

MCI participants, p<0.05. However, no significant difference was found in other all lipids/lipoproteins between the cognitively-normal and the MCI groups See Table 4.

Cognitive impairment poses a huge challenge to the public health sector, with future generations at increased risk of developing dementia. Moreover, the disease is incurable until now, therefore, it is important to find ways to detect cognitive decline at the earliest to prevent or slow down the progression of the disease. There is little we can do to change non-modifiable risk factors such as gender, genetic factors and age. However, modifiable risk factors provide a potential target for the prevention of dementia.

The present study examined global cognition of individuals attending a clinic for a regular check-up. We used the MMSE despite the availability of numerous instruments used for assessing cognitive impairment. The reason being, MMSE is frequently used and cited instrument in the literature (Aerts, 2017; de Souto Barreto et al., 2018). Moreover, it has demonstrated good internal consistency and reliability (Baek et al., 2016). It has also been translated and validated in many languages (Ganguli et al., 1995; Kim et al., 2010; Ideno et al., 2012). In addition, a few studies have been published from India, utilizing the MMSE (Vedak et al., 2015; Vasantharekha et al., 2016).

Participants in this study were relatively younger compared to a similar study (Hishikawa et al., 2017). Even though most studies on cognitive impairment are conducted in people aged 65 years or older, we recruited patients aged 55 years and above. This is because several studies have shown that initial stages of dementia begin in people in their fifth decade of life. Therefore, we considered this age group as pre-elderly and recruited them into the study. The present study revealed the prevalence of MCI to be 28.8% which is in contrast to the study on incidental MCI that had a prevalence of 13.5% (Hishikawa et al., 2017).

Elevated serum total cholesterol levels are associated with the risk of cognitive impairment. Brain cholesterol modulates the synthesis and clearance of amyloid-beta. Amyloid-beta accumulation, commonly seen in Alzheimer's disease, is triggered by disruption of cholesterol metabolism (Sponne et al., 2004). In this study, we observed higher concentrations of total cholesterol in midlife, which decreased with age as the participant's age increased. Concentrations of lipids in the peripheral system change with the age of individuals. This is evident from this study where the concentrations are different in early adulthood and late-life. A previous study found that elevated midlife cholesterol levels increase the risk of Alzheimer's disease later in life (Solomon et al., 2009). This is consistent with the present study where cholesterol levels were the highest in midlife and lowest in the oldest participants. Declining total cholesterol levels are associated with increased risk of dementia (Beydoun et al., 2011).

HDL-C is projected to be 'good cholesterol' and is associated with a decreased risk of cognitive impairment (Stukas et al., 2014). In this study, HDL-C levels were lower in MCI participants when compared to cognitively-normal participants. This is consistent with previous findings where low HDL-C levels were associated risk of increased probable Alzheimer's disease (Reitz et al., 2010). However, one study found no difference in serum HDL-C concentrations between MCI and control groups (Ohtani et al., 2018).

Evidence from animal studies indicates that elevated triglyceride levels modulate accumulation of amyloid in the brain, consequently, cognitive impairment is trigged (Burgess *et al.*, 2006). In the current study, MCI participants had lower levels of triglycerides compared to the cognitively-normal group. Previous research links higher TG levels with increased risk of MCI and Alzheimer's disease (Sims *et al.*, 2008). Verbal memory decline is evident in hypertriglyceridemic individuals (de Frias *et al.*, 2007) . This study found similar findings to those from a study that found lower odds of MCI in participants with high triglyceride levels (Yin *et al.*, 2012). However, some studies failed to find the association between TG and cognitive impairment (Huang *et al.*, 2009).

Education provides a buffer against cognitive decline (Sims *et al.*, 2008). In the present study, more cognitively-normal group participants attained higher education when compared to MCI participants. Interestingly, more participants in the cognitively-normal group had longer durations of diabetes and hypertension when compared to the MCI participants. However, they performed better on cognition test than the MCI participants. This could be because attaining higher education levels may have protective effects against cognitive impairment. In addition, better education might have influenced the cognitively-normal participants to seek medical care and improved their lifestyle conditions. Indeed, cognitive reserve compensates for the changes in the brain due to aging, thereby, slowing down the rate of cognitive decline (Milgram *et al.*, 2006). In contrast, a recent study did not find the effect of education in delaying the onset of MCI in participants (Ramakrishnan *et al.*, 2017). The present study did not exclude the use of antihypertensives and anti-diabetes medications from the analysis, which could have confounded the cognitive outcome.

This study has several strengths. The present study explores the differences between the lipid profiles of patients with MCI and normal patients. Even though the profile of lipids tends to change with age, differences in the levels of serum lipids were observed between the two groups. This study estimated the prevalence of MCI in the Kothagiri and Coonoor regions of the Nilgiris District, showing that even smaller towns are at risk of cognitive impairment just like bigger cities elsewhere.

Some of the limitations of this study must be considered. Due to its cross-sectional nature causality cannot be established. The sample size was small, limiting to the generalizability of the data. In addition, determination of mild cognitive impairment was done using MMSE. We could not determine the ApoE genotypes of the participants, and therefore exclude its influence from the analysis. Without imaging, the study could not exclude other causes of cognitive impairment in the participants. Imaging of the brain would have increased the accuracy of the diagnosis. However, this was not possible due to the huge costs incurred, which were beyond the scope of the study.

In summary, the present study investigated cognitive functions in pre-elderly and elderly population receiving regular health check-up. Serum lipid concentrations differed between cognitively-normal and mild cognitive impairment patients. Significant differences were observed between the two groups which warrant further investigation on roles of lipids in cognitive decline, and if they can be used to predict the onset of cognitive decline. By observing the results of this study, we are of the opinion that several factors affect the cognitive levels in the elderly, as reported from previous studies. However, we observed a significant impact of lower education and lower HDL-C levels, adversely affecting our population. Future investigations are warranted to explore the effects of other variables affecting cognition.

CONCLUSIONS

The present study demonstrates that serum lipid/lipoproteins concentrations vary considerably between cognitively normal and mild cognitive impairment individuals. In addition, education could provide a buffer against cognitive decline. Controlling vascular risk factors such as diabetes and hypertension could slow down the rate of cognitive decline. A longitudinal study with a larger number of participants may be warranted to confirm the findings of this study.

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Declaration of Interest

The authors declare no conflict of interest.

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