IJPSR (2019), Volume 10, Issue 9 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 July 2019; received in revised form, 05 August 2019; accepted, 13 August 2019; published 01 September 2019

PREVALENCE OF COGNITIVE IMPAIRMENT IN METABOLIC SYNDROME PATIENTS IN URBAN INDIA

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Keywords:

Cognitive impairment, Metabolic syndrome, Diabetes, Dyslipidemia, Blood pressure, Obesity

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ABSTRACT: Background: The association between metabolic syndrome and cognitive impairment is not well established. The aim of the present study was to estimate the prevalence of cognitive impairment in adults with metabolic syndrome (MetS). **Methods:** Cross-sectional observational study conducted in patients with metabolic syndrome (n=185). All patients were subjected to written informed consent, anthropometric measurements, neuropsychological assessments using Mini-Mental State Examination (MMSE). MetS was diagnosed using the definition by the National Cholesterol Education Program-Third Adult Treatment Plan. The main outcome measure was cognitive impairment (<24 on the MMSE scale). Mean, standard deviation and students t-test were used to carry out the analyses. **Results:** The prevalence of cognitive impairment in MetS patients was 24%. Patients age ranged between 20-75 years and 45% (n= 83) of them were female. MMSE scores were lower in female patients compared to male, however, the difference was not significant (p=0.06). College graduates had significantly higher MMSE scores than patients with just a high school education (p<0.05). Patients with high levels of triglycerides had significantly lower MMSE scores compared to those with borderline high triglycerides (p=0.02). **Conclusion:** MetS is associated with cognitive impairment, and further longitudinal studies are required to understand the risk of cognitive impairment especially in the elderly population.

INTRODUCTION: Metabolic syndrome (MetS) is a combination of metabolic disturbances related to cardiovascular risk involving abdominal obesity, glucose, and lipid dysregulation and raised blood pressure [1]. Estimates of the prevalence of MetS around the world range between 10% to 41.6% [2-4]. The global prevalence of the MetS is on the increase due to lifestyle changes such as decreased physical activity and increasing prevalence of obesity.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(9).4367-73

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(9).4367-73

In India, studies have been conducted estimating the prevalence of MetS in both rural and urban settings [5, 6]. The widely used criteria for the diagnosis of MetS are defined by the National Cholesterol Education Program - Adult Treatment Plan III (NCEP ATP III), the World Health Organization (WHO), and the International Diabetes Federation (IDF) [7-9].

Prevalence of MetS is high in midlife. Even though a number of studies have been conducted to find out the role of MetS in cognitive impairment, most of the results are heterogeneous and inconsistent [10]. In one longitudinal population study, glycemia but not MetS was associated with the risk of cognitive impairment [11]. MetS increase the risk of progression to dementia in patients with MCI when compared to MCI patients without MCI [12].

In adolescents, MetS were associated with smaller hippocampal sizes and decreased attention [13]. Normal aging causes little unnoticed changes in cognitive function, especially in elderly people. MetS and its components increase the risk of cognitive impairment [5, 10]. However, only a few studies have explored the association between MetS and cognitive impairment [15]. Previous studies have associated individual components of MetS such as dyslipidemia, hyperglycemia, increased blood pressure and obesity with cognitive impairment. Elevated blood pressure in mid-life increases the risk of dementia in late-life [16]. Executive function is decreased in hypertensive patients with arterial stiffness [17]. High triglycerides levels are also associated with a decline in executive function [18].

The prevalence of MetS is soaring high among the Indian population due to change in lifestyle and social habits [19]. Cardiovascular risk factors of MetS are well researched. However, the impact of MetS on mental functions is least explored especially among South Indian population who are more vulnerable to MetS.

Therefore, in this study, we seek to estimate the prevalence of cognitive impairment in MetS patients from an urban setting in Ernakulam City, Kerala.

MATERIALS AND METHODS:

Study Site: Lakshmi Hospital, Diwans Road, Ernakulam, Kerala, India.

Study Design: Cross-sectional observational study

Source of Data: Patient interview and medical records.

Study Period: 6 months (September 2016 to March 2017).

Sampling: Purposive sampling.

Selection of Patients: Male and female Patients attending Lakshmi Hospital aged between 20 to 75 years. The patients were screened and MetS diagnosis was confirmed with the help of Dr. Mani G Pillai, an endocrinologist. This study was approved by the Ethics Committee in Lakshmi Hospital, Diwans Road, Ernakulam, Kerala. IEC no. JSSCP/DPP/IRB/10/2016-17.

Demographic and Medical Variables: The data collection form was designed in such a way to obtain data on key variables like age, education, sex, lifestyle, medical history, and pharmacological treatment given.

Sample Size: A total of 185 patients were enrolled.

Assessment of Cognitive Function: Cognitive function was assessed using Mini-Mental State Examination (MMSE). The MMSE scale is an 11-question, 30-point scale that assesses five cognitive domains: orientation, registration, attention and calculation, memory, language, and visuospatial skill. It is widely accepted and frequently used for screening cognitive impairment. Scores of less than 24 indicate the presence of cognitive impairment [20].

Inclusion Criteria:

- Patients above 20 years.
- Patients who gave written informed consent form.
- Patients who met NCEP ATP III Panel criteria for MetS were included in the study. The NCEP-ATP III is included in **Table 1** [21].

TABLE 1: NCEP ATP III CRITERIA FOR METABOLIC SYNDROME

Risk factor	Values
Central obesity	Men ≥ 90cm and Women ≥ 80cm (for Indian population), plus any two of the following four factors.
Raised TG	≥ 150mg/dl (1.7mmol/L)
Reduced HDL	< 40mg/dl (1.03 mmol/L) in males < 50mg/dl (1.29 mmol/L) in females
Raised BP	Systolic BP ≥ 130 or Diastolic BP ≥ 85mmHg
Raised FPG	≥ 100mg/dl (5.6 mmol/L)

BP; blood pressure, FPG; fasting plasma glucose, HDL; high-density lipoprotein; TG; triglycerides

Exclusion Criteria: The subjects with a history of the following were excluded from the study: Neurological disorders, traumatic brain injury, significant visual or hearing impairment, stage 3-5 Chronic Kidney Disease (CKD), Human Immunodeficiency Virus, thyroid disorders, malignancy, pregnancy, poisoning, drug abuse, chronic alcoholics, any disorders affecting central nervous system functioning, and use of neurotic or psychiatric medications.

Study Procedure:

- Patients were selected from the endocrinology outpatient department of Lakshmi Hospital. A total of 256 patients were screened out of which 183 patients fulfilled the inclusion and exclusion criteria.
- Each participant was briefed on the purpose and procedure of the study and if willing, signed the written consent form.
- Clinical information was collected from the patient's case notes and necessary records.
- Information such as name, age, gender, social habits, duration of disease and comorbidities was recorded.
- Cognitive function was assessed by using Mini-Mental State Examination.
- Diabetes was determined by use of anti-diabetes medications, or fasting glucose levels of more than 100 mg/dL.
- MetS diagnosis was diagnosed using NCEP ATP III criteria.

Statistical Analysis: The collected data were entered into MS Excel sheet and double-checked to eliminate duplication and other data errors. Mean and the standard deviation was used for continuous data. Independent student test was used to compare differences between the two groups.

In the case of more than two groups, ANOVA was used to calculate the differences between multiple groups. All statistical analyses were performed using SPSS version 25.

RESULTS:

General Observations: In the current study 296 patients were screened based on inclusion and exclusion criteria. A total of 185 patients fulfilled the criteria and were enrolled in the study. Females made up 45% of the patients.

Table 2 describes the demographic characteristics of the patients. More than half of the patients were new cases of diabetes mellitus (less than 5 years). More than three-fourths of the patients had at least college education and were cognitively normal.

TABLE 2: GENERAL CHARACTERISTICS OF METABOLIC SYNDROME PATIENTS AT BASELINE

Description of variables (N=183)		Frequency (n)	Percentage (%)
Age group	20-30	6	3.24
	31-40	26	14.05
	41-50	45	24.32
	>51	108	58.38
Gender	Female	83	45
	Male	102	55
Social habits	Smoking	6	3.24
	Alcohol	49	26.49
	Smoking and alcohol	20	10.81
	None	110	59.46
Duration of diabetes	<5 years	102	55.13
	5-10 years	76	41.08
	11-15 years	7	3.78
MMSE scores	<24	42	23.78
	24-30	141	76.22
Education	High School	41	22.16
	College	144	77.84

MMSE; Mini-Mental State Examination

TABLE 3: MMSE SCORES BETWEEN DIFFERENT AGE-GROUPS IN PATIENTS WITH METABOLIC SYNDROME

Age Group (years)	Frequency	Percentage (%)	MMMSE (Mean ± SD)
21-30	6	3.27	26.03 ± 1.38
31-40	26	13.11	25.79 ± 1.24[a]
41-50	45	24.59	24.97 ± 1.62[ab]
>50	108	59.01	23.89 ± 1.95[abc]

MMSE; Mini-Mental State Examination. (a indicates P<0.05 when compared to age group >50 years, b indicates p<0.001 when compared with age group >50 years, c indicates p<0.01 when compared to age group 41-50)

The patients were categorized into different age groups. Patients aged 50 years and above had the lowest mean MMSE scores. Significant difference in MMSE scores was observed between age groups 31-40 and >50 years, p<0.001 see **Table 3**.

TABLE 4: MMSE SCORES BETWEEN GENDER IN PATIENTS WITH METABOLIC SYNDROME

Gender	Frequency	Percentage %	MMSE (Mean ± SD)
Female	83	45.86	24.68 ± 1.89
Male	102	54.14	25.21 ± 1.96

MMSE; Mini-Mental State Examination, SD; standard deviation, p=0.06

Female patients had lesser MMSE scores compared to male patients. However, the difference between their MMSE scores was not significant (p=0.06) See **Table 4**.

TABLE 5: MMSE SCORES BASED ON EDUCATION LEVEL

	Frequency (n)	Percentage (%)	MMSE (Mean ± SD)
High school	41	21.31	23.21 ± 1.71
College	144	78.69	24.01 ± 1.84

MMSE; Mini-Mental State Examination, SD; standard deviation, P<0.05

Significant difference was observed between MMSE scores of college graduates and high school educated patients (p<0.05), see **Table 5**.

The patients had 3 parameters in common, namely: BMI (>25 kg/m^2), high fasting blood glucose (100 mg/dL) and high blood pressure (systolic BP ≥ 130 or diastolic BP ≥ 85mmHg). This was kept as a standard for all MetS patients enrolled. The other 2 metabolic components (low HDL-C and elevated triglycerides) were considered as variables with two groups: MetS + elevated TG and MetS + low HDL-C (see **Table 6**).

TABLE 6: MMSE SCORES IN METABOLIC SYNDROME PATIENTS WITH MULTIPLE COMPONENTS

Parameter	Frequency	Percentage	MMSE (Mean ± SD)
MS + TG	41	66.13	24.51 ± 1.62
MS + HDL-C	22	33.87	25.18 ± 1.34

MMSE; Mini-Mental State Examination, SD; standard deviation, P=0.08; TG; triglycerides

Metabolic syndrome patients with higher triglyceride level had lower MMSE scores than the MetS patients with low HDL levels; however the difference in their scores was not significant (p=0.08).

TABLE 7: MMSE SCORES IN METABOLIC SYNDROME PATIENTS WITH VARYING LEVELS OF TRIGLYCERIDES

Parameter (mg/dL)	Frequency	Percentage (%)	MMSE (Mean ± SD)
MetS + TG (139-159)	19	46.34	25.13 ± 1.25
MetS + TG (160-189)	25	53.66	24.20 ± 1.43

Met S; metabolic syndrome, MMSE; Mini-Mental State Examination, SD; standard deviation, P=0.02

Significant difference, p=0.02, was observed in MMSE scores between MetS patients with high TG compared to MetS patients with borderline TG.

DISCUSSION: The present study enrolled patients from Ernakulam city, Kerala. All the patients were urban dwellers, attending a diabetic clinic for a health check-up. Although Kerala tops the country in terms of health care, MetS pose a real challenge for the health planners. Studies from India, have shown a high prevalence of MetS in urban dwellers with estimates ranging from 33% in men to 40% in women [6]. The ever-increasing prevalence of MetS may be due to changes in lifestyle, urbanization with poor planning, consumption of high-calorie food, and decreased physical activity levels among urban dwellers [22]. In this study, we seek to estimate the prevalence of cognitive impairment in MetS patients in from Ernakulam City, Kerala.

Organizations such as the National Cholesterol Education Programme- Third Adult Treatment Panel, International Diabetes Federation and the World Health Organization have defined MetS with little differences in their criteria. We opted to use NCEP ATP III criteria to screen patients for MetS, which has been used in previous studies in Indian population [5, 23-25]. NCEP ATP III defines MetS as presence of at least three of the five risk factors of MetS in a patient [21]. In the present study, MetS diagnosis was ascertained by the help of a physician.

We assessed the cognitive function in MetS patients, using MMSE, a widely used scale to screen patients for cognitive impairment. In India, MMSE has is widely used and has shown good internal consistency and reliability. The MMSE has been translated into several Indian languages with a number of studies published from India [26, 27]. In the current study, we found the prevalence of cognitive impairment to be 24% in MetS patients. The oldest group of patients had the lowest MMSE scores compared to all other groups. Indeed, as people grow older, the risk of cognitive impairment increases. The MMSE scores from this group differed significantly with all other groups (p<0.05).

When patients were grouped into levels of education, college graduates had better MMSE scores compared to high school goers. The scores in MMSE between the two groups differed significantly (p<0.05). Education provides a buffer against cognitive impairment in later life. Inouye *et al.,* found a strong association between education and memory performance in high-functioning

community dwellers [28]. Education, through the concept of the cognitive reserve, may mask the effects of cognitive impairment in individuals with higher levels of education [29, 30]. On the contrary, education failed to delay the onset of mild cognitive impairment in normal individuals [31].

In the present study, men scored higher than women on MMSE scale. However, the difference between the scores of men and women was not significant (p=0.06). Previous studies have reported lower scores in women compared to men [32]. Women experience a greater cognitive decline in executive functions and long-term memory, which could be a reason why the women in this study had lower scores compared to men [33]. Moreover, women undergo hormonal changes with age, which may influence the trajectory of cognitive impairment. In addition, a study from an urban setting in India found that the prevalence of MetS was higher in women compared to men [34].

All patients in the present study had three common components of MetS: high fasting glucose, elevated blood pressure, and high BMI. We compared the patients based on triglyceride levels and HDL-C levels. Patients with MetS plus high triglycerides had lower MMSE scores than the patients with MetS and low levels of HDL-C, however, the difference was not significant (p=0.08). A previous study found an association between higher levels of HDL-C and preserved cognitive function [35]. HDL-C has other pleiotropic properties such as anti-inflammatory and antioxidation. HDL-C helps remove reactive oxygen species which may induce pathogenesis of cognitive impairment. Low levels of HDL-C are associated with increased risk of Alzheimer's disease [36].

NCEP ATP III defines borderline high triglycerides to be between 131-59 mg/dL and high triglycerides between 160-189 mg/dL [7]. In our study, a comparison between MMSE scores of MetS patients with borderline high triglyceride and high triglyceride levels showed a significant difference (p=0.02). Individuals with higher levels of triglycerides are at risk of mild cognitive impairment and Alzheimer's disease [37, 38]. However, this association is unclear with some studies failing to find any relationship between triglycerides and cognitive impairment [39, 40].

The present study has several strengths worth mentioning. First, the study was conducted in an urban population, who are at increased risk of MetS. All the patients were from Kochi city. Urbanization has been linked to increased risk of MetS in India. Higher occupational status is associated with the risk of MetS [6]. Second, this study estimates the prevalence of cognitive impairment in MetS patients.

We have to acknowledge the limitations of the present study. The sample size was relatively small, limiting the findings to generalization. This was a cross-sectional study; therefore, we could not establish causality from our findings. Assessment of cognitive impairment was done using only MMSE, without any imaging studies, thereby we could not exclude other causes of cognitive impairment. This was because of the huge costs of doing magnetic resonance imaging which was beyond our study.

CONCLUSION: MetS patients are at risk of cognitive impairment. The examination of cognitive function in MetS patients may be recommended to find patients at risk of MetS-related vascular dementia and Alzheimer's diseases. These assessments which should be encouraged on a regular basis could help health care professionals formulate policies that could help prevent or slow down MetS and its associated cognitive impairment.

This study is one of a kind to be conducted in MetS patients in an urban setting in Kerala. Further research is required involving a larger population to understand if MetS or its individual components are responsible for cognitive impairment.

ACKNOWLEDGEMENT: The authors would like to thank Mr. Roni and the participants involved in this study.

CONFLICT OF INTEREST: The authors declare no competing interests.

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How to cite this article:
Menge DM, Nair NK and Kumar PRAV: Prevalence of cognitive impairment in metabolic syndrome patients in urban India. Int J Pharm Sci & Res 2019; 10(9): 4367-73. doi: 10.13040/IJPSR.0975-8232.10(9).4367-73.