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Obesity and Predictors Affecting the Occurrence of Mild Cognitive Impairment.

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ABSTRACT

Mild cognitive impairment is a cognitive decline beyond normal healthy aging but short of meeting diagnostic criteria of dementia. To assess its prevalence among obese adults, study its relation with life style risk factors and identify the most significant predictor risk factors. This study was carried out on 161 obese subjects and 69 control subjects. All participants were subjected to cognitive function assessment, measurement of weight, height, hip and waist circumference, blood pressure and laboratory assessment of fasting blood sugar, total cholesterol, fibronectin and complement 1 inhibitor levels. The prevalence of objective mild cognitive impairment was over 30% among obese compared to 14.2% among controls. A significant difference was detected between all grades of obesity and controls as regards mean total ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III score, memory, and fluency. The total ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III score showed a significant positive correlation with attention, memory, fluency, language, shape recognition and a significant negative correlation with fasting blood sugar and fibronectin levels. This study revealed no significant difference between different cognitive domains as regards obesity. The fasting blood sugar was the only positive predictor risk factor for mild cognitive impairment.
Keywords: obesity, MCI, Fibronectin, Complement 1 inhibitor.

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INTRODUCTION

Cognitive impairment (CI) is the degree of cognitive dysfunction that exists between normal ageing and dementia. Mild cognitive impairment (MCI) is defined as cognitive deterioration beyond normal healthy aging but short of meeting diagnostic criteria of dementia (1). It denotes an early but measurable stage of CI. It encompasses a wide range of cognitive deficits affecting episodic memory and semantic memory and it could be regarded as prodromal phase of Alzheimer's disease (AD) (2).The risk of developing Alzheimer's disease from its prodromal phase (MCI) is higher in the presence of metabolic syndrome (impaired glucose tolerance, central or abdominal obesity, hypertension, Hypertriglyceridemia and decreased level of high-density lipoprotein cholesterol (HDL-C)(3).Population-based research shows MCI prevalence rates ranging from 10% to35% (4-6) with annual incidence rates ranging from 5%to 10% for community-based studies and 10% to 15% in clinical samples (7,8).Obesity and diabetes, combined with aging, contribute to a person's susceptibility to Alzheimer's disease (9). Diabetes is associated with a 50–100% increased risk of Alzheimer's disease and a 100–150% increased risk of vascular dementia (10). The cause of diabetes-related cognitive dysfunction is frequently associated with several comorbidities as cerebrovascular disease (11). Some plasma proteins have been reported as potential biomarkers for MCI and AD. A previous study revealed a significant decrease in plasma levels of two potential biomarkers; fibronectin (FN) and complement 1 inhibitor (C1INH) is evident at the MCI stage (12).

Aim of the work:

To evaluate the prevalence of MCI among obese adults, to study the life style risk factors related to MCI, to evaluate the relation between MCI and DM, hypertension and dyslipidemia among obese and to identify the most significant predictor risk factors for MCI among obese.

Subjects and Methods:

A case control study was carried out on 161subjects aged 40 to 60 years from both sexes randomly recruited from National Research Center (NRC) out-patient clinics and 69 healthy subjects served as a control group.

Any subject suffering from cerebro-vascular stroke, organ failure, malignancy, autoimmune diseases or pregnant females were excluded from the study.

A closed ended questionnaire module was designed for data collection. All studied participants provided written informed consent before study activities. A face to face interview was conducted to fill in the questionnaire with special emphasis on demographic data specially tobacco smoking, full medical history, physical activity, dietary habits, and vitamin supplementation. Neuropsychological assessment was carried out for all studied population for cognitive function with its domains by using the Arabic version of the ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III.(13).The original Addenbrooke's Cognitive Examination (ACE) was developed in the Medical Research Council Cognition and Brain Sciences Unit in Cambridge in the late 1990s as a simple bedside test battery designed to detect mild dementia and differentiate Alzheimer's disease from fronto-temporal dementia (14). It was further developed to the ACE III which is a sensitive, valid and reliable 100-point questionnaire that is used to measure cognitive impairment (15). It examines functions including registration, attention and calculation, recall, language, ability to follow simple commands and orientation. The maximum score is 100 points.

Assessment of cognitive function with its domains

The case definition of MCI was based on the recommendations of the National Institute on Aging–Alzheimer's Association (16).

It includes the following core clinical criteria for the diagnosis of MCI:

- Subjective Concern regarding a change in cognition. There should be an evidence of concern about a change in cognition in comparison with the person's previous level.

- Objective Impairment in one or more cognitive domains. There should be an evidence of lower performance in one or more cognitive domains that is greater than would be expected for the patient's age and educational background. This change can occur in a variety of cognitive domains including memory, executive function, attention, language and visuo-spatial skills.
- Preservation of independence in daily functional abilities such as paying bills, preparing a meal, or shopping.
- Accordingly the following criteria were applied in the current study:

I: Objective MCI: To promote generalizability to other samples. We utilized the operational definition for objective cognitive impairment in MCI established as 1 SD below the normative mean by (17).So to estimate the normative mean of ACE-III, we studied also 69 normal healthy non obese individuals from NRC workers of comparable age, sex and education to the studied obese subjects. We found that mean score of ACE-III among controls was 89.6 ± 6.5. So, the cutoff used to identify objective MCI was score 83 (1 SD below normal mean)(17).

II: The final definition of MCI according to subjective, objective and preservation of independence in daily functional abilities

All studied population was subjected to thorough clinical examination was carried out for height and weight in order to estimate the body mass index as a measure of obesity. Obesity was defined as a BMI greater than or equal to 30. Obesity was further divided into grade 1 (BMI < 35), grade 2 (BMI 35- 39.99), and grade 3 (BMI ≥40) (18). Measurement of hip and waist circumference as hip/waist ratio is a measure of central obesity. Systolic and diastolic blood pressures were measured to the nearest even digit from the right arm of the seated participant. Hypertension is defined as repeatedly elevated blood pressure exceeding 140 over 90 mmHg-a systolic pressure above 140 or a diastolic pressure above 90 or on current use of antihypertensive medications. Measurement of fasting blood sugar (FBS), diabetes mellitus is defined as FBS ≥126 mg/dL, total cholesterol (TC) level(hypercholesterolemia as TC level >240mg/dL), triglyceride (TG) level (high triglyceride level as), high density lipoprotein-cholesterol and assessment of fibronectin (FN)and complement 1 inhibitor (C1INH) levels.

Blood sampling: 6mL of fasting venous blood were withdrawn under complete aseptic condition from all participants and were placed in two plain vacutainers. One was used for immediate analysis of FBS and TC after 8-10 hours fasting and the other was used for assessment of FN and C1INH levels by quantitative sandwich Enzyme Linked Immunosorbent Assay (ELISA) technique. Blood was allowed to clot for 30 minutes, and then centrifuged at 3000g for 10 minutes; sera were stored at -20^{o}C till analysis.

Analytical methods: FBS, TC, TG, HDL-C and LDL-Cwere assessed by enzymatic colorimetric method using Erba XL-300 .

The C1INH level was assessed using MyBioSource ELISA kit with detection range (1.56ng/ml-100ng/ml), the minimum detectable level was 0.5ng/ml, no cross-reaction with other factors was detected, the intra-assay precision ≤ 8% and inter-assay precision ≤ 12%.

The FN level was measured using Quantikine ELISA kit (RnD systems)with detection range (0.062-0.579), intra-assay precision was 5.3 and inter-assay precision was 5.5.

Statistical analysis

Statistical program for social science (SPSS) version 18 for windows SPSS; Inc. Chicago IL was used for data analysis. Continuous data were expressed as mean and standard deviation Number and percent were used to describe categorical data. Student t test was used for comparing between two means and ANOVA for comparing between more than two means and chi square test for comparing between two qualitative variables Non Parametric test was used when data not normally distributed using Mann-Whitney U test.To correlate between two continuous variables Pearson correlation test was used. Multiple regression analysis was done to identify the most significant predictor variable for objective MCI among obese. P value when < 0.05 is statistically significant.

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RESULTS

One hundred and sixty one obese subjects participated in the study; with mean age 52.1±5.4, males were 8.1% and 44.7% had secondary education (data not shown). The controls were 69 subjects with mean age 51.3 ± 6.4; males were 42.0% and 30.4% had secondary education (data not shown). There was significant difference between obese and controls as regards sex only **(P< 0.001), Table (1)**.**Table (2)** shows that among the obese, 69 (42.9%) had objective MCI and 92 (57.1%) individual had normal cognition. The prevalence of objective MCI was 42.2%,47.2%, and 38.6% among obesity grade I, II & III respectively compared to 11.6% among controls. The difference was statistically significant between grade I, II and III obesity compared to controls with odds ratios 5.5, 6.8, and 4.8 respectively.

Table 1: The relation between some socio-demographic variables among the studied groups

Variables	Controls N=69	Grades of obesity			P value
		Grade I N=64	Grade II N=53	Grade III N=44	
	N (%)	N (%)	N (%)	N (%)	
Age in years					
<45	15 (21.7)	6 (9.4)	5 (9.4)	4 (9.1)	
45-	16 (23.2)	14 (21.9)	16 (30.2)	9 (20.5)	0.203
50-	21 (30.4)	19 (29.7)	10 (18.9)	13 (29.5)	
≥55	17 (24.6)	25 (39.1)	22 (41.5)	18 (40.9)	
Sex					
Male	29 (42.0)	11 (17.2)	0 (0.0)	2 (4.5)	0.00**
Female	40 (58.0)	53 (82.8)	53 (100)	42 (95.5)	
Education					
Secondary	21(30.4)	27 (42.2)	24 (45.3)	21 (47.7)	0.21
University	48 (69.6)	37 (57.8)	29 (54.7)	23 (52.3)	

****P< 0.001**

Table 2: Objective MCI according to ACE III score in relation to obesity

Variables	Objective MCI N=77	Normal cognition N=153	Crude Odds Ratio
	N (%)	N (%)	
Controls	8 (11.6)	61(88.4)	-
Grade I obesity	27(42.2)	37(57.8)	5.56 (2.28- 13.52)**
Grade II obesity	25 (47.2)	28(52.8)	6.8 (2.7 – 16.96)**
Grade III obesity	17(38.6)	27 (61.4)	4.8 (1.8 – 12.47)**

MCI: Mild cognitive Impairment

****P< 0.001 significant difference between controls and each grade of obesity**

Table (3) shows a significant difference between all grades of obesity and controls as regards mean total ACE III, memory and fluency **(P<0.05)**. No significant difference was detected between different cognitive domains as regards different degree of obesity. MCI was presented in tables 4-5-6 according to subjective, objective and preservation of independence in daily functional abilities among the studied obese.As shown from **tables (4 & 5),**none of the studied risk factors were found to be significantly related to MCI **(P > 0.05)**.**Table (6)** shows the mean and SD of different clinical and laboratory risk factors related to MCI, none of them were significantly associated with MCI.Only the mean ofFBS was significantly higher among MCI obese compared to those with no MCI **(P < 0.05)**.The FBS level was the only significant predictor of lower objective MCI using ACE III by using multiple regression analysis (data not shown).A significant positive correlation was found between total ACEIII score and the 5 scales (Attention, memory, Fluency, language and shape recognition) (**P<0.001)**.

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Table 3: Mean ACE III score and its five cognitive domains among different grades of obesity and controls

Variables	Controls N= 69	Level of obesity (BMI)			P value
		Grade I obesity N=64	Grade II obesity N= 53	Grade III obesity N= 44	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Total ACE III score	91.0 ±5.4 **Ω©®**	86.0±7.2	84.4±6.3	84.6±8.0	0.000
Attention	17.3±1.2	17.0±1.5	17.1±1.4	16.9±1.4	0.486
Memory	23.7±2.4 **Ω©®**	22.4±3.0	22.2±2.4	22.5±3.1	0.012
Fluency	9.5±2.1 **Ω©®**	8.0±2.9	7.7±2.2	7.6±2.6	0.000
Language	25.6±0.9	24.2±1.8	24.0±2.3	23.9±2.0	0.000
Shape Recognition	15.0±1.4	14.5±1.6	13.4±2.0	13.8±2.2	0.000

BMI: Body mass index

Ω Significant difference between controls and grade I obesity (p< 0.05)
© Significant difference between controls and grade II obesity (p< 0.05)
® Significant difference between controls and grade III obesity (p< 0.05)

Table 4: Some Risk Factors for Mild Cognitive Impairment among the obese subjects

Variables	Total N=161	Cognition		P value
		Objective MCI N=69	Normal cognition N=92	
	N	N (%)	N (%)	
Grades of Obesity				
Grade I	64	27 (42.2)	37 (57.8)	0.69
Grade II	53	25 (47.2)	28 (52.8)	
Grade III	44	17 (38.6)	27 (61.4)	
Age				
<45 years	15	8 (53.3)	7 (46.7)	0.119
45-	39	11 (28.2)	28 (71.8)	
50-	42	17 (40.5)	25 (59.5)	
≥ 55 years	65	33 (50.8)	32 (49.2)	
Sex				
Male	13	8 (61.5)	5 (38.5)	0.242
Female	148	61 (41.2)	87 (58.8)	
Education				
Secondary	72	32 (44.4)	40 (55.6)	0.750
University	89	37 (41.6)	52 (58.4)	
Smoking (Out of 142)				
Never smoking	131	63 (48.1)	68 (51.9)	0.669
Smoking or Ex-smoking	11	5 (45.5)	6 (54.5)	

Table 5: Clinical risk factors for Mild Cognitive Impairment among the obese subjects

Variables	Total obese N=161	Cognition		P value
		Objective MCI N=69	Normal cognition N=92	
	N	N (%)	N (%)	
Diabetes Mellitus				
Yes	40	22 (55.0)	18 (45.0)	0.097
No	121	47 (38.8)	74 (61.2)	
Hypertension				
Yes	54	22 (40.7)	32 (59.3)	0.73
No	107	47 (43.9)	60 (56.1)	
Heart disease				
Yes	7	2 (28.6)	5 (71.4)	0.700

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No	154	67 (43.5)	87 (56.5)	
Kidney disease				
Yes	25	13 (52.0)	12 (48.0)	0.277
No	136	56 (41.1)	80 (58.9)	
Head trauma				
Yes	127	54 (42.5)	73 (57.5)	0.54
No	34	15 (44.1)	19 (55.9)	

MCI: Mild cognitive Impairment

Table 6: Mean blood pressure level and some laboratory results in relation to objective MCI among the obese group

Variables	Total obese N= 161 Mean ± SD	Objective MCI N= 69 Mean ± SD	Normal cognition N= 92 Mean ± SD	P value
Systolic Blood Pressure	126.7 ±16.3	126.3 ±16.5	127.0 ±16.1	0.781
Diastolic Blood Pressure	80.4±9.4	80.4 ±8.9	80.4 ±9.9	0.953
Fasting blood sugar level (mg/dl)	103.3 ±45.1	109.9 ±47.1	97.3 ±42.7	0.156
Cholesterol level (mg/dl)	211.7± 45.2	208.6 ±50.3	214.5 ±40.6	0.499
C1INH level (ng/ml)	46.2 ±21.1	47.8 ±21.2	44.6 ±21.2	0.482
Insulin level (µIU/mL)	17.4 ±12.2	16.3 ±10.6	18.7 ±13.7	0.512
Fibronectin level (ng/mL)	0.2 ±0.1	0.2 ±0.1	0.2 ±0.2	0.779

Table 7: Correlation between ACE III score and its five cognitive domains and different factors among the obese group

	ACE III score	Attention	Memory	Fluency	Language	Shape recognition
ACE III score	1	**0.503****	**0.783****	**0.717****	**0.656****	**0.556****
Attention	**0.503****	1	**0.301****	**0.245****	**0.212****	0.135
Memory	**0.783****	**0.301****	1	**0.385****	**0.394****	**0.308****
Fluency	**0.717****	**0.245****	**0.385****	1	**0.346****	**0.224****
Language	**0.656****	**0.212****	**0.394****	**0.346****	1	**0.198***
Shape recognition	**0.556****	0.135	**0.308****	**0.224****	**0.198***	1
Fasting blood sugar level (mg/dl)	**-0.236***	-0.193	-0.149	-0.202	-0.037	-0.147
Insulin level (µIU/mL)	-0.028	0.125	-0.018	-0.057	**-0.214***	0.131
BMI	-0.090	-0.132	0.058	-0.141	-0.090	-0.035
Fibronectin level(ng/mL)	-0.054	-0.074	-0.080	-0.024	-0.017	0.736
C1INH level (ng/ml)	-0.079	-0.088	-0.021	-0.168	-0.078	0.110

C1INH: complement 1 inhibitor; *P < 0.05; **P < 0.01

A significant negative correlation was detected between total ACE III score and FBS, also, between insulin level and language scale **(P< 0.05), Table (7).**

DISCUSSION

The prevalence of overweight and obesity is increasing throughout the world. The number of overweight and obese adults is expected to be 1.35 billion and 573 million respectively by 2030 [2].

This study examines the prevalence of MCI in a sample of obese adults. A total of 161 obese participants were aged from 40 to 60 years with mean age (52.6 ± 5.5 years) completed cognitive testing. The prevalence of objective MCI was over 30% among obese reaching 35% among morbid obesity compared to

14.2% among non-obese controls. No significant difference was detected between different grades of obesity, or between male and females. Rochette et al reported higher prevalence of objective MCI (53.8%) among obese especially those with BMI ≥ 35**(1)**.Moreover, in a study done by Ahmadi and Kiyani (2011), the overweight and obese groups were more subjected to minimal CI as compared to the group with normal weight with no significant difference between male and female(19). Similar to the present study, there was no meaningful difference among the average scores of obese men and women. The results of present study is consistent with those of Gustafson (2003), Lachsinger (2005) and Elias (2005)(20,21,22, respectively).

In the present study, age and sex were not associated with increased risk of obesity or MCI. These results are inconsistent with Paradise et al, who found that male gender and low level of education increased the risk of early memory changes by about two folds (6).

Education and reading are protective factors for cognitive function (23). In the present study, subject educated till university and more had lower percent of MCI compared to subject educated till secondary school (41.6 and 44.1% respectively) yet the difference is not significantly different. These results are consistent with previous studies done by Sabia and co-workers (2012)(24)and Martin et al.(2015)(25).

Saturated fatty acids stimulate an inflammatory response in the hypothalamus that could influence the glial activation in the brain by crossing the blood brain barrier, this may be one of the mechanisms by which obesity causes cognitive dysfunction[2]. In the present study, no significant difference was found between objective MCI and normal cognition as regard BMI and cholesterol level($P>0.05$).

Vascular risk factors are considered well established risk factors in MCI development, they include obesity, DM, heart diseases, hypertension, hypercholesterolemia and smoking (2,3,4,5). Results of the current study controversies the previous studies except for DM as none of the studied risk factors including level of obesity were found to be predictors of MCI. Rochette et al reported that age, sex, the presence of hypertension or diabetes are not predictors of MCI among obese (1).

In the current study, only FBS was revealed to be a significant predictor of MCI by multivariate analysis. Paradise et al. found out that subjective memory complaints were associated with diabetes, smoking, and hypercholesterolemia. Whereas, in multivariate analysis, none of the vascular factors showed association with early memory changes (6). The lack of association of the vascular factors with early memory changes is consistent with Jorm et al, who stated that heart troubles, history of strokes and diabetes were not associated with memory changes in their study (7). This is also in agreement with Stewart et al, who found that in a sample of Afro-Caribbean population, diabetes, cardiac ischemia, triglyceride, and cholesterol levels were not associated with memory changes (8).

Blood based markers could add a signal in the stage of MCI, among which are the complement system and fibronectin. The complement component profile has been used as an indicator in the studies of various diseases (10). C1INH has been demonstrated in the brain of MCI patients (11). Results of the present study revealed that there was no association between C1INH or fibronectin and the occurrence of MCI. Another study by Loeffler et al, found no difference between normal and MCI patients regarding the presence of complement activation products in the brain (26). However, Muenchhoff et al(2015), found that the plasma level of these two biomarkers was significantly decreased at the MCI stage (12). Also, Zanijani and co-workers, reported in their study that early complement activation products increased in the temporal cortex of patients of very mild to severe clinical Alzehimer disease (27).

CONCLUSION

This study revealed no significant difference between different cognitive domains as regards different degree of obesity. In addition, the studied risk factors (age, sex, education, hypertension) and the studied laboratory markers (fibronectin, complement 1 inhibitor, Cholesterol, Triglyceride, HDL-C, LDL-C)showed no evidence of significant association with MCI among obese, except fasting blood sugar, which was the only positive predictor risk factor for MCI.

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Declaration

The authors declare that the manuscript is original and is not published or communicated for publication elsewhere either in part or full.

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