Assessment of serum Levels of Adiponectin and Leptin in a cohort of elderly Egyptian Patients with Dementia

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Abstract:

Background/Aim: Dementia is a chronic progressive deterioration of cognitive function. About 50 million cases of dementia worldwide, 5-8% of elders aged 60 years and more have dementia. Adiponectin is an adipokine and presents in the humans' brains and is linked to multiple functions in the central nervous system. Leptin is a cytokine that was thought to be associated with a decline in cognitive function. The present study aimed to assess adiponectin and leptin levels in elderly demented patients.

Materials and methods: the current study included 60 subjects of both genders aged 65 years and more; Group (I): 40 patients with dementia, and Group (II): 20 healthy control subjects. We excluded participants with chronic renal or hepatic diseases, diabetics, hypertensive, dyslipidemic patients, those with thyroid disorders, and those who were morbidly obese. MMSE and MOCA tests were done on all subjects, levels of adiponectin and leptin were assessed in participants' sera using the ELISA test.

Results: Higher levels of adiponectin, but low levels of leptin were detected in patients with dementia. MMSE and MOCA scores were significantly correlated with serum adiponectin (negatively), and with serum leptin (positively). **Conclusion:** In elderly patients with dementia**,** serum adiponectin and leptin were strongly associated with the degree of dementia, which may help us to understand the underlying pathophysiology of this untreatable disease.

Keywords: Adiponectin, Leptin, Dementia, elderly

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Introduction:

Dementia is a general term described as a collection of symptoms related to cognitive impairment as memory impairment and deterioration in intellectual mental functions. Dementia is considered a major cognitive disorder [1]. Previously, dementia was classified into three consecutive stages: mild, moderate, and severe [2]. Recently, dementia was classified into seven stages: 1. No impairment, 2. Very mild cognitive decline, 3. Mild cognitive decline, 4. Moderate cognitive decline, 5. Moderately severe cognitive decline, 6. Severe cognitive decline, and 7. Very severe cognitive decline. The prevalence of dementia in Egypt varies between 2.01% - 5.07%, with a higher prevalence in illiterates [3]. Prevalence increases consistently with age, from about 0.34% to 9.74% in people aged less than 70 to those who are more than 80s respectively [4].

Alzheimer's disease followed by vascular dementia, and dementia with Lewy bodies are by far the commonest causes of dementia. Less common causes are frontotemporal dementia, and Creutzfeldt-Jakob disease [5].

Clinically, dementia symptoms can be categorized in three domains [6]; (1) Impaired cognition, (2) Disturbed behavior [7]. (3) Affection of daily life activities [8].

Multiple risk factors are associated with dementia as; female gender, advanced age, genetic or family history, diabetes mellitus, hyperhomocystenemia, hypercholesterolemia, and atherosclerosis [9].

Till now, no modality to diagnose dementia for sure. Diagnosing dementia depends on history taken from the patients, clinical examination, and assessment of cognitive functions. Neuroimaging is advised in selected cases most probably to exclude organic brain lesions [10].

Adiponectin is an adipocyte-derived hormone [11]. Adiponectin is not only expressed in adipocytes, but it is also found in hepatic cells, cardiac cells, muscles, osteoblasts, and epithelial cells. Firstly, adiponectin was identified as a physiological regulator of food intake and weight control in the brain via AdipoR1-AMPK signaling [12]. In experimental rats with low levels of Adiponectin, the following pathological changes were found; a significant decrease in hippocampus volume, with lower gray matter volume, and reduced cerebral glucose metabolism in the temporal lobes [12,13].

Later, a lot of functions of adiponectin were discovered. Adiponectin can bind to 3 receptors: adiponectin receptor 1 (AdipoR1), adiponectin receptor 2 (AdipoR2), and T-cadherin. AdipoR1 and AdipoR2 are expressed in different areas of the brain [14]. Adiponectin has important functions in the central nervous system as it modulates insulin sensitivity in the brain thus it modulates energy expenditure and hence cognitive function [15]. A negative correlation between insulin resistance, obesity, diabetes mellitus, atherosclerosis and adiponectin was reported [16]. All these factors are risk factors for dementia. It was suggested that metabolic diseases, such as diabetes mellitus and obesity are associated with Alzheimer's disease. The underlying pathophysiology may be an alteration of insulin receptors and obesity-related adiponectin [17,18].

Also, adiponectin modulates the behavior of interleukins by decreasing the expression of

proinflammatory interleukins while increasing the expression of anti-inflammatory interleukins [19,20].

Leptin is another adipocyte of white adipose tissue [21]. Firstly, leptin was considered an anti-obesity protein but later, it is implicated in a decline in cognitive functions. Most previous studies had been limited to animal models [22], and few observational studies studied leptin levels in patients with dementia [23].

There are a growing set of promising diagnostic approaches in the present study, we aimed to determine the levels of adiponectin and leptin in the sera of elderly patients with dementia and determine their association with cognitive assessment tests.

Materials and Methods:

The present study included sixty subjects of both genders aged 65 years and more, divided into two groups; Group I: forty demented patients, who attended the outpatient clinic at Al-Ma'mora Mental Health Hospital, and Group II: (control group) twenty healthy subjects. The nature, steps, and aim of the study were explained to all participants, and a written informed signed consent was obtained. The study was conducted after the approval of the Medical Ethics Committee of Alexandria Faculty of Medicine.

Exclusion criteria of participants were:

Dyslipidemia, hypertension, diabetes mellitus, chronic hepatic or renal diseases, thyroid disorders, morbid obesity (BMI>30 kg/m2). Participants receiving narcotic analgesics and sedative-hypnotics were excluded from the study.

A thorough history was taken from all subjects, full clinical examination including neurological examination, and routine laboratory investigations include complete blood picture, fasting blood glucose, hepatic panel, renal panel, and thyroid function tests.

Body mass index was assessed by measuring weight of the patient while wearing light clothes to the nearest kilogram divided by the square height while the patient stands with bare feet to the nearest meter.

Serum levels of Adiponectin [24], and leptin [25] were determined for all participants using ELISA kits. Dementia was diagnosed according to the Mini-Mental State Examination (MMSE) [26] and The Montreal Cognitive Assessment (MOCA) [27].

MMSE includes 11-questions that measure the range of mental skills. The questions assess orientation to time and place, registration, attention and solving simple mathematical operations, recall, language and

comprehension, repetition, and complex commands. The total score of questions is 30. A score of 24 and more indicates normal cognition. Scores ≤9 points indicate severe dementia, Scores from 10–18 points indicate a moderate form of dementia, and scores from 19–23 points indicate mild cognitive impairment.

MOCA assesses several cognitive functions include short-term memory recall, visuospatial skills using three-dimensional cube copy and clock-drawing task, attention, concentration, abstract reasoning, and orientation. The score ranges from 0-30 with a score of 26 and more considered normal.

Statistical evaluation:

Data were collected and fed to the computer and analyzed using IBM SPSS software package version 20.0. Numerals and percentages were used to describe qualitative data. Range, mean, standard deviation, and median were used to describe quantitative data. The significance level of results was judged at the 5% level. Comparison between different groups was done using the Chi-square test (x^2). comparison between groups regarding quantitative variables was done using Student t-test (t). Abnormally quantitative variables comparison between two studied groups was done using Mann Whitney test. Spearman coefficient was used to detect the correlation between abnormally quantitative variables.

Results:

Sixty subjects were involved in the current study, divided as Group (I): forty demented patients, and Group (II): twenty healthy subjects (control group).

The mean age of the group (I) was 69.70 ± 1.95 years and was 69.10 ± 2.67 years in the group (II), no significant difference was detected between the two groups (p=0.326).

Regarding gender distribution, Group I (demented patients) included 22 males (55%), and 18 females (45%), group II (control group) included 12 males (60%), and 8 females (40%). Comparison between the two groups does not show any significant difference (p=0.713).

In Group (I), 19 (47.5%) patients were within the normal weight range, 20 (50%) patients were overweight, and only one patient (2.5%) was severely obese with a mean BMI of 25.82 ± 2.26 Kg/m^2. In group (II), 12 (60%) subjects were within the normal weight range, and 8 (40%) subjects were overweight, with a mean BMI of 25.84 ± 2.22 Kg/m2. No statistically significant difference was noted between both groups.

Table 1

Table 1: Body mass index (BMI) of groups I and II:

	Group I Demented patients (n =40)		Group II Control group (n =20)		Test of Sig.	P-value
	No.	%	No.	%		
BMI (kg/m^2)						
Normal weight (18.5 – <25)	19	47.5	12	60.0		
Overweight (25 – <30)	20	50.0	8	40.0		
Obese (30 – <35)	0	0.0	0	0.0	χ^2=1.175	^{MC}p=0.721
Severely Obese (35 – <40)	1	2.5	0	0.0		
Morbidly obese (≥ 40)	0	0.0	0	0.0		
Min. – Max.	21.77 – 29.74		23.32 – 29.73			
Mean ± SD.	25.82 ± 2.26		25.84 ± 2.22		t=0.042	0.966
Median	25.09		24.77			

BMI: body mass index. *P* is significant at ≤ 0.05.

X^2: Chi-square test t: Student t-test

Table 2: Comparison between the studied groups MMSE, and MOCA scores:

	Group I (n =40)		Group II (n =20)		Test of Sig.	p
	No.	%	No.	%		
MMSE						
Normal Cognition (≥27)	0	0.0	20	100.0		
Mild Cognition impairment (19 -24)	28	70.0	0	0.0	χ^2=60.000*	<0.001*
Moderate Cognition impairment (1- 18)	12	30.0	0	0.0		
Min. – Max.	16.0 – 23.0		27.0 – 30.0			
Mean ± SD.	19.53 ± 1.96		28.85 ± 1.09		t=23.649*	<0.001*
Median	19.0		29.0			
MOCA						
Normal (≥26)	0	0.0	20	100.0	χ^2=60.000*	<0.001*
Abnormal	40	100.0	0	0.0		
Min. – Max.	14.0 – 22.0		26.0 – 30.0			
Mean ± SD.	18.03 ± 2.18		28.20 ± 1.11		t=24.008*	0.001*
Median	18.0		28.0			

MMSE: the mini-mental state examination; MOCA: The Montreal Cognitive Assessment.

*: Statistically significant at p ≤ 0.05.

X2: Chi-square test t: Student t-test

Table 2 shows the comparison between the two studied groups regarding the score of MMSE, and MOCA tests. In group I, 28 patients (70%) had mild cognitive impairment, and 12 patients (30%) had moderate cognitive impairment. In group II (control group), all subjects showed normal cognition. The mean MMSE score of the group (I) was 19.53 ± 1.96, while it was 28.85 ± 1.09 for the group (II). Both groups differed statistically (p <0.001). In the MOCA test, all

patients in the group (I) showed an abnormal score with a mean of 18.03 ± 2.18, while all subjects in the group (II) showed a normal score with a mean of 28.20 ± 1.11.A. We detected a significant difference between both groups (p =0.001).

Table 3: Serum adiponectin levels in group I and II:

	Group I (n =40)		Group II (n =20)		Test of Sig.	p
	No.	%	No.	%		
Adiponectin (ng/ml) Normal (6.33 – 10.83) Abnormal	 0 40	 0.0 100.0	 18 2	 90.0 10.0	χ^2=51.429*	<0.001*
Min. – Max. Mean ± SD. Median	24.30 – 90.40 42.11 ± 16.97 36.40		6.30 – 10.90 8.91 ± 1.66 9.15		Z=6.273*	<0.001*

χ2: Chi-square test; Z: Z value for Mann Whitney test
*: Statistically significant at p ≤ 0.05

Table 3 represents the serum adiponectin levels of both groups. The mean serum level of adiponectin was 42.11 ± 16.97 ng/ml in the group (I), while it was 8.91 ± 1.66 ng/ml in the group (II). Both groups differed significantly (p <0.001).

Table 4: Serum levels of leptin in group I and II:

	Adiponectin		Leptin	
	r_s	p	r_s	p
Demented patients (group I) MOCA MMSE	 -0.383* -0.453*	 0.015* 0.003*	 0.357* 0.378*	 0.024* 0.016*
Control group (group II) MOCA MMSE	 -0.302 -0.339	 0.195 0.144	 -0.262 0.210	 0.264 0.373

rs: Spearman coefficient
*: Statistically significant at p ≤ 0.05

Table 4 represents the serum leptin levels in both groups. The mean level in the group (I) was 1.25 ± 0.67 ng/ml, while it was 6.76 ± 2.53 ng/ml in the group (II). Both groups differed significantly (p<0.001).

Table 5: The relation between serum levels of adiponectin, and leptin and cognitive assessment tests in groups I and II:

	Adiponectin		Leptin	
	r_s	p	r_s	p
Demented patients (group I) MOCA MMSE	 -0.383* -0.453*	 0.015* 0.003*	 0.357* 0.378*	 0.024* 0.016*
Control group (group II) MOCA MMSE	 -0.302 -0.339	 0.195 0.144	 -0.262 0.210	 0.264 0.373

Table 5 represents the correlation between serum levels of leptin and adiponectin and tests of dementia in both studied groups. Serum levels of adiponectin negatively correlated with scores of both MMSE and MOCA (p=0.003 and 0.015 respectively). While serum levels of leptin were positively correlated with both MMSE and MOCA scores

(0.016 and 0.024 respectively). No significant correlation was noted in the controls (group II).

Discussion:

Dementia is a chronic progressive deterioration of cognitive function that markedly affects daily life activities [1]. The estimated prevalence of dementia in Egypt is about 1% for those aged 50 years and more, rising to 9.7% for people aged > 80 years [28].

We investigated 60 elderly subjects of both genders divided into two groups; Group I included 40 patients with dementia; 22 (55%) males, and 18 (45%) females their mean age was 69.70± 1.95 years, and group II included 20 healthy controls; 12 (60%) males, and 8 (40%) females, their mean age was 69.10± 2.67 years. No statistical difference was noted between both groups. Increasing age was a risk factor for dementia in several studies [9].

In our study,19 (47.5%) patients in group (I) were within the normal weight range, 20 (50%) patients were overweight, and only one patient (2.5%) was severely obese with a mean BMI of 25.82 ± 2.26 Kg/m2. In group (II), 12 (60%) subjects were within the normal weight range, and 8 (40%) subjects were overweight, with a mean BMI of 25.84 ± 2.22 Kg/m^2. No statistically significant difference was noted between both groups. A recent follow-up study had demonstrated a negative correlation between BMI and dementia in elders aged 65 years and more [29]. Adiponectin is a protein hormone that modulates several metabolic processes [30]. It is secreted from adipose tissue and acts via its receptors, which are widely distributed in the brain [31]. In our study, high levels of adiponectin were detected in elderly patients with dementia in both genders, with a mean of 42.11 ± 16.97 ng/ml. Following our results, Van Himbergen et al. [22] investigated 541 elderly women and followed them for 13 years, they stated that adiponectin is positively correlated with increased incidence of dementia. This finding was confirmed in another Japanese study [12]. Body resistance to high levels of adiponectin may explain the association between dementia and increased levels of Adiponectin. It was hypothesized that adequate adiponectin activity may reduce the risk of developing dementia, the explanation was that levels of adiponectin may rise as a protective mechanism to changes occurring in the brain of demented patients.

However, hormone resistance may prevent the body from getting benefit from this protective increase in adiponectin levels [20]. Shafique K et al., [33] stated that high levels of adiponectin detected in patients with dementia may be due to underlying vascular or morphological dysfunction that may arise as an explanation to the underlying pathophysiology of dementia. On the contrary, Kitagawa K et al [34], failed to confirm the correlation between dementia an adiponectin between adiponectin in 466 studied patients of both genders.

Leptin is an adipokine that regulates energy balance by inhibiting hunger [35]. In the current study, patients with dementia had low serum levels of leptin (mean level of 1.25 ± 0.67 ng/ml). Following our results, Holden KF et al. [36], stated an inverse relationship between leptin levels and deterioration of cognitive function. Furthermore, Zeki Al Hazzouri A et al. [37], found an association between higher levels of serum leptin and dementia in normal weighted very old females. A cross-sectional study has shown that patients with AD had lower levels of serum leptin compared to healthy ones [38]. On contrary to our results, Oania R et al. [39], failed to prove an association between leptin and dementia in the studied population.

In our study, in group I; 28 patients (70%) had mild cognitive impairment, and 12 patients (30%) had moderate cognitive impairment, with a mean MMSE score of 19.53 ± 1.96, and mean MOCA score was18.03 ± 2.18. In group II (control group), all subjects showed normal cognition with normal MMSE and MOCA scores. Both groups differed significantly. Serum levels of adiponectin were negatively correlated with both MMSE and MOCA scores (p=0.003 and 0.015 respectively). While serum levels of leptin were positively correlated with MMSE and MOCA scores (0.016 and 0.024 respectively).

Conclusion:

In conclusion**,** a high prevalence of dementia can be seen in the elders. With a lack of definite treatment, it mandates a search for new hormones linked to its pathogenesis to understand its pathophysiology and the emergence of medications that can control or treat this devastating disease. In this instance, serum adiponectin and leptin were detected to be strongly associated with dementia in our study. A large, longitudinal studies are recommended to validate our results.

Abbreviations:

Adipo-R1: adiponectin receptor 1
Adipo-R2: adiponectin receptor 2
BMI: body mass index
IL-10: interleukin-10
MMSE: mini-mental state examination
MOCA: The Montreal Cognitive Assessment
TNF-α: tumor necrosis factor-alpha
VaD: vascular dementia

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Conflicts of interest

There are no conflicts of interest.

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