Serum Levels of high Molecular Weight Adiponectin and Leptin in Elderly Patients with Dementia

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Abstract
Dementia is a progressive impairment of cognitive function sufficient to cause functional decline. It may affect up to 28 million individuals world-wide; 30% of those older than 85 years. Adiponectin is a cytokine released by the adipose tissue, and presents in the cerebrospinal fluid of human. It has important functions in the central nervous system. Leptin is another cytokine was implicated in cognitive decline and dementia processes. We aimed in the present study to determine the serum levels of adiponectin and leptin in elderly patient with dementia. 60 subjects aged 65 years and older were involved, divided into two groups; Group (I): 40 demented patients, and Group (II): 20 age and sex matched healthy subjects as a control group. Participants with dyslipidemia, hypertension, diabetes mellitus, chronic liver diseases, chronic kidney diseases, thyroid disorders, or morbid obesity were excluded from the study. All participants were subjected to MMSE and MOCA tests, serum adiponectin and leptin were measured. Serum adiponectin was higher, while leptin levels were lower in demented patients. A significant negative correlation between serum levels of adiponectin and both MMSE and MOCA scores, while a high positive correlation was noted between serum levels of leptin and both MMSE and MOCA scores. We concluded that serum adiponectin and leptin were strongly associated with dementia in elderly patients, which may help in understanding of its pathogenesis and emergence of new drugs for better outcome of this devastated disease.

Introduction
Dementia is defined as a progressive acquired impairment of cognitive function sufficient to cause functional decline, and occurring in a relatively normal level of consciousness (¹).

Dementia demonstrates memory impairment, disturbance in executive functioning i.e. planning, organizing, sequencing, and abstracting, decline in emotional control or motivation, or a change in social behavior, and absence of clouding of...
Dementia must be distinguished from so-called mild cognitive impairment (MCI), which appears to represent an intermediate stage between normal aging and dementia. Unlike those with dementia, MCI patients do not show significant impairment in activities of daily living (2).

Dementia may affect as many as 28 million individuals worldwide. Of the total number of demented individuals worldwide, the largest proportion (5.2 million, or 18.5%) lives in China (3). The estimated prevalence of all dementias together is about 5% in the general population older than 65 years, and 30% in those older than 85 years (1). Racial variations in incidence of dementia have reported high rates of dementia among African-Americans. Women generally have higher rates of dementia than men, largely because women live longer. However, vascular dementia appears to be more common in men (4).

Alzheimer’s disease (AD) represents about 75% of total cases of dementia. Other forms include Lewy body dementia, vascular dementia, fronto-temporal dementia, progressive supra-nuclear palsy, cortico-basal degeneration, normal pressure hydrocephalus, and Creutzfeldt-Jakob disease (5). The course of dementia is slow and progressive. Dementia affects the brain’s ability to think, reason and remember clearly. The most common affected areas include memory, visual-spatial, language, attention, and executive function i.e. problem solving. Additional psychological and behavioral problems that often affect people who have dementia include disinhibition, impulsivity, balance problems, tremor, speech and language difficulty, trouble eating or swallowing, delusions or hallucinations, memory distortions, and wandering or restlessness (6). Depression affects 20-30% of people who have dementia, and about 20% have anxiety (7). Psychosis (often delusions of persecution) and agitation/aggression also often accompany dementia (8).

Risk factors for dementia include: advanced age (9), female gender (10), physical inactivity (11), drugs as benzodiazepines (12), while some drugs have protective effect as Statins (13), low level of education (14), heavy alcohol consumption (15), weight gain (16), comorbidities as: hypertension (17), diabetes mellitus (18), stroke (19), recurrent infections (20). Environmental factors are also linked to dementia as Aluminum, iron, copper, and zinc, and low levels of vitamin D (21).

Causes of dementia can be divided into reversible and irreversible causes. Reversible causes may be structural brain lesions or metabolic, infectious, toxic, autoimmune, paraneoplastic or psychiatric disorders (22). The most common cause of irreversible dementia is Alzheimer’s disease (23) followed by vascular causes (24). Other less common causes include; Creutzfeldt-Jakob disease (25), Cortico-basal degeneration (26), Progressive Supra-nuclear Palsy (23), and Lewy bodies (23).

Adiponectin is an adipo-cytokine released by the adipose tissue. Adiponectin acts by binding to its receptors; adiponectin receptor type 1 and type 2. Adiponectin receptors are expressed in skeletal muscle, liver, hypothalamus and vascular endothelial cells of brain (27). Adiponectin was shown to be present in the cerebrospinal fluid of rodents (28), and human (29). Adiponectin has important functions in the central nervous system; it modulates the sensitivity of insulin in brain (30), decreases the expression of pro-inflammatory cytokines as tumor necrosis factor-α (TNF-α) (31), and increases the expression of anti-inflammatory molecules such as interleukin (IL)-10, IL-1 receptor antagonist (32). Adiponectin modulates brain metabolism and sensitivity of insulin (33), regulating memory and cognitive function (34), and it also regulates inflammation observed in mild cognitive impairment and Alzheimer's disease (35). In particular, adiponectin contributes to dysregulated glucose metabolism and mitochondrial dysfunction observed in Alzheimer's disease (36). Insulin dysregulation contribute to Alzheimer's disease pathologies by several mechanisms from reduced brain glucose utilization to neurofibrillary tangle formation and increased amyloid β aggregation by insulin degrading enzyme inhibition (37). Amyloid β accumulation induces the oxidative stress and mitochondrial dysfunction,
which induces Alzheimer's disease pathogenesis. Adiponectin modulates amyloid β in Alzheimer's disease and so improves cognition. Previous studies demonstrate that the insulin sensitizing action of adiponectin may be another mechanism of neuroprotection in Alzheimer's disease. On contrary, other studies had found that high adiponectin levels were associated with mild cognitive impairment and Alzheimer's disease.

Leptin is produced primarily in the adipocytes of white adipose tissue. Although leptin was originally considered an anti-obesity protein because of its regulatory role in maintenance of body weight; a growing body of evidence suggests that leptin is implicated in cognitive decline and dementia processes. The majority of work has been limited to animal models. The few observational studies of older adults have reported that higher leptin was associated with less risk of cognitive decline and dementia. In the present study, we aimed to determine the serum levels of adiponectin and leptin in elderly patient with dementia.

Materials and Methods

The present study included 60 subjects aged 65 years and older, divided into two groups; Group I: 40 demented patients, who attended the outpatient clinic at Al-Ma'mora Mental Health Hospital, and Group II: 20 age and sex matched healthy subjects as a control group. The aim, purpose, and benefits of the study were explained to all participants and an informed written consent was obtained. The proposal was accepted by the ethical committee of faculty of medicine-Alexandria University. Participants with following diseases were excluded from the study; dyslipidemia, hypertension, diabetes mellitus, chronic liver diseases, chronic kidney diseases, or thyroid disorders. Obese persons with body mass index (BMI) more than 30 kg/m² were excluded. Participants received drugs such as narcotic analgesics and sedative hypnotics were also excluded from the study. All participants were subjected to a thorough history taking, full clinical examination, and routine laboratory investigations including thyroid function testes. Serum levels of Adiponectin, and leptin were determined to all participants using ELISA kits. Dementia was diagnosed according to the mini-mental state examination (MMSE) and The Montreal Cognitive Assessment (MOCA). MMSE includes 11-questions measure five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. MOCA assesses multiple cognitive domains including attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation, and orientation. A score of 23 or lower is indicative of cognitive impairment.

Data were collected and fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. Chi-square test was used for categorical variables, to compare between different groups. Student t-test was used for normally quantitative variables, to compare between two studied groups. Mann Whitney test was used for abnormally quantitative variables, to compare between two studied groups. Spearman coefficient was used to correlate between two abnormally quantitative variables.

Results

The present study included 60 participants aged 65 years and older, divided into two groups; Group (I): 40 demented patients with mean age of 69.70 ± 1.95 years, and Group (II): 20 age and sex matched healthy subjects served as a control group, their mean age was 69.10 ± 2.67 years, with no statistical significant difference between both groups (p=0.326). Group I (demented patients) included 22 males (55%), and 18 females (45%), group II (control group) included 12 males (60%),
and 8 females (40%) with no statistical significant difference between both groups (p=0.713).

Table 1 represents a comparison between both groups regarding body mass index (BMI). In Group (I), 19 (47.5%) patients were within 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 normal weight range, and 8 (40%) subjects were overweight, with a mean BMI of 25.84 ± 2.22 Kg/m2. No statistical significant difference was noted between both groups.

Table 1: Comparison between the studied groups regarding body mass index (BMI):

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Group I Demented patients (n =40)</th>
<th>Group II Control group (n =20)</th>
<th>Test of Sig.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight (18.5 – &lt;25)</td>
<td>19 (47.5)</td>
<td>12 (60.0)</td>
<td>χ²=1.175</td>
<td>MC p=0.721</td>
</tr>
<tr>
<td>Over weight (25 – &lt;30)</td>
<td>20 (50.0)</td>
<td>8 (40.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese (30 – &lt;35)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely Obese (35 – &lt;40)</td>
<td>1 (2.5)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidly obese (≥ 40)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>21.77 – 29.74</td>
<td>23.32 – 29.73</td>
<td>t=0.042</td>
<td>0.966</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>25.82 ± 2.26</td>
<td>25.84 ± 2.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>25.09</td>
<td>24.77</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI: body mass index.  

Table 2 represents a comparison between the demented group and the control group regarding the mini-mental state examination (MMSE), and The Montreal Cognitive Assessment (MOCA). 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 group (I) was 19.53 ± 1.96, while it was 28.85 ± 1.09 for group (II). A high statistical significant difference was noted between both groups (p <0.001). In MOCA test, all patients in group (I) showed abnormal score with a mean of 18.03 ± 2.18, while all subjects in group (II) showed normal score with a mean of 28.20 ± 1.11. A high statistical significant difference was noted between both groups (p =0.001).

Table 2: Comparison between the studied groups regarding the mini-mental state examination (MMSE), and The Montreal Cognitive Assessment (MOCA):

<table>
<thead>
<tr>
<th>MMSE</th>
<th>Group I (n =40)</th>
<th>Group II (n =20)</th>
<th>Test of Sig.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Cognition (≥27)</td>
<td>0 (0.0)</td>
<td>20 (100.0)</td>
<td>χ²=60.000</td>
<td>&lt;0.001°</td>
</tr>
<tr>
<td>Mild Cognition impairment (19 -24)</td>
<td>28 (70.0)</td>
<td>0 (0.0)</td>
<td>χ²=60.000</td>
<td>&lt;0.001°</td>
</tr>
<tr>
<td>Moderate Cognition impairment (1-18)</td>
<td>12 (30.0)</td>
<td>0 (0.0)</td>
<td>χ²=60.000</td>
<td>&lt;0.001°</td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>19.0 ± 1.96</td>
<td>27.0 ± 3.00</td>
<td>t=23.649°</td>
<td>&lt;0.001°</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>19.0 ± 1.96</td>
<td>28.85 ± 1.09</td>
<td>t=23.649°</td>
<td>&lt;0.001°</td>
</tr>
<tr>
<td>Median</td>
<td>19.0</td>
<td>29.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (≥26)</td>
<td>0 (0.0)</td>
<td>20 (100.0)</td>
<td>χ²=60.000</td>
<td>&lt;0.001°</td>
</tr>
<tr>
<td>Abnormal</td>
<td>40 (100.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>14.0 ± 2.20</td>
<td>26.0 ± 3.00</td>
<td>t=24.008°</td>
<td>0.001°</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>18.03 ± 2.18</td>
<td>28.20 ± 1.11</td>
<td>t=24.008°</td>
<td>0.001°</td>
</tr>
<tr>
<td>Median</td>
<td>18.0</td>
<td>28.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*: Statistically significant at p ≤ 0.05.
Table 3 represents a comparison between the two studied groups regarding the serum adiponectin levels. The mean serum level of adiponectin was 42.11 ± 16.97 ng/ml in group (I), while it was 8.91 ± 1.66 ng/ml in group (II) with a high statistical significant difference between both groups (p <0.001).

**Table 3:** Comparison between the two studied groups regarding the serum adiponectin levels:

<table>
<thead>
<tr>
<th></th>
<th>Group I (n =40)</th>
<th>Group II (n =20)</th>
<th>Test of Sig.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (6.33 – 10.83)</td>
<td>0</td>
<td>18</td>
<td>χ²=51.429*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Abnormal</td>
<td>40</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>24.30 – 90.40</td>
<td>6.30 – 10.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>42.11 ± 16.97</td>
<td>8.91 ± 1.66</td>
<td>Z=6.273*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median</td>
<td>36.40</td>
<td>9.15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Table 4 represents comparison between the studied groups regarding serum levels of leptin. The mean level of leptin in group (I) was 1.25 ± 0.67 ng/ml, while it was 6.76 ± 2.53 ng/ml in group (II), with high statistical significant difference between both groups (p<0.001).

**Table 4:** Comparison between the studied groups regarding serum levels of leptin

<table>
<thead>
<tr>
<th></th>
<th>Group I (n =40)</th>
<th>Group II (n =20)</th>
<th>Test of Sig.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
<td>18</td>
<td>χ²=36.746*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Abnormal</td>
<td>36</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>0.20 – 2.80</td>
<td>4.0 – 11.20</td>
<td>Z=6.275*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>1.25 ± 0.67</td>
<td>6.76 ± 2.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.20</td>
<td>5.50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Table 4 represents the correlation between serum levels of leptin and adiponectin and tests of dementia in both studied groups. A significant negative correlation between serum levels of adiponectin and both MMSE and MOCA scores (p=0.003 and 0.015 respectively). While a high positive correlation was noted between serum levels of leptin and both MMSE and MOCA scores (0.016 and 0.024 respectively). No significant correlation was noted in the controls (group II).

**Table 4:** Correlation between serum levels of adiponectin, and leptin with MOCA and MMSE in studied groups.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Demented patients (group I)</th>
<th>Control group (group II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adiponectin</td>
<td>Leptin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>Demented patients (group I)</td>
<td></td>
<td>-0.383*</td>
<td>0.015*</td>
</tr>
<tr>
<td>MOCA</td>
<td></td>
<td>0.357*</td>
<td>0.024*</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td>0.378*</td>
<td>0.016*</td>
</tr>
<tr>
<td>Control group (group II)</td>
<td></td>
<td>-0.302</td>
<td>0.195</td>
</tr>
<tr>
<td>MOCA</td>
<td></td>
<td>0.210</td>
<td>0.373</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td>0.339</td>
<td>0.144</td>
</tr>
</tbody>
</table>

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

Dementia is defined as a progressive acquired impairment of cognitive function sufficient to cause functional decline and occurring in a relatively normal level of consciousness \(^{(1)}\), the estimated prevalence of dementia is 5% in the general population older than 65 years, and 30% in those older than 85 years \(^{(1)}\). Commonest causes of dementia are Alzheimer’s disease (AD), and vascular dementia (VaD).

The current study was conducted on 60 elderly subjects of both genders divided into two groups; Group I (demented patients) included 40 patients; 22 (55%) males, and 18 (45%) females, with a mean age of 69.70± 1.95 years, and group II (control group) included 20 age and sex matched subjects; 12 (60%) males, and 8 (40%) females, with a mean age of 69.10± 2.67 years. No statistical difference was noted between both groups. Several cohort studies have shown the risk of dementia increases with age. This association has been observed in all subtypes of dementia in a Spanish group \(^{(9)}\).

In our study, 19 (47.5%) patients in group (I) were within normal weight range, 20 (50%) patients were over-weight, 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 normal weight range, and 8 (40%) subjects were overweight, with a mean BMI of 25.84 ± 2.22 Kg/m\(^2\). No statistical significant difference was noted between both groups. A recent follow up studies has demonstrated a reverse association between BMI and risk of dementia in persons older than 65 years of age \(^{(51)}\). Another study stated that steady annual weight loss of 1 kg/m\(^2\) in older people was related to 35% increase in AD risk, as compared with individuals without BMI changes \(^{(52)}\).

Adiponectin is a protein hormone that modulates a number of metabolic processes \(^{(53)}\). It is secreted from adipose tissues and acts via its receptors, which are widely distributed in the brain \(^{(54)}\). 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. In accordance with our results, Van Himbergen et al \(^{(41)}\) found that after adjustment for dementia risk factors, high levels adiponectin were associated with an increased risk of dementia, and this was observed in both genders. A recent cross-sectional study from Japan also found that high levels of adiponectin were associated with mild cognitive impairment and AD \(^{(29)}\). The explanation for association of high levels of adiponectin and dementia may be that the human body can become resistant to adiponectin. Thus, adequate adiponectin activity may reduce the risk of developing dementia, and adiponectin levels may have risen as a protective response to vascular damage or changes in brain morphology. However, hormone resistance may prevent the body from getting benefit from this protective increase in adiponectin level \(^{(41)}\). Shafique K et al \(^{(55)}\) found high levels of adiponectin are possibly reflective of underlying subclinical vascular or neuro-degenerative dysfunction, and may play an important role in the pathogenesis of dementia.

On contrary, Kitagawa K et al \(^{(56)}\), found that the risk of incident dementia in patients with high or low levels of adiponectin are almost similar, thus they stated that serum adiponectin has a little association with future dementia.

Leptin is a hormone synthesized by adipose tissue and regulate energy balance by inhibiting hunger \(^{(57)}\). In our study, we found low levels of leptin in patients with dementia, with a mean serum leptin level of 1.25 ± 0.67 ng/ml. in accordance with our results, Holden KF et al \(^{(58)}\), in their studies on older adults had reported that higher levels of leptin was associated with less risk of cognitive decline and dementia. Also, Zeki Al Hazzouri A et al \(^{(59)}\), in their cohort study of very old women, they found that higher levels of serum leptin was prospectively associated with lower odds of dementia in women with normal body mass index. A cross-sectional study had shown that patients with AD had lower levels of serum leptin than patients without AD \(^{(60)}\). On contrary to our results; Oania R et al \(^{(61)}\), found that baseline cognitive ability did not differ as a function of leptin level, nor were higher levels
associated with reduced hazard of developing dementia.

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 was 18.03 ± 2.18. In group II (control group), all subjects showed normal cognition with normal MMSE and MOCA scores. A high statistical significant difference was noted between both groups (p = 0.001). A significant negative correlation was found between serum levels of adiponectin and both MMSE and MOCA scores (p=0.003 and 0.015 respectively). While a high positive correlation was noted between serum levels of leptin and both MMSE and MOCA scores (0.016 and 0.024 respectively). In conclusion; dementia has high prevalence in elderly population. That mandates search for new hormones linked to its pathogenesis for better understanding of its pathophysiology and emergence of medications that can control or treat this devastated disease.

References


