Original Article

The Blood Level of Leptin in Alzheimer's Patients and Healthy Individuals

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Abstract

Background: Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by accumulation of extracellular amyloid-β plaques and intracellular neurofibrillary tangles tau protein. Obesity significantly increases the risk of developing AD. Leptin is a peptide hormone secreted by adipocytes. In the present study the serum levels of leptin in AD was evaluated. ***Material and method:*** This study was performed on 12 Alzheimer patients referred to Zanjan Vali-e-Asr Hospital, and 12 healthy individuals. Serum levels of leptin were measured by ELISA method. ***Results:*** Our results show that the level of leptin was significantly different in AD patients and control group. Considering the relationship between leptin levels and the age, oldest the patients, the lowest the levels of leptin hormone, in both male and female. Also, the severity of disease was related to the level of leptin hormone. ***Conclusion:*** There presumably could be a cause and effect relationship between AD progress and reduction in the serum level of leptin. It may also point to the potential usage of measuring the leptin concentration in finding a biomarker for the disease.

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Introduction

Alzheimer's disease is very common type of dementia in senility. A considerable body of search has revealed that the main component of neurofibrillary tangles and senile plaques in the brain are the amyloid beta peptide and tau protein and (1,2). Formation of the amyloid plaques by beta amyloid linked to the structure of lipid membrane. When this molecule is placed in the lipid raft of the membrane, its access to beta–secretase enzyme and thus to amyloid will be increased. Otherwise, if it is located outside the lipid raft, it would be more available for alpha-secretase. In this condition entering a rout other than amyloid membrane becomes more probable. The role of cholesterol in the lipid membrane may explain why high amounts of cholesterol and apolipoprotein-E adversely affect the brain in Alzheimer's disease (3). In addition, hormones such as insulin and leptin have potential effects on the brain, and are shown to have altered the function of the hippocampus. Changes in lipid metabolism are associated with neurodegenerative diseases, Particularly Alzheimer's. Clinical studies have revealed that patients with type II diabetes are at risk of Alzheimer's disease which reveals the hormone-related diseases and neurodegenerative process. Moreover, the relationship between obesity and signaling mechanisms of insulin, retains a high potential for neurodegenerative process. Leptin is a kind of adipokine which is a factor in protein's hydrolysis (4). Leptin is composed of 167 amino acids and molecular weight of 16 kilo Dalton (KDa) similar to what exists in some cytokines (5). Leptin is produced mainly in the white adipose tissue, it exists in bloodstream in free form and its biological effects on target tissues are exerted almost in the same way.

Several studies have shown that the hypothalamus is a leptin target tissue. The leptin target neurons in the core arcuate, are those expressing neuropeptide Y. Neuropeptide Y in involved in increasing the appetite, desire to eat and reducing energy consumption hence resulting in the accumulation of fat in the body and finally causing obesity and weight gain. Leptin would stop such functions through inhibiting the production and release of the neuropeptide Y(6,7) .

The imperfection of messaging in leptin leads to leptin resistance, which is a first factor of obesity. The cause of this resistance is a defect in the transmission of leptin from of blood – brain barrier. The second reason is the deficiency in transferring the leptin message in neurons. In obese patients leptin transmission from blood – brain barrier is damaged. The permeability of this barrier to leptin which is decreased in obese rats is induced by fat diet, despite the rise in plasma leptin (8). Hyperleptinemia can be seen either in age – related obesity or as a result of fatty diet. It seems that increase in blood levels of leptin which decreases appetite is a reflection of leptin levels boost in the CSF. If leptin directly reaches the brain, it will reduce the appetite, while its existence or its increase in blood would not necessarily impact on reducing the appetite. The imperfection of transfer of leptin messages in hypothalamus is derived from different factors such as lack of enough leptin for transferring to hypothalamus, limitation of leptin entrance from blood – brain barrier and the primary replication of hyperglycemia and hyperinsulinemia. Findings reveal that the lipid molecules in the brain are associated with beta amyloid in a complex pathology. Leptin hormone is an important factor in lipid homoeostasis. Similar to methyl beta – cyclodextrin, leptin decreases the amount of beta – secretase in nervous system through changes in the lipid composition of the lipid raft. Leptin can also increase the absorption of beta amyloid which is dependent on the apolipoprotein E, and can decrease the extracellular of amyloid. Leptin and adipokine are peripheral signs of adipose tissues that interact with the arcuate nucleus of hypothalamus. These interactions stimulate the release of low appetite and high appetite peptides. Leptin and adipokine can increase the flexibility of synapses. In the primary and clinical stages of Alzheimer's disease, amyloid deposits around hypothalamus particularly the arcuate nucleus which strongly interferes with normal physiological effects of leptin and adipokine. The effects of fat tissue may explain the relationship between overweight and obesity in adults with dementia.

The pathological effects of Alzheimer on some areas of the brain which is involved in the regulation of homeostasis may also explain the weight loss in the early stages of dementia(9).

It has been observed that high levels of leptin in transgenic animals with Alzheimer significantly decrease beta – amyloid in the brain. So, it can be said that leptin under special treatment, will be able to adjust beta – amyloid in Alzheimer. In Alzheimer's disease weight loss is observed before the onset of dementia. Now the question is whether leptin and the pathway of leptin signaling related. Studies have shown that weight gain and obesity in mid – life is associated with dementia in elderly(10). Leptin, in addition to hypothalamus, also has functions in the hippocampal CA1, an area involved in learning and memory(11). Weight loss is known as one of the symbols of the clinical stage of Alzheimer in the last years of life, so, the increased level of leptin in the primary stages of Alzheimer may be considerably important. On the other hand, the high concentration of leptin may decrease this disease. Leptin levels show an inverse relationship with Alzheimer's and dementia. The amount of leptin which crosses the blood – brain barrier is much less than what can be found in the surrounding tissues. Recent research showed that leptin moderates the production and removal of amyloid-beta. Also, the reduction of leptin is associated with the cognitive impairment in elderly. As mentioned before, these patients lose weight and experience a drop in the level of circulating leptin(12).

The aim of this study was to measure the amount of serum leptin in patients suffering from Alzheimer's disease. Besides, we aimed at investigating and evaluating the levels of this hormone and its changes in patients' blood as compared to the healthy subjects. The data was obtained from patients of Vali-e-Asr Hospital in Zanjan in 2013 from the patients referred to these clinics.

Materials and methods

In this study 12 patients with Alzheimer's disease with an average age of 76.9 years were enrolled and blood-sampled in a consecutive sampling method. Patients were referring to the neurology clinic of Vali-e-Asr Hospital, Zanjan city.

In parallel, 8 aged healthy control (AC) subjects with the average age of 67.8 years and 4 young

healthy control subjects (YC) with the average age of 29.2 years were randomly selected.

All controls and patients had to be without hypertension and diabetes. Their lipid profile had to fall within normal limits. All cases in the present study received a comprehensive clinical evaluation. Histories of patient's diseases were provided and they were neurologically examined and scored using the MMSE. The consumption of drugs with healthy and patients were evaluated and brain scans of patients were reviewed. In order to confirm the diagnosis with reference to the previous records of patients, the Criteria of National Association of Neuroscience, Infectious Diseases, Association of Alzheimer's Disease, NINCDS-ADRD were used. Based on such criteria, patients were defined based on three stages of mild, moderate and severe. In this study, the amount of leptin hormone in peripheral blood serum of patients and healthy subjects were measured by means of ELISA (Human leptin ELISA E07, mediagnost). Data were analyzed using the SPSS version 19.

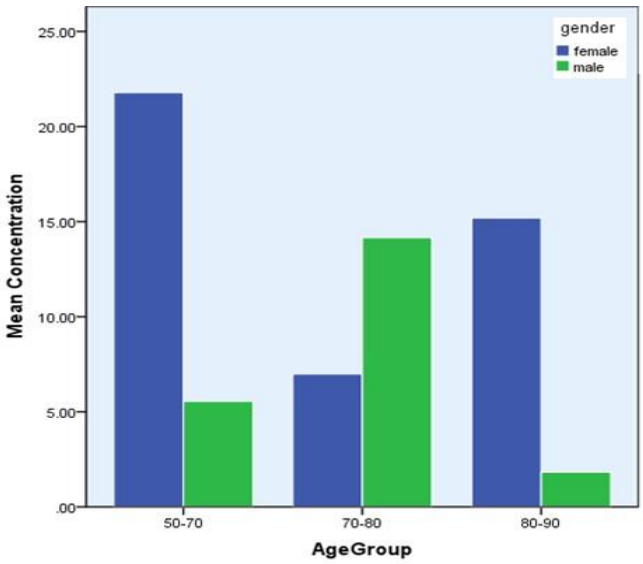

Figure 1. The concentration of leptin hormone in AD patients and the control group.

Results

In this study, 12 patients with Alzheimer's disease and 12 healthy subjects were selected. The results of the measurement indicated the less density of leptin hormone in patients, as compared to the healthy subjects(Figure 1). In addition, in patients' samples, along with age and the severity of disease, an increased fluctuation was observed in the peripheral blood serum (Figures 2 and 3). Results revealed that in women who suffer from Alzheimer's, the amount of this hormone in peripheral blood serum was less, as compared to the women in other groups. This result was also similar in men. Also, in this study the levels of this hormone was reviewed in women with Alzheimer's as compared to those in men. The results showed this level was increased in women compared to men (Figure 4). Based on the statistical analysis, there was a significant relationship between leptin level and sex, ($p<0.001$), confirming that the mean level of leptin in females out-weighted that of males.

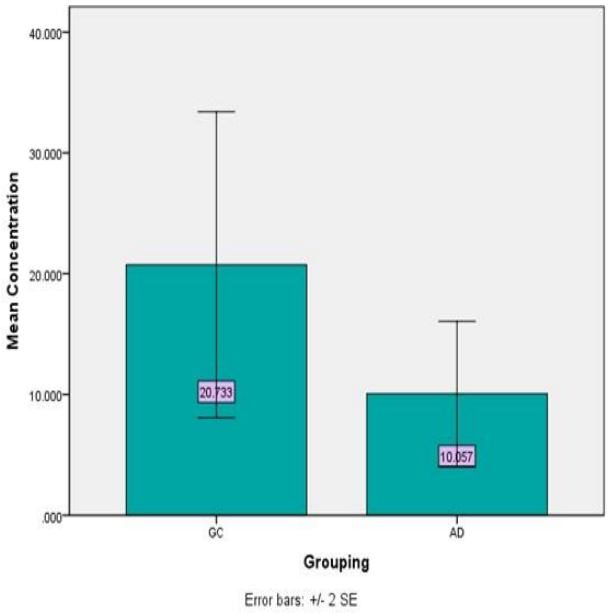

Figure 2. The concentration of leptin hormone in men and women with AD based on severity of disease.

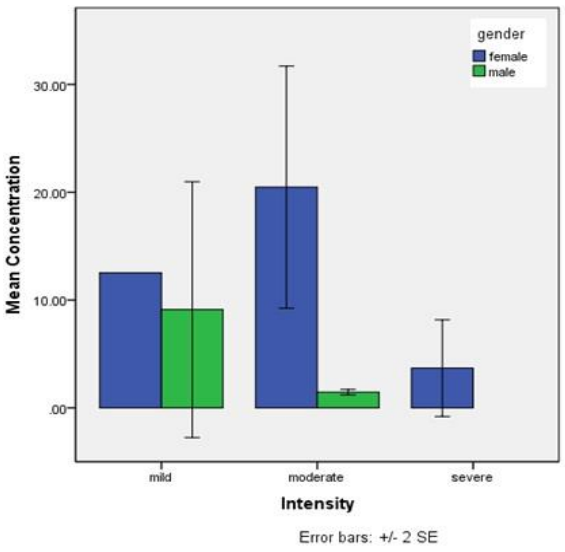

Figure 3. The concentration of leptin hormone in men and women with AD based on the age groups.

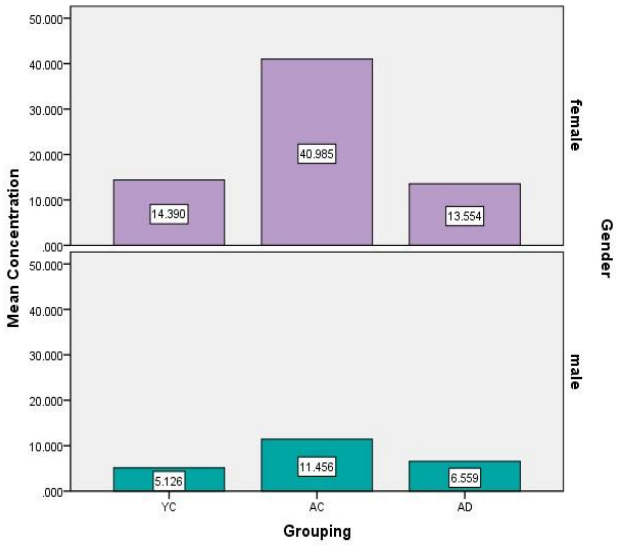

Figure 4. The comparison of leptin levels in male and female patients and healthy groups.

Discussion

In the current study, serum levels of leptin were measured in 12 AD patients and 12 healthy subjects. There was an inverse relationship between the level of leptin and Alzheimer's disease. In this regard the level of leptin was increased at the initial stages of the disease. This can be the sign of cognitive impairment relationship between leptin level and Alzheimer's disease. The results may reveal the involvement of leptin in the pathogenesis of Alzheimer's disease. Our hypothesis is that both high and low levels of leptin serum may be a reflection of inadequate leptin in cell surface which may leads to inaccurate signaling. In addition, serum levels of leptin in the brain may be linked to negative feedback on inadequate leptin in the brain. Therefore, the transfer of leptin to the central nervous system changes in the hyperleptinemia conditions. Hyperleptinemia is usually associated with leptin resistance in the brain. The leptin in the central nervous system is mainly derived from the environment.

Physiologically, the reduction of leptin in blood leads to the limitation of crossing this hormone from brain-blood barrier and reducing its amount in the brain. The redaction of leptin in the central nervous system leads to the reduction of leptin signals.

Based on our findings, the reduction of this hormone in blood serum of patients, as compared to healthy subjects may confirm the hypothesis.

The question may be raised as whether leptin affects amyloid beta homeostasis. According to a study by Steven Greco et al. (2008), at first, neurons and neuronal cells were treated with a density of leptin at different times and it was found that in all cells, tau protein phosphorylation in areas related to amyloid beta pathology is decreased.

In another experiment which was performed by this group, first the expressions of leptin receptors were examined. They found that the expression of this receptors show no significant changes. Then, they investigated whether leptin affects the phosphorylation of tau protein. They found that during a period of 1 to 4 hours, treated cells with leptin showed a significant decrease in tau phosphorylation (serine 396) (13,14). In another experiment which was conducted in 2012 by Dana M. Niedowicz and his colleagues, they investigated the role of leptin in the regulation of beta-amyloid gamma secretase. In this experiment which was conducted on H4 Neuroglioma cells, the effect of different doses of leptin on these cells decreased the production of beta amyloid in cells which were treated with leptin. The results of this study revealed that leptin limits the gamma secretase enzyme and decreases the beta-amyloid(15). Based on a subpopulation of the Framingham cohort, Lieb and colleagues suggested that higher levels of leptin are associated with reduced incidence of dementia and AD, correlated with positive associations between leptin levels and total brain and hippocampal volumes. Leptin was measured in nonfasting plasma.

However, leptin levels have ultradian and circadian rhythmicity, and measuring leptin at different times of the day creates a possible confounding factor. In addition, statistical significance for the association between leptin levels and AD was present only in nonobese individuals. Despite their hyperleptinemia, obese individuals, may not be protected from developing AD, possibly because of high leptin resistance in the brain(16). However, reductions in body weight is a harbinger of AD even before clinical symptoms of dementia are detected, suggesting that loss of body weight may be a manifestation of early brain dysfunction. Furthermore, lower body mass indexes (BMIs) are associated with abnormal CSF Amyloid-beta and tau levels and with increased CNS pathology at autopsy including neurofibrillary tangles and amyloid plaques. Thus, weight loss is a consistent feature of AD dementia and correlates with the presence of abnormal biomarkers and increased brain pathology (17). Other studies have proposed that leptin presents neuroprotective properties, which could be explained by inhibiting the amyloidogenic process, reducing the levels of tau protein phosphorylation and improving the cognitive function (18). Moreover, the upregulation of leptin has been proposed as a method of therapeutic intervention for AD (19). However, the status of the leptin signaling pathway in hippocampus and cerebral cortex and the vulnerable regions of AD, have less been determined.

Our Findings shows an inverse relationship between leptin level and Alzheimer disease. Although leptin concentrations would significantly decrease in women after the age of menopause; the amount of leptin in men and women, significantly differed from each other, favoring higher levels of leptin hormones in females than males. This dimorphism is regardless of the Body Mass Index (BMI), and related to sex hormones, fat mass and distribution of body fat. In women there is no tendency to accumulate peripheral fat, while men tend to have accumulation of abdominal fat. The amount of mRNA expression in the subcutaneous adipose tissue is more than abdominal fat tissue, which can partly explain the high concentration of leptin in women. Sex steroids are more effective than hormones and cytokines in leptin secretion(5).

Conclusion

The present findings may suggest that leptin can provide a positive view on preventing Alzheimer's disease. There presumably could be a cause and effect relationship between AD progress and reduction in the serum level of leptin. This study could be regarded as another evidence for the potential role of hormones, in general, and leptin specifically, in the pathogenesis of AD. We may also point to the potential usage of measuring the leptin concentration in blood serum to distinguish biomarkers for the disease.

Regarding the genetic and environmental factors, and also considering the lifestyle, the changes in various populations may largely differ. Further study on these indicators with a bigger sample size and different ethnic groups, would make its role more clear both on the occurrence and severity of AD, and may possibly offer an indicator to optimize clinical approaches in treating this devastating disease. In order to obtain clearer insights about such a causal relationship, more studies with prospective design and further samples are required. On the other hands, evaluation of the relationship between this hormone and Alzheimer's disease necessitates attention to BMI, leptin resistance and disorders of leptin signaling pathway in the brain.

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