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Evaluation of Melatonin, and Adipokines in Patients with Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is one of the most common causes for the development of Dementia in the elderly. In past two decades there has been abundant research in pathogenesis of AD and possible prevention and treatment. The objective of this study is to evaluate the level of melatonin, and adipokines in patients with AD and control group. The study included 52 patients with AD and 52 healthy subject as control group. The results showed that serum melatonin, leptin, adiponectin, levels of patients with AD were significantly lower than the levels found for control participants ($P < 0.0001$). Patients with AD had significantly higher mean serum ghrelin, and resistin levels than the controls ($P < 0.0001$), there was positive correlation between adiponectin with leptin, and ghrelin. In conclusion, the results of this study showed that Circulating melatonin, leptin, and adiponectin were associated with a reduced incidence of AD, Resistin levels may be considered as a predictor of AD and it may predict activation of the immune system in AD pathophysiology.

Keywords: Alzheimer disease, melatonin, leptin, adiponectin, ghrelin, and resistin

Introduction

Disease is an untreatable [(1)], multifactorial, chronic, progressive, neurodegenerative disorder which is the principal cause of dementia throughout the world and the fourth cause of death in developed economies after cancer, cardiovascular diseases, and vascular stroke [(2)]. AD is characterized by three primary groups of symptoms. The first group (cognitive dysfunction) includes memory loss, language difficulties, and executive dysfunction (i.e. loss of higher level planning and intellectual coordination skills). The second group comprises psychiatric and behavioral disturbances such as depression, hallucinations, delusions, and agitation, collectively termed as non-cognitive symptoms [(3)]. The third group comprises difficulties with performing activities of daily living (deemed "instrumental" for more complex activities such as driving and shopping and "basic" for dressing and eating unaided). White adipose tissue is a dynamic endocrine organ that releases several adipokines and pro-inflammatory factors[(4)].

Leptin is a protein with 146 amino acid and a multi-functional polypeptide hormone which is produced from fat cells and bone marrow cells [(5)]. Leptin is involved in learning and memory [(6,7)] Leptin has effects on the brain. Brain size is reduced in congenital leptin deficiency in humans and rodents and restored by leptin treatment [(8,9)]. Leptin regulates neuronal and glial proteins, increases long-term potentiation in the hippocampus and synaptic plasticity in hippocampus and hypothalamus, improves memory in rodents models of aging and Alzheimer disease, enhances the clearance of β-amyloid, and has a neuroprotective effect in stroke and seizure rodent models [(8-13)].

Ghrelin is a multifunctional hormone produced in a wide variety of tissues, which has been associated with the progression of obesity and metabolic syndrome, but has been also linked to neuromodulation, neuroprotection and memory and learning processes. In addition, ghrelin system also acts in an autocrine/paracrine fashion where the majority of its components [ghrelin variants (native ghrelin, In1-ghrelin), acylation enzyme (GOAT) and receptors (GHS-Rs)] are expressed in the different regions of central nervous system [14].

Melatonin (N-acetyl-5-methoxytryptamine), a tryptophan metabolite, is synthesized mainly by the pineal gland. It is important direct free radical scavenger and indirect antioxidant [15-18]. Melatonin is shown to be significantly effective at reducing oxidative damage in experimental models of the brain [17]. In addition to reduced melatonin secretion during aging, more prominent decreases are reported in dementia [16,19].

Interleukin-6 (IL-6) is a multi-functional inflammatory cytokine that plays an important role in the response to environmental stress and has been implicated in the pathogenesis of many chronic diseases associated with aging .Under physiologic conditions, the main source of IL-6 are cells of the immune system, vascular endothelial cells, and adipocytes .In vitro, endogenously produced cytokines could influence beta amyloid peptide accumulation and tangle formation. Conversely, beta amyloid and tau proteins stimulate microglia, astrocytes, and oligodendrocytes to overproduce inflammatory mediators, therefore generating a ‘‘vicious cycle’’ leading to irreversible synaptic loss [20-22].

The objective of our study was to investigate the adipokines and pro-inflammatory factors markers on a group of patients with Alzheimer's disease and compare its parameters with a control group composed of healthy subjects in Tikrit Governorates.

Materials and Methods

A cross-sectional study was conducted from the beginning of February 2013 until the end of March 2014 among 52 patients with AD (mean age 64 ±13.21 years; 53 women and 17 men). For the comparison, a total of 52 apparently healthy control subjects (mean age 61.4±11.4 years; 28 women and 24 men). All individuals were randomly recruited from Tikrit Teaching Hospital in Tikrit Governorates.

Blood collection and laboratory analysis. From each patient and control, five ml venous blood were aspirated from a suitable vein. Samples were collected between (8-9 A.M.) after 10 hours fast. Blood samples were transferred to sterile plain tubes for storage until assayed.

Serum melatonin concentrations were measured using the Melatonin Direct Radioimmunoassay (Sigma Chemical Co., St.Louis, MO), leptin, adiponectin, ghrelin, IL-6, and resistin were measured by using ELISA kits from United States Biological-Company.

Diagnosis: Alzheimer's disease, according to criteria International Statistical Classification of Diseases, and Diagnostic and Statistical Manual of Mental Disorders [23,24]. A minimal score on the Mini Mental State Exam (MMSE) of 25 points.

Exclusion criteria for the control group: Concurrent neurological issues Severe anemia (hemoglobin < 9 g/dL), Severe and unchecked arterial hypertension, Severe malnutrition, Concurrent psychiatric issues or a history of psychological illness, Mental deficiency, System diseases (cancer, HIV-AIDS), Stroke (cerebrovascular accident CVA) in the last 6 months, and Alcoholism.

Statistical analysis

Statistical analysis was performed using SPSS-21 (Statistical Packages for Social Sciences, version 21). Data were tested for normality and Shapiro test confirmed its normality. Unpaired test was performed to assess significant difference between means. $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the demographic features in patients with AD and controls. Patients and controls were age matched, the mean age of patients with AD was (64 ±13.21 years) lightly higher as compared to controls (61.4±11.4 years).

The data for measured biomarkers (melatonin, leptin, adiponectin, ghrelin, and resistin) are presented in Table 2. All results are presented as means ± standard deviation.

Melatonin levels were significantly lower in the AD group than in the control group (8.591 ± 0.17 versus 9.972 ± 0.19 pg/mL respectively) (P < 0.0001).

The resistin levels were significantly higher in the AD group than in the control group (89.46 ± 0.74 versus 69.62 ± 1.09 respectively) (P < 0.0001).

In the current study the mean serum ghrelin level was higher in AD than controls (16.93 ± 0.42 versus 11.51 ± 0.31 pg/ml respectively) with statistical significant difference (<0.0001). The serum levels of leptin in studied patients (4.950 ± 0.23 ng/ml) were significantly decreased than in the control group (7.687 ± 0.44 ng/ml), (p<0.001).

The serum levels of adiponectin in studied patients (3.504 ± 0.20 µg/ml) were significantly (p<0.001) decreased than in the control group (8.461 ± 0.17 µg/ml). The results showed that there was positive correlation between adiponectin with leptin, and ghrelin in AD group (r=0.3), (r=0.3) respectively as show in figure (1,2).

Serum level of IL-6 was significantly (< 0.0001) increased in AD patients (125.8 ± 2.62pg/ml) as compared with controls (70.25 ± 3.08pg/ml).

Table 1: Demographic characteristics of AD, & control patients

Variables	Alzheimer's disease	Control
No. of subjects	52	52
Sex (M/F)	17/35	24/28
Age (years)	64 ±13.21	61.4±11.4

Table 2: Biochemical parameters of patients with Alzheimer's disease and the controls

Parameter	Control group	AD group	P-value
Melatonin(pg/mL)	9.972 ± 0.19	8.591 ± 0.17	< 0.0001
Resistin (pg/mL)	69.62 ± 1.09	89.46 ± 0.74	< 0.0001
Ghrelin (pg/ml)	11.51 ± 0.31	16.93 ± 0.42	<0.0001
Leptin(ng/ml)	7.687 ± 0.44	4.950 ± 0.23	< 0.001
Adiponectin (µg/ml)	8.461 ± 0.17	3.504 ± 0.20	<0.001
Interleukin-6(pg/ml)	70.25 ± 3.08	125.8 ± 2.62	< 0.0001

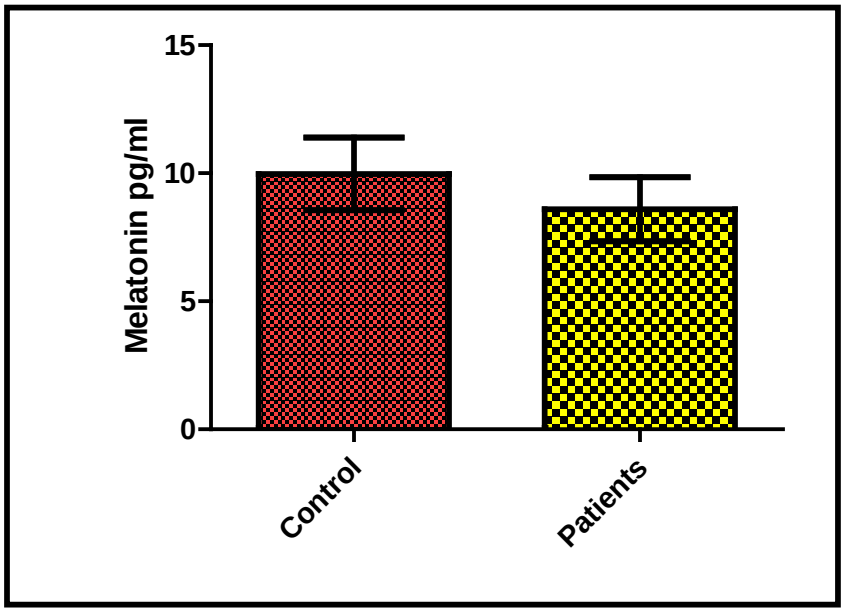

Figure 1: Serum melatonin in patients with AD and the controls

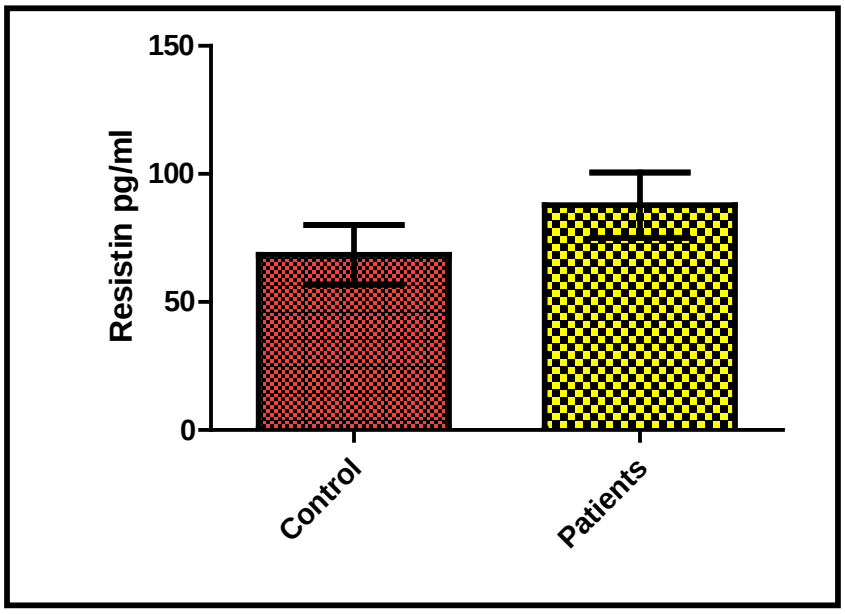

Figure 2: Serum resistin in patients with AD and the controls

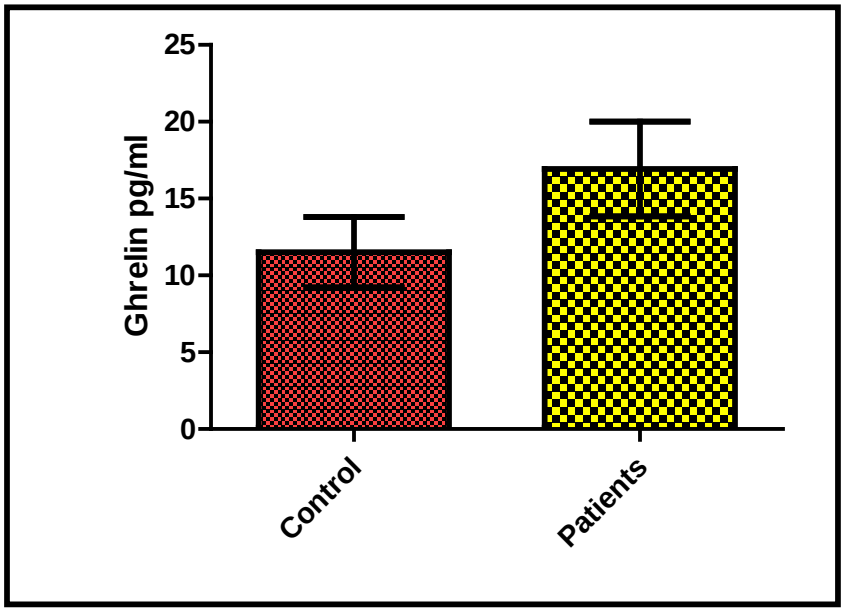

Figure 3: Serum ghrelin in patients with AD and the controls

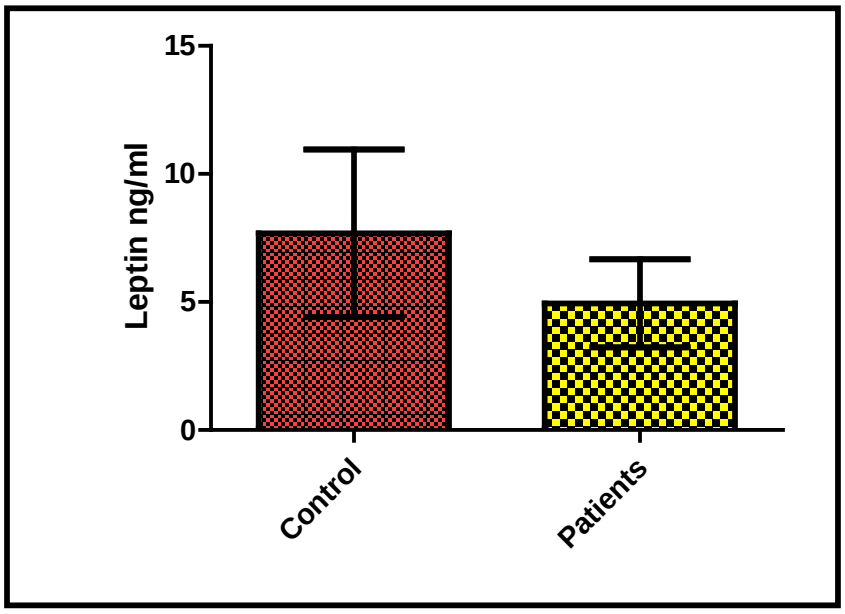

Figure 4: Serum leptin in patients with AD and the controls

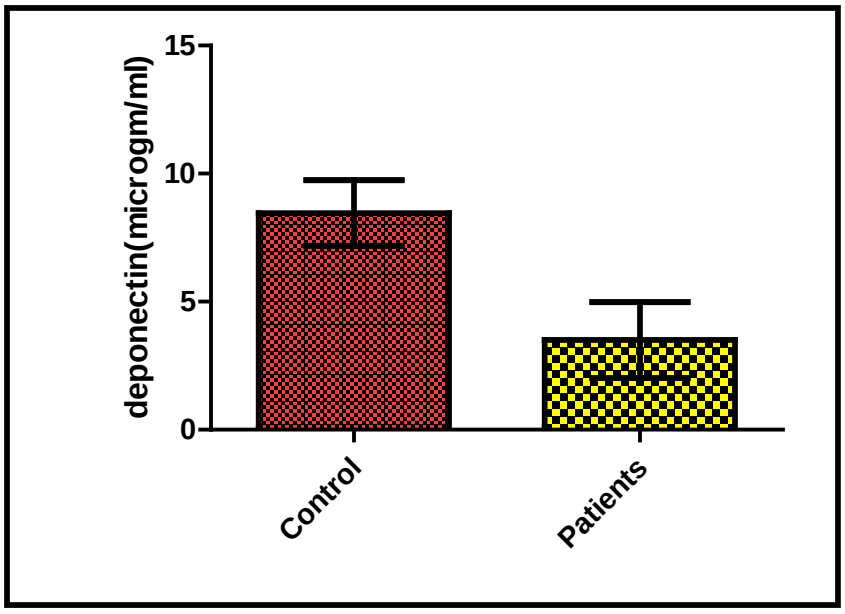

Figure 5: Serum adiponectin in patients with AD and the controls

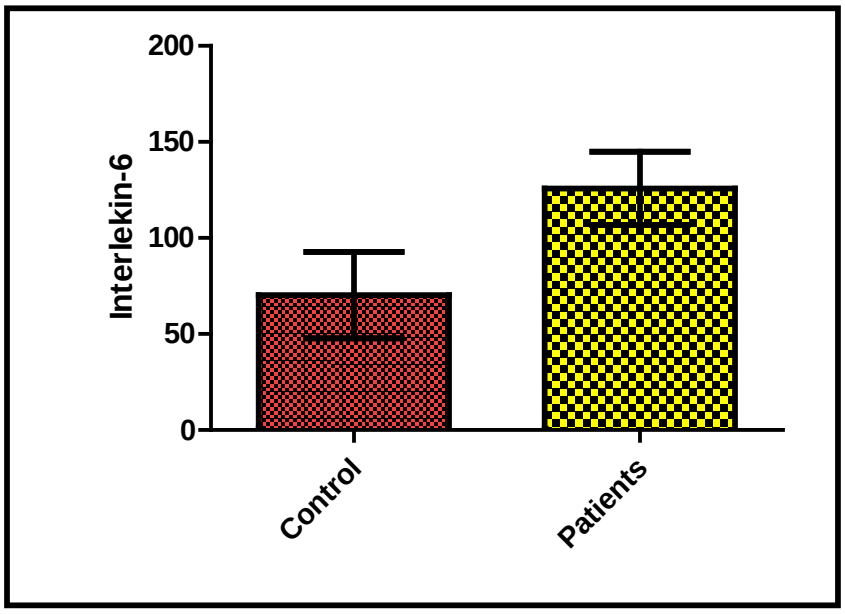

Figure 6: Serum inteleukin-6 in patients with AD and the controls

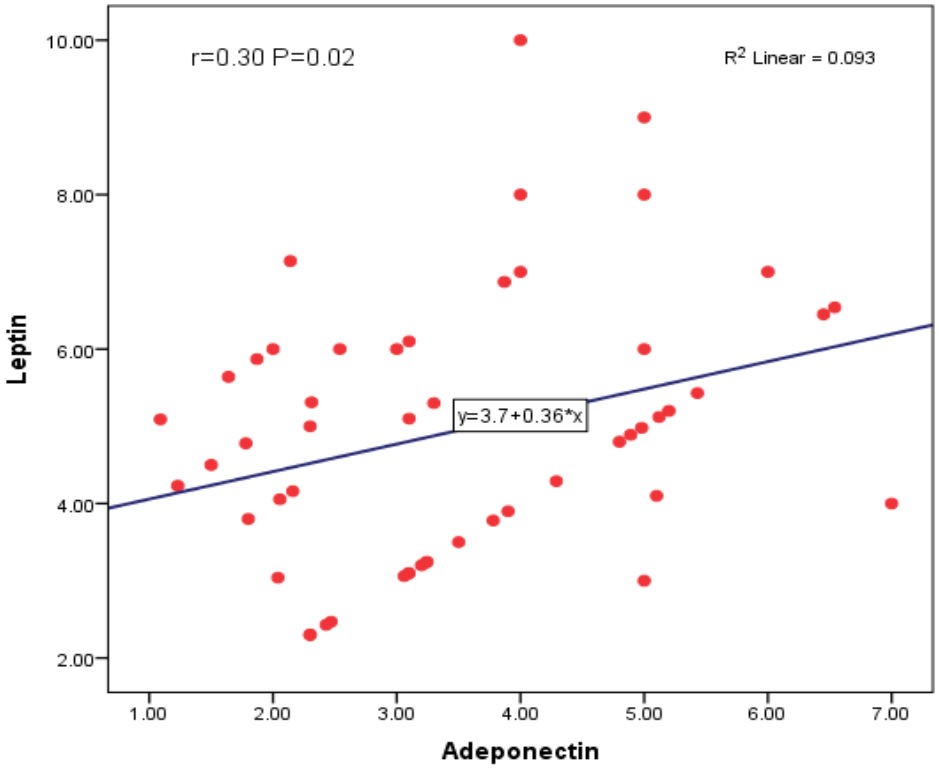

Figure 7: Correlation between adiponectin and leptin in patients with AD.

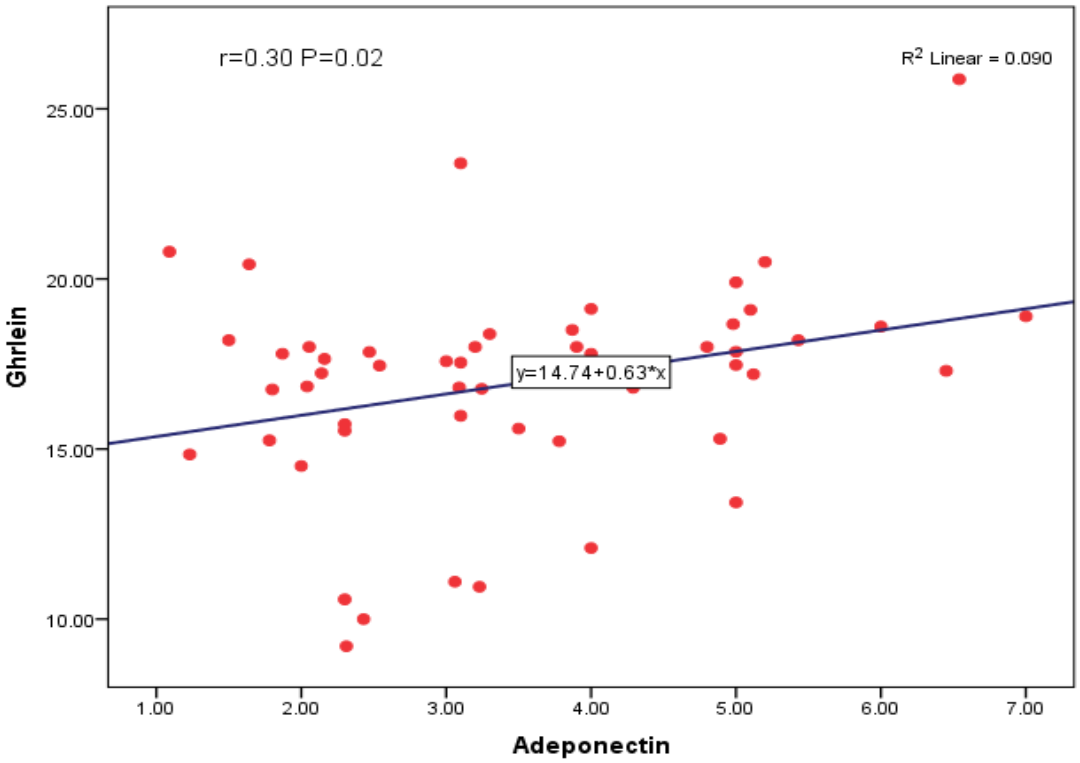

Figure 8: Correlation between adiponectin and ghrelin in patients with AD

Discussion

In present data, melatonin level of AD patient groups showed a significant decrease as compared with the control group. Melatonin regulates amyloid precursor protein (APP) metabolsim and can efficiently protect cells against Aβ toxicity, oxidative damage and cell death in vitro and in vivo [25]. None of the related studies further explained how melatonin exerts its inhibitory effect on Aβ generation. One explanation of why aged mice are immune to melatonin might be in the process of melanogenesis, i.e. a failure in light/melanin/water system would be a cause rather than effect of AD has been proposed [26]. The decrease in melanins ability to dissociate water (human photosynthesis) in age-related macular degeneration (AMD) [27] and or AD has been proposed to be a cause of these diseases is a simplistic overview of the bioenegetic mechanism related to these diseases.

In our view hypometabolism, likely due to decline in both intra- and extra-mitochondrial OXPHOS functioning are indeed fundamental to the understanding of pathological processes in these related diseases and that there is a homeostatic mechanism of energy balance related to relationship of melatonin versus Aβ through the regulation of mitochondrial fidelity. Melatonin protective role in AMD and AD may be a result of its action on mitochondrial physiology as suggested by its presence in mitochondrial circadian and seasonal variations in the brain and retina [28]. Locally produced melatonin in the surrounding of photoreceptors protects these cells thanks to its antioxidant capacity or by activation of melatonin receptors [29]. Melatonin can increase membrane fluidity, as well as the activity of the electron transfer chain (ETC) and ATP production, mitochondria membrane potential, while reducing oxidative stress [30]. Important pathological properties of Aβ, such as neurotoxicity and resistance to proteolytic degradation, depend on the ability of peptides to form β-sheet structures and/or amyloid fibrils [25]. Intervention in the Aβ aggregation process can be considered an approach to stopping or slowing the progression of AD and new investigation AMD. Melatonin can interact with Aβ40 and Aβ42 and inhibit the progressive formation of β-sheet and/or amyloid fibrils [31,32].

Melatonin could promote the conversion of β-sheets into random coils by disrupting the imidazole-carboxylate salt bridges and thus prevent Aβ fibrillogenesis and aggregation. It is therefore possible that by blocking the formation of the secondary β-sheet conformation, melatonin

may not only reduce neurotoxicity but also facilitate clearance of the peptide via increased proteolytic degradation.

Numerous relationships are shown between melatonin and mitochondria in which protection of ETC proteins are crucial [30]. The hypothesis herein exposed has concentrated on the melatonin-Aβ axis in mitochondrial age related processes leading to AD. Still, there is a more complex view of this axis which is not in the scope of this paper, i.e. first, melatonin functions exceeds its role as hormone that mediates signal ''darkness'', second melanocytes are viewed as ''neurons of the skin'' with sensory and regulatory properties which can detect and transform external and internal signals/energy into organized regulatory networks for the maintenance of skin homeostasis [33] and melanogenesis and its product melanin is by itself an pigment that has extraordinary properties [34]. The most important property is melanin participation in electron transfer reactions, reducing and oxidizing other molecules. Also, its key monomer, indolequinone, exhibits photodriven proton transfer cycles [35].

In present data, ghrelin level of AD patient groups showed a significant rise as compared with the control group. The first evidence showing a direct effect of ghrelin on AD-like alterations was reported in a mouse model widely used to examine the pathophysiology of early defects seen in AD. The senescence-accelerated mouse prone8 (SAMP8) mice develop early abnormalities in learning and memory related to abnormalities in septo-hippocampal function, which are due to overproduction of β-amyloid. In this mouse model, ghrelin was able to improve retention of T-maze foot shock avoidance in 12 and 14 month-old mice, compared to their controls [36].

More recently, a different mouse model has been used to analyze in more detail the role that ghrelin plays in AD-related endpoints. This model was generated by intrahippocampal injection of oligomeric forms of the Aβ peptide (AβO), which have been directly related with AD-associated damage [37]. Results of this study revealed that systemic injection of ghrelin rescues memory deficits observed following intrahippocampal AβO injection, using two independent behavioral paradigms (Y-maze and passive avoidance tasks). In addition, the AD-associated neuropathological abnormalities observed in these AβO mice were also attenuated by ghrelin. Indeed, ghrelin inhibited the reactive microgliosis originated by AβO, thus preventing the inflammatory response. Ghrelin also prevented AβO-induced neuronal cell loss in the dentate gyrus and increased the density of hippocampal synaptic and cholinergic nerve fibers. Collectively, these data show that systemic injection of ghrelin rescue cognitive impairments induced by AβO, possibly through inhibition of both, microgliosis and impairment of neuronal integrity [37].

In spite of the growing body of evidence pointing out the strong relationship between ghrelin system and metabolism, inflammation, neuroprotection, and memory and learning processes, only few studies have been conducted to date to unveil the potential implication of the ghrelin system in human Alzheimer's disease. In 2002, it was reported that mean plasma ghrelin concentrations in older normal weight subjects were significantly lower than those present in young normal weight subjects, providing the first evidence for an age related decline of plasma ghrelin concentrations [38]. Nevertheless, a more recent study has reported that ghrelin levels do not vary in the cerebrospinal fluid of AD patients compared with age-matched controls [39].

Gahete *et al*[40] showed, for the first time, that AD patients have a reduction in local brain ghrelin production, as compared with age-matched controls also, revealed that GHS-R1a, which is expressed at high levels in all regions of the temporal lobe, is altered in AD patients, showing a region-dependent reduction in its expression levels. Of note, human GHS-R1a is encoded by a gene that also produces an alternative spliced variant (GHS-R1b), which may serve as a dominant negative inhibitor of GHS-R1a [41]. Interestingly, GHS-R1b was found to be clearly expressed in the three different regions of the temporal lobe, at levels comparable to that of GHS-R1a; however, its expression level was clearly increased in all the regions of AD patients [40].

The serum leptin levels were significantly decreased in patients with AD as compared to controls. The association of high leptin levels with protection from AD remained significant after adjustment for other factors like age, sex, weight and smoking. The only factor that could affect leptin levels, was antipsychotic drugs. The overall findings support the hypothesis that one possible reason for the presence of AD may be an acquired resistance to effects of leptin, including its neuroprotective effects [42].

Leptin was found to reduce Aβ generation and tau phosphorylation in vitro [43,44], and leptin replacement therapy induces hippocampal neurogenesis [45] and improves cognitive performance

[43] in transgenic models of AD. Initially described for its role in satiety and long-term body weight maintenance, leptin has recently been proposed to regulate cognition, axonal growth, and synaptogenesis in extrahypothalamic regions [46]. Lower plasma levels of leptin have been associated with a fourfold increased risk of development of AD in a 12-year follow-up period compared with patients in whom leptin levels were greater [47].

Although a small cross-sectional study showed that leptin is elevated in midlife obesity and declines during Alzheimer disease, [47], it is uncertain whether leptin reduces the risk of Alzheimer disease. Lieb et al [47], measured plasma leptin concentrations in 785 participants without dementia in the Framingham Heart Study between 1990 and 1994 .Total cerebral brain volume and temporal horn volume were measured prospectively in 198 participants without dementia between 1999 and 2005. During a median follow-up of 8.3 years, 111 participants developed dementia and 89 were diagnosed with Alzheimer disease.There was a strong inverse association between the logarithm of leptin concentration and incidence of dementia and Alzheimer disease after adjusting for central obesity (waist to hip ratio) and cardiovascular risk factors.The absolute risk of Alzheimer disease during 12 years of follow-up was 12% for participants with the lowest leptin quartile and 6% for the highest quartile. Higher leptin levels were associated with increased total cerebral brain volume and reduced temporal horn volume.

The strengths of the study by Lieb *et al*[47] are the moderate sample size and prospective assessment of cognitive function and brain structure. Overall, the results are consistent with growing evidence that shows beneficial effects of leptin on brain structure and function[9-13]. Leptin receptors are present in the hippocampal cornu ammonis1 (CA1) region[11]. Leptin stimulates synaptic plasticity and memory function in leptin-deficient rodents[12].

Nonetheless, this community-based, prospective study does not establish a causal role for leptin in Alzheimer disease. High leptin level is often indicative of leptin resistance in obesity; therefore, it is unclear how a high leptin level is capable of signaling in the brain to prevent Alzheimer disease in a subset of apparently Leptin-resistant people[48,49]. A major methodological flaw is the reliance on a single baseline measurement of leptin that ignores the fact that leptin is influenced by fat stores as well as changes in energy homeostasis [50].

A better approach is to measure plasma leptin longitudinally in relation to neuropsychiatric evaluation and structural brain assessments. Leptin has circadian and pulsatile rhythms that are disrupted in pathological conditions,eg, amenorrhea and sleep and eating disorders[51,52]. Leptin and insulin act in a dose-dependent and synergistic manner to decrease hyper phosphorylation of tau, the primary component of the neurofibrillary tangle, the second major histopathological hallmark of AD [43]. Most interesting is an observation that chronic leptin treatment improved memory performance in transgenic animal models of AD [41,53].

In this study, the serum Adiponectin level of AD was found to be significantly lower than of control group. Adiponectin also seems to play a role in the development of all-cause dementia and particularly AD. A recent study [54] proved that increased plasma adiponectin levels are an independent risk factor for the development of AD in women. Furthermore, another study [54,55] found higher adiponectin levels both in plasma and CSF in subjects with AD,suggesting a critical role of this molecule in the onset of AD.

In present data, resistin level of AD patient groups showed a significant rise as compared with the control group. In humans, resistin is mainly expressed in bone marrow, monocytes, macrophages, and the spleen, and proinflammatory mediators such as tumor necrosis factor alpha-α, interleukin - 6, or lipopolysaccharide can strongly increase the expression of resistin in peripheral blood mononuclear cells [56-58]. In vitro and in vivo resistin is produced with a potent inflammatory character itself and also promotes the activation of mononuclear cells in a nuclear kappa á-dependent manner. Although the current literature data have demonstrated that resistin has various effects on distinct disease states, the relationship between resistin and AD is still obscure. In this respect, high plasma resistin levels that are found in AD patients suggest action through cytokine release during monocyte-macrophage differentiation as playing a key role in the inflammation process [59].

In AD patients, IL-6 is further increased locally around amyloid plaques and in the CSF [60-63], as well as in several AD animal models [64,65].The expression of IL-6 around the plaques precedes the neuropathological changes [61].indicating it is probably not a mere consequence of neurodegeneration. Based on the elevated IL-6 levels in AD patients, there have been attempts to

prove the validity of IL-6 levels in the serum or cerebrospinal fluid as a biomarker for AD [66-70]. However, up to now, there is no conclusive proof substantiating the use of IL-6 as an AD biomarker [71].Aβ triggers IL-6 production in both microglia and astrocytes. The toll-like receptor (TLR2) can bind Aβ and this is associated with induction of IL-6 production. Concomitantly, IL-6 induces astrogliosis and microgliosis. In astrocytes, IL-6 induces proliferation and hypertrophy, and expression of the chemokine (C–X–C motif) 4 receptor (CXCR4), leading to astrocyte chemotaxis. IL-6 also induces the production of inflammatory mediators in astrocytes. Furthermore, IL-6 leads to APP upregulation in neurons and, possibly, tau hyperphosphorylation. IL-6 also triggers differentiation of microglia to a phagocytic M2 phenotype, which is associated with acidification of their lysosomes, enabling them to degrade Aβ [72].

In conclusion, our study provides good evidence for an association between the circulating concentrations of melatonin, leptin, and adiponectin and the presence of AD. Although further research is required to address the precise cellular mechanisms underlying the reduced incidence of AD when melatonin, leptin, and adiponectin concentrations are high, it is possible that melatonin, leptin, and adiponectin good indicator of susceptibility to AD in the elderly population. Serum levels of resistin, and ghrelin was higher in AD patients compared to the control group. Increased serum resistin levels may be related to ongoing inflammatory processes during AD development.

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