Original paper
Originalni naučni rad

EVALUATION OF RENAL FUNCTION IN ALZHEIMER'S DISEASE AND GERIATRIC PATIENTS: RESULTS FROM A TURKISH TWO-CENTER STUDY

PROCENA BUBREŽNE FUNKCIJE U ALCHAJMEROVOJ BOLESTI I KOD GERIJATRIJSKIH PACIJENATA: REZULTATI TURSKE STUDIJE IZ DVA CENTRA

Zubeyde Erbayraktar[1], Ahmet Turan Evlice[2], Gokhan Yilmaz[3],
Canan Yazici[4], Gorsev Yener[5], Nuriye Nuray Ulusu[6]

[1]Dokuz Eylul University, Faculty of Medicine, Department of Biochemistry, Izmir
[2]Cukurova University, Faculty of Medicine, Department of Neurology, Adana
[3]University College London (UCL), Institute of Child Health, London
[4]Baskent University, Faculty of Medicine, Department of Biostatistics, Ankara
[5]Dokuz Eylul University, Faculty of Medicine, Department of Neurology, Izmir
[6]Koc University School of Medicine, Department of Biochemistry, Istanbul

Summary

Background: Alzheimer's disease (AD) is a severe multifactorial neurodegenerative proteopathy associated with advanced age. Discrepancies in the renal function of these patients compared to geriatric patients with dementia have rarely been reported. In this study, we aimed to disclose the importance of associated renal changes for the pathogenesis of AD.

Methods: Patients with AD (n=107) and geriatric patients with dementia and without dementia (n=124) (231 patients in total) from Dokuz Eylul and Cukurova University Hospitals were enrolled in the study. We measured serum Na, K, Cl, Ca, BUN, creatinine, total protein levels and MDRD [eGFR] in all groups.

Results: From Izmir Center, the first study arm consisted of patients with AD dementia (n=74), and the second arm included geriatric patients with dementia (n=79). From Adana, 78 patients were recruited to the study, of which 33 were with AD and 45 were geriatric patients without dementia. When we analyzed comparatively the AD and geriatric dementia patients study arms, a statistically significant difference was observed both in the median age

Kratak sadržaj

Uvod: Alchajmerova bolest (AB) predstavlja tešku multifaktorijalnu neurodegenerativnu proteopatiju koja je povezana sa starenjem. Dosad nije bilo mnogo izveštaja o razlikama u bubrežnoj funkciji kod obolelih od AB i kod gerijatrijskih pacijenata sa demencijom. U ovoj studiji, cilj je bio da se otkrije važnost povezanih promena bubrežne funkcije u patogenezi AB.

Metode: Studija je obuhvatila obolele od AB (n=107) i gerijatrijske pacijente sa demencijom i bez demencije (n=124) (ukupno 231 pacijent) iz bolnica Dokuz Eylul i Univerziteta Cukurova. U svim grupama, izmerili smo serumske nivoe Na, K, Cl, Ca, BUN, kreatinina, ukupnog proteina i MDRD (eGFR).

Rezultati: Iz centra Izmir, kao jednog od dva centra u kojima je studija sprovedena, uključeni su pacijenti sa demencijom AB (n=74) i gerijatrijski pacijenti sa demencijom (n=79). Iz centra Adana, u studiju je uključeno 78 pacijenata, od kojih je 33 imalo AB, dok su 45 bili gerijatrijski pacijenti bez demencije. Kada smo uporedo analizirali pacijente sa AD i gerijatrijskom demencijom, uočene su statistički značajne razlike kako u prosečnoj dobi (p<0,001) tako i u biohe-

Address for correspondence:

N. Nuray Ulusu
Koç University, School of Medicine
Professor of Biochemistry
Rumelifeneri Yolu
Sarıyer, Istanbul –Turkey
Phone: +90 (212) 338 11 60
Fax: +90 (212) 338 11 68
e-mail: nulusu@ku.edu.tr

(p<0.001), as well as in the biochemical parameters from Izmir Center: Na (p<0.001), K (p<0.001), Cl (p<0.05), Ca (p<0.001), BUN (p<0.05), creatinine (p<0.001), total protein (p<0.001) and MDRD [eGFR] (p<0.001). However, these were not significantly different between AD and geriatric patients without dementia in the Adana group.
Conclusions: Our results indicate that renal function is prone to alterations in different age groups of patients with AD. However, there is no conclusive evidence that renal function is one of the risk factors in AD.

Keywords: Alzheimer's disease, dementia, renal function

mijskim parametrima iz centra Izmir: Na (p<0,001), K (p<0,001), Cl (p<0,001), Ca (p<0,001), BUN (p<0,05), kreatinin (p<0,001), ukupni protein (p<0,001) i MDRD (eGFR) (p<0,001). Međutim, ovi parametri se u grupi Adana nisu značajno razlikovali između obolelih od AB i gerijatrijskih pacijenata bez demencije.
Zaključak: Naši rezultati ukazuju na to da je bubrežna funkcija podložna alteracijama u različitim starosnim grupama obolelih od AB. Međutim, nema čvrstih dokaza da je bubrežna funkcija jedan od faktora rizika za AB.

Ključne reči: Alchajmerova bolest, demencija, bubrežna funkcija

Introduction

The proportion of older people in the general population is steadily increasing worldwide in both developed and developing nations (1). However, a rapidly aging population also has important implications on healthcare and the age-related comorbidities including Alzheimer's disease (AD) which is a very complex, progressive, irreversible neurodegenerative disease and is the most common type of dementia (2). This neurodegenerative disease has been associated with three main structural changes in the brain: diffuse loss of neurons, intracellular protein deposits termed neurofibrillary tangles, and extracellular protein deposits termed amyloid or senile plaques, surrounded by dystrophic neurites (3). It has been known that cortical atrophy, neuron degeneration, neuronal loss, accumulation of extracellular (amyloid β containing) plaques and accumulation of intracellular (tau) neurofibrillary tangles are the dominant factors behind the cognitive decline of patients with AD (4–8). During the aging process, biochemical events such as defective cell signaling, oxidative damage, and aberrant tau protein phosphorylation eventually drive cells to apoptosis which in turn may prelude to AD. AD finally reaches to episodic short-term memory deficits and progress to further decline and loss of general cognitive functioning during the late dementia stage (9). Although the exact mechanisms behind AD are still poorly understood and it is usually considered as a complex disease with environment-gene interactions, there are various proposed distinct and interrelated triggering factors such as aberrant phosphorylation of tau proteins that triggers apoptotic pathway and neuronal loss. In addition to accumulation of Aβ plaques, intrusions that disturb normal cellular function which are essential for elimination or reduction of oxidative stress, such as vitamin deficiencies, might have a key role in AD. Furthermore, the ε4 allele of Apolipoprotein E (ApoEε4) is the only known major risk factor for late onset AD in a variety of ethnic groups (9–15).

It is known that the pathophysiologic link between brain and kidney injury is strong and complex (16). Elimination of toxic, water-soluble nitrogenous compounds of protein and nucleotide metabolisms by urinary extraction are quintessential for normal neu-rological function of the brain. In fact, a declining renal function could in turn create a further burden for an already inflammatory brain in AD. Previous studies have tried to address this complex, interdependent pathophysiological link, and identified that chronic kidney disease is also one of the risk factors for dementia and cognitive impairment (17–20).

Here, we aimed to evaluate and discern the changes in renal function in AD and geriatric patients based on the results from two different geographic regions in Turkey.

Materials and Methods

This study based on serum biochemistry was carried out to investigate the variations in kidney function tests in patients with AD and geriatric patients with dementia. Study population consisted of individuals aged 65 years and older from Dokuz Eylul and Cukurova University Hospitals. Patients were excluded from the study for multiple infections, clinically documented malignancies including brain tumor, drug and/or alcohol abuse or if a concurrent disease was likely to affect serum biochemistry.

In all clinical laboratory investigations, we used Beckman Coulter AU5800 and Beckman Coulter DXI devices according to manufacturer's guidelines.

In all centers, biochemical measurements were performed according to the following rules. All patients' blood samples were collected after a 10–12 hours fasting period. Venous blood samples, which were drawn between 9 a.m. and 11 a.m., were stored at 4 °C. Serum Na, K, Cl, Ca, BUN, creatinine and total protein levels were determined according to manufacturer's guidelines. Estimated Glomerular Filtration Rate [eGFR] was calculated according to the MDRD formula. To this end, Isotope Dilution Mass Spectrometry (IDMS) was employed with a value of 175 in a calibrated-creatinine method.

Statistical analysis

Shapiro-Wilk's test was used to assess the normality of distributions of the variables. Homogeneity

of groups' variances was checked by Levene's test. When the parametric test assumptions were not met, in comparisons of two independent groups, Mann-Whitney U test was employed.

Data analyses were performed using the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago IL, USA). P values < 0.05 were considered as statistically significant. The results of statistical analysis were expressed as number of observations (n), mean±standard deviation ($\bar{x}$±Sx), median and minimum–maximum values [M (min–max)].

Ethics and Dissemination

This study was approved by the Koc University Ethics Committee (2014.087.IRB3.063).

Results

In this study, we evaluated serum Na, K, Cl, Ca, BUN, creatinine, total protein levels and MDRD [eGFR] in AD and geriatric patients with dementia. We have selected our patients from two different geographic regions of Turkey; Izmir is from the Aegean region, and Adana is from the Mediterranean. We aimed to determine if there was a correlation between kidney disease and AD. Two hundred thirty-one female and male geriatric subjects were enrolled.

We evaluated the electrolyte panel, besides the glomerular and tubular function parameters, which is effective in a thorough assessment of renal function. These parameters act as an indicator of biological and/or pathologic processes, or pharmacologic responses to a therapeutic intervention and are routinely used for monitoring the effect of treatment on a known imbalance that is affecting bodily kidney function.

Reference ranges for the studied blood tests were as follows: serum sodium (Na): 136–145 mmol/L; serum potassium (K): 3.5–5.1 mmol/L; serum chloride (Cl): 98–107 mmol/L; serum calcium (Ca): 2.2–2.7 mmol/L; blood urea nitrogen (BUN): 2.9–8.2 (mmol/L); creatinine: 59.2–103.4 μmol/L; total protein: 66–83 g/L; MDRD [eGFR]: 90 mL/min.

From Izmir Center, 153 patients were recruited to the study, of which 95 were female and 58 were male. Furthermore, patients were assigned to two different arms; while the first study arm consisted of patients with AD (n=74), the second arm included geriatric patients with dementia (n=79). In the AD arm, 51 patients were female, and 23 patients were male.

The median age in the first arm in the AD arm was 76.16± 6.54 years (66–91). Our evaluation of the electrolyte panel is shown in *Figure 1*. The mean Na level was 144.98±4.70 mmol/L (129–155). The mean K level was 3.51±0.22 mmol/L (3.01–3.98) (*Figure 2*). The mean Cl level was 105.68±6.08 (93–119) (not shown in the the *Figure*). The mean Ca level was 2.04±0.15 mmol/L (1.75–2.33) mmol/L (not shown in the *Figure*). The mean serum BUN level in AD patients was 5.59±1.09 (3.2–8.2) mmol/L (*Figure 4*). The mean serum BUN level in geriatric patients with dementia was 5.98±0.87 (3.53–8.1) mmol/L (*Figure 4*). The mean eGFR level in patients from Dokuz Eylul University with AD was 66.01± 5.45 (55–77) (*Figure 5*). The mean eGFR level in geriatric patients from Dokuz Eylul University was 94.09±3.36 (88–99) (*Figure 5*). The mean serum total protein level in patients from Izmir with AD was 56.8±3.1 (50.1–64) g/L (*Figure 6*). The mean serum total protein level in geriatric patients from Izmir was 67.9±3 (60.6–75.3) g/L (*Figure 6*).
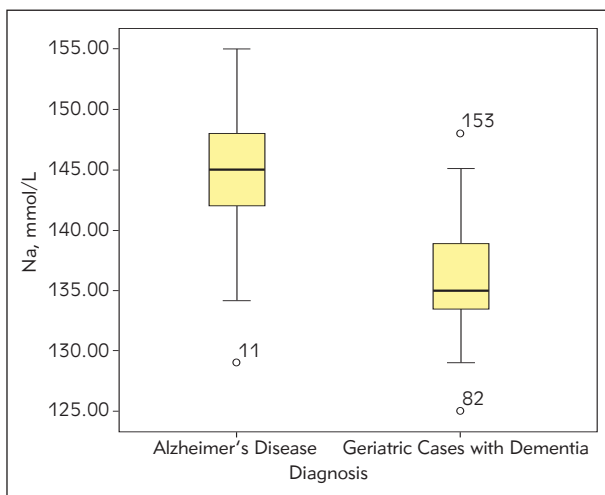

Figure 1 Results of serum sodium levels in patients with AD and other types of dementias from the Aegean Region, Izmir, Dokuz Eylul University Hospital.
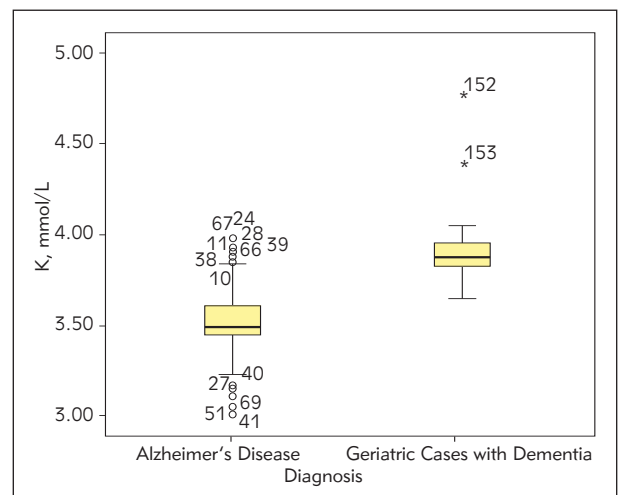

Figure 2 Results of serum potassium levels in patients with AD and other types of dementias from the Aegean Region, Izmir, Dokuz Eylul University Hospital.
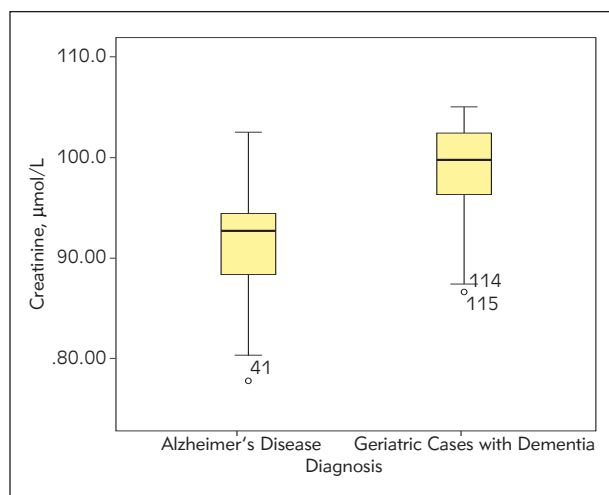
Figure 3 Results of serum creatinine levels in patients with AD and other types of dementias from the Aegean Region, Izmir, Dokuz Eylul University Hospital.
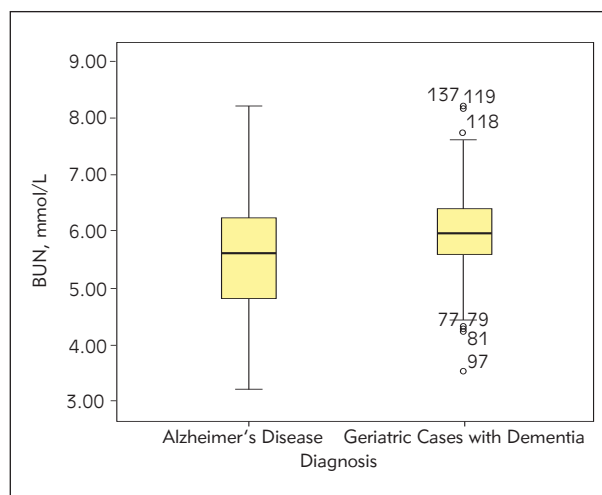

Figure 4 Results of serum BUN levels in patients with AD and other types of dementias from the Aegean region, Izmir, Dokuz Eylul University Hospital.
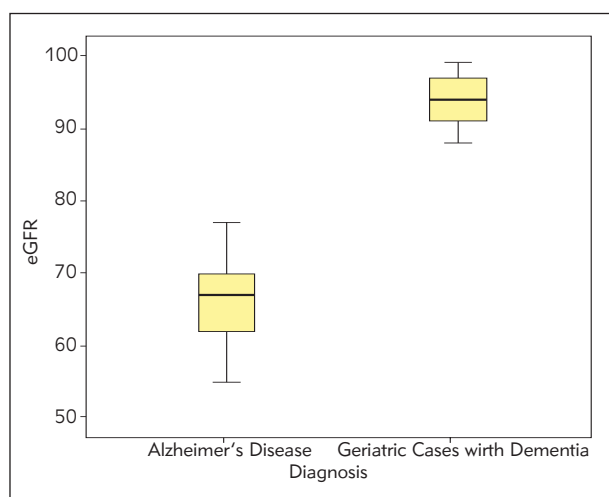

Figure 5 Results of serum eGFR levels in patients with AD and other types of dementias from the Aegean region, Izmir, Dokuz Eylul University Hospital.
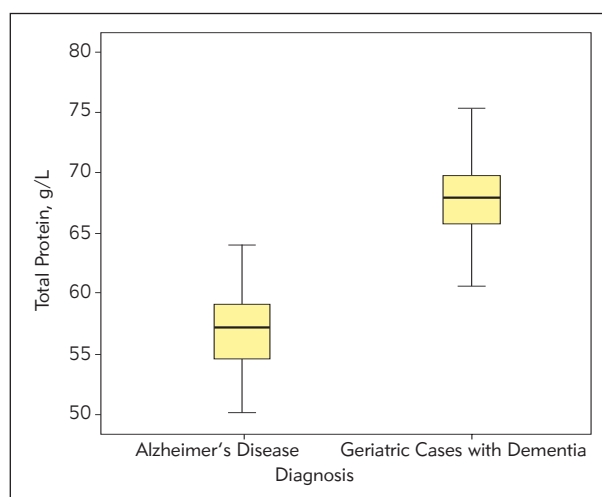

Figure 6 Results of serum total protein levels in patients with AD and other types of dementias from the Aegean region, Izmir, Dokuz Eylul University Hospital.

In the second arm (geriatric patients with dementia), the median age was 79.85±6.27 years (68–95). Analysis of biochemical parameters showed that the mean Na level was 136.13±4.09 mmol/L (125–148) (*Figure 1*), the mean K level was 3.88± 0.15 mmol/L (3.65–4.75) (*Figure 2*), the mean Cl level was 103.59±3.98 mmol/L (93–110) (data not shown), and the mean Ca level was 2.32±0.1 mmol/L (1.9–2.5) mmol/L (data not shown).

The creatinine results of the patients with AD and geriatric patients with dementia are shown in *Figure 3*. The mean creatinine level in patients with AD was 91.05±5.3 (77.8–102.5) μmol/L (*Figure 3*). The mean creatinine level in geriatric patients was 99.0±5.3 (86.6–105.2) μmol/L (*Figure 3*).

Mean serum concentrations of these tests were in the normal range, but group values were statistically divergent from normal reference values. In addition, when two different study arms were compared, a statistically significant difference was observed both in the median age (p<0.001), as well as in biochemical parameters: Na (p<0.001), K (p<0.001), Cl (p<0.05), Ca (p<0,001), BUN (p<0.05), creatinine (p<0.001), MDRD [eGFR] (p<0.001) and total protein (p<0.001).

The mean Na and Cl levels were higher in the first arm, compared to the second arm; on the other hand, the mean K, Ca, BUN, creatinine, total protein and MDRD [eGFR] values were found to be lower.
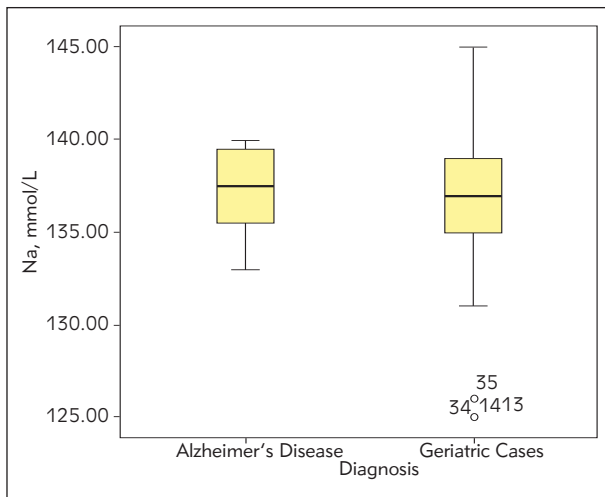
Figure 7 Results of serum sodium levels in patients with AD and geriatric patients without dementia from the Mediterranean Region, Adana, Cukurova University Hospital.
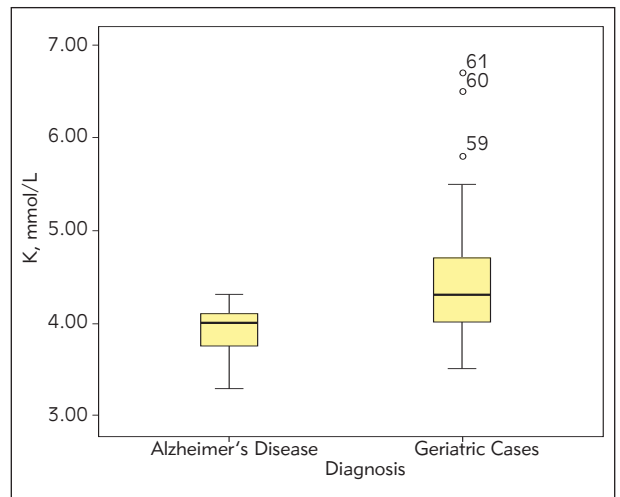

Figure 8 Results of serum potassium levels in patients with Alzheimer's and geriatric patients without dementia from the Mediterranean Region, Adana, Cukurova University Hospital.
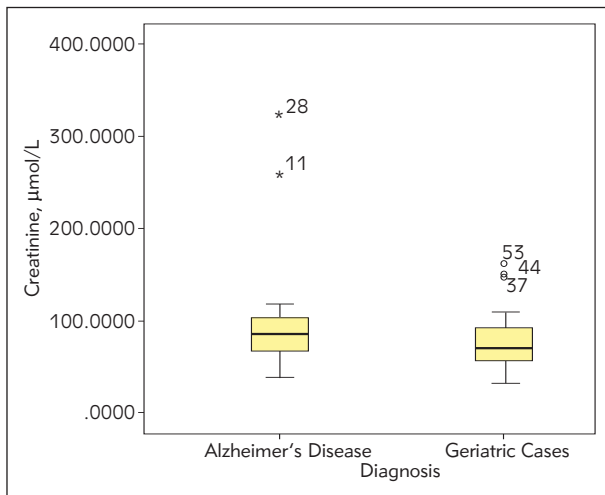

Figure 9 Results of serum creatinine levels in patients with AD and geriatric patients without dementia from the Mediterranean region, Adana, Cukurova University Hospital.
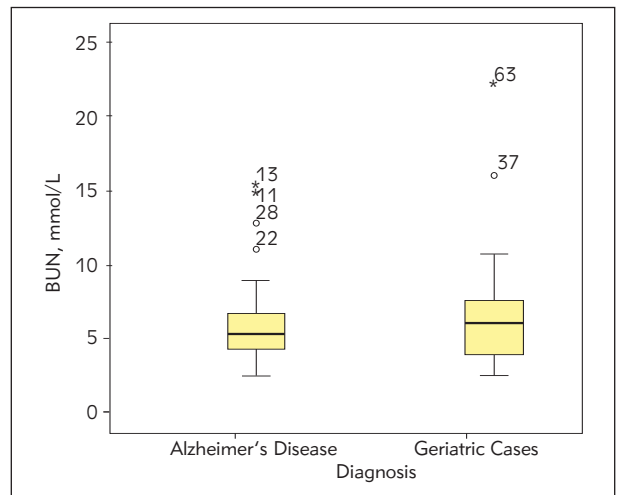

Figure 10 Results of serum BUN levels in patients with AD and geriatric patients without dementia from the Mediterranean region, Adana, Cukurova University Hospital.

From Adana Center (Cukurova University, Faculty of Medicine, Neurology Clinic), we evaluated clinical biochemical test results for renal function and in our study, we recruited patients over the age of 65 with previously diagnosed AD as well as geriatric patients without dementia to evaluate BUN and creatinine levels (in our evaluation, we used a Beckman Coulter DXI device according to the guidelines of the manufacturer).

From Adana Center, 78 patients were recruited to the study, of which 33 were with AD and 45 were geriatric patients with dementia. In the AD arm, 22 of the patients were male, whereas 11 of them were female, with a median age of 76.42±9.96 years (55–91). Evaluation of clinical biochemistry test results for discerning renal function was noted as follows: Na: 137.54±2.50 (132–141) mmol/L (*Figure*

7), K: 4.30±0.54 (3.30–5.40) mmol/L (*Figure 8*). The mean creatinine and BUN levels were 95.3±54.85 (40.66–323.54) μmol/L, 6.1±3.3 (2.5–15.4) mmol/L, respectively (*Figure 9* and *Figure 10*). The mean Cl level was 108.57±2.68 (93–110) mmol/L (data not shown), and the mean Ca level was 2.1±0.1 (1.9–2.5) (data not shown) mmol/L. The mean MDRD [eGFR] level was 46.02±5.15 (55.0–77.0) mL/min (not shown in the *Figure*). Finally, the mean total protein level was 56.86±15.74 (15–72) g/L.

In the geriatric arm, 21 of the patients were male, and 24 were female, with a median age of 71.98±6.14 years (68–88). The median sodium level was 136.95±3.98 (125–145) mmol/L (*Figure 7*). The mean potassium level was 4.54±0.71
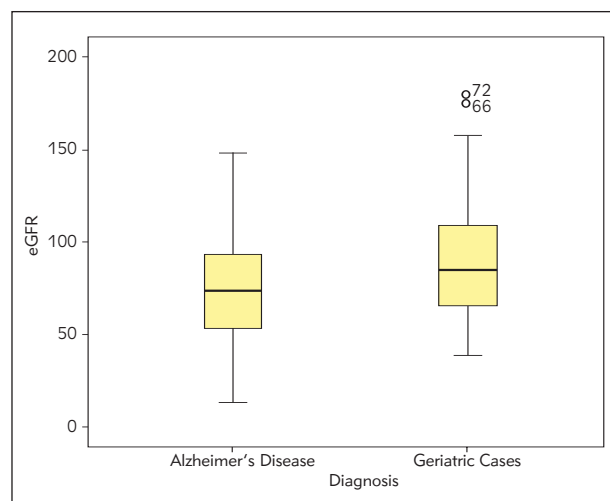
Figure 11 Results of serum eGFR levels in patients with AD and geriatric patients without dementia from the Mediterranean region, Adana, Cukurova University Hospital.

Figure 12 Results of serum total protein levels in patients with AD and geriatric patients without dementia from the Mediterranean region, Adana, Cukurova University Hospital.

(3.50–6.70) mmol/L (*Figure 8*). The mean creatinine level was 78.11±28.66 (33.59–161.77) μmol/L (*Figure 9*), and the mean BUN level was 6.4±3.5 (2.6–22.1) mmol/L (*Figure 10*). The mean Cl level was 105.29±3.67 (93–110) mmol/L (data not shown), and the mean Ca level was 2.3±0.1 (1.9–2.5) mmol/L (data not shown). The mean eGFR level in patients from Adana with AD was 75.94±29.43 (13.11–148.57) mL/min (*Figure 11*). The mean eGFR level in geriatric patients from Adana was 89.92±32.84 (38.76–179.54) mL/min (*Figure 11*). The mean serum total protein level in patients from Adana with AD was 56.9±15.7 (15–72 g/L (*Figure 12*). The mean serum total protein level in geriatric patients without dementia from Adana was 63.6±8 (47–78) (*Figure 12*).

When we compared the age of the groups, the median age in the AD arm was significantly higher compared to the geriatric arm (p=0.004).

On the other hand, BUN, creatinine, sodium, potassium, chloride, calcium, total protein and MDRD [eGFR] levels did not show significant differences between the groups (p=0.96, p=0.259, p=0.220, p=0.215, p=0.84, p=0.46, p=0.27, p=0.25 respectively).

Urinary protein levels were omitted as they were found to be in normal ranges. In this study, we have used serum concentrations such as: creatinine, blood urea nitrogen (BUN), as well as electrolytes, to determine renal function.

Discussion

Renal disease is a risk factor for vascular diseases and for dementia, and renal insufficiency can in fact be a complication of AD as emerging evidence
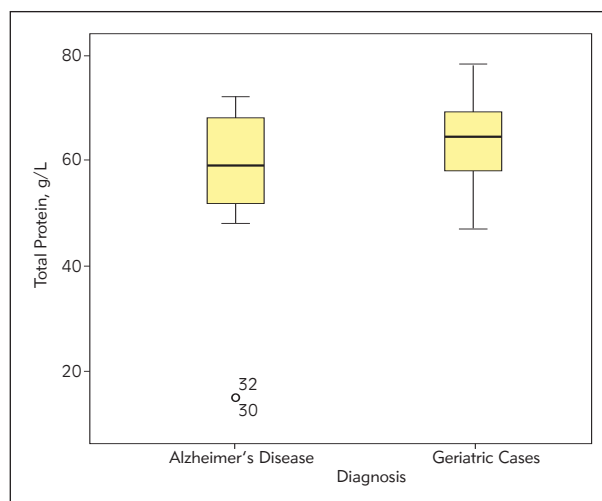
suggests that vascular mechanisms mediate the link between renal disease and dementia (1). We began our evaluation by first keeping in mind that healthy aging is a complex phenomenon with the interplay of many modifiable as well as heritable factors including but not limited to genetic and environmental factors, dietary habits, socioeconomic factors such as access to proper healthcare, degree of exposure to exogenous toxins etc. Multi-morbidity is common among older adults; however, for many aging-related diseases, population-based statistical data, including the statistics for U.S population that is commonly used as a model population, fell short in shedding light on how early these conditions begin to appear in life (21).

Definitive pathologies of AD are not well understood yet. It is usually proposed to be the sum of many factors such as genes, environment, lifestyle, and any kind of stress has a triggering effect in the occurrence of tangles and senile plaques. A previous population-based study has shown that individuals with decreased kidney function, as measured by low glomerular filtration rate, have smaller brain volume, smaller deep white matter volume, and more white matter lesions (1, 22–26). In addition, glomerular filtration rate is related to white matter lesions, subcortical atrophy, and to a lesser extent lacunar infarcts (24, 26). Therefore, poor kidney function is highly prevalent in the general elderly population (27–29). Electrolytes have enormous roles, such as modification of brain functions. In a previous study, it was demonstrated that exercise leads to increased serum calcium levels, and the calcium is transported to the brain. This in turn enhances brain dopamine synthesis through a calmodulin-dependent system, and increased dopamine levels regulate various brain functions (30). In addition, electrolytes are correlated with brain energy metabolism and it has been reported that a decline in cognitive functions may be miti-

gated by incorporating nutraceuticals in the diet (31). Dementia has been defined by Qui C as a clinical syndrome, which is characterized by a cluster of symptoms and signs manifested by difficulties in memory, disturbances in language and other cognitive functions, changes in behavior, and impairments in activities of daily living (24). Recent studies aimed at discerning a connection between cognitive brain functions and renal function have proposed that there is an observable decline in renal function in patients with AD, which in turn can create a risk (1, 22).

In this study, we evaluated and presented a clinical biochemistry panel of selected serum tests which are widely used for monitoring kidney function. We found that renal function, in fact, differed in geriatric dementia and patients with AD. These results may be correlated with the advanced age group of our patient population. Also, although we observed significant difference between patients with AD and geriatric dementia patients' results in Izmir Center, the same statistical pattern did not emerge in patients recruited from Adana Center. However, Adana Center also included geriatric patients without clinical dementia as a control group. This, in turn, can be attributed to the geographical differences, including access to healthcare and dietary habits.

Nonetheless, when we compared the study arms of AD and geriatric patients, although the median age was found to be lower in Izmir Center, we did not observe a significant difference between these study arms for renal function in our selected serum samples. However, the progressive decline of renal function with aging is not inevitable and there is an age-related decrease in glomerular filtration rate in elderly people with diabetes, hypertension (33, 34). Various researchers have proposed different ways to define GFR (35). Therefore, it is essential in clinical evaluations to include every variable and factor when clinically examining an organ function or an enzyme in all aspects of health (37–39).

Conclusion

From a public health perspective, Turkey still lacks valuable statistical data for age-related diseases, which are highly relevant in observing emerging comorbidities and clinical correlations when monitoring such fragile populations. We examined the associations between AD and renal dysfunction in geriatric patients as reflected by our selected serum routine tests for normal renal function in a Turkish population from two distinct geographical centers with palpable differences in lifestyles including dietary habits. We conclude that renal function differs significantly in various age groups of AD and geriatric patients in our population.

In order to discern valuable and practical data that could later be translated to patient care, we proposed that geriatric patients should be grouped by age, per decades – i.e. 65–74 as the first group, 75–84 as the second group, 85–95 as the third group and finally the fourth group of more than 95 years of age. We need further randomized, controlled studies for this classification to recalculate new indicators of aging based on the cutoff ages as stated above between these groups.

Our study showed that age-associated decline in renal function in elderly subjects and patients with AD is correlated with co-occurrence even though our findings are not conclusive that renal function is one of the risk factors in AD due to limitations in our sample size.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

References

1. Ulusu NN, Yilmaz G, Erbayraktar Z, Evlice AT, Aras S, Yener G, Avci A. A Turkish three-center study evaluation of serum folic acid and vitamin B12 levels in Alzheimer's Disease. Turk J Med Sci 2015; 45(5): 59–66.

2. Hampel H, Lista S, Teipel SJ, Garaci F, Nisticò R, Blennow K, et al. Perspective on future role of biological markers in clinical therapy trials of Alzheimer's disease: a long-range point of view beyond 2020. Biochem Pharmacol 2014; 88(4): 26–49.

3. Tonelli M, Riellae M. Chronic kidney disease and the aging population. Arab J Nephrol Transplant 2014; 7(1): 7–11.

4. Fändrich M, Schmidt M, Grigorieff N. Recent progress in understanding Alzheimer's β-amyloid structures. Trends Biochem Sci 2011; 36: 38–45.

5. Galan A, Carletti BE, Morgaz J, Granados MM, Mesa I, Navarrete R, et al. Comparative study of select biochemical markers in cerebrospinal fluid of healthy dogs before and after treatment with nutraceuticals. Vet Clin Pathol 2014; 43(1): 2–7.

6. Ikram MA, Vernooij MW, Hofman A, Niessen Wiro J, van der Lugt A, Breteler MMB. Kidney function is related to cerebral small vessel disease. Stroke 2008; 39(1): 55–61.

7. Murray AM. Cognitive impairment in the aging and chronic kidney disease populations: an occult burden. Adv Chronic Kidney Dis 2008; 15: 23–32.

8. Murray AM, Knopman DS. Cognitive impairment in CKD: no longer an occult burden. Am J Kidney Dis 2010; 56: 5–8.

9. Shin RW, Ogomori K, Kitamoto T, Tateishi J. Increased tau accumulation in senile plaques as a hallmark in Alzheimer's disease. Am J Pathol 1989; 134: 65–71.

10. Sutoo D, Akiyama K. Regulation of brain function by exercise. Neurobiol of Dis 2003; 13(1): 1–14.

11. Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci 2009; 11(2): 11–28.

12. Ulusu NN, Yılmaz G, Erbayraktar Z, Evlice A, Genç M, Aras S, et al. A Comparative Study on Thyroid Function in Alzheimer's Disease: Results From a Turkish Multi-Center Study. J of Neurological Sci [Turkish] 2015; 32(2): 35–47.

13. Ulusu NN. Curious Cases of the Enzymes. J Med Biochem 2015; 34 (3): 71–81.

14. Sambamurti K, Greig NH, Utsuki T, Barnwell EL, Sharma E, Mazell C, et al. Targets for AD treatment: conflicting messages from Y-secretase inhibitors. J Neurochem 2011; 117: 59–74.

15. Yamamoto K, Takeshita K, Saito H. Plasminogen Activator Inhibitor-1 in Aging. Semin Thromb Hemost 2014; 40(6): 2–9.

16. Ulusu NN. Glucose-6-Phosphate Dehydrogenase Deficiency and Alzheimer's Disease: Partners In Crime? Med Hypotheses 2015; 85(2): 19–23.

17. De Ferrari GV, Inestrosa NC. Wnt signaling function and Alzheimer's disease. Brain Res Rev 2000; 33: 1–12.

18. Hampel H, Prvulovic D, Teipel S, Jessen F, Luckhaus C, Frölich L, et al. German Task Force on Alzheimer's Disease (GTF-AD). The future of Alzheimer's disease: the next 10 years. Prog Neurobiol 2011; 95(4): 18–28.

19. Hickman SE, El Khoury J. TREM2 and the neuroimmunology of Alzheimer's disease. Biochem Pharmacol 2014; 88(4): 5–8.

20. Yu J, Gattoni-Celli M, Zhu H, Bhat NR, Sambamurti K, Gattoni-Celli S, Kindy MS. Vitamin D3-enriched diet correlates with a decrease of amyloid plaques in the brain of AβPP transgenic mice. J Alzheimers Dis 2011; 25: 295–307.

21. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145(4): 47–54.

22. Richardson C, Nilforooshan R, Gard PR, Weaving G, Tabet N. Impaired renal function and biomarkers of vascular disease in Alzheimer's disease. Curr Alzheimer Res 2014; 11(3): 3–8.

23. Tonelli M, Riella M. Chronic kidney disease and the aging population. Curr Opin Organ Transplant 2014; 19(4): 3–7.

24. Gowda S, Desai PB, Kulkarni SS, Hull VV, Math AA, Vernekar SN. Markers of renal function tests. N Am J Med Sci 2010; 2(4): 70–3.

25. Bugnicourt JMI, Godefroy O, Chillon JM, Choukroun G, Massy ZA. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. J Am Soc Nephrol 2013; 24(3): 53–63.

26. Madero M, Gul A, Sarnak MJ. Cognitive function in chronic kidney disease. Seminars in Dialysis [Wiley online library] 2008; 21(1): 29–37.

27. Kerr E, Craig D, McGuinness B, Dynan KB, Fogarty D, Johnston JA, Passmore AP. Reduced estimated glomerular filtration rate in Alzheimer's disease. Int J Geriatr Psychiatry 2009; 24(9): 27–32.

28. Koushik NS, McArthur SF, Baird AD. Adult chronic kidney disease: neurocognition in chronic renal failure. Neuropsychol Rev 2010; 20: 33–51.

29. Cho EB, Seo SW, Kim H, Lee JM, Yoon U, Im K, et al. Effect of kidney dysfunction on cortical thinning in patients with probable Alzheimer's disease dementia. J Alzheimers Dis 2013; 33(4): 1–8.

30. Hüttenrauch M, Baches S, Gerth J, Bayer TA, Weggen S, Wirths O. Neprilysin deficiency alters the neuropathological and behavioral phenotype in the 5XFAD mouse model of Alzheimer's disease. J Alzheimers Dis 2015; 44: 291–302.

31. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002; 297: 3–6.

32. Evlice A, Ulusu NN. Glucose-6-phosphate dehydrogenase a novel hope on a blood-based diagnosis of Alzheimer's disease. Acta Neurol Belg. 2016 Jul 4. [Epub ahead of print] DOI: 10.1007/s13760-016-0666-6.

33. Fliser D. Assessment of renal function in elderly patients. Curr Opin Nephrol Hypertens 2008; 17: 4–8.

34. Aucella F, Guida CC, Lauriola V, Vergura M. How to assess renal function in the geriatric population. J Nephrol 2010; 23: 46–54.

35. Delanaye P1, Schaeffner E, Ebert N, Cavalier E, Mariat C, Krzesinski JM, Moranne O. Normal reference values for glomerular filtration rate: what do we really know? Nephrol Dial Transplant 2012; 27: 64–72.

36. Grewal GS, Blake GM. Reference data for 51Cr-EDTA measurements of the glomerular filtration rate derived from live kidney donors. Nucl Med Commun 2005; 26: 1–5.

37. Popević S, Šumarac Z, Jovanović D, Babić D, Stjepanović M, Filipović S, Šobić-Šaranović D, Gvozdenović B, Omčikus M, Milovanović A, Videnović-Ivanov J, Radović A, Žugić V, Mihailović-Vučinić V. Verifying sarcoidosis activity: chitotriosidase versus ACE in sarcoidosis. A case control study. J Med Biochem 2016; 35: 390–400.

38. Erten-İşeri ÖS, Dikmen ZG, Ulusu NN. Comparison of spectrophotometric and fluorimetric methods in evaluation of biotinidase deficiency. J Med Biochem 2016; 35: 3–9.

39. Krnjeta T, Mirković L, Ignjatović S, Tomašević D, Lukić J, Topalov D, Soldatović I, Majkić-Singh N. Protective Role of Maternal P.VAL158MET Catechol-O-methyltransferase Polymorphism against Early-Onset Preeclampsia and its Complications. J Med Biochem 2016; 35: 312.