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ORIGINAL ARTICLE

# Thiazide therapy is not related to any changes in cognitive function in older hypertensive patients with or without dementia: a 26-week follow-up study

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## Abstract

**Aim:** The study aimed to evaluate the effect of thiazide diuretics, a first-line antihypertensive therapy, on cognitive function in elderly hypertensive patients with or without cognitive impairment.

**Methods:** This retrospective and observational study assessed 286 elderly patients with hypertension. Patients were divided based on thiazide diuretic usage and then into dementia and non-dementia groups. The comprehensive geriatric assessment was performed for all patients. All participants were re-evaluated after a 26-week period.

**Results:** In total, 133 patients, including 62 with dementia, took thiazide. There were no significant differences between baseline and follow-up laboratory findings, comprehensive geriatric assessment parameters, including detailed neurocognitive assessment, or electrolytes in the thiazide group, the non-thiazide group, and the dementia group ($P > 0.05$).

**Conclusion:** Thiazide therapy does not show any effect on cognitive function in older hypertensive adults regardless of dementia status.

## INTRODUCTION

Cognitive impairment is one of the most important considerations for older adults.[1] The current literature has demonstrated that several cardiovascular risk factors such as diabetes, hypertension (HT), obesity, and high cholesterol level, which are common in older adults, are likely to play a role in the development of cognitive impairment.[2] Accordingly, the hypothesis 'what's good for the heart is good for the brain' has become the focus of much study,[3,4] and the management of those risk factors has become particularly important in geriatric practice.

HT is a modifiable risk factor for age-related dementia, the most common types of which are Alzheimer's disease (AD) followed by vascular dementia. HT is also a risk factor for cerebrovascular diseases and for vascular dementia.[5] Although AD is considered a neurodegenerative disease, chronic and episodic hypoperfusion is also responsible for AD development.[6] In most studies, midlife blood pressure elevation was associated with late-onset cognitive impairment, while in some studies, late-in-life low diastolic blood pressure and very high systolic blood pressure accompanied dementia and cognitive impairment.[5]

It was reported that HT might affect cognitive function through several mechanisms.[7] Moreover, antihypertensive medications, such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and diuretics, reduced the risk of dementia in several studies.[8–10] In an observational study, it was reported that potassium-sparing diuretics had a greater effect on verbal learning and memory in an HT group than in a non-HT group.[11] However, the Cache County Study reported that thiazide and potassium-sparing diuretics were associated with a decreased risk of AD, but that thiazide monotherapy did not reduce the risk.[12] In contrast, another study demonstrated that

thiazides might ameliorate AD-type neurodegeneration because of their direct vasodilator effect.[13] Many studies have shown the relationship between diuretic therapy and cognitive function; nonetheless, the effects of thiazide diuretics on cognitive function in the elderly have not been detailed in the literature.

The aim of this study was to detect the effect of thiazides on cognitive function in older adults with and without dementia.

## METHODS

### Patients

In this study, a total of 286 older adults with HT who had been admitted to a geriatrics clinic between January 2013 and November 2016 were included in this study. All were evaluated retrospectively based on medical records. Patients were divided into two groups: those taking thiazide diuretics and those taking other antihypertensive drugs without diuretics. In addition, each of the two groups was further divided into two subgroups according to whether a diagnosis of dementia was present. Dementia was diagnosed in accordance with *The Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, released in 2013.[14] All patients were re-evaluated after 26 weeks. This study conformed to the Declaration of Helsinki and was approved by the local ethics committee.

#### *Exclusion criteria*

Patients were excluded for the following reasons:

- taking diuretics other than thiazide diuretics
- having uncontrolled HT (systolic blood pressure >160 mmHg and/or diastolic blood pressure > 90 mmHg) or hypotension (systolic blood pressure < 100 mmHg and/or diastolic blood pressure < 60 mmHg)
- having had a recent cardiovascular or neurological event (New York Heart Association (NYHA) stage 3–4 heart failure, angina pectoris, stroke, transient ischaemic attack, or cerebrovascular event)
- having a metabolic diseases, such as uncontrolled diabetes mellitus or severe hypothyroidism/hyperthyroidism that could affect cognitive function
- having a psychotic disease (e.g. schizoaffective disorder) and/or treatment-resistant major depressive disorder
- having delirium during evaluation
- having a malignancy
- engaging in alcohol and drug abuse
- taking medications that are likely to affect cognitive function, such as corticosteroids, benzodiazepines, and antipsychotics
- being under 60 years of age.

All the patients who applied to the geriatric clinic for any reason and did not meet the exclusion criteria were included in the study.

#### Patient characteristics:

Patients were evaluated for their age, gender, marital status, living environment, years of education, comorbidities except for HT (e.g. diabetes mellitus, peripheral arterial disease, thyroid disease, ischaemic heart disease, congestive heart failure, and chronic obstructive pulmonary disease), weight, body mass index, and the number of medications. The number of medications was recorded again at the 26-week follow-up. To calculate body mass index, height was measured to the nearest centimetre and weight was measured to the nearest half-kilogram (kg) with the same stadiometer.

#### Comprehensive geriatric assessment (CGA)

Cognitive function was evaluated by the Mini-Mental State Examination, the Cognitive State Test, and the Montreal Cognitive Assessment Scale.[15] In addition, scores from the Geriatric Depression Scale, Mini Nutritional Assessment-Short Form, Basic Activities of Daily Living index, Instrumental Activities of Daily Living index, and the Tinetti Performance-Oriented Assessment of Mobility were also recorded for each patient.

#### Laboratory findings

Some laboratory tests, such as renal and liver function, fasting blood glucose, haemogram, thyroid-stimulating hormone, glycated haemoglobin, high-density lipoprotein, low-density lipoprotein, uric acid, vitamin D, vitamin B12, and folic acid levels, were performed to evaluate the biochemical, metabolic, and nutritional status of the patients. All tests were obtained by the auto-analyzer diagnostic modular system (E170 and P-800; Roche Diagnostics, Basel, Switzerland). Serum 25-hydroxy vitamin D was measured by radioimmunoassay.

### Follow-up

Each patient's blood pressure status was evaluated at 3 and 6 months from baseline. The CGA was administered again at week 26.

### Statistical analysis

Data analysis was performed by SPSS for Windows 15 package program (SPSS Inc., Chicago, IL, USA). Descriptive statistics are shown as mean ± SD for variables with normal distribution, median (minimum–maximum) for non-normal distributions, and the number of cases and percentage for nominal variables. When two groups were compared, the significance of differences between the groups in terms of averages was investigated by *t*-test and, in terms of median values, by the Mann–Whitney *U*-test. Nominal variables were assessed by Pearson's $\chi^2$ or Fisher's exact test. $P < 0.05$ was considered statistically significant. Changes between the visits were calculated by subtracting the baseline value from the follow-up value. The relationship of changes between visits with thiazide use and the use of other antihypertensive drugs was assessed by the Kruskal–Wallis test. Paired *t*-test was used to compare values between baseline and the 26-week follow-up.

## RESULTS

Baseline characteristics of thiazide and non-thiazide patients are summarized in Table 1. Of the 286 patients, 133 took a thiazide diuretic. The mean ages did not differ between the groups ($P > 0.05$). Most of the patients were women in both groups (thiazide: 75.9%; non-thiazide: 65.4%; $P = 0.051$). Years of education, body mass index, percentage of comorbidities, laboratory findings, baseline blood pressure, and change in blood pressure were also similar in both groups ($P > 0.05$). Baseline CGA

**Table 1** Baseline characteristics of patients

| | Thiazide (–) ($n$ = 152) | Thiazide (+) ($n$ = 133) | $P$-value |
|---|---|---|---|
| Age (years), mean ± SD | 75.58 ± 8.17 | 75.47 ± 8.40 | 0.906 |
| Female (%) | 65.4 | 75.9 | 0.051 |
| Education (years), mean ± SD | 7.53 ± 4.73 | 14.91 ± 7.58 | 0.228 |
| BMI (kg/m$^2$), mean ± SD | 29.06 ± 4.80 | 29.95 ± 5.07 | 0.140 |
| SBP (mmHg), mean ± SD | 140.29 ± 19.32 | 136.83 ± 19.96 | 0.142 |
| DBP (mmHg), mean ± SD | 77.61 ± 12.46 | 75.34 ± 12.26 | 0.125 |
| Comorbidities (%) | | | |
| Falls | 29.4 | 27.1 | 0.661 |
| Dementia | 26.1 | 17.3 | 0.072 |
| Forgetfulness | 83.0 | 79.7 | 0.473 |
| CVD | 9.2 | 9.0 | 0.970 |
| Depression | 30.1 | 33.1 | 0.584 |
| DM | 29.4 | 37.1 | 0.167 |
| Hyperlipidaemia | 32.7 | 23.3 | 0.079 |
| CAD | 26.1 | 21.1 | 0.313 |
| CHF | 7.8 | 3.8 | 0.145 |
| COPD | 7.8 | 9.8 | 0.564 |
| Hypothyroidism | 20.3 | 24.8 | 0.357 |
| Osteoporosis | 23.5 | 24.8 | 0.800 |
| Orthostatic hypotension | 36.1 | 29.9 | 0.373 |
| Laboratory findings, mean ± SD | | | |
| Albumin (g/L) | 4.11 ± 0.44 | 4.07 ± 0.36 | 0.453 |
| LDL cholesterol (mg/dL) | 126.24 ± 36.33 | 128.21 ± 35.75 | 0.657 |
| Triglycerides (mg/dL) | 145.67 ± 76.69 | 136.98 ± 59.86 | 0.310 |
| HDL cholesterol (mg/dL) | 54.96 ± 12.86 | 55.03 ± 12.31 | 0.965 |
| Na (mmol/L) | 138.57 ± 2.67 | 138.68 ± 2.59 | 0.730 |
| K (mmol/L) | 4.54 ± 0.46 | 4.43 ± 0.43 | 0.059 |
| Ca (mg/dL) | 9.53 ± 0.46 | 9.60 ± 0.49 | 0.222 |
| 25(OH)D (ng/mL) | 19.13 ± 16.67 | 18.61 ± 12.66 | 0.772 |

25(OH)D, 25-hydroxy vitamin D; BMI, body mass index; Ca, calcium; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein; K, potassium; LDL, low-density lipoprotein; Na, sodium; SBP, systolic blood pressure.

parameters did not differ between the thiazide and non-thiazide groups ($P > 0.05$) (Table 2).

There were no significant differences between the thiazide and non-thiazide groups in terms of baseline and 26-week follow-up laboratory findings or in terms of scores on the Mini-Mental State Examination, Cognitive State Test, Montreal Cognitive Assessment Scale, Mini Nutritional Assessment-Short Form, and the clock-drawing test ($P > 0.05$). Only Basic Activities of Daily Living and Instrumental Activities of Daily Living were significantly decreased at the 26-week follow-up compared to baseline ($P < 0.05$) (Table 2).

Of the 62 dementia patients, 23 were treated with thiazide diuretics. In patients with dementia, changes in CGA parameters and in thyroid-stimulating hormone, folic acid, uric acid, vitamin B12, high-density lipoprotein, low-density lipoprotein, and sodium and potassium values did not differ between the thiazide and non-thiazide groups ($P > 0.05$) (Table 3). The laboratory tests were also similar in non-dementia patients ($P > 0.05$).

## DISCUSSION

In this retrospective observational study, it was demonstrated that 26-week thiazide therapy was not related to any changes in cognitive function in older hypertensive adults with or without dementia. The effects of thiazide might be independent of blood pressure as well.

HT may affect cognitive function through various pathophysiological mechanisms, such as orthostatic hypotension, reduction in brain volume, vascular remodelling, vascular stiffness and cerebral atherosclerosis, impaired cerebral perfusion and autoregulation, endothelial dysfunction, altered functional hyperaemia, and oxidative stress between high blood pressure and cognitive function.[7] However, the effect of antihypertensive treatment on cognitive function has not been conclusively determined thus far.[9] It was reported that candesartan, an angiotensin receptor blocker, had no effect on cognitive function in patients with HT,[16] whereas nitrendipine, a calcium channel blocker, reduced dementia incidence by 55%.[17] Furthermore, in another study, perindopril and indapamide therapy was associated with reduced risks of dementia and cognitive decline.[18] In contrast, the results of the Hypertension in the Very Elderly Trial suggested that perindopril plus indapamide treatment in elderly patients did not reduce the incidence of dementia.[19] These conflicting findings have affected subsequent meta-analyses and reviews. For example, one meta-analysis reported that antihypertensive treatment had no effect on the

**Table 2** Comparison of the patients' characteristics at baseline and follow-up

| | Thiazide (–) $n = 152$ | | | Thiazide (+) $n = 133$ | | | |
|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | *P*-value[†] | Baseline | Follow-up | *P*-value[‡] | *P*-value[§] |
| Geriatric assessment | | | | | | | |
| MMSE | 23.38 ± 6.04 | 22.99 ± 6.73 | 0.324 | 24.66 ± 4.97 | 24.60 ± 5.45 | 0.859 | 0.180 |
| COST | 22.03 ± 6.27 | 21.90 ± 6.68 | 0.843 | 21.44 ± 6.83 | 21.63 ± 7.45 | 0.658 | 0.736 |
| MOCA | 24.20 ± 4.24 | 24.06 ± 4.81 | 0.652 | 23.92 ± 4.02 | 23.95 ± 5.01 | 0.945 | 0.749 |
| Clock-drawing test | 3.96 ± 1.51 | 3.87 ± 1.63 | 0.359 | 4.13 ± 1.39 | 4.03 ± 1.43 | 0.606 | 0.365 |
| BADL | 90.96 ± 14.95 | 90.19 ± 17.14 | 0.024 | 92.11 ± 10.95 | 91.16 ± 13.33 | 0.040 | 0.914 |
| IADL | 16.85 ± 6.59 | 16.56 ± 7.13 | 0.005 | 17.28 ± 5.92 | 17.01 ± 6.12 | 0.028 | 0.458 |
| MNA-SF | 11.49 ± 2.44 | 11.82 ± 2.27 | 0.111 | 11.53 ± 2.13 | 12.08 ± 1.89 | 0.041 | 0.560 |
| Number of drugs | 5.82 ± 3.03 | 5.30 ± 2.32 | 0.008 | 6.48 ± 3.32 | 5.37 ± 2.45 | <0.001 | 0.084 |
| Laboratory findings | | | | | | | |
| TSH (uIU/mL) | 1.46 ± 1.05 | 2.20 ± 7.36 | 0.264 | 1.54 ± 1.09 | 1.84 ± 2.53 | 0.238 | 0.528 |
| Folic acid (ng/mL) | 9.36 ± 5.18 | 8.62 ± 4.94 | 0.230 | 9.38 ± 5.36 | 8.87 ± 4.65 | 0.302 | 0.976 |
| Vitamin B12 (pmol/L) | 504.77 ± 394.33 | 509.78 ± 278.31 | 0.832 | 536.74 ± 392.47 | 463.59 ± 245.21 | 0.033 | 0.496 |
| Glucose (mg/dL) | 108.76 ± 33.43 | 109.02 ± 33.21 | 0.660 | 106.95 ± 29.19 | 112.50 ± 45.14 | 0.203 | 0.637 |
| HbA1c (%) | 6.87 ± 1.32 | 6.98 ± 1.20 | 0.311 | 6.73 ± 1.14 | 6.83 ± 0.99 | 0.721 | 0.573 |
| Uric acid (mg/dL) | 5.74 ± 1.57 | 6.01 ± 1.64 | 0.800 | 5.97 ± 1.56 | 6.06 ± 1.45 | 0.310 | 0.370 |
| eGFR (MDRD) | 70.20 ± 21.62 | 71.18 ± 20.30 | 0.345 | 68.33 ± 19.10 | 70.71 ± 18.80 | 0.070 | 0.445 |

[†] For comparisons of baseline and follow-up in patients who were not treated with thiazide. [‡] For comparisons of baseline and follow-up in patients who were treated with thiazide. [§] For baseline comparisons of patients treated with and without thiazides. BADL, Basic Activities of Daily Living (0 (worst)–100 (best)); COST, Cognitive State Test (0 (worst)–30 (best)); eGFR (MDRD), estimated glomerular filtration rate (modification of diet in renal disease); HbA1c, glycated haemoglobin; IADL, Instrumental Activities of Daily Living (0 (worst)–17 (best)); MMSE, Mini-Mental State Examination (0 (worst)–30 (best)); MNA-SF, Mini Nutritional Assessment-Short Form (0 (worst)–14 (best)); MOCA, Montreal Cognitive Assessment (0 (worst)–30 (best)); TSH, thyroid-stimulating hormone.

**Table 3** Comparison of the changes in characteristics of patients at baseline and follow-up

| | Patients with Dementia *n* = 62 | | | Patients without Dementia *n* = 223 | | |
|---|---|---|---|---|---|---|
| | Thiazide (–) *n*=39 | Thiazide(+) *n*=23 | *P*-value | Thiazide (–) *n* = 113 | Thiazide (+) *n* = 110 | *P*-value |
| Geriatric assessment | | | | | | |
| ΔMMSE | −1.31 ± 4.01 | −1.46 ± 3.79 | 0.919 | −0.04 ± 2.93 | 0.27 ± 2.32 | 0.551 |
| ΔCOST | −1.30 ± 4.21 | −0.28 ± 2.13 | 0.418 | 0.76 ± 2.99 | 0.35 ± 2.18 | 0.630 |
| ΔMOCA | −1.71 ± 3.14 | 0.66 ± 3.05 | 0.326 | 0.08 ± 2.21 | −0.02 ± 2.29 | 0.821 |
| ΔCDT | −0.45 ± 1.02 | 0.21 ± 1.31 | 0.108 | 0.01 ± 1.13 | 0.08 ± 0.85 | 0.473 |
| ΔCDR | 0.12 ± 0.29 | 0.13 ± 0.46 | 0.933 | | | |
| ΔGDS | −0.60 ± 2.64 | −1.73 ± 3.41 | 0.261 | −0.76 ± 2.40 | −0.53 ± 2.88 | 0.539 |
| ΔBADL | −4.27 ± 9.31 | −4.1 ± 10.76 | 0.953 | −0.14 ± 4.49 | −0.91 ± 6.80 | 0.335 |
| ΔIADL | −1.02 ± 2.70 | −1.05 ± 2.01 | 0.974 | −0.40 ± 2.21 | −0.31 ± 2.18 | 0.786 |
| ΔMNA-SF | 0.14 ± 2.03 | −0.50 ± 1.63 | 0.272 | 0.31 ± 1.96 | 0.52 ± 1.86 | 0.458 |
| Laboratory findings | | | | | | |
| ΔTSH (uIU/mL) | 2.51 ± 14.49 | −0.18 ± 0.56 | 0.398 | 0.11 ± 1.42 | 0.33 ± 2.32 | 0.455 |
| ΔFolic acid (ng/mL) | −1.22 ± 5.62 | −1.98 ± 9.72 | 0.703 | −0.30 ± 5.41 | −0.29 ± 5.28 | 0.996 |
| ΔVitamin B12 (pmol/L) | −65.66 ± 481.77 | −174.17 ± 510.06 | 0.405 | 33.67 ± 441.03 | 64.93 ± 426.94 | 0.098 |
| ΔUric acid | −0.67 ± 1.92 | 0.27 ± 1.15 | 0.175 | 0.42 ± 0.88 | 0.12 ± 1.17 | 0.294 |

Δ, change in; BADL, Basic activities of Daily Living; CDR, Clinical Dementia Rating; CDT, clock-drawing test; COST, Cognitive State Test; eGFR(MDRD), estimated glomerular filtration rate (modification of diet in renal disease); GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; MNA-SF, Mini Nutritional Assessment-Short Form; MOCA, Montreal Cognitive Assessment; TSH, thyroid-stimulating hormone.

incidence of cognitive decline or dementia.[20] However, antihypertensive medications such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and diuretics were reported to reduce the risk of dementia in other reports.[8–10]

Among these antihypertensive medications, thiazides, which are safe, effective, and well-tolerated, are used commonly in the elderly as monotherapy or combined with other medications.[21–24] Although thiazides are commonly used in elderly patients with HT, and many studies have demonstrated the relationship between diuretic therapy and cognitive function, the effect of thiazide diuretics on cognitive function in the elderly has not been conclusively determined yet. In a community cohort of 1810 older adults (including 225 dementia cases), it was reported that all kinds of diuretics could protect against dementia, and they reduced the risk of dementia by 30% in adults over the age of 75 years.[13] It has been suggested that HT medications may reduce senile plaque and neurofibrillary tangles and that thiazides differ from the other medications because their direct vasodilator effect on vessel walls may reduce the toxic effect of β-amyloid proteins.[13] Additionally, Chuang *et al*. reported that both potassium-sparing and thiazide diuretics may have decreased the risk of AD over the course of 7.1 years.[12] Although these studies had a longer follow-up period and larger sample size than the present study, they did not offer any details regarding comorbidities, drugs other than antihypertensive medications, and laboratory parameters or blood pressure measurements before and after treatment. Moreover, we were able to exclude many factors affecting cognitive function, such as orthostatic hypotension, vitamin D deficiency, depression, malnutrition, and hyperuricemia, because the comorbidities and laboratory parameters of patients were detailed in the records.[25–27] Therefore, the present study is one of the rare studies to evaluate the effects of thiazides on cognition in older patients with or without dementia.

A large randomized, double-blind, and active-controlled clinical trial emphasized that thiazides improve cerebrovascular disease, heart failure, and combined cardiovascular outcomes.[28] Therefore, we think that the previously reported improvement in cognitive function attributed to thiazides may be related to their antihypertensive effect. In this study, we demonstrated that 26-week thiazide therapy had no effect on activities of daily living, mood, or nutrition parameters in older hypertensive adults with or without dementia.

In contrast to the previous findings, it is remarkable that this study did not demonstrate that thiazides have any effect on uric acid levels in older patients with HT. They also had no effect on sodium, potassium, glycose, and lipid profiles, all of which are

related to cognitive impairment in older adults. Therefore, thiazides can be safely used as an antihypertensive medication for older adults with or without dementia.

This study had several strong aspects. First, this study did not include any non-hypertensive patients. Therefore, the groups were alike in terms of HT, which increases the risk of dementia. Second, diuretics other than thiazides were excluded. Because all thiazide diuretics have similar metabolic and physiological effects, their cognitive effects are similar too. The limitations of the study were the short follow-up period, the non-standardized hydrochlorothiazide doses, and the small number of dementia cases. Also, subjects were not divided according to the other antihypertensive drug classes they were taking.

In conclusion, 26-week thiazide therapy does not seem to affect cognitive function in older hypertensive adults regardless of dementia status. Moreover, thiazides can be safely used as a hypertensive medication because they have no effect on uric acid levels, metabolic parameters, and electrolyte balance in older adults with or without dementia.

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