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*Article*

# Effects of Thiazide Diuretics for Add-on Therapy versus Monotherapy in Non-diabetic Patients with Essential Hypertension

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**Abstract:**
Background: Previous studies have shown the effects of thiazide diuretics as first-line monotherapy on blood pressure (BP) and metabolism; however, the effects of thiazide diuretics as an add-on therapy are relatively unknown.Methods: Non-diabetic patients with treated and untreated hypertension were enrolled in this study if they did not previously take diuretics and if their office systolic BP (SBP) was  140 mmHg or diastolic BP (DBP) was  90 mmHg. Changes in their diet and modification of their life style were advised in addition to the concomitant medication for 2 weeks. Additional hydrochlorothiazide (50 mg) was given once every morning for another 2 weeks.Results: Twenty-four patients were treated for 2 weeks; 12 patients were treated with add-on therapy, and 12 patients, with monotherapy. Significant changes in the office BP (SBP, -14.1 mmHg; $p < 0.001$ and DBP, -7.0 mmHg; $p < 0.001$) were noted for both patient groups. In the add-on therapy group, asymmetric dimethylarginine (ADMA) levels significantly decreased ($p = 0.042$) and NOx (nitrate and nitrite) levels significantly increased ($p = 0.002$) after the treatment; moreover, changes in NOx/ADMA ratio ($p = 0.013$) were noted. In the monotherapy group, significant increases in the expression of adiponectin ($p = 0.025$) and decreases in Homeostatic Model Assessment Index-Insulin Resistance (HOMA-IR) ($p = 0.049$) were noted after treatment.Conclusion: Hydrochlorothiazide is appropriate as either mono- or add-on therapeutic agent. In addition to BP reduction, metabolic profiles were improved by monotherapy, whereas endothelial function was highly improved by add-on therapy.

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**Keywords:** add-on therapy, ambulatory blood pressure monitoring, hypertension, thiazide.

## 1. Introduction

The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) and other pivotal hypertension studies have established that use of thiazide-type diuretics leads to

significant reductions in stroke and cardiovascular events[1–5]. To date, thiazide diuretics remain one of the most widely recommended first-line therapeutic agents for hypertension, although its dominance is being challenged by the beneficial effects of other agents[6,7].

However, the influence of antihypertensive therapy on several metabolic pathways was recently recognized as an important factor in evaluating the global cardiovascular risk among hypertensive patients. Impairment of the metabolic status by increase in insulin resistance, deterioration of the plasma lipid profile, and less pronounced weight loss may weaken the benefits obtained from blood pressure (BP) reduction[8]. Concerns have been raised regarding diuretic use because they have unfavorable effects on insulin sensitivity, increase the risk of new-onset diabetes and have adverse clinical outcomes[9–11].

Previous studies mainly focused on the effects of thiazide diuretics as a first-line monotherapeutic agent. In contrast, the effects of thiazide diuretics as an add-on therapeutic agent are relatively unknown. Besides, the effects of thiazide diuretics on the circadian rhythm and changes in biomarkers have not yet been assessed. Our study investigated the effects of thiazide diuretics by monitoring office and ambulatory BP, and by measuring the changes in biomarkers in patients on or not on concomitant medications.

## 2. Methods and Materials

### *2.1. Study Patients*

Stable patients who were previously treated or untreated for essential hypertension were prospectively included in the study if all of the following criteria were fulfilled: (1) age between 25 and 65 years; (2) a sitting office systolic BP (SBP) of 140–180 mmHg and/or a diastolic BP (DBP) of 90–110 mmHg on 3 different occasions within 3 months before the study; (3) a fasting plasma sugar level < 126 mg/dl; (4) no clinical evidence of secondary hypertension and serial studies, including blood chemical test, renal function test, endocrine examination, abdominal sonogram, and/or renal arteriogram, were conducted to exclude the possibility of chronic renal disease, renal arterial stenosis, primary aldosteronism, Cushing syndrome, pheochromocytoma, thyroid disorder, and coarctation of the aorta.

Patients with the following characteristics were excluded: (1) current diuretic use (2) history of diabetes mellitus; (3) history of major systemic disease in the last 3 months before the study; (4) a body mass index of > 30 kg/m$^2$; (5) renal dysfunction with a plasma creatinine level of > 1.7 mg/dL; (6) liver dysfunction with liver enzyme activity of more than double the normal upper limit; (7) congestive heart failure with New York Heart association function class II-IV; (8) pregnancy.

This study was performed in accordance to the tenets of the Declaration of Helsinki. The study protocol was approved by the ethics committee of the Taipei Veterans General Hospital. Written informed consent was obtained from all participants before data collection.

### *2.2. Study Design*

Patients who fulfilled the inclusion criteria were studied by a comprehensive examination of the patient history and physical examination at the hypertension clinic of the hospital. The patients' office BPs, including SBP and DBP, were measured and their waist-hip circumference ratios and body mass indexes were determined. They were also requested to undergo a series of tests, including blood sampling. The patients were then observed with their regular cardiovascular medications over 2 weeks. Normal salt intake was maintained at the approximately 100 mmol NaCl (6g) per day as suggested by the research nurse. During their visits to the clinic, they were interviewed again and questioned about their daily lifestyle and eating habits. Both the office BP and ambulatory BP were measured. If the SBP was still between 140 and 180 mmHg and/or the DBP was between 90 and 110 mmHg, they were given hydrochlorothiazide (50 mg) once every morning in addition to their usual medications for the next 2 weeks. When they returned after 2 weeks, blood sampling was repeated followed by

examination of the patient history and physical examination. Their office BP and ambulatory BP were also rechecked to determine their response to the thiazide treatment.

## *2.3. Office BP measurement*

Office BP was measured according to a standardized protocol by a well-trained nurse with an electronic BP monitor in the morning hours after the patients were instructed to sit for 10 min in a quiet room. During each measurement, both SBP and DBP were recorded. Three consecutive BP measurements were performed on the same upper arm. Each measurement was separated by an interval of 30 s. The average value of the last 2 measurements was considered as the BP record.

## *2.4. Ambulatory BP monitoring*

In addition to conventional sphymomanometry, all patients underwent 24-h ambulatory BP monitoring (ABPM) before and after the 2 weeks of hydrochlorothiazide treatment. The monitoring device was an Oscar oscillometric AMBP (Sun Tech Medical Instruments, Oakfield Industrial Estate, Stanton Harcourt Rd. Eynsham Oxfordshire, OX29 4TS, United Kingdom). All patients were connected to the device between 0800 hours and 1000 hours. The device was programmed to record BP every 15 min between 0600 hours and 2200 hours (awake BP) and every 30 min from 2200 hours to 0600 hours (sleep BP).

## *2.5. Laboratory Measurements*

Fasting whole blood samples of the patients were obtained by venipuncture after 10-min rest in a supine position in the morning, typically between 0730 hours and 0900 hours. The participants were instructed to take all routine medications. The blood samples were centrifuged, and the serum/plasma fraction was stored between –70°C and –80°C until it was thawed for analysis. Serum levels of adiponectin (adiponectin ELISA kit; BioSource Europe S.A., Rue de l'Industrie, 8-B-1400 Nivelles, Belgium), insulin (Mercodia Insulin ELISA kit; Mercodia AB, Sylveniusgtan 8A, SE-754 50, Uppsala, Sweden), asymmetric dimethylarginine (ADMA) (ADMA ELISA kit; DLD Diagnostika GmbH, Adlerhorst 15, D-22459 Hamburg, Germany), oxidized LDL (ox-LDL) (ox-LDL ELISA kit; Mercodia AB, Sylveniusgtan 8A, SE-754 50, Uppsala, Sweden), monocyte chemoattractant protein (MCP)-1 (Quantikine Human MCP-1 Immunoassay; RD Systems, Minneapolis, MN, USA), and high-sensitivity C-reactive protein (hs-CRP) (Human CRP ELISA Kit; Immunology Consultants Laboratory, Inc., 141 N. Elliott Rd, Newberg, OR 97132, USA) were measured using enzyme-linked immunosorbent assay (ELISA). Insulin resistance was calculated using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). Serum levels of nitrate and nitrite (NOx) were determined by the chemiluminescence method described by Braman and Hendrix[12] by using an NO analyzer (Model 280; Sievers, Boulder, CO, USA).

## *2.6. Statistical Analysis*

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software (Version 21.0, SPSS Inc., Chicago, Illinois, USA). All data were expressed as mean ± standard deviation (SD) or frequency (percentage). Parametric continuous data between different response groups were compared using the unpaired Student t-test, and nonparametric data using the Mann-Whitney U test. Categorical data between different response groups were compared using the Chi-square test with Yates' correction or Fisher's exact test, where appropriate. The BP parameters and laboratory data before and after treatment were compared using a paired t-test. All tests were two-sided, and the level of significance was established as $p < 0.05$.

## 3. Results

Twenty-four consecutive patients, 19 men and 5 women with a mean age of 45 years, were enrolled due to either their unsatisfactory response to current antihypertensive treatment (add-on, n = 12) or newly diagnosed hypertension (monotherapy, n = 12). Each patient was treated with hydrochlorothiazide (50 mg) once every morning for 2 weeks in addition to their current antihypertensive medications. Table 1 shows the baseline characteristics of the 2 groups. The baseline office BP parameters, ambulatory BP parameters, biochemistry results, and biomarkers for the 2 groups were similar. In the patients that received the add-on therapy, the concomitant medications included beta-blockers (91.7%), calcium channel blockers (33.3%), alpha-blockers (8.3%), and angiotensin-converting enzyme inhibitors (8.3%).

**Table 1.** Baseline characteristics of all hypertensive patients and patients treated with thiazide diuretics as add-on therapy or monotherapy

| | **All patients (n=24)** | **Add-on therapy (n=12)** | **Monotherapy (n=12)** | **p-value** |
|---|---|---|---|---|
| Baseline Characteristics | | | | |
| Age (years) | 45.1 ± 10.7 | 45.8 ± 9.8 | 44.4 ± 12.0 | >0.999 |
| Onset of hypertension (years) | 37.9 ± 11.6 | 36.7 ± 10.3 | 39.2 ± 13.2 | 0.623 |
| Male (n, %) | 19 (79.2%) | 8 (66.7%) | 11 (91.7%) | 0.158 |
| Body weight (kgs) | 78.0 ± 12.5 | 78.4 ± 14.3 | 77.6 ± 10.9 | 0.902 |
| BMI (kg/m2) | 27.4 ± 3.3 | 28.6 ± 3.3 | 26.2 ± 2.9 | 0.073 |
| Waist-hip ratio | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.9 ± 0.1 | 0.149 |
| | | | | |
| Office BP parameters | | | | |
| Office SBP (mmHg) | 144.0 ± 15.6 | 147.3 ± 16.2 | 140.6 ± 14.9 | 0.623 |
| Office DBP (mmHg) | 95.7 ± 8.2 | 97.0 ± 9.8 | 94.4 ± 6.3 | 0.158 |
| Office HR (beat/minute) | 79.8 ± 15.4 | 76.4 ± 11.6 | 83.6 ± 18.6 | 0.902 |
| | | | | |
| AMBP parameters | | | | |
| SBP (mmHg) | 138.8 ± 12.9 | 138.2 ± 15.7 | 139.4 ± 10.0 | 0.908 |
| DBP (mmHg) | 91.0 ± 9.0 | 90.3 ± 9.8 | 91.8 ± 8.6 | 0.603 |
| Awake SBP (mmHg) | 142.8 ± 13.4 | 142.0 ± 16.3 | 143.7 ± 10.3 | 0.817 |
| Awake DBP (mmHg) | 94.2 ± 9.6 | 93.2 ± 10.7 | 95.1 ± 8.8 | 0.453 |
| Sleep SBP (mmHg) | 127.4 ± 13.6 | 128.4 ± 16.0 | 126.4 ± 11.4 | 0.908 |
| Sleep DBP (mmHg) | 82.2 ± 9.8 | 82.8 ± 10.1 | 81.5 ± 9.8 | 0.686 |
| Nocturnal change (%) | 10.7 ± 5.7 | 9.5 ± 5.8 | 11.9 ± 5.5 | 0.225 |
| | | | | |
| Laboratory data | | | | |
| BUN (mg/dL) | 12.3 ± 5.5 | 13.1 ± 5.1 | 11.5 ± 6.0 | 0.309 |
| Cr (mg/dL) | 0.9 ± 0.3 | 1.0 ± 0.3 | 0.9 ± 0.2 | 0.620 |
| Na (mmol/L) | 142.8 ± 1.8 | 142.9 ± 2.3 | 142.7 ± 1.4 | 0.322 |
| K (mmol/L) | 4.3 ± 0.3 | 4.2 ± 0.3 | 4.3 ± 0.3 | 0.977 |
| Cl (mmol/L) | 104.1 ± 2.8 | 104.8 ± 2.3 | 103.4 ± 3.1 | 0.109 |
| Fasting glucose (mg/dL) | 100.0 ± 13.8 | 103.4 ± 11.3 | 96.7 ± 15.6 | 0.112 |
| Cholesterol (mg/dL) | 212.4 ± 47.2 | 213.1 ± 45.7 | 211.7 ± 50.6 | 0.729 |
| Triglyceride (mg/dL) | 164.6 ± 83.1 | 159.0 ± 77.4 | 170.2 ± 91.6 | 0.954 |
| LDL-C (mg/dL) | 130.9 ± 33.4 | 126.5 ± 35.5 | 135.3 ± 32.1 | 0.470 |
| HDL-C (mg/dL) | 45.4 ± 13.1 | 48.5 ± 14.5 | 42.3 ± 11.3 | 0.272 |
| ALT (U/L) | 42.8 ± 34.3 | 52.1 ± 42.8 | 33.6 ± 21.0 | 0.402 |

| | | | | |
|---|---|---|---|---|
| AST (U/L) | 27.1 ± 16.1 | 26.6 ± 15.8 | 27.7 ± 17.1 | 0.908 |
| NOx (mM) | 70.8 ± 40.1 | 59.1 ± 22.9 | 82.5 ± 50.4 | 0.603 |
| ADMA (mM/ml) | 0.7 ± 0.1 | 0.7 ± 0.1 | 0.7 ± 0.1 | 0.773 |
| NOx/ADMA ratio | 102.3 ± 58.0 | 87.3 ± 43.6 | 117.3 ± 68.0 | 0.564 |
| Adiponectin (mg/ml) | 4.4 ± 2.6 | 5.1 ± 3.0 | 3.8 ± 2.0 | 0.166 |
| ox-LDL (U/L) | 63.5 ± 18.1 | 63.2 ± 17.5 | 63.8 ± 19.5 | 0.862 |
| MCP-1 (pg/mL) | 161.0 ± 62.1 | 164.0 ± 40.9 | 158.0 ± 79.7 | 0.488 |
| hs-CRP (mg/L) | 3.6 ± 5.7 | 4.9 ± 7.6 | 2.2 ± 2.8 | 0.204 |
| Insulin (mU/L) | 13.1 ± 5.7 | 14.0 ± 4.5 | 12.1 ± 6.8 | 0.447 |
| HOMA-IR | 3.3 ± 1.8 | 3.6 ± 1.4 | 3.0 ± 2.0 | 0.387 |
| | | | | |
| Concomitant medication | | | | |
| No | 12 (50.0%) | | 12 (100%) | |
| Yes | 12 (50.0%) | 12 (100%) | | |
| B-blocker | 11 (45.8%) | 11 (91.7%) | | |
| Alpha-blocker | 1 (4.2%) | 1 (8.3%) | | |
| CCB | 4 (16.7%) | 4 (33.3%) | | |
| ACEI | 1 (4.2%) | 1 (8.3%) | | |

ACEI, angiotensin converting enzyme inhibitor; ADMA, asymmetric dimethylargine; ALT, alanine aminotransferase ; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; BUN, blood urine nitrogen; CCB, calcium channel blocker; Cl, chloride; Cr, creatinine; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; K, potassium; LDL-C, low-density lipoprotein cholesterol; MCP-1, monocyte chemoattractant protein-1; Na, sodium; NOx, Nitrate and nitrite; ox-LDL, oxidized LDL; SBP, systolic blood pressure

### *3.1. Changes in office BP and ambulatory BP in patients who received add-on therapy vs monotherapy*

Table 2 and Fig. 1 show the changes in the office BP and ambulatory BP in the group that received either add-on therapy or monotherapy. After 2 weeks of thiazide treatment, a significant decrease in the office SBP (-14.1 mmHg, $p < 0.001$) and DBP (-7.0 mmHg, $p < 0.001$) was noted in both groups. In the add-on therapy group, there were significant changes in ambulatory BP, including average SBP, average DBP, awake SBP, awake DBP, sleep SBP, and sleep DBP. In the monotherapy patients group, there were only significant ambulatory BP changes in the average SBP (-4.6 mmHg, $p = 0.024$) and awake SBP (-5.0 mmHg, $p = 0.016$).

### *3.2. Changes in the biochemical parameters and biomarkers in patients who received add-on therapy or monotherapy*

Table 3 and Fig. 2 show the changes in the biochemical parameters and biomarkers in both the add-on therapy and monotherapy groups. After 2 weeks of thiazide treatment, significant decreases in potassium (from 4.3 ± 0.3 mmol/L to 4.0 ± 0.5 mmol/L, $p = 0.004$) and chloride levels (from 104.1 ± 2.8 mmol/L to 102.1 ± 3.6 mmol/L, $p = 0.003$) were noted in both groups. There were significant decreases in the levels of ADMA (-17.9%, $p < 0.001$) and ox-LDL (-6.9%, $p = 0.042$), and significant increases in the NOx/ADMA ratio (+88.7%, $p = 0.007$) and adiponectin levels (+50.6%, $p = 0.006$). There were no significant changes in insulin levels and HOMA-IR after 2 weeks of thiazide treatment in either group.

In patients who received add-on therapy, there were significant decreases of chloride (from 104.8 ± 2.3 mmol/L to 102.8 ± 3.2 mmol/L, $p = 0.018$) but not potassium levels. There were significant decreases of ADMA (-16.5%, $p = 0.002$), increases of NOx (+74.1%, $p = 0.042$) and in the NOx/ADMA ratio (+112.6%, $p = 0.013$). Adiponectin, ox-LDL, MCP-1, hs-CRP, insulin, and HOMA-IR did not show significant differences after two weeks of treatment.

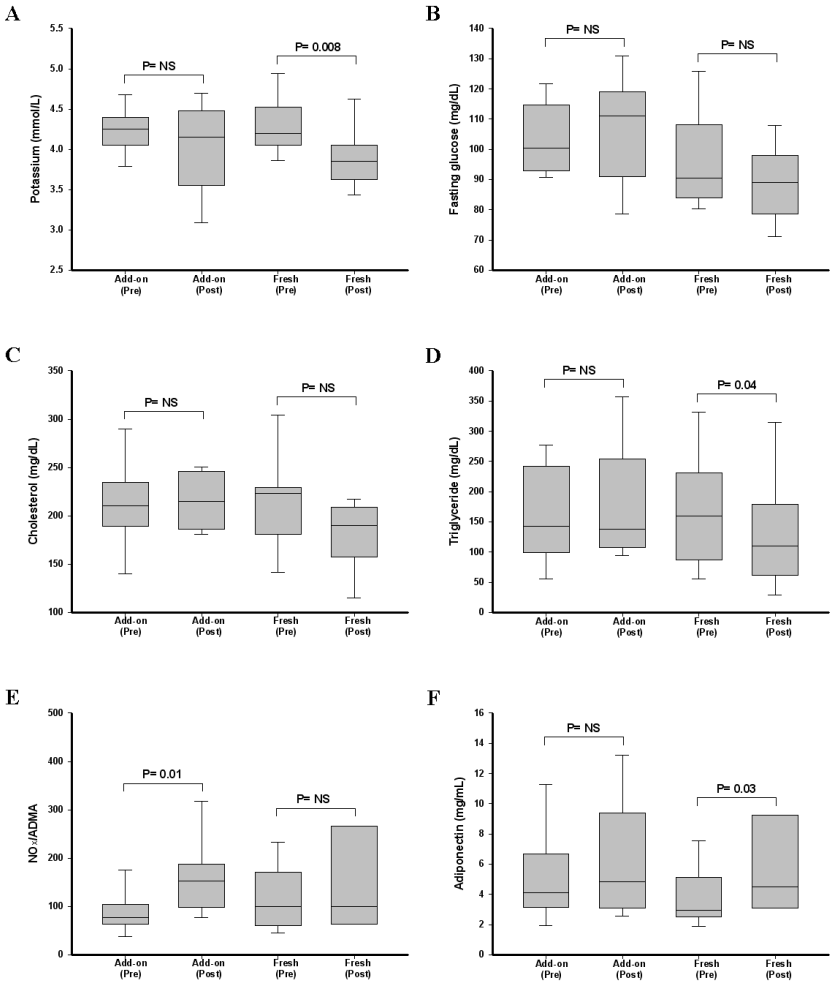


**Figure 1.** Blood pressure (BP) parameters before and after two weeks of hydrochlorothiazide treatment in patients receiving add-on therapy or monotherapy. (A) Office systolic BP (SBP), (B) office diastolic BP (DBP), (C) awake SBP, (D) awake DBP, (E) sleep SBP, (F) sleep DBP.

In patients who received monotherapy, there were significant decreases in potassium (from 4.3 ± 0.3 mmol/L to 3.9 ± 0.4 mmol/L, p = 0.008), triglycerides (170.2 ± 91.6 mg/dL to 129.8 ± 87.8 mg/dL, p = 0.044), and ADMA levels (-19.7%, p = 0.001), as well as significant increases in adiponectin levels (+77.2%, p = 0.025). Although fasting sugar and insulin levels were similar after 2 weeks of thiazide treatment, there was a significant decrease in HOMA-IR (-20.5%, p = 0.049). Otherwise, NOx, the NOx/ADMA ratio, ox-LDL, MCP-1, and hs-CRP did not show significant differences after 2 weeks of treatment.

## 4. Discussion

Ambulatory BP has been shown to be a better predictor of cardiovascular morbidity and mortality than office BP[13–16]. It is also important to recognize that ABPM is a better surrogate measure of response to antihypertensive drug therapy than office BP measurement[17–19]. A patient who appears to have responded well to a given antihypertensive drug when being examined using post-treatment office BP may be a non-responder when being examined using ABPM; conversely, a patient who does not appear to have responded according to office BP may actually be a good responder when being examined using ABPM[17–19]. Different classes of antihypertensive drugs have variable effects on ABPM results. However, the effects of thiazide diuretics on the ABPM were rarely reported. Morgan et

**Table 2.** Blood pressure parameters before and after two weeks of hydrochlorothiazide treatment as add-on therapy or monotherapy.

| | **Female (n=42)** | | | **Male (n=42)** | | | **Male (n=42)** | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before | After | p-value | Before | After | p-value | Before | After | p-value |
| Office BP parameters | | | | | | | | | |
| Office SBP (mmHg) | 143.9 ± 15.6 | 129.8 ± 12.9 | <0.001 | 147.3 ± 16.2 | 129.3 ± 12.5 | <0.001 | 140.6 ± 14.9 | 130.3 ± 13.8 | 0.011 |
| Office DBP (mmHg) | 95.7 ± 8.2 | 88.7 ± 8.9 | <0.001 | 97.0 ± 9.8 | 87.8 ± 8.8 | 0.001 | 94.4 ± 6.3 | 89.5 ± 9.4 | 0.025 |
| AMBP parameters | | | | | | | | | |
| SBP (mmHg) | 138.8 ± 12.9 | 131.9 ± 14.0 | 0.002 | 138.2 ± 15.7 | 129.0 ± 16.9 | 0.022 | 139.4 ± 10.0 | 134.8 ± 10.3 | 0.024 |
| DBP (mmHg) | 91.0 ± 9.0 | 87.4 ± 9.3 | 0.020 | 90.3 ± 9.8 | 84.3 ± 9.3 | 0.034 | 91.8 ± 8.6 | 90.4 ± 8.6 | 0.349 |
| Awake SBP (mmHg) | 142.8 ± 13.4 | 135.5 ± 14.3 | 0.001 | 142.0 ± 16.3 | 132.4 ± 17.0 | 0.015 | 143.7 ± 10.3 | 138.6 ± 11.0 | 0.016 |
| Awake DBP (mmHg) | 94.2 ± 9.6 | 90.4 ± 9.6 | 0.016 | 93.2 ± 10.7 | 87.0 ± 9.4 | 0.027 | 95.1 ± 8.8 | 93.7 ± 8.9 | 0.350 |
| Sleep SBP (mmHg) | 127.4 ± 13.6 | 120.5 ± 13.6 | 0.006 | 128.3 ± 16.0 | 118.3 ± 16.2 | 0.019 | 126.4 ± 11.4 | 122.7 ± 10.7 | 0.158 |
| Sleep DBP (mmHg) | 82.2 ± 9.8 | 77.8 ± 9.1 | 0.016 | 82.8 ± 10.1 | 75.7 ± 9.2 | 0.018 | 81.5 ± 9.8 | 80.0 ± 8.9 | 0.441 |
| Nocturnal change (%) | 10.7 ± 5.7 | 11.0 ± 5.4 | 0.757 | 9.5 ± 5.8 | 10.7 ± 5.6 | 0.510 | 11.9 ± 5.5 | 11.4 ± 5.4 | 0.677 |

BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure

al[20]. analyzed the ABPM results to 4 drug classes (hydrochlorothiazide, felodipine, atenolol, and peridonpril) in patients older than 65 years. The data concerning hydrochlorothiazide and felodipine were relatively consistent over 24 h; atenolol caused no significant decline in sleep or morning SBP; the decline in sleep BP with peridopril was higher than with other drugs. In the current study, the study population consisted of relatively young Chinese patients. Patients in both the add-on therapy and monotherapy groups had significant changes in office BP after 2 weeks of hydrochlorothiazide treatment. In the group that received the add-on therapy, there were significant ambulatory BP changes in SBP and DBP, whether awake or asleep. However, in the group that received monotherapy, there were only significant changes in the ambulatory BP responses in average SBP and awake SBP.

The influence of thiazide diuretics on changes in nocturnal BP was controversial. In the study by Morgan et al.[20], hydrochlorothiazide did not affect the diurnal changes in SBP. In another study by Uzu and Kimura[21], hydrochlorothiazide did not affect the reduction of nocturnal BP in dippers, but it enhanced the reduction of nocturnal BP in nondippers, shifting their circadian BP rhythm toward the dipper pattern. In the current study, we did not detect a nocturnal BP change before and after 2 weeks of treatment in either of the groups.

Asymmetrical dimethylarginine (ADMA) has been proposed as a novel risk marker of cardiovascular disease[22,23] due to its possible role in endothelial dysfunction[24–26], a process thought to be pivotal in the development of arteriosclerosis[27]. ADMA is an endogenous competitive inhibitor of nitric oxide synthase[24,28]. Therefore, raised levels of ADMA lead to reduced nitric acid production and impaired endothelial function. There was limited data about the effect of thiazide diuretics on endothelial function. One animal study[29] showed that thiazide diuretics neither reduce oxidative stress, improve endothelial function, nor prevent the expression of proatherogenic molecules. Another human study[30] showed that flow-mediated dilation of the brachial artery showed significant improvement after treatment of essential hypertension in patients. However, improvement in the flow-mediated dilation of the brachial artery was observed only in patients who were treated with nifidipine but not in those treated with hydrochlorothizide. In the current study, we found only decreases in the ADMA but not increases in the NOx levels in new cases after treatment. However,

**Table 3.** Laboratory data before and after two weeks of hydrochlorothiazide treatment as add-on therapy or monotherapy.

| | **Female (n=42)** | | | **Male (n=42)** | | | **Male (n=42)** | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before | After | p-value | Before | After | p-value | Before | After | p-value |
| Laboratory data | | | | | | | | | |
| BUN (mg/dL) | 12.3 ± 5.5 | 13.9 ± 5.3 | 0.335 | 13.1 ± 5.1 | 16.5 ± 4.8 | 0.178 | 11.5 ± 6.0 | 10.7 ± 4.2 | 0.633 |
| Cr (mg/dL) | 0.9 ± 0.3 | 0.9 ± 0.2 | 0.320 | 1.0 ± 0.3 | 1.0 ± 0.3 | >0.999 | 0.9 ± 0.2 | 0.9 ± 0.2 | 0.193 |
| Na (mmol/L) | 142.8 ± 1.8 | 143.0 ± 1.8 | 0.485 | 142.9 ± 2.3 | 143.4 ± 2.0 | 0.236 | 142.7 ± 1.4 | 142.7 ± 1.7 | >0.999 |
| K (mmol/L) | 4.3 ± 0.3 | 4.0 ± 0.5 | 0.004 | 4.2 ± 0.3 | 4.0 ± 0.6 | 0.182 | 4.3 ± 0.3 | 3.9 ± 0.4 | 0.008 |
| Cl (mmol/L) | 104.1 ± 2.8 | 102.1 ± 3.6 | 0.003 | 104.8 ± 2.3 | 102.8 ± 3.2 | 0.018 | 103.4 ± 3.1 | 101.3 ± 3.9 | 0.069 |
| Fasting glucose (mg/dL) | 100.0 ± 13.8 | 97.9 ± 17.3 | 0.339 | 103.4 ± 11.3 | 105.4 ± 17.9 | 0.872 | 96.7 ± 15.6 | 88.7 ± 11.6 | 0.065 |
| Cholesterol (mg/dL) | 212.4 ± 47.2 | 202.2 ± 35.1 | 0.159 | 213.1 ± 45.7 | 218.4 ± 27.8 | 0.881 | 211.7 ± 50.6 | 182.3 ± 34.1 | 0.055 |
| Triglyceride (mg/dL) | 164.6 ± 83.1 | 162.2 ± 95.3 | 0.703 | 159.0 ± 77.4 | 188.6 ± 96.9 | 0.437 | 170.2 ± 91.6 | 129.8 ± 87.8 | 0.044 |
| LDL-C (mg/dL) | 130.9 ± 33.4 | 126.0 ± 26.2 | 0.455 | 126.5 ± 35.5 | 131.4 ± 24.3 | 0.926 | 135.3 ± 32.1 | 119.3 ± 28.4 | 0.236 |
| HDL-C (mg/dL) | 45.4 ± 13.1 | 43.8 ± 12.6 | 0.109 | 48.5 ± 14.5 | 49.3 ± 12.9 | 0.506 | 42.3 ± 11.3 | 37.1 ± 8.8 | 0.107 |
| ALT (U/L) | 42.8 ± 34.3 | 44.7 ± 31.5 | 0.408 | 52.1 ± 42.8 | 55.2 ± 38.6 | >0.999 | 33.6 ± 21.0 | 31.9 ± 12.7 | 0.223 |
| AST (U/L) | 27.1 ± 16.1 | 25.9 ± 9.9 | 0.248 | 26.6 ± 15.8 | 28.2 ± 10.8 | 0.977 | 27.7 ± 17.1 | 23.0 ± 8.5 | 0.177 |
| NOx (mM) | 70.8 ± 40.1 | 89.7 ± 53.7 | 0.084 | 59.1 ± 22.9 | 93.3 ± 48.4 | 0.042 | 82.5 ± 50.4 | 84.0 ± 65.0 | 0.998 |
| ADMA (mM/ml) | 0.7 ± 0.1 | 0.6 ± 0.1 | <0.001 | 0.7 ± 0.1 | 0.6 ± 0.1 | 0.002 | 0.7 ± 0.1 | 0.6 ± 0.1 | 0.001 |
| NOx/ADMA ratio | 98.0 ± 58.9 | 157.8 ± 93.7 | 0.007 | 88.4 ± 45.6 | 160.2 ± 75.7 | 0.013 | 113.0 ± 77.0 | 154.1 ± 123.6 | 0.271 |
| Adiponectin (mg/ml) | 4.4 ± 2.6 | 6.0 ± 3.5 | 0.006 | 5.0 ± 3.0 | 6.3 ± 3.8 | 0.125 | 3.8 ± 2.0 | 5.5 ± 3.2 | 0.025 |
| ox-LDL (U/L) | 63.5 ± 18.1 | 56.3 ± 12.5 | 0.042 | 63.2 ± 17.5 | 57.0 ± 9.2 | 0.326 | 63.8 ± 19.5 | 55.2 ± 16.7 | 0.069 |
| MCP-1 (pg/mL) | 161.0 ± 62.1 | 161.3 ± 72.7 | 0.959 | 164.0 ± 40.9 | 146.8 ± 42.8 | 0.208 | 158.0 ± 79.7 | 181.3 ± 100.9 | 0.165 |
| hs-CRP (mg/L) | 3.5 ± 5.7 | 2.7 ± 2.8 | 0.354 | 4.9 ± 7.6 | 2.7 ± 2.2 | 0.198 | 2.2 ± 2.8 | 2.6 ± 3.7 | 0.647 |
| Insulin (mU/L) | 13.1 ± 5.7 | 13.5 ± 8.2 | 0.455 | 14.0 ± 4.5 | 13.2 ± 6.7 | 0.586 | 12.1 ± 6.8 | 13.8 ± 10.4 | 0.643 |
| HOMA-IR | 3.3 ± 1.8 | 3.2 ± 2.4 | 0.185 | 3.6 ± 1.4 | 3.5 ± 2.1 | 0.765 | 3.0 ± 2.0 | 2.8 ± 2.7 | 0.049 |

ADMA, asymmetric dimethylargine; ALT, alanine aminotransferase ; AST, aspartate aminotransferase; BUN, blood urine nitrogen; Cl, chloride; Cr, creatinine; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; K, potassium; LDL-C, low-density lipoprotein cholesterol; MCP-1, monocyte chemoattractant protein-1; Na, sodium; NOx, Nitrate and nitrite; ox-LDL, oxidized LDL

increase in NOx, decrease in ADMA, and increase in NOx/ADMA ratios were observed after treatment in the add-on therapy group. At the same time, there was a more significant ambulatory BP change in the add-on therapy group. We also found a correlation between the SBP change and the increase of NOx ($r = -0.486$, $p = 0.04$). This may reflect improved endothelial function due to a more significant BP

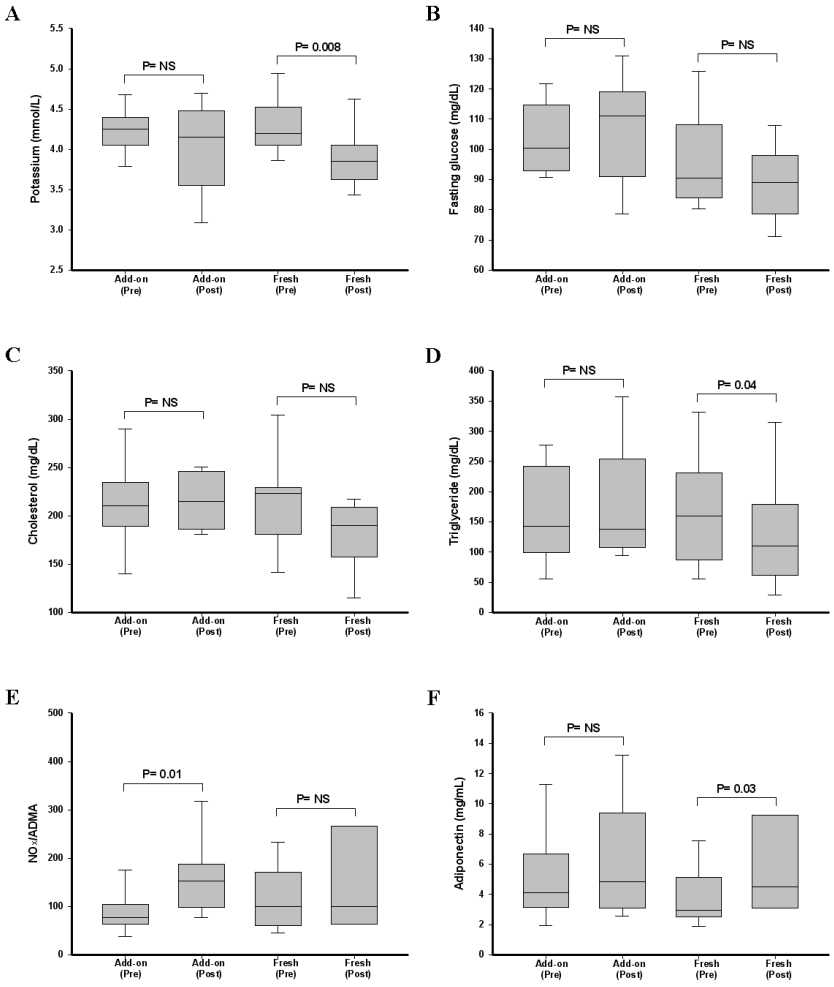


**Figure 2.** Metabolic profiles and biomarkers before and after two weeks of hydrochlorothiazide treatment in patients receiving add-on therapy or monotherapy. (A) Potassium, (B) fasting sugar, (C) cholesterol, (D) triglyceride, (E) NOx/ADMA ratio, (F) adiponectin.

change after two weeks of hydrochlorothiazide treatment. Therefore, only add-on therapy patients, but not monotherapy patients, had improved endothelial function.

Adiponectin is an adipokine mainly derived from adipose tissue[31]. It plays an important role in the development of metabolic syndromes and coronary arterial disease[32–34]. In animals, injections of adiponectin have been shown to improve insulin sensitivity and reduce plasma glucose and fatty-acid levels[34]. According to previous data[35–37], several antihypertensive regimens increased plasma adiponectin levels. However, the effect of thiazide diuretics on plasma adiponectin were rarely discussed. Only one small study[38] reported decreases of adiponectin after indapamide treatment. In the current study, we focused on another kind of thiazide diuretic, namely hydrochlorothiazide. For monotherapy patients, there were significant increases of adiponectin levels after treatment. The improvement of both fasting glucose and the lipids profile may reflect improvement of metabolic profiles after two weeks of treatment with hydrochlorothiazide in the monotherapy group.

There were some limitations in the present study. First, only patients without diabetes mellitus were enrolled in this study. Since thiazide has been suggested as one of the drugs of choice for the treatment of hypertension in diabetic patients[7], further evaluation of the use of thiazide in diabetic patients may be required. Second, our sample size was small. However, we evaluated BP change with both office BP measurement and ABPM, which made the data more reliable. There were also significant changes in serum biomarkers after treatment.

# 5. Conclusion

In new hypertensive patients, both awake SBP and serum potassium concentrations were reduced and metabolic profiles were improved by hydrochlorothiazide used as first-line monotherapeutic agent. On the other hand, hydrochlorothiazide used as an add-on therapeutic agent significantly reduced both office BP and ambulatory BP, and improved endothelial function, suggesting that hydrochlorothiazide could be appropriate as an add-on therapeutic agent for better BP control in patients who are non-diabetic and have essential hypertension. Further large-scaled studies are necessary to confirm the long-term clinical effects of thiazide diuretics.

**Conflicts of Interest:**
The authors declare no conflict of interest.

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