Association of Thiazide-Type Diuretics With Glycemic Changes in Hypertensive Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials

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Patients receiving thiazide diuretics have a higher risk of impaired glucose tolerance or even incident diabetes, but the change of blood glucose level varies across different trials. The aim of this study was to investigate the glycemic changes in hypertensive patients with thiazide-type diuretics. Twenty-six randomized trials involving 16,162 participants were included. Thiazide-type diuretics were found to increase fasting plasma glucose (FPG) compared with nonthiazide agents or placebo or nontreatment (mean difference [MD], 0.27 mmol/L [4.86 mg/dL]; 95% confidence interval [CI], 0.15–0.39). Patients receiving lower doses of thiazides (hydrochlorothiazide or chlorthalidone ≤25 mg daily) had less change in FPG (MD, 0.15 mmol/L [2.7 mg/dL]; 95% CI, 0.03–0.27) than those receiving higher doses (MD, 0.60 mmol/L [10.8 mg/dL]; 95% CI, 0.39–0.82), revealed by the subgroup analysis of thiazides vs calcium channel blockers. Thiazide-type diuretics are associated with significant but small adverse glycemic effects in hypertensive patients. Treatment with a lower dose might reduce or avoid glycemic changes. *J Clin Hypertens (Greenwich).* 2016;18:342–351. © 2015 Wiley Periodicals, Inc.

Thiazide-type diuretics, which include thiazide diuretics such as hydrochlorothiazide (HCTZ) and thiazide-like diuretics such as chlorthalidone (CTD) and indapamide, are a classic class of antihypertensive medications. Studies over decades have demonstrated a reduction in morbidity and mortality of cardiovascular events in patients who receive thiazide-type diuretics.[1,2] This class has been widely used for more than 40 years and is still recommended as one of the first-line treatments in the latest guidelines for the management of hypertension.[3]

However, despite the strong evidence of benefits, there are some adverse effects of thiazide diuretics that have led to debates over their wide use. Randomized trials and observational studies have demonstrated multiple metabolic abnormalities such as dysglycemia, new-onset diabetes, hypokalemia, hyponatremia, hyperuricemia, and hyperlipidemia.[4–7] Among these adverse metabolic effects, glycemic dysregulation is the greatest concern. Although there has been agreement that patients receiving thiazide diuretics have a higher risk of impaired glucose tolerance or even incident diabetes, the change of blood glucose level in hypertensive patients varies across different trials. We propose that it is essential to quantify the glycemic effect of thiazide diuretics by reviewing trials that used diverse doses and types of thiazides. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials to assess the effects of thiazide-type diuretics on glycemic metabolism in hypertensive patients.

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METHODS

Search Strategy

We searched PubMed and Web of Science for relevant articles until November 2014, using the following search items: ("thiazide" OR "HCTZ") AND ("diabetes" OR "glucose"). Species were limited to humans. We also manually checked the reference lists of eligible studies and relevant reviews for further information. The design and conduction of this review followed the recommendations of the Cochrane Collaboration[8] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[9]

Study Selection and Data Extraction

Studies were considered eligible if they met the following inclusion criteria: (1) randomized controlled clinical trial in hypertensive patients; (2) comparing thiazide or thiazide-like diuretics with other hypertensive agents or placebo or nontreatment; (3) assessing one or more glycemic parameters, including fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and glycated hemoglobin (HbA_{1c}); and (4) reporting data both before and after intervention or values changed with intervention, expressed as mean±standard deviation (SD). Trials in normotensive patients were excluded since they might have different metabolic characteristics from hypertensive patients. In studies with multiple doses or duration of treatment, only data on the largest dose and longest duration were extracted. Trials with a crossover design were also excluded to avoid overestimation of their effects. Trials using thiazides in combination with other types of antihypertensive agents were excluded to prevent possible bias caused by the interaction or synergistic effects. Information including type and dose of thi-

azide-type diuretics and treatment in the control group, duration of intervention, sample size, percentage of diabetes, data of glycemic and other metabolic parameters, and baseline characteristics of participants were extracted independently by two reviewers. Consensus was reached through discussion and repetitive review of the details in cases of discrepancies.

Assessment of Risk of Bias

The risk of bias of included studies was assessed according to the recommendations of the Cochrane Handbook of Systematic Reviews of Interventions[8] in the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias.

Statistical Analysis

For outcome comparison between two groups, the mean differences (MDs) with SDs measuring the changes from baseline, were pooled across studies using the random-effects model. In case of a missing SD for the changes, we followed the Cochrane Handbook[8] and the recommendations of Musini and colleagues.[10] Heterogeneity was examined by Cochran Q test (considered significant when $P<.10$) and quantified by I^2 statistic (considered substantial when $I^2 \geq 50\%$). Sensitivity analyses were performed by successively excluding studies. To explore the reasons for heterogeneity, we performed subgroup analyses based on age of patients, type and dose of medication, and duration of treatment. Publication bias was assessed by Begg's funnel plot and Egger's regression test. A P value $<.05$ was considered statistically significant. Statistical analyses were conducted by Review Manager (RevMan) version 5.2 (The Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 (STATA, College Station, TX).

RESULTS

Characteristics of Included Studies

The initial literature search retrieved 1369 relevant articles. Of these, 26 studies met the inclusion criteria and were selected in the meta-analysis, which included a total of 16,162 participants (Figure S1). Seven trials contained more than one study group except for thiazide and one trial contained two study groups receiving different kinds of thiazides. We included these outcomes and regarded them as different comparisons in the pooled analysis. The basic characteristics of included studies are shown in the Table. The number of participants ranged from 19 to 7703 across the trials,[11–36] of which only three enrolled obese participants.[12,14,31] The longest duration of treatment was 6 years,[35] but most trials lasted less than half a year. Intervention with HCTZ was the most commonly reported. CTD, bendrofluazide, and indapamide were also included. The dose of treatment varied across different trials (HCTZ 12.5–100 mg/d, CTD 6.25–50 mg/d, bendrofluazide 2.5–10 mg/d, and indapamide 1.25–2.5 mg/d).

The Risk of Bias and Publication Bias

We determined the risk of bias in seven domains using the criteria of the Cochrane handbook.[8] Most studies did not report the process of randomization or allocation concealment and we therefore judged them as having an unclear risk of bias (Figure S2 and Figure S3). Funnel plots for FPG suggested asymmetry visually (Figures S4–S6) while Egger's tests did not show sufficient evidence of publication bias (thiazide vs nonthiazide: $P=.421$; thiazide vs placebo or nontreatment: $P=.643$; thiazide vs angiotensin-converting enzyme inhibitor or angiotensin receptor blocker: $P=.395$).

Outcomes

Fasting Plasma Glucose. All trials reported the changes of FPG. Thiazide or thiazide-like diuretics were found to increase FPG level compared with nonthiazide agents or placebo or nontreatment (MD, 0.27 mmol/L [4.86 mg/dL]; 95% confidence interval [CI], 0.15–0.39 [$P<.0001$]) (Figure 1). Heterogeneity was substantial in the pooled analysis ($I^2=97\%$, $P<.00001$). Since different kinds of hypertensive agents with different pharmacology were included, we performed subgroup analysis based on types of medication in control groups. In addition, after classifying the studies into five categories including placebo or nontreatment, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACE) inhibitor or angiotensin receptor blocker (ARB), β-blocker, and α-blocker, we performed further analysis in these groups, respectively. Thiazide-type diuretics did not significantly increase FPG level when compared with placebo or nontreatment or β-blockers (thiazide vs placebo or nontreatment: MD, 0.21 mmol/L [3.78 mg/dL]; 95% CI, 0.00–0.41 [$P=.05$] and thiazide vs β-blocker: MD, 0.23 mmol/L [4.14 mg/dL]; 95% CI, −0.14 to 0.59 [$P=.22$]). However, subgroup analysis did not show a significant difference between different kinds of control groups (Figure S7). Subgroup analysis of the CCB group based on dose of medication significantly reduced heterogeneity and indicated that patients receiving lower doses of thiazides (HCTZ or CTD ≤25 mg daily, n=5148) had less change in FPG (MD, 0.15 mmol/L [2.7 mg/dL]; 95% CI, 0.03–0.27) compared with patients receiving higher doses (n=130) (MD, 0.60 mmol/L [10.8 mg/dL]; 95% CI, 0.39–0.82) ($P=.0003$) (Figure 2). Patients with a longer duration of treatment (≥6 months, n=221) also had less glycemic change (MD, −0.01 mmol/L [−0.18 mg/dL]; 95% CI, −0.47 to 0.45) than patients with short treatment duration (n=114) (MD, 0.50 mmol/L [9.0 mg/dL]; 95% CI, 0.36–0.64), revealed by the subgroup analysis of thiazide vs β-blocker ($P=.04$) (Figure 3). Sensitivity analyses did not significantly reduce the heterogeneity.

TABLE. Baseline Characteristics of Included Trials

Study	Group	Patients	Number	Duration	Age, y[a]	Women, %	Baseline SBP/DBP, mm Hg[a]	Diabetic Patients, %	BMI, kg/m2[b]	Changed FPG, mmol/L[b]	Changed PPG, mmol/L[b]	Changed $HbA1_c$, %[b]
Thiazide vs placebo or empty control												
Chrysant 1994 A[11]	HCTZ 25 mg/d	Patients with hypertension	84	12 weeks	53	71.8	155/104	0	–	0.5±2.3	–	–
	Placebo		81		53		155/103		–	0.1±2.2	–	–
Carlsen 1990[18]	Bendrofluazide 10 mg/d	Patients with mild to moderate hypertension	51	10 weeks	59	45.1	166.9±2.7/103.7±0.8	–	–	0.27±0.15	–	–
	Placebo		52		57	55.8	161.9±1.9/101.8±0.5	–	–	−0.08±0.09	–	–
Fiddes 1997[22]	Indapamide 1.25 mg/d	Patients 65 y or older with mild to moderate hypertension	103	8 weeks	69.4	48	–/98.8	–	–	0.194±1.51	–	–
	Placebo		100		69.7	42	–/99.8	–	–	−0.0556±1.15	–	–
Fuenmayor 1997 A[14]	HCTZ 100 mg/d	Obese patients with mild to moderate hypertension	14	1 week	50±2	–	150±2/103±2	–	29±1	0.3±0.2	–	–
	Placebo		14		50±2	–	148±3/103±2	–	30±1	0.1±0.2	–	–
Hall 1994[23]	Indapamide 1.25 mg/d	Patients with mild to moderate hypertension	82	8 weeks	–	–	–/100.1	–	–	0.2±1.5	–	–
	Placebo		90		–	–	–/99.6	–	–	0.2±1.2	–	–
Jounela 1994[13]	HCTZ 25 mg/d	Patients with mild to moderate hypertension	23	6 weeks	46.4	60.9	147.0/97.6	–	–	−0.14±0.82	–	–
	Placebo		22		48.5	59.1	152.5/99.8	–	–	−0.03±0.50	–	–
Mersey 1993 A[21]	HCTZ 12.5 mg/d	Patients with mild to moderate hypertension	69	8 weeks	48.2	36.9	143.5/97.3	–	–	−0.12±0.26	–	–
	Placebo		70		50.7	40.9	142.8/97.6	–	–	−0.02±0.27	–	–
Oslo 1984[15]	HCTZ 50 mg/d	Male patients with mild hypertension	125	5 y	40–49	0	–	–	–	0.18±0.59	–	–
	Nontreatment		277		57	55.8	–	–	–	0.13±0.68	–	–
Pool 1993 A[19]	HCTZ 12.5 mg/d	Patients with hypertension	67	6 weeks	52.7±10.6	27	153.4±2.2/100.2±0.5	–	–	0.35±0.80	–	–
	Placebo		57		53.5±10.5	40	152.9±1.9/99.9±0.5	–	–	0.028±0.66	–	–
Reisin 1997 A[12]	HCTZ 12.5–50 mg/d	Obese hypertensive patients	76	12 weeks	51±10	46.1	148±14/98±5	0	32.5±3.8	0.31±0.99	–	–
	Placebo		79		49±10	40.5	146±13/96±4	–	32.2±3.8	−0.16±0.90	–	–
SHEP 1998[16]	CTD 12.5–25 mg/d	Patients older than 60 y with isolated systolic hypertension	860	3 y	71.6±6.7	56.3	170.5±9.5/76.7±9.6	10	27.5±4.9	0.51±1.69	–	–
	Placebo		803		71.5±6.7	57.4	170.1±9.2/76.5±9.8	10.2	27.5±5.1	0.31±1.42	–	–
Siegel 1994 A[20]	HCTZ 50 mg/d	Hypertensive men aged 35–79 y	147	2 months	60.8±7.7	0	–	–	27.8±3.9	0.1±0.13	–	–
	Placebo		27		60.8±8.5	40.9	–	–	28.0±3.6	0.3±0.14	–	–
Siegel 1994 B[20]	CTD 50 mg/d	Hypertensive men 35–79 y	28	2 months	61.4±7.8	0	–	–	28.0±4.7	0.7±0.28	–	–
	Placebo		27		60.8±8.5	42	–	–	28.0±3.6	0.3±0.14	–	–
Vardan 1987[17]	CTD 25 mg/d	Patients with mild hypertension	60	12 weeks	21–69	34.2	143.4±1.6/93.7±0.7	0	–	0.61±0.15	–	–
	placebo		59				145.7±1.8/93.6±0.7	–	–	−0.1±0.13	–	–
Thiazide vs CCB												
ALLHAT 2006 A[26]	CTD 12.5–25 mg/d	Patients with hypertension	4972	4 y	66.9±7.7	47.0	146±16/84±10	36.2	29.7±6.2	0.16±3.09	–	–
	Amlodipine 2.5–10 mg/d		2954		66.9±7.7	47.3	146±16/84±10	36.7	29.8±6.3	0.03±3.09	–	–
Calvo 2000[24]	HCTZ 50–100 mg/d	Patients older than 60 y with hypertension	100	8 weeks	67.6±5.9	64	177.8±1.2/87.1±0.7	–	27.4±3.9	0.28±1.22	–	–
	Amlodipine 5–10 mg/d		97		69.0±6.4	69	178.4±1.3/87.1±0.7	–	27.4±4.3	−0.60±1.22	–	–
Fuenmayor 1997 B[14]	HCTZ 100 mg/d	Obese patients with mild to moderate hypertension	14	1 week	50±2	–	150±2/103±2	–	29±1	0.3±0.2	–	–
	Verapamil 160 mg/d		14		49±2	–	149±2/100±1	–	30±1	−0.3±0.2	–	–
Jansen 1989[28]	HCTZ 50 mg/d	Hypertensive patients older than 70 y	16	12 weeks	74.9±4.0	75	–	–	–	0.3±0.2	–	–
			15		72.3±2.4	73	–	–	–	−0.1±0.5	–	–

TABLE. Baseline Characteristics of Included Trials (Continued)

Study	Group	Patients	Number	Duration	Age, y[a]	Women, %	Baseline SBP/DBP, mm Hg[a]	Diabetic Patients, %	BMI, kg/m2[b]	Changed FPG, mmol/L[b]	Changed PPG, mmol/L[b]	Changed $HbA1_c$, %[b]
	Nitrendipine 20 mg/d											
Pareek 2008 A[25]	CTD 6.25 mg/d	Patients with stage I hypertension	100	4 weeks	46.44±11.79	40.0	149.43±6.99/93.81±4.33	17	–	0.24±2.14	−0.11±3.21	–
	Amlodipine 2.5 mg/d		102		48.98±10.83	40.2	149.66±7.20/93.50±4.48	16.7	–	−0.26±1.52	−0.71±2.82	–
Piecha 2007 A[27]	Indapamide 2.5 mg/d	Patients with mild to moderate hypertension	9	6 months	44.8±12.2	67	154±5/137±10	0	30.8±6.0	0.4±0.9	–	–
	Amlodipine 5–10 mg/d		10		49.6±11.4	20	161±10/145±13	–	30.0±3.8	0.6±0.5	–	–
Pool 1993 B[19]	HCTZ 12.5 mg/d	Patients with hypertension	67	6 weeks	52.7±10.6	27	153.4±2.2/100.2±0.5	–	–	0.35±0.80	–	–
	Diltiazem 120 mg/d		63		55.4±9.2	36	152.7±1.6/99.4±0.3	–	–	0.18±0.69	–	–
Thiazide vs ACE inhibitor/ARB												
ALLHAT 2006 B[26]	CTD 12.5–25 mg/d	Patients with hypertension	4972	4 y	66.9±7.7	47.0	146±16/84±10	36.2	29.7±6.2	0.16±3.09	–	–
	Lisinopril 10–40 mg/d		2731		66.9±7.7	46.2	146±16/84±10	35.5	29.8±6.2	−0.08±2.85	–	–
Chrysant 1994 B[11]	HCTZ 25 mg/d	Patients with hypertension	84	12 weeks	53	71.8	155/104	0	–	0.5±2.3	–	–
	Lisinopril 10 mg/d		85		54		154/104		–	0.1±0.8	–	–
Fuenmayor 1997 C[14]	HCTZ 100 mg/d	Obese patients with mild to moderate hypertension	14	1 week	50±2	–	150±2/103±2	–	29±1	0.3±0.2	–	–
	Captopril 100 mg/d		13		49±2	–	144±4/100±1	–	30±1	0.4±0.1	–	–
Grassi 2003[31]	HCTZ 25 mg/d	Obese hypertensive patients	59	12 weeks	50.2±11.2	62.7	146.2±12.6	–	35.1±3.2	0.15±0.82	–	0.13±0.6
	Candesartan cilexetil 8 mg/d		68		51.2±9.5	58.8	98.8±3.7	–	33.7±2.6	0.13±0.92	–	0.07±0.5
Mersey 1993 B[21]	HCTZ 12.5 mg/d	Patients with mild to moderate hypertension	69	8 weeks	48.2	36.9	143.5/97.3	–	–	−0.120±0.256	–	–
	Captopril 25 mg/d		68		52.0	49.2	146.6/96.7	–	–	0.0367±0.264	–	–
Piecha 2007 B[27]	Indapamide 2.5 mg/d	Patients with mild to moderate hypertension	9	6 months	44.8±12.2	67	154±5/137±10	0	30.8±6.0	0.4±0.9	–	–
	Enalapril 10–20 mg/d		10		50.0±9.9	60	163±10/98±9		27.9±2.1	0.7±0.6	–	–
Pollare 1989[29]	HCTZ 40±12 mg/d	Patients with hypertension	50	18 weeks	58±10	34.6	166±16/101±4	2.0	27±4	0.6±1.4	–	0.7±1.5
	Captopril 81±24 mg/d		48		58±12	29.2	165±14/101±4		28±4	−0.2±1.1	–	0.1±0.7
Reisin 1997 B[12]	HCTZ 12.5–50 mg/d	Obese hypertensive patients	76	12 weeks	51±10	46.1	148±14/98±5	0	32.5±3.8	0.31±0.99	–	–
	Lisinopril 10–40 mg/d		77		51±11	48.1	147±25/98±6	–	32.3±3.7	−0.21±0.71	–	–
Stimpel 1998[33]	HCTZ 25 mg/d	Postmenopausal women with mild to moderate hypertension	41	12 weeks	62±5	100	158.8±12.7/100.5±3.9	–	–	0.61±0.23	–	–
	Moexipril 15 mg/d		43		61±8	100	159.0±13.7/100.5±4.7	–	–	−0.13±0.11-	–	–
Weinberger 1985[30]	HCTZ 37.5 mg/d	Patients with hypertension	67	6 weeks	–	–	146.1±2.6/97.7±0.9	–	–	0.55±0.17	–	–
	Captopril 75 mg/d		69		–	–	149.5±2.7/99.6±0.9	–	–	−0.06±0.17	–	–
Zappe 2008[32]	HCTZ 12.5–25 mg/d	Hypertensive patients with cardiometabolic syndrome	158	16 weeks	48.8±11	58	141.7±9/91.4±5	–	37.4±7	0.22±0.9	–	0.2±0.6
	Valsartan 320 mg/d		164		50.0±11	62	143.5±9/91.5±5	–	36.2±7	0.17±0.9	–	0.1±0.5
Thiazide vs β-blocker												
Berglund 1981[35]	Bendrofluazide 2.5–5 mg/d	Middle-aged men with mild to moderate hypertension	38	6 y	47–54	0	–	–	–	0.0±1.0	–	–
	Propanolol 160 mg–320 mg/d		37		48.49±12.98	43.9	–	–	–	0.4±1.6	–	–
Fuenmayor 1997 D[14]	HCTZ 100 mg/d	Obese patients with mild to moderate hypertension	14	1 week	50±2	–	150±2/103±2		29±1	0.3±0.2	–	–
	Atenolol 100 mg/d		14		50±2	–	140±2/99±1		30±1	−0.2±0.2	–	–
Pareek 2008 B[25]	CTD 6.25 mg/d	Patients with stage I hypertension	100	4 weeks	46.44±11.79	40.0	149.43±6.99/93.81±4.33	17.0	–	0.24±2.14	−0.11±3.21	–
	Atenolol 25 mg/d		98		48.49±12.98	43.9	149.47±7.69/93.23±3.62	14.3	–	−0.26±1.05	−0.48±1.80	–
	Indapamide 2.5 mg/d		9	6 months	44.8±12.2	67	154±5/137±10	0	30.8±6.0	0.4±0.9	–	–

TABLE. Baseline Characteristics of Included Trials (Continued)

Study	Group	Patients	Number	Duration	Age, y[a]	Women, %	Baseline SBP/DBP, mm Hg[a]	Diabetic Patients, %	BMI, kg/m^2[b]	Changed FPG, mmol/L[b]	Changed PPG, mmol/L[b]	Changed HbA_{1c}, %[b]
Piecha 2007 C[27]	Metoprolol 50–200 mg/d	Patients with mild to moderate hypertension	11		50.3±10.5	54	157±9/140±13	0	28.1±3.0	−0.2±0.6	–	–
Veterans	HCTZ 50–200 mg/d	Hypertensive men	174	1 y	49.8±9.9	0	146.5±15.8/101.3±4.5	–	–	0.26±1.61	1.44±4.12	–
1985[34]	Propranolol 80–640 mg/d		119		49.6±9.8		146.0±14.4/101.6±4.6	–	–	0.36±1.02	1.01±2.27	–
Thiazide vs α-blocker												
Alderman 1986[36]	HCTZ 25–50 mg/d	Patients with hypertension	9	1 y	53.4±8.8	23.3	150.8±14.2/107.6±8.5	–	–	0.49±0.82	–	–
	Prazosin 1–2 mg/d		10		51.4±9.8	15.6	152.2±13.8/105.8±5.2	–	–	−0.17±0.64	–	–
Fuenmayor 1997 E[14]	HCTZ 100 mg/d	Obese patients with mild to moderate hypertension	14	1 week	50±2	–	150±2/103±2	–	29±1	0.3±0.2	–	–
	Prazosin 6 mg/d		13		49±2	–	142±2/100±1	–	30±0.4	0.0±0.1	–	–

Abbreviations: ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CTD, chlorthalidone; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HCTZ, hydrochlorothiazide; PPG, postprandial plasma glucose; SBP, systolic blood pressure; SHEP, Systolic Hypertension in the Elderly Program; – data unavailable. [a]Mean or mean±standard deviation or range. [b]Mean±standard deviation.

Postprandial Plasma Glucose. Only three studies reported PPG changes, thus the sample size was relatively small (thiazide: n=245, nonthiazide: n=234). Change in PPG was not significantly different between patients receiving thiazides and patients receiving other treatments (MD, 0.46 mmol/L [8.28 mg/dL]; 95% CI, −0.05 to 0.97 [*P*=.07]) (Figure 4). There was no evidence of heterogeneity (I^2=0%, *P*=.92).

Glycated Hemoglobin. The comparison only included three studies, involving 547 hypertensive patients (thiazide: n=267, nonthiazide: n=280). No significant increase in HbA_{1c} level was observed in patients receiving thiazides compared with other patients (MD, 0.15%; 95% CI, −0.04 to 0.34 [*P*=.12]) (Figure 5). Heterogeneity was substantial among the studies (I^2=57%, *P*=.10). Exclusion of the study by Pollare and colleagues[30] reduced I^2 to 0, which might be explained by the largest dose of HCTZ in this study.

Moreover, we found decreasing trends in metabolic parameters including high-density lipoprotein cholesterol, potassium, and sodium. On the other hand, uric acid and major lipid parameters except high-density lipoprotein cholesterol showed a tendency to increase. We generated pooled estimates for the aforementioned metabolic changes, but the level of heterogeneity was statistically significant and could not be explained through subgroup or sensitivity analyses. Therefore, we did not present these outcomes.

DISCUSSION

The present study reveals an increase in FPG level in patients receiving thiazide-type diuretics, which is consistent with findings from previous studies.[4] Adverse glycemic effects of thiazides have been reported since the application of these medications. Significantly greater concern was generated when thiazides were found to be associated with significantly higher risk of incident diabetes as compared with other antihypertensive medications.[5,37] However, since the glycemic change was small in most included studies and in the pooled outcome (FPG 0.27 mmol/L [4.86 mg/dL]) and no significant changes in PPG or HbA_{1c} were found in the meta-analysis, we wonder how these small changes are able to translate into a higher incidence of new-onset diabetes. In fact, it remains undefined whether the small glycemic changes or the incident diabetes during thiazide therapy has a strong impact on cardiovascular or other major outcomes. Some researchers compared the 4-year cumulative incidence of new-onset diabetes in patients assigned to CTD and those assigned to amlodipine in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and argued that 85% of cases of diabetes associated with a thiazide diuretic was not induced by the diuretic itself.[38] Moreover, diabetes diagnosed during thiazide therapy was not found to be related to an increase in cardiovascular outcomes or mortality.[39]

The mechanism of the adverse glycemic effect of thiazide diuretics has not yet been fully elucidated. Several hypotheses exist. Hypokalemia is a classic hypothesis most frequently mentioned by researchers. The inverse relationship between potassium and glucose was confirmed and potassium supplementation was correlated with a smaller increase in serum glucose.[40] Abdominal obesity and impaired insulin release were found to be involved in this process. Thiazide-induced hyperuricemia may also be responsible for some adverse metabolic effects and may be associated with increased cardiovascular risk and renal injury. Other possible mechanisms related to dysglycemia include visceral fat accumulation, changes in renin-angiotensin-aldosterone system (RAAS) activity, hepatic insulin resistance, and genetic variations.[41]

It seems that thiazide diuretics influence glucose metabolism in a dose-dependent manner. Lower doses of thiazides have therefore been recommended by international guidelines to reduce adverse effects.[42] In this meta-analysis, we found that serum glucose levels were significantly lower in patients receiving low doses of thiazides (HCTZ or CTD ≤25 mg daily) than in those receiving high doses. Similar results were presented in previous studies.[43] Apart from the relatively favorable metabolic outcomes, low-dose thiazides are also effective in controlling blood pressure and preventing cardiovascular events.[10,44] A recent systematic review demonstrated that low-dose HCTZ could effectively lower blood pressure. For thiazide diuretics other than HCTZ, the lowest doses could lower blood pressure maximally and higher doses did not exhibit increased

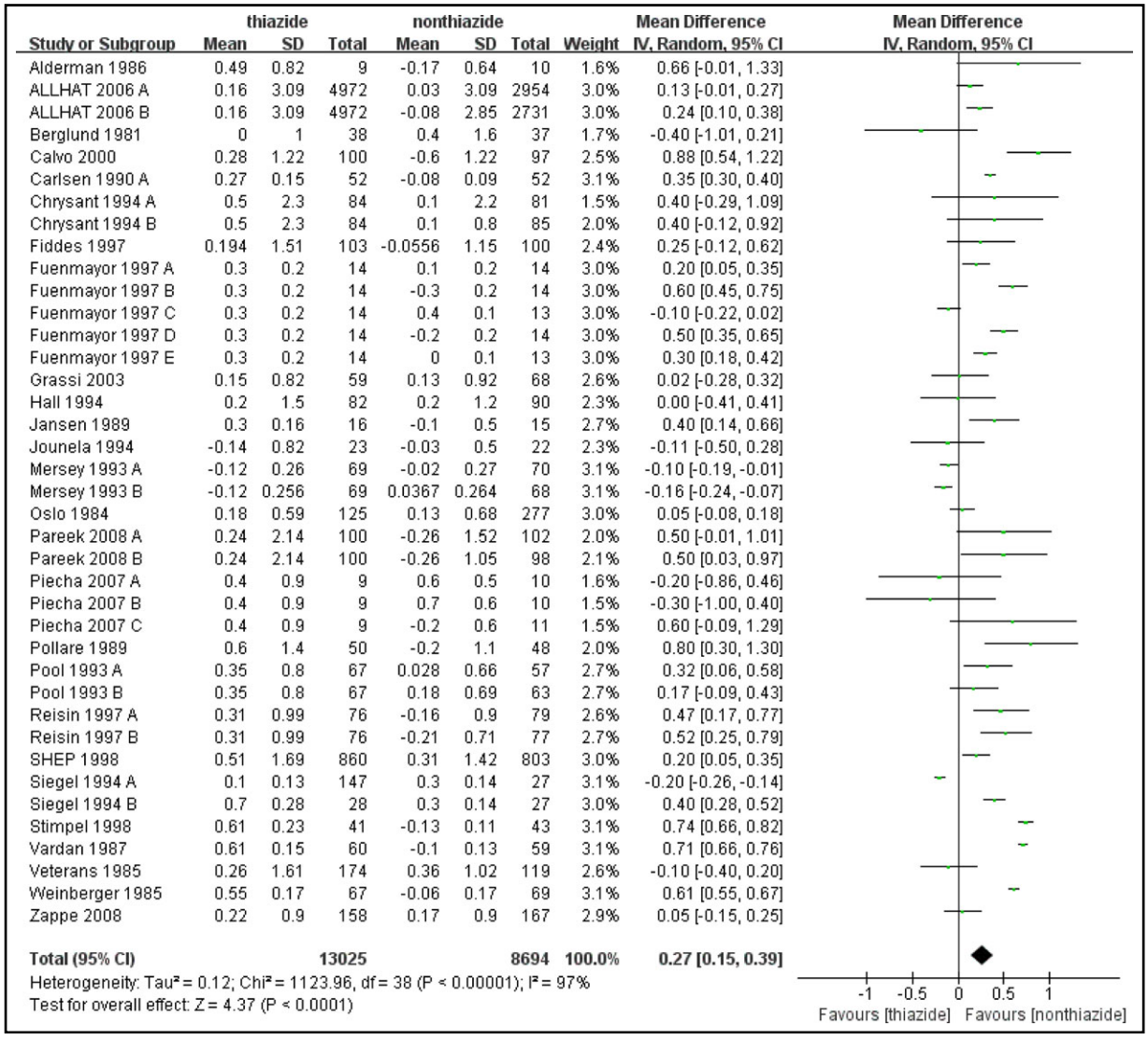

FIGURE 1. Forest plot for the mean difference (MD) of the change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with nonthiazide medications or placebo or nontreatment. MDs from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval (CI) of the study.

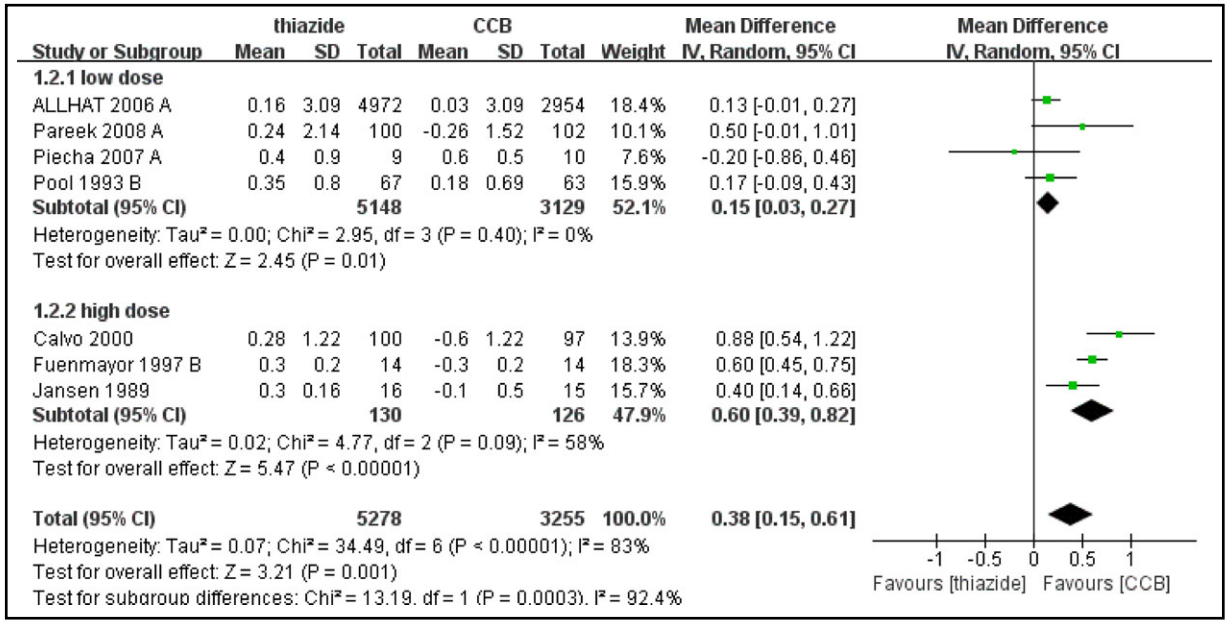

FIGURE 2. Forest plot for subgroup analysis of change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with calcium channel blockers (CCBs) based on dose of treatment. Mean differences (MDs) from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval (CI) of the study.

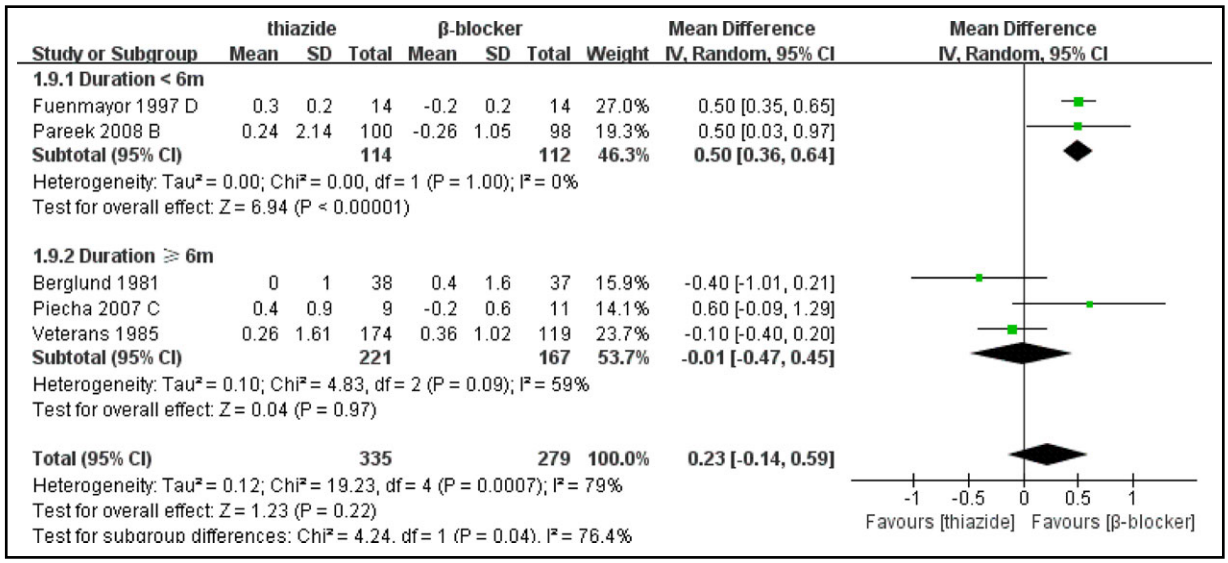

FIGURE 3. Forest plot for subgroup analysis of change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with β-blockers based on duration of treatment. Mean differences (MDs) from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval (CI) of the study.

effects on blood pressure.[10] Low-dose thiazide treatment has been proven to be well-tolerated and could significantly reduce cardiovascular outcomes for hypertensive patients.[44] Another finding of our meta-analysis is that patients with longer duration of treatment had less glycemic change compared with patients with short-term treatment. However, this result should be cautiously interpreted given the specific comparative agent (β-blocker) and the few number of studies and participants included. For patients with hypertension, blood glucose levels tend to increase over time. According to the results of randomized trials, changes in blood glucose were most evident in the first 1 or 2 years in patients receiving thiazides. This disparity in blood

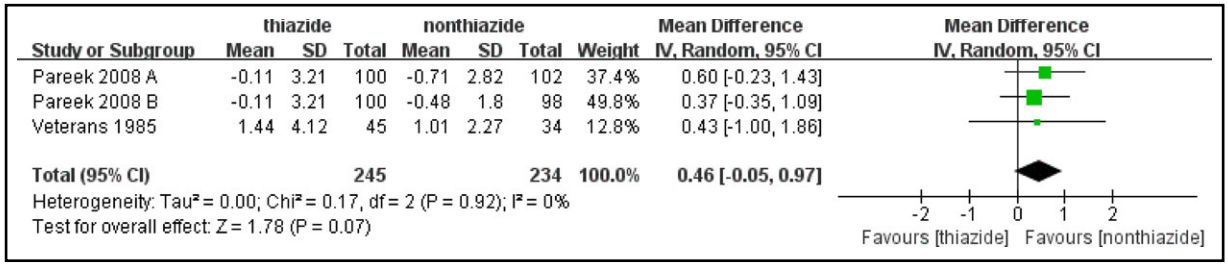

FIGURE 4. Forest plot for the mean difference (MD) of the change in postprandial plasma glucose (PPG) comparing thiazide-type diuretics with other treatments. MDs from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval (CI) of the study.

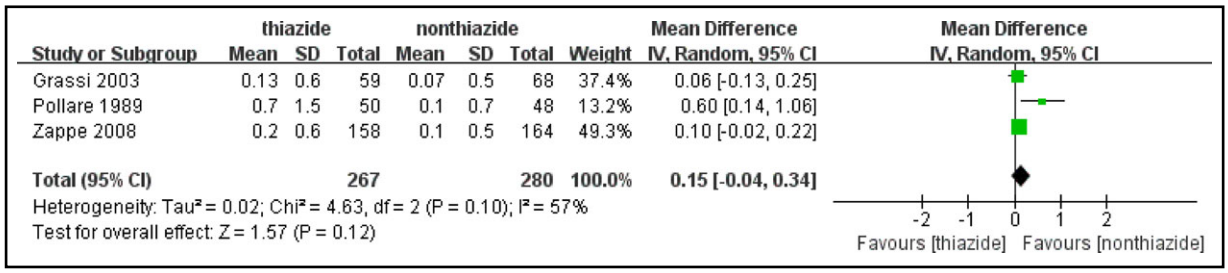

FIGURE 5. Forest plot for the mean difference (MD) of the change in glycated hemoglobin (HbA_{1c}) comparing thiazide-type diuretics with other treatments. MDs from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval (CI) of the study.

glucose between patients receiving thiazides and patients receiving other treatments appeared to wane over time.[16,26] Nevertheless, an observational study published recently indicated that prolonged duration of thiazide treatment was associated with increased fasting glucose.[45] Long-term randomized clinical trials are needed for more accurate comparisons regarding treatment duration.

Diabetic patients receiving thiazides were shown to have a moderate increase in serum glucose. A recent meta-analysis[46] reported a higher increase in FPG (MD, 1.69 mmol/L [30.42 mg/dL]; 95% CI, 0.69–2.69) in diabetic patients taking thiazide diuretics compared with that in our study. Considering the impaired glucose metabolism of existing diabetes, it can be assumed that the use of thiazides in diabetic patients needs to be more cautiously monitored.

Similar to thiazide diuretics, ACE inhibitors and ARBs are medications widely used and also recommended as first-line antihypertensive medications. These classes showed beneficial effects on glucose metabolism in contrast to thiazide diuretics,[5] probably because of their inhibition of RAAS. The combinations of low-dose thiazides and ACE inhibitors or ARBs were demonstrated to be effective and well-tolerated in hypertensive patients without apparent adverse effects on glucose and lipid profiles,[47] suggesting complementary impacts of these drugs. Based on the neutral or less-adverse glycemic effects, these combinations might be considered for patients with impaired glucose metabolism. On the contrary, β-blockers were not recommended to be used in combination with thiazide-type diuretics. Because of the negative impacts of both classes on glucose metabolism, patients at increased risk for diabetes should avoid using these combination regimens.

A meta-analysis by Mukete and Rosendorff[48] investigated the glycemic effects of thiazide diuretics and showed that low-dose thiazide diuretics were associated with significantly increased FPG.[48] However, only 10 studies were included and no comparison based on doses of thiazides was shown in this study. Although the total sample size was larger than our study, some nonrandomized trials and some trials using combination therapies containing thiazides were included.

STUDY LIMITATIONS

There are some limitations to our study. First, except for seven trials,[15,16,22,23,26,32,34] the other included studies were small, with fewer than 200 participants. Second, most studies measured only the changes of FPG without referring to other glycemic parameters, which led to a small sample size in the pooled analysis of PPG and HbA_{1c}. In addition, despite the positive findings in subgroup analyses, the sample sizes of the high-dose thiazide subgroup and both subgroups in the analysis based on duration of treatment are relatively small. Third, most studies did not clearly report the process of randomization, which might increase the risk of bias. Finally, since glycemic outcome was not the major endpoint in some trials and most trials lasted less than a

year, further randomized controlled trials with longer duration and larger populations are needed for more conclusive results. In fact, some recommendations have been released by a national working group of the United States to encourage more research on thiazide-induced dysglycemia.[49] Previous evidence suggests that there may be no increased cardiovascular risk in patients with dysglycemia or incident diabetes during thiazide therapy.[39] However, a study with a 15-year follow-up reported that diabetes associated with diuretic use was linked to significant cardiovascular risk. In addition, patients with incident diabetes receiving antihypertensive treatment that included diuretics were shown to have higher cardiac morbidity rates than those without diabetes.[50] Since antihypertensive treatment is usually a persistent or even lifelong process, further studies are needed to evaluate long-term consequences of the glycemic effects of thiazides, especially their impact on major cardiovascular outcomes.

CONCLUSIONS

This meta-analysis demonstrated a significant but small magnitude of glycemic abnormalities associated with thiazide-type diuretics in hypertensive patients. Treatment with lower doses might reduce or avoid adverse effects. Further investigations are needed to clarify whether these metabolic changes are of clinical significance.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flowchart of literature search and selection.

Figure S2. Risk of bias of included studies.

Figure S3. Risk of bias summary.

Figure S4. Begg's funnel plot for the mean difference of the change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with nonthiazide medications or placebo or nontreatment.

Figure S5. Begg's funnel plot for the mean difference of the change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with calcium channel blockers (CCBs).

Figure S6. Begg's funnel plot for the mean difference of the change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Figure S7. Forest plot for subgroup analysis of change in fasting plasma glucose (FPG) comparing thiazide-type diuretics with nonthiazide medications or placebo or nontreatment based on types of medication in control groups. Mean differences (MDs) from the individual studies are presented by squares and the size of the square represents the statistical weight of the study in the summary estimate. The horizontal line indicates the 95% confidence interval of the study.