Thiazide Diuretic–Induced Change in Fasting Plasma Glucose: a Meta-analysis of Randomized Clinical Trials

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BACKGROUND: Prior meta-analyses measuring thiazide-induced glycemic change have demonstrated an increased risk of incident diabetes; however, this measure's definition has changed over time.

AIM: To determine the magnitude of change in fasting plasma glucose (FPG) for thiazide diuretics.

DATA SOURCES: A research librarian designed and conducted searches in Medline®, EMBASE, and EBM Reviews-Cochrane Central Register of Controlled Trials (inception through July 2018) and International Pharmaceutical Abstracts (inception to December 2014).

STUDY SELECTION: Randomized, controlled trials comparing a thiazide or thiazide-like diuretic to any comparator reporting FPG were identified. Trials enrolling < 50 participants, those with a follow-up period of < 4 weeks, and conference abstracts were excluded.

DATA EXTRACTION: Independent duplicate screening of citations and full-text articles, data extraction, and assessment of risk of bias was conducted.

DATA SYNTHESIS: Ninety-five studies were included ($N = 76{,}608$ participants), with thiazides compared with placebo, beta-blockers, calcium channel blockers, renin-angiotensin-aldosterone-system inhibitors, potassium-sparing diuretic, and others alone or in combination. Thiazide diuretics marginally increased FPG (weighted mean difference 0.20 mmol/L (95% CI 0.15–0.25); $I^2 = 84\%$) (1 mmol/L = 18 mg/dL). Results did not change substantially when considering dose or duration, comparing thiazides with placebo or an active comparator, or using thiazides as monotherapy or combination therapy, even when combined with a potassium-correcting agent.

CONCLUSION: Thiazide diuretics have a small and clinically unimportant impact on FPG.

KEY WORDS: fasting plasma glucose; meta-analysis; randomized controlled trial; thiazide diuretic.

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INTRODUCTION

Thiazide (e.g., hydrochlorothiazide) and thiazide-like (e.g., chlorthalidone, indapamide) diuretics (hereafter called "thiazide diuretics") are considered first-line therapy for the management of hypertension.[1, 2] However, the use of thiazide diuretics has been associated with concerns of adverse metabolic effects, including glycemic change and incident diabetes.[3, 4]

Thiazides are proposed to influence blood glucose by several mechanisms, including impaired insulin sensitivity, increased hepatic glucose production, and impaired peripheral uptake.[5] Thiazides decrease serum potassium by 0.2–0.6 mEq/L (1 mEq/L = 1 mmol/L) in a dose-dependent manner,[3, 6] which has been shown retrospectively in aggregate to correlate with increased mean plasma glucose;[7] however, this has not been consistently demonstrated. A pre-specified analysis of the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study in 202 patients on hydrochlorothiazide 12.5–25 mg for 9 weeks did not demonstrate a significant correlation between fasting plasma glucose (FPG) and potassium levels.[8] Controversy also exists as to the potential impact of thiazide-induced glycemic change and incident diabetes on long-term adverse cardiovascular event rates and associated health care costs.

Previously published meta-analyses concerning thiazide-induced glycemic change have demonstrated an increased risk of incident diabetes ranging from an odds ratio of 1.16 to 1.30 as compared with placebo, calcium channel blockers (CCB), angiotensin-converting enzyme (ACE) inhibitors, and/or angiotensin receptor blockers (ARB).[9–11] However, this measure's definition has changed over time; thus, we aimed to determine the magnitude of change in fasting plasma glucose (FPG).

METHODS

We conducted a systematic review with meta-analysis of the effects of thiazide and thiazide-like diuretics on changes in FPG according to PRISMA (Preferred Reporting Items for

Systematic Reviews and Meta-Analyses) guidance on meta-analyses using a pre-specified study protocol.[12]

Data Sources and Searches

Randomized, controlled trials comparing a thiazide or thiazide-like diuretic with any comparator that did not fit this classification reporting any measure of blood glucose were identified. A research librarian designed and conducted searches in the following databases: Medline®, EMBASE, and EBM Reviews-Cochrane Central Register of Controlled Trials (between July 2012 and July 2018), as well as International Pharmaceutical Abstracts (up to December 2014 as the institutional subscription had been canceled). The detailed search strategy is described in eTable 1. Searches were restricted using randomized controlled trial study design filters for each database, as well as to English language, humans, and adults. Reference lists of included studies were searched to identify any additional eligible trials and authors were contacted for additional information to enable study inclusion.

Study Selection

Randomized controlled trials comparing the effect of any thiazide diuretic at any dose as a first-line agent on fasting plasma glucose were included. We excluded trials enrolling less than 50 participants, those with a follow-up period of less than 4 weeks, and those reported only as conference abstracts; however, we did not restrict based on patient characteristics (age, sex, presence of hypertension, diabetes, or other metabolic disorders) or primary outcome measured. Studies evaluating children (< 18 years) and those not in English were excluded.[13, 14] Authors of trials that mentioned a measure of glycemia but did not directly report data were contacted to acquire data where possible.

Data Extraction and Quality Assessment

Two reviewers screened the titles, abstracts, and subsequent full-text articles independently to identify relevant articles. Discrepancies were resolved by consensus or with consultation from a third reviewer if required. Data regarding patient population, intervention in the treatment and control group (drug, dose), study primary outcome, duration of follow-up, and baseline and endpoint measure of FPG were extracted and then independently verified, with discussion of any incongruity. FPG was extracted as mean and standard deviation at baseline and end of follow-up (to a maximum of 1 year [metabolic changes expected within 4 weeks]) where possible, and mean change and standard deviation of change within groups during the study period otherwise.

Two reviewers used the Cochrane tool to independently assess risk of bias within included trials.[15] Selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting) were rated as low, unclear, or high risk and used to provide an overall assessment of the trial's risk of bias.

Data Synthesis and Analysis

The primary outcome measure was the weighted mean difference (WMD) in FPG (1 mmol/L = 18 mg/dL) comparing thiazide diuretic with any comparator, with a clinically important change defined as 0.4–0.5 mmol/L, equating to a 0.3% change in A1c.[16] In studies where more than one thiazide diuretic arm may have been evaluated (i.e., low versus high dose, or thiazide alone or in combination with other agents), data from the study arm with the highest dose utilized and thiazide use as monotherapy was preferred to maximize any potential signal related to glucose changes while also minimizing any confounding of the thiazide with other agents.

To summarize the effects of thiazide therapy on changes in FPG, we pooled estimates across studies using random effects models with inverse variance weighting (as recommended by Cochrane) as heterogeneity between the studies due to the difference in thiazide diuretic dose, comparator arms, and length of follow-up was expected. Heterogeneity was assessed using the I^2 statistic, with an I^2 statistic > 75% being considered as high heterogeneity. There was not an a priori degree of heterogeneity that precluded pooling. In studies that employed multiple comparison arms (e.g., a beta-blocker arm and a calcium channel blocker arm), a single combined comparator arm was created using the methods and formulas recommended by Cochrane for continuous data.[15]

In addition to the overall effect of thiazide diuretics, we a priori evaluated their effect in a number of subgroups based on comparator arm (placebo or any active comparator) as well as in specific active comparators (ACEi, ARB, or aliskiren; beta-blockers (BB); or CCB). An analysis of thiazides in combination with a potassium-correcting agent (potassium-sparing diuretic; ACEi, ARB, or aliskiren; or potassium supplement) was also conducted. Additional analyses according to thiazide dose (standard doses of thiazides defined as hydrochlorothiazide ≤ 25 mg, chlorthalidone ≤ 25 mg, indapamide ≤ 2.5 mg, trichlormethiazide ≤ 4 mg, altizide ≤ 15 mg, bendroflumethiazide ≤ 2.5 mg, hydroflumethiazide ≤ 25 mg) were also explored in subgroup and meta-regression approaches.

After initial pooling of study results, 3 additional sensitivity analyses were completed post hoc to explore the impact of specific studies on the estimates or to explore issues related to heterogeneity. Specifically, we evaluated the effect of thiazides overall in studies of a < 6-month duration and in those with ≥ 6-month duration. Second, we removed several studies that appeared to be outliers based on the magnitude of effect observed (positive or negative). Specifically studies by Foder et al., Cicero et al., and Rubio-Guerra et al. were excluded in these analyses.[17–19] Finally, we removed the 2 largest studies, Antihypertensive and Lipid-Lowering Treatment to Prevent

Heart Attack Trial (ALLHAT) and Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH), which had the most weight in the pooled results and repeated the analysis.[20, 21]

Publication bias was assessed via visual inspection of a funnel plot and the use of an Egger test. All analyses were conducted using Stata MP Version 15 (College Station, TX 77845).

RESULTS

Study Characteristics

In total, 13,343 records were identified, with 7674 screened by title and abstract after removal of duplicates and 1692 full-text articles assessed for eligibility (Fig. 1). Of these, 1597 were excluded, the majority because they did not report fasting glucose data. Overall, 95 studies were included, all but 2 of which enrolled patients with hypertension, with a total of 76,608 participants (33,357 of whom were enrolled in ALLHAT). The mean age of participants was 58 years (range of the means 43–74 years) and on average, 55% of the participants were male. Participants were followed for a mean of 35 weeks (range of the means 4–260 weeks).

Thiazides were compared with the placebo ($n = 15$ comparisons),[22–36] BB ($n = 13$),[37–49] CCB ($n = 12$),[17, 20, 25, 39, 42, 48, 50–55] RAASi ($n = 28$),[20, 23, 39, 42, 48, 50, 56–74] potassium-sparing diuretic ($n = 4$)[75–78] or others (none, diet, alpha-blocker, loop diuretic, sodium glucose cotransporter-2 inhibitors) ($n = 10$)[18, 79–87] alone or to any combination ($n = 30$)[19, 21, 52, 88–111] (Table 1, eTable 2). Thiazide diuretics were commonly utilized as monotherapy ($n = 59$),[17, 18, 20, 23, 25–28, 30–35, 38–45, 47–49, 51, 53–55, 57, 59, 61, 63–65, 67, 68, 70, 72, 73, 75–86, 102] dual therapy (with BB ($n = 4$),[43, 84, 91, 101] CCB ($n = 1$),[25] RAASi ($n = 36$),[19, 21, 23, 46, 52, 60, 62, 65, 68, 69, 71, 88, 90, 92–97, 99, 100, 103, 105–108, 110, 111] potassium-sparing diuretics ($n = 12$),[22, 24, 28, 29, 58, 66, 74–77, 81, 87] potassium supplements ($n = 4$)),[37, 50, 98, 117] and other combinations ($n = 11$)[22, 28, 31, 36, 56, 84, 89, 102–104, 109] (Table 1, eTable 2).

Trials were generally judged to be of low to moderate risk of bias (Fig. 2, eTable 3). Few trials were at high risk of bias for blinding of participants, personnel, and/or assessors (14 to 29%) or selective reporting (1%); a large number had unclear risk of bias for random sequence generation (66%) and/or allocation concealment (77%).

Effect of Thiazides on Fasting Plasma Glucose

Overall, in pooled analyses, thiazide diuretics were found to marginally increase FPG (WMD 0.20 mmol/L (95% CI 0.15–0.25)) (Fig. 3, eFigure 1). Heterogeneity was relatively high ($I^2 = 84\%$, $p < 0.001$) and decreased with the removal of the 3 outlying studies (WMD 0.16 mmol/L (95% CI 0.12–0.21), $I^2 = 61\%$).[17–19] A sensitivity analysis removing ALLHAT[20] and ACCOMPLISH,[21] the 2 largest studies, did not impact the results (WMD 0.21 mmol/L (95% CI 0.15–0.26), $I^2 = 83\%$) (Fig. 3). Assessment of the funnel plots indicated asymmetrical suggesting the presence of publication bias (Eggers test $p < 0.001$) (eFigure 2).

A subgroup analysis of thiazides utilized as monotherapy and as combination therapy produced similar results (WMD 0.17 mmol/L (95% CI 0.10–0.24), $I^2 = 83\%$ (eFigure 3) and WMD 0.23 mmol/L (95% CI 0.14–0.32), $I^2 = 80\%$ (eFigure 4), respectively). Studies evaluating a duration of treatment ≥ 6 months (WMD 0.15 mmol/L (95% CI 0.09–0.20), $I^2 = 68\%$) (eFigure 5) and < 6 months (WMD 0.29 mmol/L (95% CI 0.19–0.40), $I^2 = 87\%$) (eFigure 6) also demonstrated a similar impact on FPG.

In analyzing studies comparing thiazides with placebo versus an active comparator (of any type), again, a similar impact on FPG was seen (WMD 0.16 mmol/L (95% CI 0.07–0.25), $I^2 = 72\%$ (eFigure 7) and WMD 0.21 mmol/L (95% CI 0.15–0.28), $I^2 = 84\%$ (eFigure 8), respectively). Sensitivity analyses of thiazides versus various drug classes (ACEi, ARB, or aliskiren; beta-blockers; and calcium channel blockers) were similar (eFigures 9–11), as were those in populations with diabetes (WMD 0.24 mmol/L (95% CI 0.07–0.41), $I^2 = 75\%$) (eFigure 12) and no history of diabetes or impaired FPG (WMD 0.25 mmol/L (95% CI 0.15–0.36), $I^2 = 80\%$) (eFigure 13).

An analysis of thiazide dose was also conducted, with standard and higher doses of thiazides demonstrating similar effects on FPG: WMD 0.21 mmol/L (95% CI 0.14–0.28), $I^2 = 80\%$ (eFigure 14) and WMD 0.18 mmol/L (95% CI 0.09–0.26), $I^2 = 80\%$ (eFigure 15), respectively. Meta-regression utilizing the weighted average for FPG and the equivalent of maximum total daily dose hydrochlorothiazide also did not demonstrate a significant relationship ($p > 0.05$, data not shown).

Finally, an analysis of thiazides in combination with a potassium-correcting agent (ACEi, ARB, or aliskiren, potassium-sparing diuretic, or potassium supplement) was conducted (WMD 0.23 mmol/L (95% CI 0.13–0.33), $I^2 = 81\%$ (eFigure 16)).

DISCUSSION

This meta-analysis (97 comparisons across 95 trials) demonstrated a statistically significant but clinically unimportant increase in FPG. Overall, heterogeneity in this main result was high and despite numerous subgroup and sensitivity analyses was not identifiable but was likely due to features of the study design (dose, duration of treatment, co-intervention) or population (diabetes/not, comorbidities),[119] rather than true outliers given their removal did not alter the result.

The magnitude of the change in FPG with thiazide diuretics was similar across subgroups and among studies utilizing standard doses, some form of potassium correction (RAAS inhibitor, potassium-sparing diuretic, or potassium

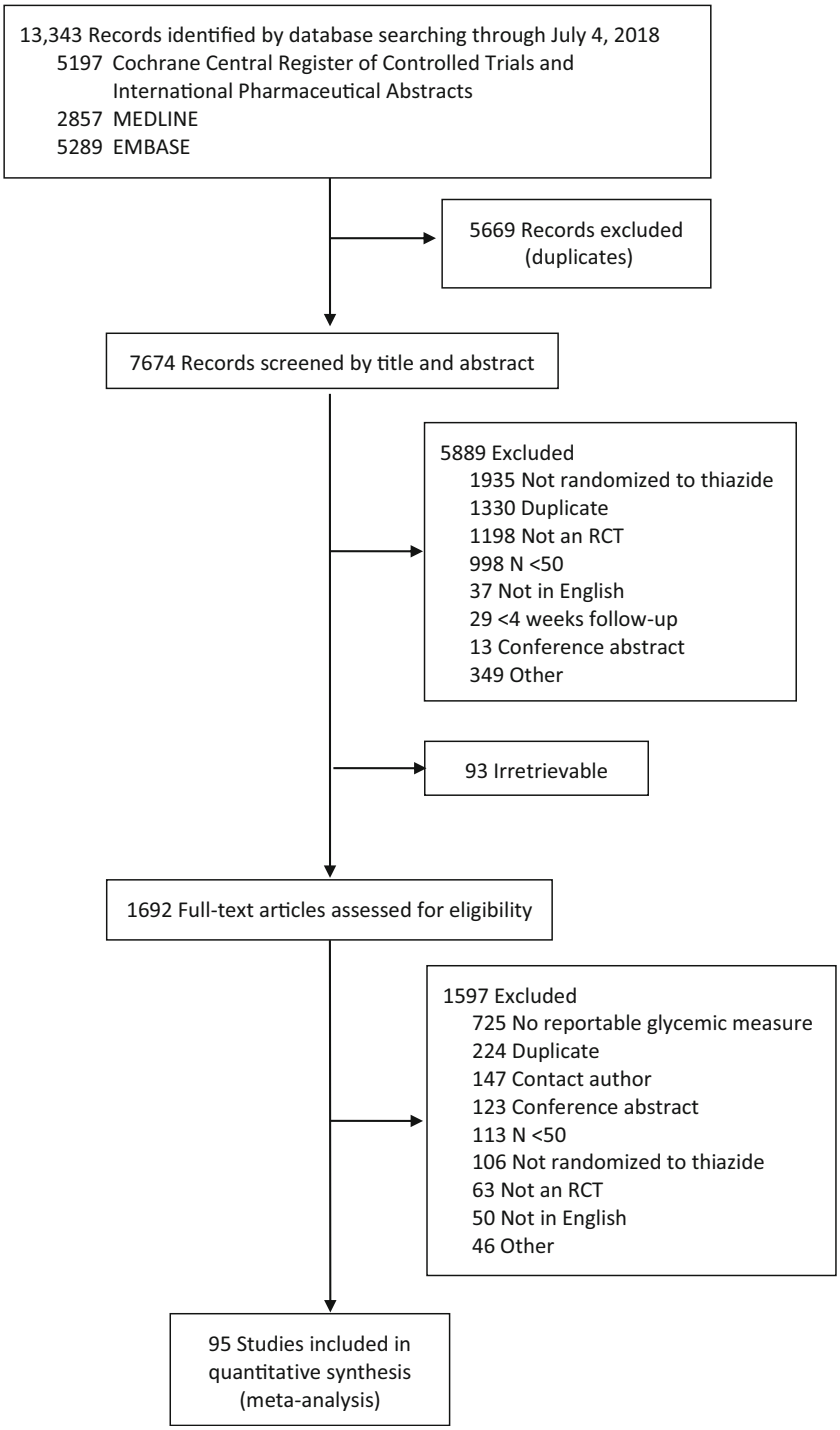

Figure 1 Summary of study retrieval and identification for meta-analysis.

supplement), and a thiazide in combination with any other drug. Although we had anticipated that the impact of standard doses of thiazide diuretics may be less than higher doses, given that they have been shown to impact potassium to a lesser degree,[120] our data suggested otherwise with respect to changes in FPG. However, in our meta-analysis, there was no clinically important change in FPG when considering subgroups or other agents that may potentially change potassium levels. Given that we did not specifically evaluate change in FPG in relation to potassium, the potential for a relationship to exist remains; our data, however, would suggest the clinical impact at the population level on FPG is negligible.

For this analysis, a follow-up was truncated at 1 year recognizing that most metabolic alterations occur during the first several weeks of therapy and most incident diabetes within the first year.[8, 121] While the magnitude of the effect for studies with a longer duration of treatment (> 6 months compared with those less than 6 months) appears to be less, this result is most likely

Table 1 Selected Characteristics of Included Studies

First author (year of publication)	Intervention arm (maximum total daily dose (mg))	Control arm (maximum total daily dose (mg))	*N* in primary analysis	Total duration of follow-up (weeks)
ALLHAT Officers and Coordinators (2002)[20] [ALLHAT]	Chlorthalidone 25	Amlodipine 10 or lisinopril 40	12,819	104
Abe (2009)[71]	Hydrochlorothiazide 12.5 + losartan 100	Losartan 100	60	24
Amery (1986) [EWPHE][22]	Hydrochlorothiazide 50 + triamterene 100 ± methyldopa 2000	Placebo	507	52
Amin (2015)[79]	Hydrochlorothiazide 12.5	Ertugliflozin 25	78	4
Bakris (2006) [STAR][105]	Hydrochlorothiazide 25 + losartan 100	Verapamil SR 240 + trandolapril 4	184	52
Berglund (1981)[37]	Bendroflumethiazide 5 + KCl 15	Propranolol 320	106	52
Bichisao (1984)[38]	Chlorthalidone 25	Metoprolol SR 200	738	4
Bosone (2017)[52]	Hydrochlorothiazide 25 + ramipril 10	Amlodipine 10 or ramipril 10 + canrenone 100	289	52
Brandao (2010)[72]	Hydrochlorothiazide 25 or indapamide 1.5	Perindopril 4	48	12
Brown (2016)[75] [PATHWAY-3]	hydrochlorothiazide 50 or hydrochlorothiazide 25 + amiloride 10	Amiloride 20	166	24
Byington (1998)[53] [MIDAS]	Hydrochlorothiazide 50	Isradipine 10	881	52
Calvo (2000)[54]	Hydrochlorothiazide 100	Amlodipine 10	197	8
Campo (2003)[80]	Hydrochlorothiazide 25	Doxazosin 8	98	16
Charansonney (1997)[81] [Eurevie]	Hydrochlorothiazide 25 or altizide 15 + spironolactone 25	Piretanide SR 6	599	24
Christogiannis (2013)[106]	Hydrochlorothiazide 12.5 + valsartan 160	Valsartan 160 + amlodipine 5	60	16
Chrysant (1994)[23] [The Lisinopril Hydrochlorothiazide Group]	Hydrochlorothiazide 12.5 or hydrochlorothiazide 25 or hydrochlorothiazide 12.5 + lisinopril 10 or hydrochlorothiazide 25 + lisinopril 10	Placebo or lisinopril 10	165	8
Cicero (2012)[18]	Hydrochlorothiazide 12.5	*Orthosiphon stamineus* 100	80	8
Damian (2016)[29]; MRC Working Party (1992)[112] [MRC elderly trial]	Hydrochlorothiazide 50 + amiloride 5	Placebo	3294	52
Deedwania (2013)[107]	Hydrochlorothiazide 25 + (lisinopril 10 or losartan 50)	Placebo + (lisinopril 10 or losartan 50)	309	12
Derosa (2015)[108]	Hydrochlorothiazide 12.5 + telmisartan 80	Losartan 100 + barnidipine 20	141	24
Ferdinand (2011)[109] [ASCENT]	Hydrochlorothiazide 25 + aliskiren 300 + amlodipine 10	Amlodipine 10 + aliskiren 300	411	8
Fiddes (1997)[30]	Indapamide 1.25	Placebo	188	8
Fodor (1997)[17]	Hydrochlorothiazide 50	Nisoldipine 40	252	12
Fogari (1995)[42]	Hydrochlorothiazide 25	Amlodipine 10 or atenolol 100 or lisinopril 20	118	8
Fogari (2007)[110]	Hydrochlorothiazide 25 + candesartan 16	Manidipine 20 + candesartan 16	174	24
Fogari (2008)[111]	Hydrochlorothiazide 25 + olmesartan 20	Manidipine 20 + delapril 30	150	48
Fogari (2008)[88]	Hydrochlorothiazide 12.5 + olmesartan 20	Manidipine 10 + delapril 30	88	24
Fogari (2014)[89]	Hydrochlorothiazide 25 + valsartan 160 + amlodipine 5	Valsartan 160 + amlodipine 5 + canrenone 50	109	24
Fonseca (2015)[73]	Hydrochlorothiazide 25 or indapamide 1.5	Perindopril 4	44	12
Fuchs (2015)[74] [PREVER]	Chlorthalidone 25 + amiloride 5	Losartan 100	607	78
Garg (2015)[56]	Hydrochlorothiazide 12.5 + KCl 10 + enalapril 20	Enalapril 20	41	24
Ghiadoni (2017)[90]	Hydrochlorothiazide 25 + enalapril 20	Enalapril 20 + lercanidipine 20	76	24
Goldman (1980)[31] [Mild Hypertension Feasibility Trial]	Chlorthalidone 100 ± reserpine 0.25	Placebo	611	52
Grimm (1981)[32]	Hydrochlorothiazide 100 or chlorthalidone 100	Placebo	117	24
Haenni (1994)[57]	Bendrofluazide 5	Lisinopril 20	61	24
Hegbrant (1989)[83]	Bendroflumethiazide 2.5	Piretanide SR 6 or piretanide SR 12	76	12
Helgeland (1984)[84] (1980)[113] [OSLO]	Hydrochlorothiazide 50 ± (propranolol 320 or methyldopa 1500)	Untreated	402	260
Holzgreve (2003)[91]	Chlorthalidone 25 + atenolol 100	Verapamil SR 180 + trandolapril 2	450	20
Jounela (1994)[33]	Hydrochlorothiazide 3 or 6 or 12.5 or 25	Placebo	45	6
Karashima (2016)[92]	Hydrochlorothiazide 6.25 + candesartan 8	Eplerenone 50 + candesartan 8	50	52
Kato (2011)[93]	Olmesartan 21.2* + (indapamide 0.96* or trichlormethiazide 1.47*)	Olmesartan 22.1* + azelnidipine 13.3*+	58	24

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Table 1. (continued)

First author (year of publication)	Intervention arm (maximum total daily dose (mg))	Control arm (maximum total daily dose (mg))	*N* in primary analysis	Total duration of follow-up (weeks)
		(amlodipine 3.5* or benidipine 4*)		
Koh (2010)[34]	Hydrochlorothiazide 50	Placebo	62	8
Lambers Heerspink (2013)[35]	Hydrochlorothiazide 25	Placebo	51	12
Lee (2012)[94]	Hydrochlorothiazide 25 + valsartan 160	Amlodipine 10 + benazepril 20	167	16
Leehey (1988)[55]	Hydrochlorothiazide 75	Diltiazem SR 360	61	10
Lin (1995)[58]	Hydrochlorothiazide 50 + amiloride 5	Captopril 150 or enalapril 40	60	52
Lindholm (2003)[59] [ALPINE]	Hydrochlorothiazide 25	Candesartan 16	392	52
Makita (2009)[60]	Hydrochlorothiazide 12.5 + telmisartan 40	Candesartan 8 or valsartan 80	64	12
Malekzadeh (2010)[36]	Hydrochlorothiazide 12.5 + ASA 81 + enalapril 2.5 + atorvastatin 20	Placebo	474	52
Maroko (1989)[24] [PHICOG]	Hydrochlorothiazide 25 + triamterene 50	Placebo	352	8
Marre (2004)[61] [NESTOR]	Indapamide SR 1.5	Enalapril 10	510	52
Martinez-Martin (2011)[95] [OLAS]	Hydrochlorothiazide 25 + olmesartan 40	Olmesartan 40 + amlodipine 10	120	78
Matsui (2011)[96] [J-CORE]	Hydrochlorothiazide 12.5 + olmesartan 20	Olmesartan 20 + azelnidipine 16	207	24
Milon (1984)[44]	Chlorthalidone 100	Atenolol 100	67	24
Momeni (2015)[77]	Hydrochlorothiazide 25 or hydrochlorothiazide 25 + spironolactone 50	Spironolactone 50	40	12
Monmany (1990)[45]	Hydrochlorothiazide 100	Metoprolol 300	37	52
Mugellini (2004)[97]	Hydrochlorothiazide 12.5 + irbesartan 150	Delapril 30 + manidipine 10	80	8
Multicenter Diuretic Cooperative Study Group (Douglas) (1981)[76]	Hydrochlorothiazide 100 or hydrochlorothiazide 100 + amiloride 10	Amiloride 10	90	12
Nielsen (1994)[98]	Bendroflumethiazide 5 + KCl 15	Enalapril 20 + KCl 15	114	20
Nishimura (2013)[62]	Hydrochlorothiazide 12.5 + losartan 50	Losartan 100	106	52
Nishiwaki (2013)[99]	Hydrochlorothiazide 12.5 + losartan 100	Losartan 100 + amlodipine 5	65	48
Obel (1984)[85]	Bendroflumethiazide 10	Furosemide SR 60	33	36
Os (1997)[46]	Hydrochlorothiazide 6 + enalapril 20	Atenolol 50	121	12
Oshikawa (2014)[100]	Hydrochlorothiazide 12.5 + losartan 100	Amlodipine 5 + losartan 100	176	52
Pareek (2008)[101]	Chlorthalidone 6.25 + atenolol 25	Amlodipine 2.5 + (atenolol 25 or atenolol 50)	125	24
Pollare (1989)[63]	Hydrochlorothiazide 50	Captopril 100	98	18
Pollavini (1984)[47]	Chlorthalidone 25	Oxprenolol SR 160	446	4
Pool (1993)[25]	Hydrochlorothiazide 12.5 + diltiazem SR 120 or hydrochlorothiazide 12.5	Placebo or diltiazem SR 120	144	6
Posadzy-Malaczynska (2015)[102]	Hydrochlorothiazide 25 ± estrogen progesterone therapy	Perindopril 4 ± estrogen progesterone therapy	50	52
Rajzer (2017)[48]	Hydrochlorothiazide 50	Quinapril 40 or amlodipine 10 or losartan 100 or bisoprolol 10	95	24
Rasmussen (2006)[50]	Bendroflumethiazide 1.25 + KCl 7.6 or bendroflumethiazide 2.5 + KCl 7.6	Amlodipine 5 or enalapril 10	181	24
Reid (2000)[26]	Hydrochlorothiazide 50	Placebo	185	104
Roman (1998)[64]	Hydrochlorothiazide 50	Ramipril 20	50	24
Rosenthal (1990)[65]	Hydrochlorothiazide 25 or hydrochlorothiazide 25 + enalapril 40	Enalapril 40	45	8
Rubio-Guerra (2017)[19], Duran-Salgado (2015)[114]	Hydrochlorothiazide 12.5 + losartan 100	Amlodipine 5 + losartan 100	60	12
Saruta (2015)[103], Ogihara (2014)[115] [COLM]	Olmesartan 40 + (indapamide 1 or trichlormethiazide 1 or hydrochlorothiazide 12 or benzylhydrochlorothiazide 2 or meticrane 75 or tripamide 7.5 or chlorthalidone 25 or mefruside 12.5)	Olmesartan 40 + (azelnidipine 16 or amlodipine 5)	5141	156
Savage (1998)[27], SHEP Cooperative Research Group (1991)[116] [SHEP]	Chlorthalidone 25	Placebo	2807	52
Scali (1992)[66]	Hydrochlorothiazide 100 + amiloride 10	Lisinopril 20	62	24
Siegel (1992)[117], (1994)[28]	Hydrochlorothiazide 50 or hydrochlorothiazide 50 + KCl 40 or hydrochlorothiazide 50 + KCl 40 + magnesium oxide or hydrochlorothiazide 50 + triamterene 100 or chlorthalidone 50	Placebo	55	8
Skoczylas (2016)[39]	Indapamide 3	Bisoprolol 10 or amlodipine 10 or candesartan 32	84	6

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Table 1. (continued)

First author (year of publication)	Intervention arm (maximum total daily dose (mg))	Control arm (maximum total daily dose (mg))	*N* in primary analysis	Total duration of follow-up (weeks)
Smith (2012)[40][PEAR]	Hydrochlorothiazide 25	Atenolol 100	569	9
Stimpel (1998)[67]	Hydrochlorothiazide 25	Moexipril 15	97	12
Takihata (2015)[51] [COAT]	Trichlormethiazide 1	Azelnidipine 16	209	48
Tani (2017)[104]	Indapamide 1 + amlodipine 5 + irbesartan 100	Amlodipine 10 + irbesartan 100	115	12
Ueda (2014)[86] [DIME]	Hydrochlorothiazide 12.5 or indapamide 1 or trichlormethiazide 1	Any antihypertensive other than thiazides	1130	229
Veterans Cooperative Study Group on Antihypertensive Agents (Freis 1979)[82]	Hydrochlorothiazide 200	Ticrynafen 1000	155	30
Veterans Cooperative Study Group on Antihypertensive Agents (Freis 1983)[43]	Bendroflumethiazide 10 or bendroflumethiazide 10 + nadolol 240	Nadolol 240	164	12
Veterans Cooperative Study Group on Antihypertensive Agents (Ramirez 1985)[49] (Freis 1982)[118]	Hydrochlorothiazide 200	Propranolol 640	294	58
Weber (2010)[21] [ACCOMPLISH]	Hydrochlorothiazide 25 + benazepril 40	Benazepril 40 + amlodipine 10	6946	130
Wicker (1986)[87]	Hydrochlorothiazide 50 + amiloride 5	Muzolimine 20	47	20
Yonga (1993)[41]	Hydroflumethiazide 50	Propranolol 160	53	12
Yutaka (2009)[78]	Trichlormethiazide 0.857*	Spironolactone 10.7*	64	24
Zappe (2008)[68] [MADE-ITT]	Hydrochlorothiazide 25 or hydrochlorothiazide 25 + valsartan 320	Valsartan 320	363	16
Zhang (2010)[69]	Indapamide 2.5 + fosinopril 20	Fosinopril 20	89	52–64
Zhang (2017)[70]	Hydrochlorothiazide 25	Telmisartan 40	1023	8

Note. KCl, potassium chloride (mEq); SR, sustained or slow release formulation; +, "and"; ±, "and/or" as additional or step up therapy after initial randomization
**Mean dose per day*

due to chance given the overlapping confidence intervals and differences in study design and population, as noted above.

Baseline blood glucose has been associated with changes in blood glucose or incident diabetes with thiazide therapy. A PEAR study analysis (hydrochlorothiazide 25 mg versus atenolol 100 mg) demonstrated that baseline blood glucose was the greatest predictor of change in blood glucose or incident impaired fasting glucose,[122] similar to that reported in the PIUMA hypertension registry, where baseline impaired FPG, higher 24-h ambulatory blood pressure, and (low-dose) thiazide diuretic use predicted incident diabetes.[123] Moreover, in an analysis of hydrochlorothiazide impact on FPG in patients with type 2 diabetes, Lin et al. also observed an increased in FPG (standardized mean difference (SMD) 0.27 (95% CI 0.11–0.43)).[124] These data are aligned with our results; however, there was no appreciable difference in the magnitude of change in patients with and without pre-existing diabetes or impaired FPG. Recognizing that this change may have different meaning to patients in either group, notably no change in FPG reached the 0.5 mmol/L change threshold for clinical importance.[16]

In comparison with a recently published meta-analysis also investigating the association of thiazide diuretics with

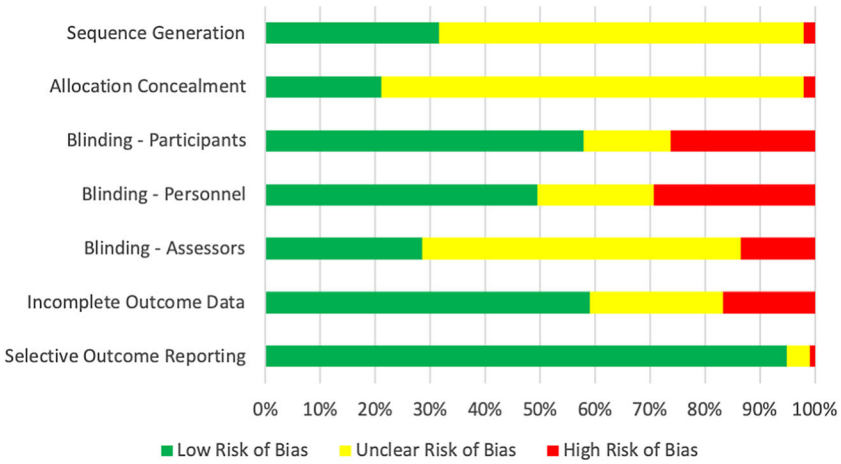

Figure 2 Summary of risk of bias for trials included in meta-analysis.

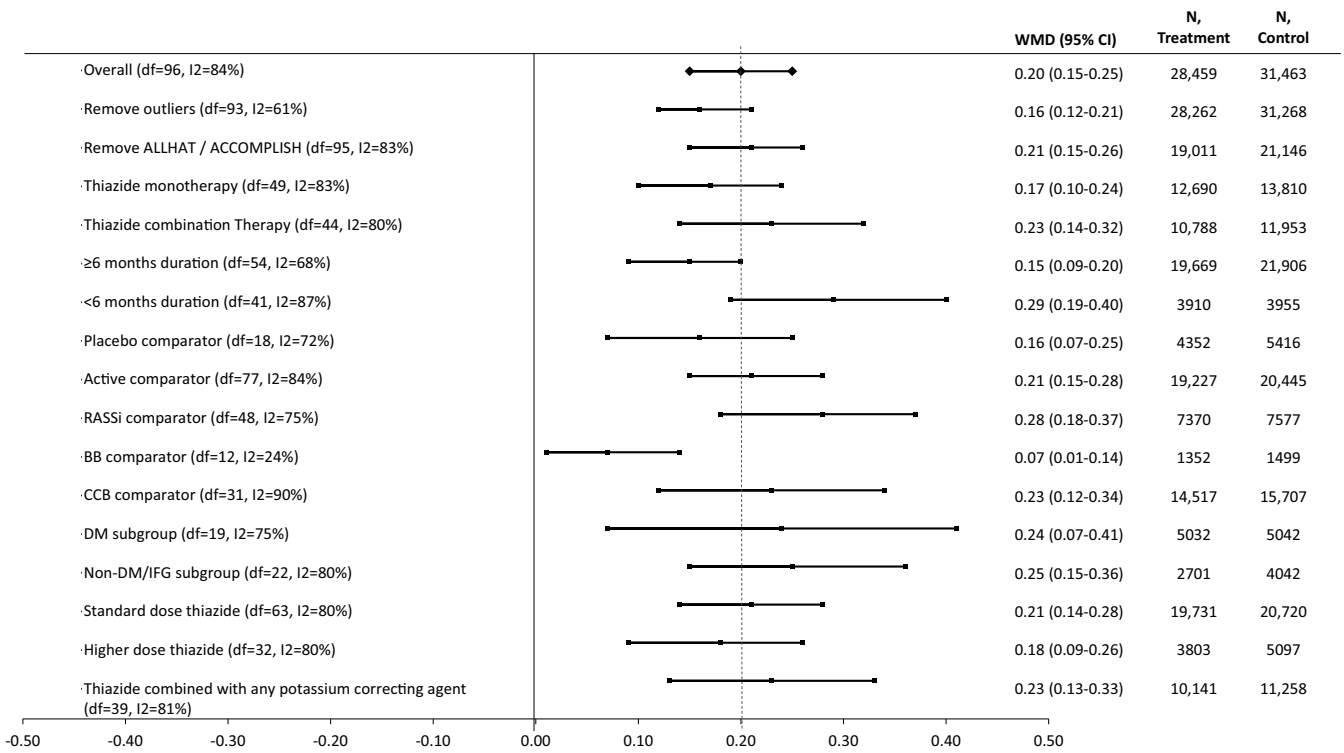

Figure 3 Summary of forest plot demonstrating the weighted mean difference in fasting blood glucose (1 mmol/L = 18 mg/dL) in patients treated with thiazide diuretics overall and in sensitivity and subgroup analyses.

glycemic changes in randomized controlled clinical trials, our study includes a larger number of trials and participants.[125] Zhang et al. concluded that thiazide-type diuretics produce a statistically significant increase in FPG (mean difference (MD) 0.27 mmol/L (95% CI 0.15–0.39)), which was mitigated in the lower dose analysis (MD 0.15 mmol/L (95% CI 0.03–0.27)) and with time (studies < 6 months MD 0.5 mmol/L, compared with studies > 6 months MD − 0.01 mmol/L). Although all 26 included trials were captured in our search, only 15 were included in our analysis primarily for follow-up and sample size reasons. Despite this, the larger number of participants in our analysis and the broader breadth of patients included allowed for a more comprehensive assessment of thiazide use on FPG, particularly among important subgroups of patients not previously assessed in the Zhang et al. paper.

There are several further strengths of our study. We were more inclusive of trial populations as compared with other systematic reviews, and with the analyses including data from 95 trials and 76,608 participants, this is the largest meta-analysis addressing this question. Concerns over the use of a weighted mean difference may exist; however, an analysis of SMD was completed, which allows for the expression of the effect size of the thiazide diuretics in each study relative to its variability despite the inconsistency in study populations and treatment strategies—results were unchanged (SMD 0.17 mmol/L (95% CI 0.12–0.21)). Utilizing FPG rather than new-onset diabetes as an outcome is also a strength, in that the latter is plagued by differing definitions over time and is limited by its low incidence and the short follow-up in individual trials. The use of FPG also enables the inclusion of results for a larger proportion of the study population and is relatively quickly responsive to any influencers; however, it was rarely the study primary outcome, and a one-time unconfirmed measurement may not be accurate and/or reflective of average blood glucose levels. Last, imbalance with respect to studies with large weighted mean differences was observed, which may be due to reporting bias, poor methodological quality, true heterogeneity, or chance.[126] As a result, our results may overestimate the effect of thiazides of FPG.

Our study is not without limitations. Given the timespan over which included studies were conducted, it was not reasonable to analyze patient-level data nor were we successful in obtaining study data (except for 1 article[73]) where papers indicated a measure of glucose without necessary details (authors were either not contactable or no longer had data of interest). The design of included studies also did not enable an analysis of confounding by co-intervention, outside of those which were assigned at randomization. Finally, we excluded non-English papers, deemed reasonable given reports that excluding non-English studies does not influence results of meta-analyses,[13, 14] and results reported only as conference proceedings, and could not access the IPA database after 2014, which may have further limited our dataset.

CONCLUSION

Thiazide diuretics have a small and clinically unimportant impact on FPG.

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