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Hydrochlorothiazide hypertension treatment induced metabolic effects in type 2 diabetes: a meta-analysis of parallel-design RCTs

J.-J. LIN[1], H.-C. CHANG[2], C.-T. KU[3], H.-Y. CHEN[4,5]

[1]Department of Pharmacy, Feng-Yuan Hospital, Ministry of Health Welfare, Taichung, Taiwan, R.O.C
[2]Department of Pharmacy, Taichung Hospital, Ministry of Health Welfare, Taichung, Taiwan, R.O.C
[3]Department of Pharmacy, Tsaotun Psychiatric Center Ministry of Health Welfare, Nantou, Taiwan, R.O.C
[4]School of Pharmacy, China Medical University Hospital, Beikang Campus, Taichung, Taiwan, R.O.C
[5]Institute of Pharmacy, China Medical University, Taichung, Taiwan, R.O.C

Abstract. – OBJECTIVE: Thiazide diuretics are still widely used as an initial therapy in essential hypertension, sometimes in both hypertensive and diabetic patients. However, the metabolic effects in type 2 diabetes treated with a thiazide diuretic have not been fully elucidated.

MATERIALS AND METHODS: Randomized controlled trials (RCTs) were identified from the electronic databases: the Cochrane Library, MEDLINE, and PubMed web of knowledge. The trials compared the metabolic effects of hydrochlorothiazide (HCTZ) versus no- HCTZ hypertension treatment in type 2 diabetes.

RESULTS: A total of 368 papers showed a match, in the keyword search. Upon screening the title, reading the abstract and the entire article, 13 parallel-design RCTs, described in 7 reports, involving 720 patients, showed fasting glucose (FG) (SMD = 0.27, 95% CI 0.11-0.43) and HbA1c (SMD = 1.09, 95% CI 0.47-1.72)significantly increased in the patients treated with HCTZ groups and high-density lipoprotein-cholesterol (HDL-C) (SMD = -0.44, 95% CI -0.81- -0.08) decreased in the patients treated with low-dose HCTZ groups. Our study showed FG, HbA1c and HDL-C significantly affected in the patients treated with low-dose HCTZ groups.

CONCLUSIONS: Our study showed FG and HbA1c increased in the patients treated with the low-dose HCTZ groups, and HDL-C decreased in the patients. While thiazide diuretics are still a recommended medication of hypertension therapy for type 2 diabetes, treatment with low-dose HCTZ should be attempted to evaluate the effectiveness and adverse metabolic effects.

Key Words:
Hydrochlorothiazide, Metabolic effects, NIDDM.

Introduction

The prevalence of diabetes with hypertension is 1.5 to 3 times greater than those without diabetes in age-matched groups. About 20-60% of type 2 diabetics suffer from high blood pressure. Research shows type 2 diabetics with hypertension are 1.5 times more common than those without diabetes[1]. Age, obesity, insulin resistance and other factors such as racial differences may have high blood pressure causes. Therefore, the complex disease management mechanism makes differences in prevalence difficult to estimate correctly.

In 2014, the Eighth Joint National Committee from many experts confirmed the lower BP treatment goal of less than 140/90 mm Hg for patients with diabetes[2]. A recent study involving patients without diabetes who had hypertension reported patients randomly assigned to a tight-control BP (systolic BP <130 mm Hg) treatment group had a significantly lower prevalence of left ventricular hypertrophy, an intermediate outcome known to be a strong predictor of cardiovascular outcomes, and a significantly reduced risk of a secondary outcome, which included cardiovascular morbidity or all-cause mortality[3]. The ACCORD BP trial evaluated the effect of targeting a systolic blood pressure of 140 mm Hg, among patients with type 2 diabetes at high risk for cardiovascular events[4].

Thiazide diuretics are still widely used as the initial therapy in essential hypertension, and are superior in preventing one or more major forms of cardiovascular disease. Studies show an advantage in cardiovascular outcomes of initial

Corresponding Author: Chen-Ting Ku, MD; e-mail: ctku@ttpc.mohw.gov.tw

therapy with low-dose thiazide diuretics[5,6]. However, the optimal dose of thiazide/thiazide-like diuretics is unclear, and the metabolic effects in NIDDM treated with a thiazide diuretic have not been fully elucidated.

An international verapamil SR-trandolapril study (INVEST)[7] showed the addition of hydrochlorothiazide (HCTZ) dose-dependently increased the risk for new-onset diabetes, not only in patients who received atenolol, but also in those who were treated with verapamil. Similarly, a valsartan antihypertensive long-term use evaluation (VALUE) trial[8] showed a greater incidence of new-onset diabetes can be tentatively explained by the greater occurrence of hypokalemia induced by the association of HCTZ.

Materials and Methods

Criteria for Considering Studies for this Review

A computerized literature search used the electronic databases: the Cochrane Library (December 2014), MEDLINE (1966-December 2014), and PubMed (1966-December 2014). Randomized controlled trials (RCTs) investigating the effect of HCTZ in the treatment of patients with type 2 diabetes and hypertension were examined. Specific endpoints, particularly death, can only be assessed with parallel group trials. Therefore crossover trials were excluded. Crossover studies did not present data in a way that could be included in the meta-analyses[9]. Patients with unstable or type 1 diabetes were not included in the study.

Literature references were manually retrieved at the same time. The keywords for the search were hydrochlorothiazide and thiazide. Other words used were non insulin-dependent diabetes mellitus, type 2 diabetes mellitus, diabetes, RCT or clinical trials. All of the literature included at least an abstract in the English language, followed by the full text.

The resulting citations were then limited to human subjects, clinical trials, and English language publications. To identify additional relevant trials, a manual search of references from reports of clinical trials or review articles was performed. Patients with unstable or insulin-dependent diabetes mellitus were not included in the study. Patients were excluded when they had severe target organ damage, active ischemic heart disease, evidence of chronic liver disease, active peptic ulcer, or any gastrointestinal disease that may affect absorption.

Trials with pre-term infants were excluded, as this patient group is covered in another Cochrane Review. Studies in animal models were excluded.

Primary Analyses

Patients were randomized into a parallel group study, with mild to moderate essential hypertension and NIDDM in a stable metabolic controlled diet, hypoglycemic agents or/and stable albuminuria throughout these studies. The utilized definition of 'HCTZ' was as given by the authors of the studies.

The inhibitors of the renin-angiotensin system (RAS) might further reduce albuminuria in hypertensive diabetic patient. In general, ACEIs and ARBs are the same pharmacologic mechanisms. Combination therapy is frequently required for optimal control of BP, and the amount of the decrease in BP by a two-drug combination is approximately the same as the sum of the decrease by each individual drug if their mechanisms of action are independent, with the exception of the combination of ACEIs and ARBs[10]. ADA recommendation[11], ABCD trial[12], and Micro-HOPE[13] have suggested that RAS may have unique advantages for initial or early therapy of hypertension in people with diabetes.

We performed a validation study to compare the high dose of HCTZ with the low dose, a dose > 25 mg per day is considered high, and is associated with a significant increase in side effects, including metabolic derangement[10].

Data Collection

The following variables were collected: blood samples for measurements of fasting glucose (FG), HbA1c, triglyceride (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), uric acid (UA), and potassium(K) between HCTZ and conventional therapy. We converted these levels to the same unit. For example: to convert LDL-C or HDL C levels from mmol/L to mg/dL, we divided the number given in mmol/L by 0.0259[14]. All analyses were not adjusted in this study.

Subgroup Analyses

In subgroup analyses we assessed the metabolic effects of HCTZ according to dose (any treatment

dose or ≤ 25 mg per day) versus no-HCTZ, and HCTZ with low dose (HCTZ+ACEI or ARB) according to pharmacologic mechanisms with no-HCTZ (ACEI+CCB, ACEI or ARB) hypertension treatment in NIDDM.

Statistical Analysis

The statistical analysis was performed using MedCalc Version 9.6 software (MedCalc Software, Belgium)[15]. Meta-analysis of studies with a continuous measure was used to test the significance of the treatment effect. MedCalc uses the Hedges g statistic as a formulation for the standardized mean difference (SMD) under the fixed effects model. The heterogeneity statistic is incorporated to calculate the summary standardized mean difference under the random effects model (DerSimonian and Laird[16]). This assumption is tested by the "Heterogeneity test". If this test yields a low *p*-value ($p<0.05$), then the fixed effects model may be invalid. SMD with 95% CI is given both for the fixed effects model and the random effects model. If the test of heterogeneity is statistically significant ($p<0.05$), then more emphasis should be placed on the random effects model. Statistical heterogeneity was assessed using the I^2 statistic and the Chi-square test for heterogeneity[17]. A two-sided significance level of 5% was considered evidence of statistical significance and corresponding confidence intervals (CI) were calculated.

Results

A total of 479 articles were identified. We excluded duplication (73 articles), review articles (8 articles), cross-over studies (37 article), studies in which patients did not receive HCTZ (11 articles), studies which did not examine the association between HCTZ and metabolic effect outcomes (32 articles), and studies which did not have a comparator (3 articles). Of the 7 publications included, 1 reported 6 separate trials, 1 reported two independent trials and 5 reported one trial within their publication. Following this, 13 parallel-design RCTs described in 7 reports involving 720 patients met our inclusion criteria (Figure 1).

Six reports were performed in western countries and one in Taiwan. Five reports were described as double-blind and two were open-label. Four reports reported participants with NIDDM and stable microalbuminuria, and three reports did not provide information on albuminuria. Six trials were described as high-dose therapy from Lacourcière et al[18] 1993 and six were low-dose therapy from others.

The characteristics of the studies included in the meta-analysis are presented in Table I.

Metabolic Effects of HCTZ Versus No-HCTZ Hypertension Treatment in NIDDM (Table II)

There were 12 trials described in 7 reports involving 696 patients that were included in the meta-analysis.

FG (SMD = 0.27, 95% CI 0.11-0.43, $p<0.05$) and HbA1c (SMD = 1.09, 95% CI 0.47-1.72, $p<0.05$) significantly increased in the patients treated with HCTZ groups, then the test of FG for heterogeneity was not heterogeneous and the fixed effects model was used.

Potassium levels were significantly decreased in the HCTZ groups with SMD -0.55 (95% CI -1.05- -0.04, $p<0.05$). The test for heterogeneity was significant.

TG, HDL-C, LDL-C and UA were not significantly affected by either treatment, while TC significantly increased (SMD = 0.53, 95% CI 0.1-0.96, $p<0.05$) in the patients treated with the HCTZ groups. The test for heterogeneity was significant.

Metabolic Effects of HCTZ with low Dose Versus no- HCTZ Hypertension Treatment in NIDDM (Table II)

There were 7 trials described in 6 reports involving 615 patients that were included in the meta-analysis.

FG (SMD = 0.27, 95% CI 0.11-0.43, $p<0.05$) and HbA1c (SMD = 0.92, 95% CI 0.3-1.55, $p<0.05$) significantly increased in the patients treated with the HCTZ groups, then the test of FG for heterogeneity was not heterogeneous and the fixed effects model was used.

Potassium levels were significantly decreased in the HCTZ groups with SMD -0.55 (95% CI -1.05- -0.04, $p<0.05$). The test for heterogeneity was significant.

TC, TG, LDL-C and UA were not significantly affected by either treatment, while HDL-C significantly decreased (SMD = -0.44, 95% CI -0.81- -0.08, $p<0.05$) in the patients treated with the HCTZ groups. The test for heterogeneity was significant.

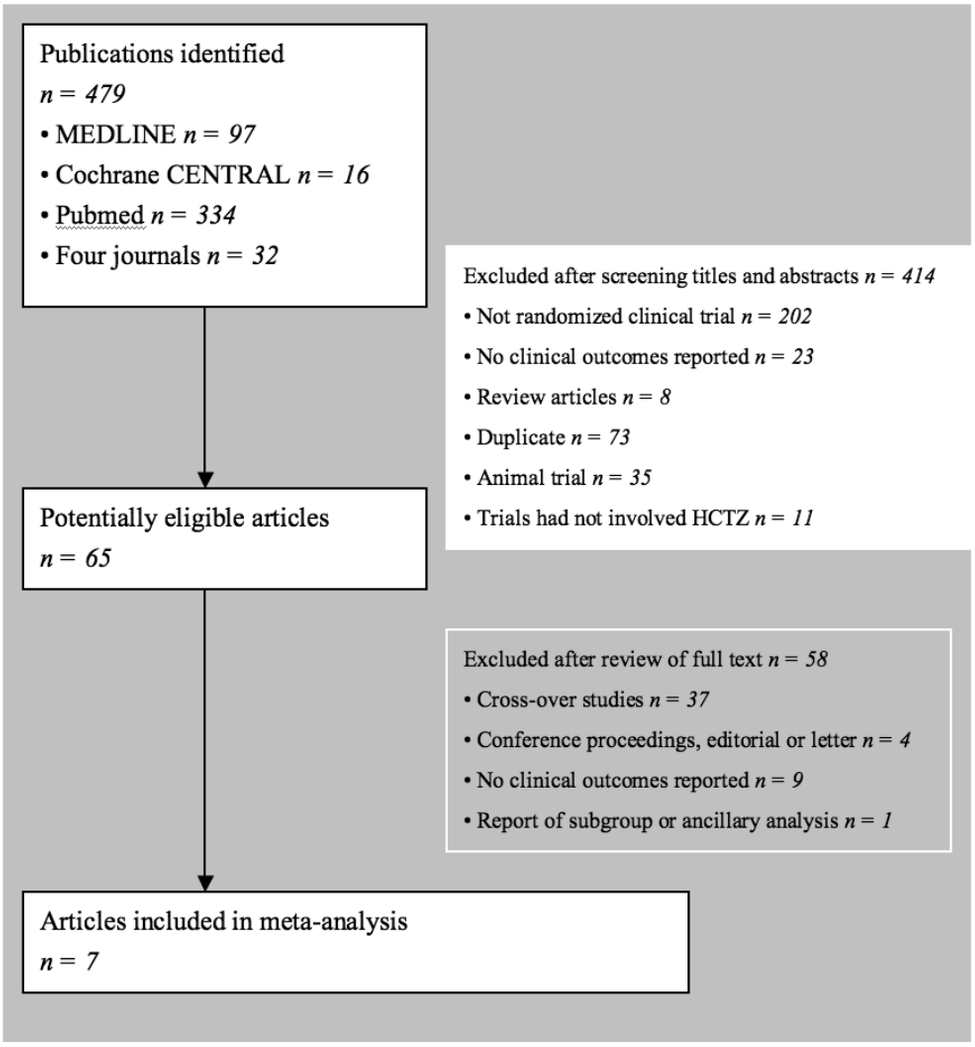

Figure 1. Diagram of study selection results.

Metabolic Effects of HCTZ with low Dose (HCTZ+ACEI or ARB) Versus no- HCTZ (ACEI+CCB) Hypertension Treatment in Type 2 Diabetes (Table III)

Four trials described in four reports involving 486 patients were included in the meta-analysis.

FG (SMD = 0.23, 95% CI 0.05-0.41, $p<0.05$) and HbA1c (SMD = 0.85, 95% CI 0.18-1.51, $p<0.05$) significantly increased in the patients treated with the HCTZ groups, then the test of FG for heterogeneity was not heterogeneous and the fixed effects model was used.

TC, TG, LDL-C, UA and potassium levels were not significantly affected by either treatment, while HDL-C significantly decreased (SMD = -0.39, 95% CI -0.76- -0.02, $p<0.05$) in the patients treated with HCTZ groups. The test for heterogeneity was significant.

Metabolic Effects of HCTZ with low Dose (HCTZ+ACEI or ARB) Versus no- HCTZ (ACEI or ARB) Hypertension Treatment in Type 2 Diabetes (Table III)

There were 3 trials described in 2 reports involving 129 patients that were included in the meta-analysis.

FG (SMD = 0.23, 95% CI 0.05-0.41, $p<0.05$) and HbA1c (SMD = 0.85, 95% CI 0.18-1.51, $p<0.05$) significantly increased in the patients treated with HCTZ groups, then the test of FG for heterogeneity was not heterogeneous and the fixed effects model was used.

Potassium levels were significantly decreased in the HCTZ groups with SMD -0.42 (95% CI -0.78- -0.05, $p<0.05$). The test for heterogeneity was not heterogeneous and the fixed effects model was used.

Table I. Characteristics of studies included in the meta-analysis.

	Lacourcière 1993[18]	Shamiss 1995[19]	Fernandez 2001[20]	Pablos-Velasco 2002[21]	Mugellini 2004[22]	Fogari 2008[23]	Lee 2012[24]
No. of cases	74	10	93	150	76	150	167
Blinding	Double blind	NR	Double blind	Open label	Double blind	Open label	Double blind
Max. dose of H (mg/d)	50	12.5	12.5	12.5	12.5	25	25
Age (years)	45-75	42-70	54.9±9.3	61±10.7	41-65	66-74	20-80
Albuminuria	MAP	NR	MAP	MAP	NR	NR	MAP
Country	Canada	Israel	Spain	Spain	Italy	Italy	Taiwan
Duration (weeks)	144	8	24	4	8	48	16
No. of trials	6	1	1	2	1	1	1
Exclusion criteria	SCr > 1.2	SCr > 1.5	SCr >3	SCr > 1.4	SCr >1.15	SCr > 1.4	SCr >2-fold
HCTZ groups	H+ACEI/ B: (1) H (2) H+ metoprolol (3) H+ captopril	H+ACEI: H+enalapril	H+ACEI: H+enalapril	H+ ARB: H+losartan	H+ARB: H +irbesartan	H+ARB: H+olmesartan	H+ARB: H+valsartan
no-HCTZ groups	ACEI/B: (1) captopril (2) metoprolol	ACEI: enalapril	ACEI+CCB: verapamil+ trandolapril	ARB: (1) losartan 50 mg (2) losartan 100 mg	ACEI+CCB: delapril+ manidipine	ACEI+CCB: delapril+ manidipine	ACEI+CCB: benazepril+ amlodipine
Jadad Quality Score	4	1	4	2	4	2	4

ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blocker, B = beta blocker, CCB = calcium channel blockers, H = HCTZ, MAP= mixed albuminuria participants, NR = no report, SCr = serum creatinine (mg/dL)

Table II. Metabolic effects of HCTZ versus no-HCTZ hypertension treatment in type 2 diabetes.

						HCTZ with low dose				
Outcome	No. of trials	SMD	95% CI	I2	*p*-value	No. of trials	SMD	95% CI	I2	*p*-value
FG	n=7	0.27	0.11-0.43	0%	0.0009	n=7	0.27	0.11-0.43	0%	0.0009
HbA1c	n=5	0.92	0.3-1.55	89%	0.004	n=5	0.92	0.3-1.55	89%	0.004
TC	n=12	0.53	0.1-0.96	85%	0.02	n=6	-0.03	-0.41-0.35	75%	0.87
TG	n=12	0.02	-0.4-0.43	84%	0.94	n=6	0.2	-0.2-0.61	79%	0.32
HDL-C	n=10	0.28	-0.29-0.85	89%	0.33	n=4	-0.44	-0.81- -0.08	65%	0.02
LDL-C	n=9	0.21	-0.21-0.63	81%	0.33	n=3	0.01	-0.57-0.6	88%	0.97
UA	n=5	0.07	-0.35-0.48	81%	0.75	n=5	0.07	-0.35-0.48	81%	0.75
K	n=5	-0.55	-1.05- -0.04	87%	0.03	n=5	-0.55	-1.05- -0.04	87%	0.03

ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blocker, B = beta blocker, CCB = calcium channel blockers, H = HCTZ, MAP= mixed albuminuria participants, NR = no report, SCr = serum creatinine (mg/dL)

Table III. Metabolic effects of HCTZ with low dose versus no-HCTZ hypertension treatment in type 2 diabetes.

						HCTZ+ ACEI/ ARB versus ACEI/ARB				
Outcome	No. of trials	SMD	95% CI	I2	*p*-value	No. of trials	SMD	95% CI	I2	*p*-value
FG	n=4	0.23	0.05-0.41	0%	0.01	n=3	0.43	0.08-0.78	0%	0.02
HbA1c	n=4	0.85	0.18-1.51	92%	0.01	n=1	1.59	0.06-3.12	-	0.04
TC	n=4	-0.05	-0.58-0.48	86%	0.85	n=3	0.02	-0.64-0.69	63%	0.95
TG	n=3	0.28	-0.28-0.84	87%	0.33	n=3	0.05	-0.49-0.59	47%	0.86
HDL-C	n=3	-0.39	-0.76- -0.02	71%	0.04	n=1	-1.31	-2.76-0.13	-	0.07
LDL-C	n=3	0.01	-0.57-0.60	88%	0.97	n=0	-	-	-	-
UA	n=3	0.28	-0.18-0.74	81%	0.23	n=2	-0.31	-0.77-0.14	34%	0.17
K	n=3	-0.63	-1.41- 0.15	93%	0.11	n=2	-0.42	-0.78- -0.05	0%	0.03

TC, TG, HDL-C and UA were not significantly affected by either treatment, and there was no report in LDL-C.

Discussion

Not only did the thiazide diuretics increase blood total cholesterol, triglycerides and low-density lipoprotein, as well have high density lipoprotein effects, but they also consistently decreased plasma potassium and the secretion of insulin, and increased blood sugar. Our study showed FG and HbA1c increased in the patients treated with HCTZ groups, even through low-dose treatment, and HDL-C decreased in the patients treated with low-dose HCTZ groups. However, these results showed the high degree of heterogeneity except FG. A high LDL to HDL ratio is a predictor of an increased risk of cardiovascular disease[25]. The relationship between insulin resistance, plasma insulin level, and glucose intolerance is mediated to a significant degree by changes in ambient plasma free-fatty acid (FFA) concentration. Patients with type 2 diabetes are also resistant to insulin suppression of plasma FFA concentration, but plasma FFA concentrations can be reduced by relatively small increments in insulin concentration[26]. The mechanism by which thiazides alter lipid profiles is poorly understood.

Other metabolic effects of thiazide diuretics include electrolyte imbalance and sexual dysfunction. Each 0.5-mEq/L decrease in serum potassium was associated with a 45% increased risk of developing diabetes throughout the course of the study[27]. A prospective study found no significant correlation between changes in serum potassium and serum glucose in HCTZ-treated patients with 12.5 or 25 mg/day for 9 weeks, but Smith et al[28] mentioned that higher doses may be prone to significantly greater adverse metabolic consequences, including more hypokalemia and hyperglycemia. Tuck[29] pointed out hypokalemia can impair glucose metabolism by reducing insulin secretion and insulin sensitivity. Diuretics are a number of side effects. However, the SHEP study[30] showed 5-year major cardiovascular disease (CVD) rate was lower for diabetic patients in low-dose diuretic-based treatment. A meta-analysis study indicated low-dose thiazide diuretics and other antihypertensive agents lowered BP to a similar degree and low-dose thiazide diuretics are the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality[31].

Diabetic nephropathy occurs in 20-40% of patients with diabetes and is the single leading cause of end-stage renal disease. Microalbuminuria is also a well-established marker of increased CVD risk[32]. A higher proportion of individuals with type 2 diabetes were found to have microalbuminuria after the diagnosis of their diabetes[33]. There are four reports including patients with stable microalbuminuria in our study, and the other three reports did not show this. The CHILI T2D Study[34] evaluated 4110 patients with type 2 diabetes, all stages of hypertension and microalbuminuria. The research showed the favourable metabolic profile of low-dose HCTZ therapy.

The optimal dose of thiazide/thiazide-like diuretics is unclear, but higher doses, that is, >25 mg hydrochlorthiazide, should be avoided because such doses will further increase the risk of metabolic abnormalities[35]. Beta-blockers can also affect blood sugar. But, low doses of HCTZ did not include beta blockers in our study, there were HCTZ, CCB, ACEI, and ARB in our subgroup analysis.

Our study has several potential limitations. First, we did not have enough information to evaluate the effect of HCTZ therapy on glucose and lipid metabolisms in the 7 publications. Second, this meta-analysis includes only small-scaled 7 trials with relatively short observation periods. Only 1 trial had the duration more than 1 year. Thirdly, 37 crossover trials were excluded. Cross-over studies did not present data in a way that could be included in the meta-analyses, we could not calculate whether 37 crossover trials may have influenced. Consequently, additional large and long observation period studies should be performed to evaluate our results and further resolve the uncertainty regarding the effect of HCTZ on glucose and lipid metabolisms in type 2 diabetes patients.

Conclusions

The risk of type 2 diabetes is higher in persons with metabolic syndrome and diabetes is a major risk factor for CVD. It also examined various criteria for a clinical diagnosis of the metabolic syndrome[36]. Thiazide diuretics were probably also the main cause of the metabolic changes observed with the high or low-dose HCTZ treat-

ment, notably an increase in FG and HbA1c and a decrease in serum potassium and HDL-C with the low-dose HCTZ groups. However, these results showed the high degree of heterogeneity except FG.

While thiazide diuretics are still a recommended medication of hypertension therapy for type 2 diabetes, treatment with low-dose HCTZ should be attempted to evaluate the effectiveness and adverse metabolic effects. Antihypertensive medications could be due to the dosages, monotherapy or in combination; they are suggested by international guidelines that reflect concerns about the risk of side effects[37].

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Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Turner, RC; Holman, RR; Matthews, DR; Bassett, PA; Coster, R; Stratton, IM; Cull, CA; Peto, R; Frighi, V; Kennedy, IA; Manley, SE; Bown, EG; Eeley, EA; Ross, I; Matthews, DR; Dornan, TL; Wright, AD; Neil, HAW; Kohner, EM; Aldington, S; Keen, N; Rose, C; Fletcher, AE; Battersby, C; Yudkin, JS; Oakes, SF; Turner, RC; Holman, RR; Stearn, MR; Palmer, SL; Hammersley, MS; Franklin, SL; Spivey, RS; Hockaday, TDR; Murchison, LE; Brunt, AHE; Williams, MJ; Macpearson, DW; Petrie, XMP; Lean, MEJ; Wright, AD; Levi, NA; Shearer, ACI; Thompson, RJW; Kohner, EM; Doddridge, MC; Hayes, JR; Henry, RW; Fetherston, MS; Hadden, DR; Kennedy, L; Atkinson, AB; Culbert, AM; Hagan, C; Spathis, AS; Nanson, ME; James, LM; Tyrell, JM; Yudkin, JS; Gould, C; Singer, J; Badenoch, M; Greenwood, RH; Wilson, J; Denholm, MJ; Temple, RC; Borthwick, LJ; Wheatcroft, DJ; Seaman, RJ; Christie, RA; Newton, RW; Jung, RT; Roxburgh, C; Kilgallan, B; Fox, CJ; Holloway, MC; Coghill, HM; Paisey, RB; Brown, NPR; Tucker, AJ; Roland, JM; Brown, DJ; Youens, J; Brown, PM; Davidson, AJM; Peacock, IDA; Culverwell, NJC; Charlton, MH; Connolly, BPS; Boulton, AJM; Robertson, AM; Young, RJ; Dornan, TL; Clyne, JRr; Burden, AC; Sellen, EM; Tooke, JE. Hypertension in Diabetic Study (HDS): Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. J Hypertens 1993; 11: 309-317.

2) James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014; 311: 507-520.

3) Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A, Mureddu G, Pede S, Maggioni AP, Lucci D, Reboldi G; Cardio-Sis investigators. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. Lancet 2009; 374: 525-533.

4) The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010; 362:1575-1585.

5) ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The antihypertensive and lipid-lowering treatment to prevent heart attack trial: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). JAMA 2002; 288: 2981-2997.

6) Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network metaanalysis. JAMA 2003; 289: 2534-2544.

7) Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW; INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): A randomized controlled trial. JAMA 2003; 290: 2805-2816.

8) Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomized trial. Lancet 2004; 363: 2022-2031.

9) Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. Int J Epid 2002; 31: 140-149.

10) Chiang CE, Wang TD, Li YH, Lin TH, Chien KL, Yeh HI, Shyu KG, Tsai WC, Chao TH, Hwang JJ, Chiang FT, Chen JH; Hypertension Committee of the Taiwan Society of Cardiology. 2010 Guidelines of the Taiwan Society of Cardiology for the Management of Hypertension. J Formos Med Assoc 2010; 109: 740-773.

11) Executive Summary: standards of medical care in diabetes. Diabetes Care 2010; 33: S4-S10.

12) Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998; 338: 645-652.

13) Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000; 355: 253-259.

14) Fauci AS, Kasper DL, Longo DL, Braunwald E, Hauser SL, Jameson JL, Loscalzo J. Harrison's principles of internal medicine17th Edition. U.S.A.: McGraw-Hill Companies; 2008. Appendix: laboratory values of clinical importance.

15) MedCalc for Windows. Statistics for biomedical research software manual. Ostend, Belgium: MedCalc Software bvba, 2011; pp. 125-126.

16) DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177-188.

17) Higgins J, Thompson S: Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.

18) Lacourcière Y, Nadeau A, Poirier L, Tancrède G. Captopril or conventional therapy in hypertensive type II diabetics. Three-year analysis. Hypertension 1993; 21: 786-794.

19) Shamiss A, Carroll J, Peleg E, Grossman E, Rosenthal T. The Effect of enalapril with and without hydrochlorothiazide on insulin sensitivity and other metabolic abnormalities of hypertensive patients with NIDDM. Am J Hypertens 1995; 8: 276-281.

20) Ferna´ndez R, Puig JG, Rodri´guez-Pe´rez JC, Garrido J, Redon J. Effect of two antihypertensive combinations on metabolic control in type-2 diabetic hypertensive patients with albuminuria: a randomised, double-blind study. J Human Hypertension 2001; 15: 849-856.

21) de Pablos-Velasco PL, Pazos Toral F, Esmatjes JE, Fernandez-Vega F, Lopez de la Torre ML, Pozuelo A, Ruilope LM. Losartan titration versus diuretic combination in type 2 diabetic patients. J Hypertens 2002; 20: 715-719.

22) Mugellini A, Preti P, Zoppi A, Corradi L, Fogari E, Derosa G, Fogari R. Effect of delapril–manidipine combination vs irbesartan–hydrochlorothiazide combination on fibrinolytic function in hypertensive patients with type II diabetes mellitus. J Human Hypertension 2004; 18: 687-691.

23) Fogari R, Derosa G, Zoppi A, Rinaldi A, Preti P, Lazzari P, Mugellini A. Effects of manidipine/delapril versus olmesartan/hydrochlorothiazide combination therapy in elderly hypertensive patients with type 2 diabetes mellitus. Hypertens Res 2008; 31: 43-50.

24) Lee IT, Hung YJ, Chen JF, Wang CY, Lee WJ, Sheu WHH. Comparison of the efficacy and safety profiles of two fixed-dose combinations of antihypertensive agents, amlodipine/ benazepril versus valsartan/hydrochlorothiazide, in patients with type 2 diabetes mellitus and hypertension: a 16-week, multicenter, randomized, double-blind, noninferiority study. Clin Ther 2012; 34: 1735-1750.

25) Millán J, Pintó X, Muñoz A, Zúñiga M, Rubiés-Prat J, Pallardo LF, Masana L, Mangas A, Hernández-Mijares A, González-Santos P, Ascaso JF, Pedro-Botet J. Lipoprotein ratios: physiological significance and clinical usefulness in cardiovascular prevention. Vasc Health Risk Manag 2009; 5: 757-765.

26) Reaven GM: Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-1607.

27) Shafi T, Appel LJ, Miller ER 3rd, Klag MJ, Parekh RS. Changes in serum potassium mediate thiazide-induced diabetes. Hypertension 2008; 52: 1022-1029.

28) Smith SM, Anderson SD, Wen S, Gong Y, Turner ST, Cooper-Dehoff RM, Schwartz GL, Bailey K, Chapman A, Hall KL, Feng H, Boerwinkle E, Johnson JA, Gums JG. Lack of correlation between thiazide-induced hyperglycemia and hypokalemia: subgroup analysis of results from the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study. Pharmacotherapy 2009; 29: 1157-1165.

29) Tuck ML: Metabolic considerations in hypertension. Am J Hypertens 1990; 3: 355S–365S.

30) Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension: Systolic Hypertension in the Elderly Program Cooperative Research Group. JAMA 1996; 276: 1886-1892.

31) Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, Lemaitre RN, Wagner EH, Furberg CD. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA 1997; 277: 739-745.

32) Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, Appleyard M, Jensen JS. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation 2004; 110: 32-35.

33) Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, Steffes MW; American Diabetes Association. Nephropathy in diabetes. Diabetes Care 2004; 27(Suppl 1): S79-83.

34) Ketelhut R and Bramlage P. CandesartanCilexetil/Hydrochlorothiazide treatment in high-risk patients with type 2 diabetes mellitus and microalbuminuria. Clin Drug Investie 2010; 30: 301-311.

35) Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM; BHS guidelines working party, for the British Hypertension Society. Guidelines for management of hypertension BHS IV. J Human Hypertension 2004; 18: 139-185.

36) Grundy SM, Hansen B, Smith SC, Cleeman JI, Kahn RA. Clinical management of metabolic syndrome. Circulation 2004; 109: 551-556.

37) Pannarale G, Licitra R, Leonetti S, Arrivi A, Corsi F, Gianturco L, Mirabelli F, Acconcia MC, Gaudio C. Efficacy and safety of evaluation of systolic blood pressure control in elderly patients with isolated systolic hypertension. Eur Rev Med Pharmacol Sci 2006; 10: 111-114.