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Impact of Abdominal Obesity on Incidence of Adverse Metabolic Effects Associated With Antihypertensive Medications

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Abstract—We assessed adverse metabolic effects of atenolol and hydrochlorothiazide among hypertensive patients with and without abdominal obesity using data from a randomized, open-label study of hypertensive patients without evidence of cardiovascular disease or diabetes mellitus. Intervention included randomization to 25 mg of hydrochlorothiazide or 100 mg of atenolol monotherapy followed by their combination. Fasting glucose, insulin, triglycerides, high-density lipoprotein cholesterol, and uric acid levels were measured at baseline and after monotherapy and combination therapy. Outcomes included new occurrence of and predictors for new cases of glucose ≥ 100 mg/dL (impaired fasting glucose), triglyceride ≥ 150 mg/dL, high-density lipoprotein ≤ 40 mg/dL for men or ≤ 50 mg/dL for women, or new-onset diabetes mellitus according to the presence or absence of abdominal obesity. Abdominal obesity was present in 167 (58%) of 395 patients. Regardless of strategy, in those with abdominal obesity, 20% had impaired fasting glucose at baseline compared with 40% at the end of study ($P < 0.0001$). Proportion with triglycerides ≥ 150 mg/dL increased from 33% at baseline to 46% at the end of study ($P < 0.01$). New-onset diabetes mellitus occurred in 13 patients (6%) with and in 4 patients (2%) without abdominal obesity. Baseline levels of glucose, triglyceride, and high-density lipoprotein predicted adverse outcomes, and predictors for new-onset diabetes mellitus after monotherapy in those with abdominal obesity included hydrochlorothiazide strategy (odds ratio: 46.91 [95% CI: 2.55 to 862.40]), female sex (odds ratio: 31.37 [95% CI: 2.10 to 468.99]), and uric acid (odds ratio: 3.19 [95% CI: 1.35 to 7.52]). Development of adverse metabolic effect, including new-onset diabetes mellitus associated with short-term exposure to hydrochlorothiazide and atenolol was more common in those with abdominal obesity. (*Hypertension*. 2010;55:61-68.)

Key Words: atenolol ■ hydrochlorothiazide ■ abdominal obesity ■ metabolic syndrome
■ new-onset diabetes mellitus ■ hypertension

It is estimated that >72 million US adults are obese, affecting 33% of men and 35% of women.¹ This epidemic is associated with increased mortality,² primarily via metabolic and cardiovascular (CV) complications. Abdominal fat accumulation increases CV disease risk independent of overall adiposity.³ The presence of abdominal obesity provides additional predictive information for the development of CV morbidity and mortality compared with increased body mass index alone.⁴ Hypertension requiring treatment is highly prevalent in those with obesity and abdominal obesity,

regardless of sex or ethnicity, and is poorly controlled.⁵⁻⁷ Some antihypertensives are associated with adverse metabolic effects (AMEs), including hyperglycemia, hypertriglyceridemia, and hyperuricemia.⁸ The predisposing factors for these AMEs are unknown, but preexisting abdominal obesity may contribute. Although there are many studies in older, high-risk populations indicating that thiazide diuretics and β -blockers increase the incidence of new-onset diabetes mellitus compared with other antihypertensive regimens,⁹ our knowledge is incomplete with regard to the development of

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R.M.C.-D. and S.W. had full access to all of the data used in this study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

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PEAR has been registered at www.clinicaltrials.gov (identifier NCT00246519).

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AMEs in those with a lower CV risk profile and the contribution of abdominal obesity to this risk.

Accordingly, we investigated early AMEs and clinical characteristics predictive of early AMEs among those with and without abdominal obesity in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) Study. We hypothesized that antihypertensive-induced AMEs develop preferentially in those with abdominal obesity.

Methods

This study includes analysis of the AME data from a contemporary population of low-risk hypertension subjects enrolled in the PEAR Study. PEAR is an ongoing, prospective, randomized, parallel group titration study undertaken primarily to evaluate the pharmacogenomic determinants of the antihypertensive and adverse metabolic responses to hydrochlorothiazide (HCTZ) and atenolol in hypertensive patients without a history of heart disease or diabetes mellitus. Details regarding study design and enrollment criteria have been published previously.¹⁰

Study Population

Men and women with mild-to-moderate essential hypertension within age 17 to 65 years are being recruited from primary care populations at the University of Florida, Emory University, and the Mayo Clinic. Enrolled subjects had newly diagnosed, untreated or treated hypertension. Those in whom hypertension was treated had antihypertensives discontinued with a minimum washout of 18 days.

Protocol

The study has been conducted in accordance with the provisions of the Declaration of Helsinki and was approved by the institutional review boards at each institution. Written, informed consent was provided by each patient before participation. Those meeting the blood pressure (BP) inclusion criteria were randomly assigned at each study site to receive HCTZ or atenolol. HCTZ and atenolol were initiated at 12.5 mg and 50.0 mg daily, respectively, and titrated to 25.0 mg and 100.0 mg daily on the basis of BP. After ≥ 6 weeks of 25 mg of HCTZ or 100 mg of atenolol or maximum tolerated dose, response to monotherapy was assessed. Then, those with BP remaining $> 120/70$ mm Hg had the second drug added and titrated to the maximum dose. Response to combination therapy was assessed after 6 weeks on both drugs at the maximum tolerated dose.

Anthropometric Measurements

Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Waist circumference was measured to the nearest 0.5 cm by placing a tape measure snugly around the abdomen at the level of the umbilicus just above the uppermost lateral border of the right iliac crest and at the normal minimal respiration with the patient in standing position and with his/her hands by the side. Patients were categorized as having abdominal obesity if their waist measured ≥ 35 in for women or ≥ 40 in for men.¹¹

Laboratory Measurements

At baseline, fasting blood samples were collected for glucose, insulin, potassium, magnesium, uric acid, and a lipid profile. Blood samples were collected again, after a 12-hour fast, at the completion of the monotherapy and combination therapy phases of the study. Insulin sensitivity using homeostasis model assessment-insulin resistance (HOMA-IR) was calculated at each time point according to a validated formula.¹² Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation.¹³

Biochemical Assays

Serum potassium, magnesium, glucose, triglyceride, high-density lipoprotein (HDL) cholesterol, and uric acid concentrations were measured on an Hitachi 911 Chemistry Analyzer (Roche Diagnos-

tics) at the central laboratory at the Mayo Clinic. Potassium and magnesium concentrations were determined by an ion selective electrode, and glucose, triglycerides, HDL cholesterol, and uric acid concentrations were determined spectrophotometrically by automated enzymatic assays. Low-density lipoprotein (LDL) cholesterol was computed. Plasma insulin was measured using the Access Ultrasensitive Insulin immunoassay system (Beckman Instruments). All of the samples were tested in duplicate, and data reported are the means of the duplicate samples.

Metabolic Outcomes

Within abdominal obesity categories, we compared the percentage of patients with glucose < 100 and ≥ 100 mg/dL, triglycerides < 150 and ≥ 150 mg/dL, and HDL < 40 for male and < 50 for female (hereafter termed "low HDL") or ≥ 40 for male and ≥ 50 for female at baseline and after monotherapy and combination therapy in the 2 treatment strategies, respectively. These categories were picked on the basis of their inclusion in the definition of metabolic syndrome (MetSyn).¹¹ In addition, we compared the percentage of patients with incident diabetes mellitus (fasting glucose: ≥ 126 mg/dL) after monotherapy and combination therapy within waist groups and treatment strategies. Lastly, we assessed the clinical characteristics that were predictive for development of these outcomes after monotherapy in those in whom the outcomes were absent at baseline.

Statistical Analysis

Nonparametric tests were used when data were nonnormally distributed. Baseline characteristics were compared between patients with and without abdominal obesity using χ^2 and Wilcoxon rank-sum tests. McNemar test was used to compare counts of dichotomous traits of MetSyn criteria in the abdominal obesity groups before and after treatment. Continuous variables repeatedly measured over time were compared using the Friedman test.

We used a multivariable logistic regression analysis to determine factors associated with having a glucose level ≥ 100 mg/dL after monotherapy among those with a level < 100 mg/dL at baseline. Patient baseline clinical characteristics and laboratory variables were entered in a backward logistic regression model. Variables with a P value of < 0.05 were retained in the model. The same logistic regression analysis was performed for triglycerides ≥ 150 mg/dL, low HDL, and new-onset diabetes mellitus. The baseline variables entered in the model were as follows: age, sex, race, treatment strategy, waist status, pulse, home BP, glucose, insulin, triglyceride, uric acid, HDL, LDL, potassium, estimated glomerular filtration rate, and current smoking status. Because potassium during treatment with HCTZ has been associated with dysglycemia, on-treatment change in potassium was also entered in the model.

All of the statistical analyses were performed using SAS 9.1 (SAS Institute). P value < 0.05 was considered significant for a single test. For multiple comparisons we used the Bonferroni adjustment, and the critical P value was 0.017 after adjustment.

Results

From a total of 418 patients who had completed the PEAR Study at the time of this analysis, we excluded those with missing waist circumference measurements ($n = 13$) and those with nonfasting laboratory measurements ($n = 10$). Baseline characteristics of the 395 patients included in this analysis are summarized in Table 1, according to the presence or absence of abdominal obesity. Among these middle-aged hypertensive patients, 58% had abdominal obesity. At baseline, compared with those without abdominal obesity, those with abdominal obesity had significantly higher fasting glucose, insulin, HOMA-IR, and triglycerides and lower HDL. They were also significantly more likely to have MetSyn compared with those without abdominal obesity (odds ratio: 10.1; 95% CI: 6.13 to 16.57). Less than one quarter of all patients had

Table 1. Baseline Characteristics of Patients According To Abdominal Obesity Status

Baseline Variable	No Abdominal Obesity (n=167)	Abdominal Obesity (n=228)	P
Atenolol strategy, n (%)	86 (51)	114 (50)	0.769
HCTZ strategy, n (%)	81 (49)	114 (50)	
Sex, n (%)	Female: 72 (43) Male: 95 (57)	Female: 150 (66) Male: 78 (34)	<0.0001
Race, n (%)	Black: 67 (40) White: 94 (56)	Black: 83 (36) White: 138 (61)	0.458
Age, mean (SD), y	49.8 (9.1)	50.2 (8.7)	0.905
BMI, mean (SD), kg/m ²	27.6 (4.2)	33.5 (5.3)	<0.0001
Weight, mean (SD), kg	80.1 (14.2)	95.8 (16)	<0.0001
Waist circumference, mean (SD), in	34.6 (3.3)	41.5 (3.9)	<0.0001
Hip circumference, mean (SD), in	41.0 (3.4)	45.8 (4.7)	<0.0001
Current smoker (%)	5	16	0.0006
Past smoker %	26	20	0.156
Ever smoker %	31	36	0.299
SBP, mean (SD), mm Hg	145.4 (10.1)	146.2 (11.4)	0.561
DBP, mean (SD), mm Hg	93.9 (6.0)	93.3 (6.8)	0.207
Pulse, mean (SD), bpm	75.0 (9.2)	78.0 (8.4)	0.0009
Years with HTN, mean (SD)	7.5 (7.3)	8.7 (8.12)	0.232
Family history of HTN (%)	75	82	0.188
Ever taken BP-lowering medications, %	88	91	0.297
Currently taking BP-lowering medications, %	77	77	0.909
Potassium, mean (SD), meq/L	4.2 (0.5)	4.3 (0.5)	0.517
Magnesium, mean (SD), mg/dL	2.1 (0.2)	2.1 (0.2)	0.295
Uric acid, mean (SD), mg/dL	5.5 (1.5)	5.6 (1.3)	0.152
GFR, mean (SD), mL/min per 1.73 m ²	96.0 (22.1)	95.0 (18.3)	0.706
Fasting glucose, mean (SD), mg/dL	90.1 (9.9)	92.4 (10.0)	0.008
Impaired fasting glucose, n (%)*	27 (16)	47 (21)	0.263
Fasting insulin, mean (SD), μ U/mL	8.0 (9.4)	10.7 (7.1)	<0.0001
HOMA-IR, mean (SD)	1.9 (2.5)	2.5 (1.8)	<0.0001
Fasting triglyceride, mean (SD), mg/dL	111.4 (76.7)	139.7 (106.2)	0.0003
HDL, mean (SD), mg/dL	52.0 (15.4)	47.6 (13.0)	0.0009
LDL, mean (SD), mg/dL	121.7 (30.5)	121.7 (31.3)	0.967
Metabolic syndrome, n (%)	27 (16.2)	151 (66.2)	<0.0001

*Impaired fasting glucose was defined as glucose \geq 100 but <126 mg/dL.

impaired fasting glucose. Mean duration of antihypertensive washout was 29 ± 16 days, and there was no difference in any of the metabolic parameters of interest at baseline comparing those who had received previous treatment with a β -blocker

and/or thiazides diuretic and those who had received other classes of antihypertensive agents. Mean duration of monotherapy and combination therapy in each of the treatment strategies was 9 weeks, resulting in a mean total follow-up of 18 weeks for all of the patients. In the atenolol strategy, 86% of patients were taking 100 mg of atenolol, and 78% of patients were taking 25 mg of HCTZ at the end of combination therapy. In the HCTZ strategy, 98% of patients were taking 25 mg of HCTZ, and 68% of patients were taking 100 mg of atenolol at the end of combination therapy. There were no significant differences comparing the percentage on maximum dose between those with and without abdominal obesity.

Table 2 summarizes mean biochemical parameters, BP parameters, and weight according to treatment strategy in those without and with abdominal obesity. In those randomized to the atenolol strategy (top half of Table 2), glucose, triglycerides, and uric acid were significantly increased during follow-up irrespective of the presence or absence of abdominal obesity at baseline. In those randomized to the HCTZ strategy (bottom half of Table 2), uric acid was significantly increased during follow-up irrespective of the presence or absence of abdominal obesity at baseline. However, in the HCTZ strategy, those with abdominal obesity at baseline also exhibited significantly increased glucose, insulin, HOMA-IR, and triglyceride levels during follow-up. Insulin and HOMA-IR were not significantly affected by monotherapy or combination therapy in either treatment strategy in the group without abdominal obesity, nor were they affected in those with abdominal obesity treatment with the atenolol strategy.

Regardless of abdominal obesity status, potassium was significantly decreased in both treatment strategies, related to the initiation or add-on of HCTZ, although mean potassium did not fall below 4.0 meq/L. There was not a difference in the potassium decrease in those with and without abdominal obesity after HCTZ monotherapy ($P=0.96$) or add-on therapy ($P=0.08$). Systolic and diastolic BPs and pulse were significantly and similarly decreased by both treatment strategies, whereas weight was not significantly affected by either strategy.

In subjects without abdominal obesity (Figure, left), the majority had glucose <100 mg/dL, high HDL, and triglycerides <150 mg/dL at baseline. Although neither treatment strategy significantly altered the proportion of patients with glucose levels \geq 100 mg/dL, drug treatment significantly increased the proportion with low HDL and triglyceride levels \geq 150 mg/dL.

In subjects with abdominal obesity (Figure, right), both treatment strategies resulted in significantly increased proportions with glucose levels \geq 100 mg/dL, approximately doubling after combination therapy. The proportion with triglyceride levels \geq 150 mg/dL increased by 30% to 50% after combination therapy. Order of initiation (atenolol versus HCTZ) did not impact the glucose or triglyceride outcomes within either abdominal obesity group.

A total of 17 patients developed new-onset diabetes mellitus during the follow-up period. In the abdominally obese patients, new-onset diabetes mellitus occurred in 13 (6%) of 224 patients, 11 patients in the HCTZ strategy and 2 patients

Table 2. Mean and SD for Biochemical, Weight, and BP Parameters in Patients With and Without Abdominal Obesity at Baseline and After Monotherapy and Combination Therapy

Variable	No Abdominal Obesity				Abdominal Obesity			
	Baseline	Atenolol	Atenolol+HCTZ	<i>P</i> *	Baseline	Atenolol	Atenolol+HCTZ	<i>P</i> *
Atenolol strategy								
Glucose, mg/dL	89.5±9.8	92.3±10.3	95.6±13.8	0.004	92.6±10.0	94.8±11.2	98.8±12.4	0.0001
Insulin, μU/mL	8.3±11.4	7.9±12.2	10.3±18.9	0.290	10.5±5.8	10.6±7.2	12.6±9.8	0.446
HOMA-IR	1.9±3.0	1.9±3.5	2.8±7.1	0.151	2.4±1.5	2.5±1.8	3.2±2.8	0.229
HDL, mg/dL	53.7±16.1	50.3±15.1	50.1±15.5	0.268	47.9±12.3	46.7±11.6	45.8±12.1	0.417
LDL, mg/dL	124.4±29.7	121.3±31.4	126.8±31.8	0.431	122.0±30.0	122.1±30.9	123.7±34.2	0.798
Triglyceride, mg/dL	108.4±82.8	121.5±66.1	149.2±119.0	0.009	126.1±72.2	137.1±81.9	155.9±88.5	0.011
Uric acid, mg/dL	5.4±1.5	5.7±1.4	6.7±1.7	<0.0001	5.5±1.1	5.8±1.1	6.8±1.6	<0.0001
Potassium, meq/L	4.3±0.5	4.3±0.5	4.1±0.5	0.001	4.3±0.4	4.4±0.5	4.1±0.5	<0.0001
Magnesium, mg/dL	2.1±0.2	2.1±0.25	2.2±0.2	0.193	2.1±0.2	2.1±0.2	2.1±0.2	0.310
GFR	97.6±25.9	94.4±25.9	91.5±26.4	0.0797	95.0±16.6	91.8±17.1	89.9±17.6	0.0618
Weight, kg	79.8±15.2	81.6±13.2	81.6±17.9	0.767	97.0±16.0	97.6±17.3	99.0±17.3	0.677
SBP, mm Hg	144.8±10.2	138.4±13.5	128.9±11.2	<0.0001	143.9±10.4	136.6±12.8	129.1±11.5	<0.0001
DBP, mm Hg	93.4±6.0	86.8±9.3	81.9±7.8	<0.0001	92.0±6.2	84.5±7.6	80.5±8.0	<0.0001
Pulse, bpm	75.2±8.2	63.2±7.4	65.6±8.3	<0.0001	78.7±8.4	66.8±8.2	68.4±8.5	<0.0001
	Baseline	HCTZ	HCTZ+Atenolol		Baseline	HCTZ	HCTZ+Atenolol	
HCTZ strategy								
Glucose, mg/dL	90.8±10.2	92.5±10.9	94.1±11.6	0.151	92.3±10.0	96.8±13.3	99.1±12.6	0.0002
Insulin, μU/mL	7.4±7.2	8.4±6.7	7.4±5.3	0.267	10.9±8.2	13.9±15.6	13.9±12.3	0.037
HOMA-IR	1.7±1.9	2.0±1.9	1.8±1.4	0.211	2.5±2.1	3.4±4.2	3.5±3.4	0.009
HDL, mg/dL	51.2±14.0	50.0±14.3	48.9±15.0	0.207	47.3±13.7	46.6±13.5	43.5±12.2	0.114
LDL, mg/dL	119.9±31.6	125.3±37.0	124.7±34.7	0.701	122.0±30.0	122.1±30.9	123.7±34.2	0.798
Triglyceride, mg/dL	114.3±73.4	122.3±86.9	156.0±162.5	0.087	153.2±130.7	168.9±143.4	191.2±186.1	0.049
Uric acid, mg/dL	5.7±1.6	6.7±2.0	6.8±2.1	0.0002	5.7±1.4	6.8±1.7	7.0±1.7	<0.0001
Potassium, meq/L	4.3±0.5	3.9±0.4	4.1±0.6	0.0002	4.3±0.5	4.0±0.5	4.0±0.5	<0.0001
Magnesium, mg/dL	2.2±0.2	2.2±0.3	2.2±0.4	0.650	2.1±0.2	2.1±0.2	2.1±0.3	0.676
GFR	93.6±16.8	90.8±16.3	89.8±17.5	0.3299	94.8±19.8	92.1±20.3	88.7±19.8	0.0438
Weight, kg	79.3±11.9	78.4±12.6	78.9±13.0	0.940	94.7±16.1	96.2±16.1	98.2±16.6	0.390
SBP, mm Hg	146.3±9.7	136.5±10.2	128.1±10.5	<0.0001	148.5±11.9	138.3±12.2	127.7±11.2	<0.0001
DBP, mm Hg	94.6±5.8	88.4±6.4	80.3±6.0	<0.0001	94.5±7.0	88.9±8.3	79.5±7.3	<0.0001
Pulse, bpm	75.1±9.9	77.3±10.1	64.7±8.8	<0.0001	76.8±8.3	79.1±8.9	65.9±8.5	<0.0001

LDL indicates low-density lipoprotein; GFR, glomerular filtration rate; SBP, systolic BP; DBP, diastolic BP.

**P* value compares the change in variable across baseline, monotherapy, and combination therapy time points.

in the atenolol strategy ($P=0.0189$). In those without abdominal obesity, 4 (2%) of 164 patients developed new-onset diabetes mellitus, 2 patients in the HCTZ strategy and 2 patients in the atenolol strategy ($P=1.00$). Of the 17 patients who developed new-onset diabetes mellitus, 13 (76%) met the criteria for MetSyn at baseline, and mean baseline fasting glucose was 101 ± 11.8 mg/dL.

Table 3 summarizes baseline predictors of developing glucose ≥ 100 mg/dL, triglycerides ≥ 150 mg/dL, low HDL, or new-onset diabetes mellitus after exposure to atenolol or HCTZ monotherapy in those in whom the condition was not present at baseline.

Discussion

Multiple randomized, controlled studies in patients with or at increased risk for CV disease have associated long-term use

of thiazide diuretics and/or β -blockers with new-onset diabetes mellitus compared with other antihypertensive medications.⁹ Our findings in a contemporary sample of hypertensives without CV disease or diabetes mellitus demonstrate that the AMEs of atenolol and HCTZ begin within 9 weeks of initiation and are most pronounced in patients with abdominal obesity with longer duration of exposure to HCTZ. Importantly, in patients with abdominal obesity, we observed a significant increase in the proportion with adverse metabolic phenotypes, including impaired fasting glucose, increased triglycerides, and low HDL, which are known to increase the risk of developing diabetes mellitus and long-term CV adverse outcomes.

In PEAR participants with hypertension and abdominal obesity, we observed significantly higher baseline values for

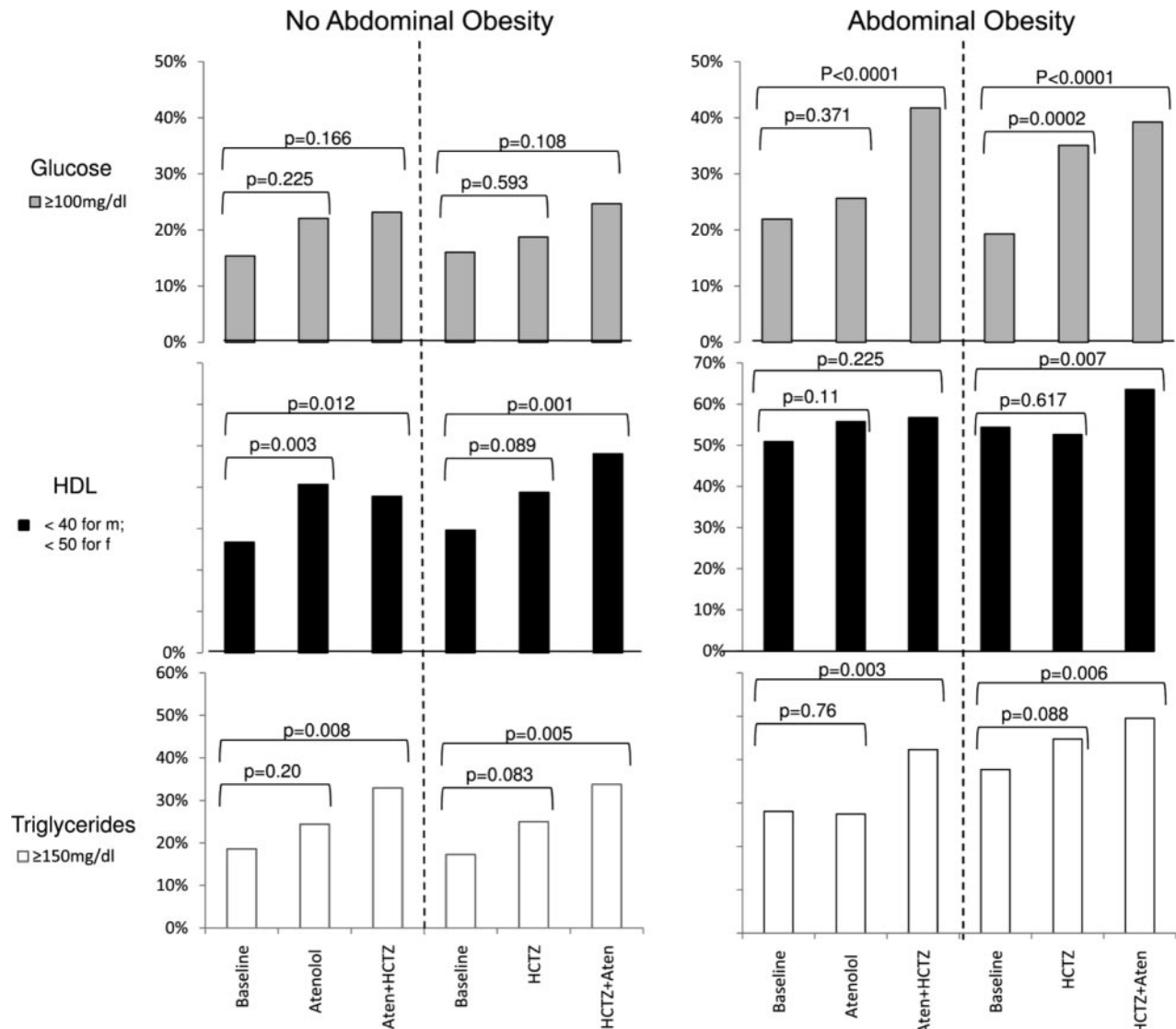


Figure. Proportion of patients with glucose, HDL, and triglyceride categories at baseline and after monotherapy and combination therapy in those without abdominal obesity (left) and with abdominal obesity (right). Results of statistical comparisons within each strategy and abdominal obesity group are included. m indicates male; f, female.

glucose, insulin, and triglycerides; lower HDL values; and a prevalence of MetSyn compared with those without abdominal obesity, indicating a population at increased risk for developing diabetes mellitus.^{14,15} After 9 to 18 weeks of exposure to 25 mg of HCTZ either alone or in combination with atenolol, patients with abdominal obesity had a significant increase in glucose and a significant increase in the proportion with glucose ≥ 100 mg/dL or impaired fasting glucose. Although the notion that treatment with thiazide diuretics increases glucose and worsens glucose tolerance is not new,¹⁶ it is considered by some to be an “innocent” adverse effect that takes many years to develop and may not be associated with adverse CV outcomes.^{17,18} Others have shown a significant association between antihypertensive associated incident diabetes mellitus and CV outcomes, including stroke, myocardial infarction, and death.^{19,20} Importantly, in patients who have both abdominal obesity and hypertension, a glucose level ≥ 100 mg/dL results in a

diagnosis of MetSyn,¹¹ resulting in a 3- to 5-fold increase in the risk for diabetes mellitus.¹⁵ The risk for long-term CV morbidity and mortality is increased 2- to 4-fold and increases proportionately with an increasing number of MetSyn components,²¹ suggesting the importance of preventing or aggressively treating each of the MetSyn criteria. Among our patients, who were exposed to short-term antihypertensive therapy, the majority who developed diabetes mellitus also had MetSyn and impaired fasting glucose at baseline.

The hyperglycemic effects of thiazide diuretics have been associated with diuretic-induced hypokalemia^{22,23}; however, we did not confirm this association in PEAR participants.²⁴ In a cross-sectional study, serum potassium was found to be independently associated with plasma glucose abnormalities in abdominally obese hypertensives treated with thiazide diuretics.²⁵ The data presented here did not confirm this finding, because neither baseline potassium nor change in potassium during treatment predicted the development of

Table 3. Baseline Predictors of the Metabolic Outcomes After Monotherapy and Combination Therapy

Glucose \geq 100 mg/dL: Baseline Variable OR (95% CI)	Triglycerides \geq 150 mg/dL: Baseline Variable OR (95% CI)	Low HDL: Baseline Variable OR (95% CI)	New-Onset Diabetes Mellitus (Glucose \geq 126 mg/dL): Baseline Variable OR (95% CI)
All patients, monotherapy			
Glucose 1.11 (1.05 to 1.17)	Triglyceride 1.05 (1.03 to 1.06)	HDL 0.80 (0.73 to 0.87)	Glucose 1.10 (1.03 to 1.18)
Insulin 1.05 (1.01 to 1.10)	Uric acid 1.87 (1.30 to 2.68)	Potassium 0.30 (0.11 to 0.83)	HCTZ strat. 13.37 (1.45 to 123)
	Black race 0.14 (0.04 to 0.46)	Smoker 4.58 (1.09 to 19.18)	Female sex 10.00 (1.63 to 62.5)
All patients, combination therapy			
Glucose 1.16 (1.09 to 1.22)	Triglyceride 1.05 (1.03 to 1.06)	HDL 0.86 (0.82 to 0.91)	Glucose 1.06 (1.00 to 1.12)
	Uric acid 1.74 (1.30 to 2.32)	HCTZ strat. 2.08 (1.01 to 4.29)	Pulse 1.08 (1.01 to 1.16)
	Black race 0.37 (0.17 to 0.80)	Pulse 1.06 (1.01 to 1.10)	
Abdominal obesity, monotherapy			
Glucose 1.13 (1.04 to 1.22)	Glucose 1.08 (1.01 to 1.16)	HDL 0.86 (0.79 to 0.95)	Glucose 1.20 (1.07 to 1.33)
	Triglyceride 1.04 (1.01 to 1.07)		Uric acid 3.2 (1.35 to 7.5)
	Uric acid 2.35 (1.23 to 4.48)		HCTZ strat. 47.0 (2.55 to 862)
Insulin 1.06 (1.01 to 1.12)	HCTZ strat. 8.32 (1.68 to 41.09)	GFR 0.95 (0.91 to 0.99)	Female sex 31.3 (2.1 to 469)
	Systolic BP 1.10 (1.03 to 1.18)		
	Black race 0.05 (0.01 to 0.34)		
Abdominal obesity, combination therapy			
Glucose 1.14 (1.06 to 1.22)	Triglyceride 1.04 (1.02 to 1.07)	HDL 0.84 (0.77 to 0.92)	Pulse 1.12 (1.02 to 1.25)
	Black race 0.24 (0.08 to 0.69)	Potassium 0.12 (0.02 to 0.63)	
		HCTZ strat. 3.75 (1.11 to 12.64)	
		Pulse 1.16 (1.06 to 1.27)	
No abdominal obesity, monotherapy			
Glucose 1.11 (1.02 to 1.21)	Triglyceride 1.07 (1.04 to 1.10)	HDL 0.77 (0.68 to 0.87)	
	Male sex 11.03 (1.78 to 68.45)	Potassium 0.17 (0.04 to 0.69)	
No abdominal obesity, combination therapy			
Glucose 1.19 (1.08 to 1.31)	Triglyceride 1.07 (1.04 to 1.10)	HDL 0.85 (0.79 to 0.92)	Glucose 1.13 (1.01 to 1.26)
Male Sex 7.72 (1.93 to 30.91)	Uric acid 1.88 (1.06 to 3.33)	Black race 4.18 (1.44 to 12.2)	
	Potassium 0.12 (0.02 to 0.71)		

OR indicates odds ratio; strat., strategy.

either impaired fasting glucose or new-onset diabetes mellitus.

Visceral fat may influence metabolism and promote insulin resistance via the liver through the portal circulation, and, recently, treatment with HCTZ for 12 weeks was associated with liver fat accumulation and fat redistribution from the subcutaneous to the visceral space in patients with abdominal obesity.²⁶ This fat redistribution was associated with aggravated insulin resistance and low-grade inflammation. This mechanism may partially explain the insulin resistance that we observed in our abdominally obese subjects assigned to the HCTZ strategy but not in those assigned to the atenolol strategy.

Although the number of cases of new-onset diabetes mellitus that we report here is small, when extrapolated to the large population of abdominally obese individuals with hypertension who are likely to be exposed to HCTZ and/or atenolol, the impact is significant. Baseline predictors of new-onset diabetes mellitus during treatment with antihypertensives in long-term observational and prospective treatment

trials consistently include age, Hispanic ethnicity, BMI, waist circumference, glucose (fasting and nonfasting), HDL, female sex, and treatment with a thiazide diuretic and/or β -blocker.²⁷ In the PEAR Study, baseline predictors of new-onset diabetes mellitus after the short-term use of antihypertensives are remarkably consistent with this list. Importantly, we add an additional predictive factor, uric acid, which was associated with a >3 -fold excess risk of new-onset diabetes mellitus. Baseline uric acid was also a significant predictor of elevated triglycerides posttreatment in the PEAR Study. In addition, during follow-up, we observed a significant increase in uric acid without regard to abdominal obesity status, particularly associated with the addition of HCTZ. This uric acid elevation may have serious long-term consequences in terms of increased risk of CV events, as well as offsetting benefits of BP lowering.²⁸

There are some limitations of this study worthy of mention. We only measured fasting glucose and not glucose tolerance on the basis of the outcome of an oral glucose tolerance test. As a result, we likely underdetected new-onset diabetes

mellitus cases that might have been diagnosed on the basis of impaired glucose tolerance, which has been associated with short-term use of HCTZ.²⁹ This may also have contributed to the wide CIs observed in Table 3 and, thus, should be interpreted with some caution. We are unable to adequately assess the impact of dose of HCTZ or atenolol on development of AMEs, because the majority of all of the patients in both treatment strategies required the highest protocol-specified dose (25 mg of HCTZ and 100 mg of atenolol). It has been suggested that the AMEs associated with HCTZ are dose related and are minimized or prevented with lower doses than those used in this study; however, PEAR data suggest that few patients achieve their BP goal with 12.5 mg of HCTZ daily.³⁰ In addition, lower doses of thiazides have been associated with neutral or negative long-term morbidity and mortality outcomes and, thus, may not be optimal long-term treatments. Similarly, because of the lack of a control (untreated) group, we are unable to detect temporal changes that might have occurred even without treatment. Lastly, we only have a single fasting blood glucose level of ≥ 126 mg/dL in patients classified as having new-onset diabetes mellitus.

In conclusion, we observed AMEs, including new-onset diabetes mellitus, in a contemporary sample of hypertensive study participants after only short-term treatment with HCTZ and atenolol. These adverse effects were more prominent in those with abdominal obesity, despite normal potassium levels. Our findings reinforce guidelines and recommendations that indicate thiazide diuretics and β -blockers be used with caution in patients with or at risk for developing impaired fasting glucose or MetSyn to prevent the development of diabetes mellitus and the associated long-term adverse consequences.^{31,32}

Perspectives

New data from the Centers for Disease Control and Prevention indicate that, in the United States, the prevalence of obesity in whites ranges from 9% to 30%. Compared with whites, blacks had 51% higher and Hispanics had 21% higher prevalence of obesity.³³ Given that $\approx 50\%$ of obese individuals also have hypertension,⁵⁻⁷ understanding the impact the AMEs on thiazide diuretics and β -blockers in this growing population is important. Our data add significantly to the growing body of literature related to the metabolic effects of antihypertensives by demonstrating that the AMEs associated with both thiazide diuretics and β -blockers occur very early in therapy in those with abdominal obesity, and, in our population of hypertensives with abdominal obesity, HCTZ was strongly associated with new-onset diabetes mellitus after just 9 to 18 weeks of exposure. Because treatment for hypertension usually requires lifelong therapy, and the likelihood of developing AMEs increases with increasing exposure duration, particularly to HCTZ, prescribers should consider not only the BP-lowering properties, but also the AMEs, which could include diabetes mellitus and it is associated CV outcomes, when developing a hypertension treatment regimen for patients with abdominal obesity and/or MetSyn.

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Disclosures

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