Demographic, Environmental, and Genetic Predictors of Metabolic Side Effects of Hydrochlorothiazide Treatment in Hypertensive Subjects

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Background: Thiazide diuretics are recommended for first-line treatment of hypertension. Although considered safe and effective, their use is associated with dyslipidemia, hyperglycemia, and an increased risk of developing type 2 diabetes. The aim of this study was to characterize interindividual variation in glucose and lipid responses to hydrochlorothiazide and to identify demographic, environmental, and genetic predictors associated with this variation.

Methods: A community-based sample of 585 adults with essential hypertension (291 African Americans [150 women and 141 men] and 294 non-Hispanic whites [126 women and 168 men]) underwent monotherapy with hydrochlorothiazide for 4 weeks. Linear regression was used to construct prediction models for the changes in plasma total cholesterol, triglyceride, and glucose concentrations.

Results: The mean changes (± standard deviation) in response to hydrochlorothiazide were 6.13 ± 22.8 mg/dL for total cholesterol, 17.21 ± 70 mg/dL for triglycerides, and 3.5 ± 9.5 mg/dL for plasma glucose. Ethnicity and baseline levels of the analytes were the only predictors that were significant for more than one response. Therefore, the mechanism for these metabolic effects are not entirely shared.

Conclusions: Taken together, demographic, environmental, and genetic factors accounted for only 13% of the total variation in total cholesterol response, 17% of the variation in triglyceride response, and 11% of the variation in glucose response to hydrochlorothiazide, and less than half of this predicted variation in response was explained by measured genotypes. Am J Hypertens 2005;18: 1077–1083 © 2005 American Journal of Hypertension, Ltd.

Key Words: Hydrochlorothiazide, side effects, cholesterol, triglyceride, glucose, pharmacogenetics.

Thiazide diuretics are recommended for the initial treatment of hypertension. Despite a reputation for safety and efficacy, metabolic abnormalities including hyperlipidemia and carbohydrate intolerance have been noted.[1] Diuretic therapy has been associated with increases in serum total cholesterol and LDL-cholesterol of up to 10% of baseline levels. High-density lipoprotein-cholesterol is not affected, whereas triglyceride concentrations can increase by 5% to 15%.[2–7] A recent meta-analysis of 11 large randomized clinical trials showed that treatment with diuretics or β-blockers was associated with a higher incidence of type 2 diabetes than treatment with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or calcium antagonists.[8] Because of the availability of many efficacious antihypertensive drugs, knowledge of the predictors of adverse metabolic responses to thiazide diuretics may help health care providers to identify patients at increased risk who would be candidates for an alternative antihypertensive drug.

The aim of this study was to characterize the magnitude of interindividual variation in plasma total cholesterol, triglyceride, and glucose responses to hydrochlorothiazide

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and to identify environmental and genetic predictors of this interindividual variation.

Methods

African Americans were recruited at the Emory University in Atlanta, Georgia, and non-Hispanic whites were recruited at the Mayo Clinic in Rochester, Minnesota. The diagnosis of essential hypertension was defined as diastolic blood pressure (BP) >90 mm Hg in the absence of known causes or a previous diagnosis of essential hypertension and use of prescription antihypertensive drugs. The study was approved by the institutional review boards of the Mayo Clinic and Emory University.

Details of the previous study protocol and the methods for genotyping have been previously described.[9] Briefly, previous BP-lowering medication was discontinued for at least 4 weeks. This was followed by 4 weeks of therapy with hydrochlorothiazide, 25 mg orally once daily. Subjects were counseled to maintain a dietary sodium intake of 2 mmol/kg/d. Dietary compliance was monitored by measurement of 24-h urine sodium excretion and dietary recall diaries. Subjects were withdrawn from the study if their diastolic BP was <90 mm Hg at the end of the washout period, or if BP increased to >180/110 mm Hg during the washout period. Blood pressure was measured and blood was obtained for biochemical measurements at the end of the washout period (baseline) and at the end of the 4-week diuretic treatment period. Blood pressure measurements were taken with subjects in the seated position after 5 min of rest by trained nurses. Blood samples were morning fasting samples after an 8-h fast. If serum potassium was <3.6 mmol/L at the screening visit, an oral potassium supplement (K-Dur, 20 mmol/d; Key Pharmaceuticals, Kenilworth, NJ) was prescribed. After 2 weeks of diuretic therapy, serum potassium concentration was remeasured; if the value was <3.6 mmol/L, an oral potassium supplement (20 to 40 mmol/d) was prescribed.

A total of 45 polymorphisms in 19 candidate genes for hypertension were measured. These genes and polymorphisms had been selected for the previous study as candidates to predict antihypertensive response to hydrochlorothiazide.[10] Genotyping was carried out by primer extension and mass spectrometry after polymerase chain reaction amplification of the target region. Genotypes were called directly from the spectra using semiautomated software (Sequenom, San Diego, CA). Primers for the amplification and extension reactions are available upon request.

Plasma glucose concentrations were determined by automated spectrophotometric methods implemented on the IL Monarch Chemistry System 760 (Instrumentation Laboratories, Lexington, MA). Cholesterol and triglyceride concentrations were determined spectrophotometrically using Roche reagents on a Cobas Mira analyzer (Roche Instrument Center, Rotkreuz, Switzerland).

Changes in total cholesterol, triglycerides, and blood glucose in response to hydrochlorothiazide were defined

Table 1. Genetic polymorphisms considered in the analyses

Gene Name	Polymorphism ID
Adducin 1	rs4963
	rs4961
Adrenergic, β-2-, receptor	hcv8950495
	rs2400707
	rs1042714
	rs1042713
	rs2400707
Adrenergic, β_1-receptor	rs1801253
Aldosterone synthase	rs4544
	rs1799998
Angiotensin II receptor, type 1	rs5186
Angiotensin-I converting enzyme	rs4339
	rs4298
	rs4314
	rs4364
Angiotensinogen	rs699
	rs7079
	rs4762
	rs5051
	rs1805090
Chloride channel Kb	hcv11647074
	rs2015352
Cytochrome P450, family 17	rs284849
Endothelial nitric oxide synthase	rs1799983
Guanine nucleotide binding protein (G protein), β polypeptide 3	rs6489738
Lipoprotein lipase	rs328
Nuclear receptor subfamily 3, group C, member 2	rs2232920
	rs5527
	rs3846306
Potassium inwardly rectifying channel, subfamily J, member 1	hcv632615
Protein kinase lysine-deficient 1	rs2277052
	rs2286007
	rs2107614
	rs1159744
	rs2277869
Renin	rs5706
	rs5705
	rs5707
	hcv116.22760
Sodium channel γ-subunit promotor	rs5729
	rs5723
	rs7200183
	hcv11894753
Sodium channel, nonvoltage-gated 1, β	rs250563
Solute carrier family 12 (Na/Cl transporters), member 3	hcv9609124
Solute carrier family 12 (Na/K/Cl q1 transporters), member 1	rs1552311

rs = NCBI SNP database (*http://www.ncbi.nlm.nih.gov/locuslink*).
hcv = Celera discovery system SNP database (*http://www.celeradiscoverysystem.com*).

as the final value (at the end of drug therapy) minus the baseline value (at the end of the washout period). Analyses considered these responses to hydrochlorothiazide as continuous variables. Mean values and standard deviations were calculated for changes in total cholesterol, triglycerides, and blood glucose. Student *t* tests were performed to determine whether the mean values were different from zero. Shapiro-Wilk tests were performed to test for normality of the distributions of the response variables. Deviations of the observed genotype frequencies from Hardy-Weinberg equilibrium (HWE) expectations were tested using a χ^2 goodness-of-fit test.

For building of the models, all potential nongenotype predictor variables measured at baseline (ie, end of the washout period) (gender, ethnicity, weight, body mass index, waist–hip ratio, age, age at diagnosis of hypertension, previous antihypertensive drug treatment, current smoking, ethanol use, systolic BP, diastolic BP, serum sodium and potassium, plasma triglycerides, total cholesterol and HDL-cholesterol, plasma glucose and insulin, plasma epinephrine, norepinephrine and dopamine, serum ACE, urine sodium, potassium, and aldosteron excretion) were considered in separate linear regression models, one for each outcome variable (ie, change in total cholesterol, change in triglycerides, and change in glucose). The stepwise method (SAS 8.2 STEPWISE [SAS Institute Inc., Cary, NC]) was used for the selection of variables. All predictors that had *P* values $< .05$ in the multiple regression model were kept in the model. All possible interaction terms between pairs of these predictors were then tested for statistical significance, and only the interaction terms with *P* values $< .05$ were retained in the model. After constructing this base model of "nongenotype" predictors, each single nucleotide polymorphism (SNP) was then entered one-at-a-time in separate linear regression models (see Table 1 for list of SNPs). Those SNPs with *P* values $< .05$ were then entered into a multiple regression model into which the previously identified nongenotype predictors were forced. Only the SNPs with *P* values $< .05$ were kept in the final model. The R^2 of the models with and without the SNPs were calculated.

Use of potassium supplements, final serum potassium, and changes in potassium values (final value minus baseline value) were tested in all models as potential predictors of the changes in total cholesterol, triglycerides, and glucose.

Results

Characteristics of the study sample, stratified by ethnicity are shown in Table 2. Fig. 1 shows the interindividual variation in responses of plasma total cholesterol, triglycerides, and glucose to hydrochlorothiazide. The mean ± standard deviation (median, interquartile range) for the change in total cholesterol, triglycerides, and glucose was 6.13 mg/dL ± 22.8 (5, 24), 17.21 mg/dL ± 70.3 (10, 52),

Table 2. Baseline characteristics of study population

Characteristic	Whole Population	African American	Non-Hispanic Whites	*P**
Number	553	282	271	
Gender (% men)	51.7	47.2	56.5	.03
Weight (kg)	92.4 ± 19.5	92.2 ± 18.5	92.7 ± 17.5	.77
Body mass index (kg/m^2)	31.4 ± 5.9	30.9 ± 5.9	30.5 ± 5.0	.25
Waist:hip	0.91 ± 0.09	0.87 ± 0.1	0.94 ± 0.1	<.0001
Age (y)	48.2 ± 6.7	47.7 ± 6.0	48.8 ± 7.3	.04
Age hypertension (y)	41.7 ± 7.0	39.8 ± 7.3	43.8 ± 5.8	<.0001
Antihypertensive drug treatment (y)	5.4 ± 6.1	6.4 ± 6.0	4.5 ± 5.4	.0002
Current smoker (%)	12.1%	17.4	6.6	.0001
Ethanol use (%)	66.7%	52.5	81.6	<.0001
Systolic blood pressure (mm Hg)	146.3 ± 14.5	149.8 ± 15.3	142.6 ± 12.5	<.0001
Diastolic blood pressure (mm Hg)	96.1 ± 5.4	96.9 ± 5.3	95.4 ± 5.3	.0010
Serum sodium (mmol/L)	138.3 ± 2.5	138.3 ± 2.6	138.3 ± 2.3	.95
Serum potassium (mmol/L)	3.9 ± 0.3	3.8 ± 0.3	4.0 ± 0.2	<.0001
Plasma triglyceride (mg/dL)	156.8 ± 88.9	129.8 ± 71.7	184.9 ± 96.1	<.0001
Total cholesterol (mg/dL)	184.1 ± 35.0	181.1 ± 38.2	187.3 ± 31.2	.04
HDL-cholesterol (mg/dL)	45.6 ± 13.5	48.4 ± 14.2	42.7 ± 12.0	<.0001
Plasma glucose (mg/dL)	95.6 ± 13.1	98.2 ± 13.3	92.9 ± 12.4	<.0001
Plasma insulin (μIU/mL)	10.2 ± 7.5	11.3 ± 8.5	9.0 ± 6.2	.0003
Plasma epi (pg/mL)	16.1 ± 14.4	15.4 ± 14.3	16.7 ± 14.4	.31
Plasma DOPA (pg/mL)	16.2 ± 21.3	16.6 ± 21.9	13.3 ± 20.3	.0014
Serum ACE (U/L)	11.9 ± 5.0	12.2 ± 5.5	11.6 ± 4.4	.14
Urine sodium (mmol/24 h)	162.6 ± 69.7	165.1 ± 66.7	160.0 ± 72.8	.39
Urine potassium (mmol/24 h)	58.7 ± 25.8	48.8 ± 20.5	66.3 ± 27.0	<.0001
Urine Aldo (μg/24 h)	9.4 ± 6.0	9.0 ± 6.0	9.9 ± 6.0	.07

* *P* value for difference between African Americans and Non-Hispanic whites derived from Student *t* test (continuous variables) or Pearson's χ^2 test (categorical variables).

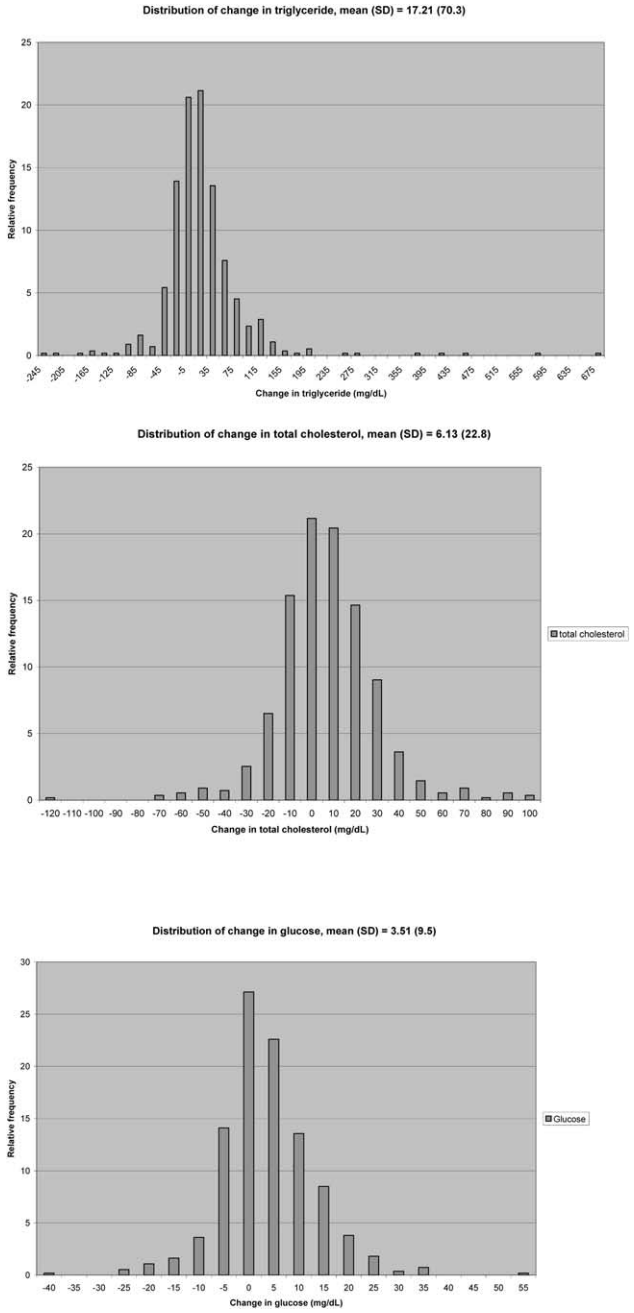

FIG. 1. Interindividual variation in glucose and lipid responses to hydrochlorothiazide.

3.51 mg/dL ± 9.5 (2.5, 10.75), respectively. Each mean change was statistically significantly different from zero ($P < .0001$), and each distribution deviated from normality and was positively skewed ($P < .0001$). The coefficient of variation was 371% for change in total cholesterol, 408% for change in triglycerides, and 271% for change in glucose.

For triglycerides and glucose, ethnicity was a significant predictor of interindividual variation in response, with African Americans having a smaller response than whites. Therefore, the potential for ethnic interaction was investigated in all subsequent analyses. For each outcome variable, sex was not a significant predictor of response. However, to help control for possible confounding gender effects, sex was included in all subsequent prediction models. Finally, the baseline level of each response measure was a significant predictor of response. When ethnicity, sex, and baseline values were considered, the R^2 value was 0.06 for change in total cholesterol, 0.03 for change in triglycerides, and 0.05 for change in glucose (P values of the models were $< .0001$, .0008, and $< .0001$, respectively).

Plasma triglycerides, total cholesterol, HDL-cholesterol, and insulin were the nongenotype predictors of total cholesterol change in response to hydrochlorothiazide (Table 3). The R^2 for this model was 0.11 (model $P < .0001$). Polymorphisms in the gene encoding the β_1-adrenergic receptor (ARB1A_rs1801253) and renin (REN_rs5705) made additional contributions to prediction of the total cholesterol change. Subjects with the GC variant of the ARB1A_rs1801253 polymorphism had a larger total cholesterol increase (+9.0) than subjects with the GG (+4.36) or CC (+4.10) genotypes (Table 3). Subjects with the GT or TT variant of the REN_rs5705 polymorphism had a smaller increase in total cholesterol (+6.01 and +5.74, respectively) than subjects with the GG variant (+15.0) (Table 3) The R^2 value of the model with baseline variables and SNPs was 0.13 (model $P < .0001$).

Ethnicity, plasma triglycerides, dopamine, urine sodium excretion, and interactions plasma triglycerides with ethnicity and with urine sodium excretion were the nongenotype predictors of triglyceride change in response to hydrochlorothiazide (Table 4). The R^2 value for this model was 0.14 (model $P < .0001$). Non-Hispanic whites had a larger increase in triglyceride levels (+25.05) than African Americans (+10.11) ($P = .0003$). Polymorphisms in the genes encoding angiotensinogen (AGT_rs7079), endothelial nitric oxide synthase (ENOSA_rs1799983), and the protein kinase lysine deficient 1 (PRKWNK1_rs2277869) were also predictors of triglyceride changes. Subjects with TT genotype of the AGT_rs7079 polymorphism had a larger mean increase in triglycerides (+43.47) than those with GG (+15.2) or TG (+14.04) genotypes. Subjects with the TT genotype of the ENOSA_rs1799983 polymorphism had a larger mean increase in triglycerides (+48.70) than those with the TC (+20.30) or the GG (+13.79) genotypes. Subjects with the CC genotype of the PRKWNK1_rs2277869 polymorphism had a decrease in plasma triglycerides (−11.75), whereas triglycerides increased in those with the TC (+25.90) and TT (+14.96) genotypes (Table 4). The R^2 of the model with the baseline variables and SNPs was 0.17 (model $P < .0001$).

Ethnicity, weight, plasma glucose, urine sodium excretion, and interactions of weight with the ethnic group and with urine sodium excretion were the nongenotype predictors of glucose change in response to hydrochlorothiazide (Table 5). The R^2 of this model was 0.09 (model $P < .0001$). Polymorphisms in the genes encoding the potassium inwardly rectifying channel (KCNJ1_hcv632615)

Table 3. Final model of predictors of total cholesterol change in response to hydrochlorothiazide $R^2 = 0.13$

Predictor	*n*	Changes in Total Cholesterol	β Coefficient	SE	*P*
Race (Non-Hispanic whites)	271	5.72 ± 20.11	Reference		
Race (African American)	282	6.52 ± 25.06	1.01	2.24	.65
Gender (male)	286	8.01 ± 21.06	Reference		
Gender (female)	267	4.11 ± 24.32	−3.53	2.04	.31
Plasma triglyceride	—	—	0.06	0.01	<.0001
Total cholesterol	—	—	−0.21	0.03	<.0001
HDL-cholesterol	—	—	0.16	0.09	.08
Plasma insulin	—	—	−0.33	0.14	.02
ARBlA_rs1801253 CC	246	4.36 ± 21.56	Reference		
ARBlA_rs1801253 GC	207	9.00 ± 24.38	5.15	2.14	.02
ARBlA_rs1801253 GG	61	4.10 ± 24.06	0.60	3.31	.86
REN_rs5705 GG	33	15.00 ± 35	Reference		
REN_rs5705 GT	159	6.01 ± 25.42	−8.71	4.35	.05
REN_rs5705 TT	327	5.74 ± 21.30	−9.90	4.26	.02

and the β_2-adrenergic receptor (ADRB2_rs2400707) made additional contributions to prediction of changes in glucose. In subjects with the KCNJ1_hcv632615 AA genotype, glucose increased (+3.75) whereas it decreased in those with the AG genotype (−4.56). Subjects with the ADRB2_rs2400707 AA genotype had a larger blood glucose increase (+5.90) than those with the AG (+3.52) or GG (+2.83) genotypes (Table 5). The R^2 of the model with the baseline variables and SNPs was 0.11 (model $P < .0001$).

Because of previous reports of an inverse relationship between serum potassium concentration and thiazide diuretic-associated hyperglycemia,[11–13] further analyses were carried out on serum potassium values. The SNPs that had a significant effect on the change in glucose levels had no significant effect on baseline serum potassium levels or the change in potassium. There was a negative association between the final value of potassium and the change in glucose ($P = .01$ and $R^2 = 0.01$), but the baseline value, the use of potassium supplements, and change in potassium were not predictive of the change in glucose.

Discussion

Small percentages of individual variation in total cholesterol change (13%), triglyceride change (17%), and glucose change (11%) could be explained by the predictors we measured. Additionally genetic predictors also accounted for only a small fraction of the explained variation

Table 4. Final model of predictors of triglyceride change in response to hydrochlorothiazide $R^2 = 0.17$

	n	Changes in Triglyceride (mean ± SD)	β Coefficient	SE	*P*
Race (Non-Hispanic whites)	257	25.05 ± 87.33	Reference		
Race (African American)	278	10.11 ± 50.29	53.12	14.62	.0003
Gender (male)	279	19.75 ± 80.77	Reference		
Gender (female)	256	14.60 ± 58.26	−3.95	6.48	.54
Plasma triglyceride	—	—	0.49	0.07	<.0001
Race plasma triglyceride	—	—	−0.36	0.09	<.0001
Dopamine	—	—	−0.05	0.14	.75
24-h urinary excretion of sodium	—	—	0.20	0.07	.005
24-h urinary excretion of sodium plasma triglyceride	—	—	−0.002	0.0003	<.0001
AGT_rs7079 GG	331	15.2 ± 58.4	Reference		
AGT_rs7079 TG	148	14.04 ± 58.21	2.68	7.36	.72
AGT_rs7079 TT	32	43.47 ± 128.57	27.68	12.86	.03
ENOSA_rs1799983 GG	362	13.79 ± 54.40	Reference		
ENOSA_rs1799983 GT	163	20.30 ± 92.51	4.44	7.04	.63
ENOSA_rs1799983 TT	23	48.70 ± 103.94	30.14	15.02	.05
PRKWNK1_rs2277869 CC	16	−11.75 ± 32.93	Reference		
PRKWNK1_rs2277869 TC	153	25.90 ± 92.08	41.31	18.63	.03
PRKWNK1_rs2277869 TT	366	14.96 ± 60.84	31.26	18.03	.08

Table 5. Final model of predictors of glucose change in response to hydrochlorothiazide $R^2 = 0.11$

	n	Changes in Glucose (mean ± SD)	β Coefficient	SE	*P*
Race (Non-Hispanic whites)	282	3.95 ± 10.33	Reference		
Race (African American)	270	3.05 ± 8.57	14.43	4.19	.0006
Gender (male)	286	2.73 ± 9.54	Reference		
Gender (female)	266	4.35 ± 9.42	1.53	0.90	.09
Weight	—	—	−0.008	0.06	.90
Plasma glucose	—	—	−0.14	0.03	<.0001
24-h urinary excretion of sodium	—	—	−0.06	0.03	.04
Race weight	—	—	−0.14	0.04	.002
Weight 24-h urinary excretion of sodium	—	—	0.0007	0.0003	.02
KCNJ1_hcv632615 AA	532	3.75 ± 9.32	Reference		
KCNJ1_hcv632615 AG	8	−4.56 ± 8.49	−8.16	3.26	.01
ADRB2_rs2400707 AA	93	5.90 ± 9.85	Reference		
ADRB2_rs2400707 AG	228	3.52 ± 10.20	−1.67	1.14	.14
ADRB2_rs2400707 GG	159	2.83 ± 8.79	−2.50	1.21	.04

(2%, 3%, and 2%, respectively). The genes in this study were chosen based on their possible influence on the BP-lowering effect of hydrochlorothiazide rather than a hypothesized effect on the drugs influence on lipids or glucose. The genetic mechanisms that may lead to the changes in total cholesterol, triglycerides, and glucose are most likely due to mechanisms unrelated to BP response. Some of the measured genes in this study have demonstrated effects on total cholesterol, triglycerides,[14,15] and glucose concentrations,[16] however, to our knowledge there is no information yet available concerning the specific effects of these genes on changes in total cholesterol, triglycerides, and glucose during short-term (4 weeks) administration of hydrochlorothiazide. Therefore, we can only hypothesize as to the underlying mechanisms for the SNP associations we found.

For the change in total cholesterol in response to hydrochlorothiazide, the statistically significant predictors were baseline total cholesterol, triglycerides, HDL-cholesterol, and insulin. Polymorphisms in the β_1-adrenergic receptor gene and in the renin gene were significant predictors of the change in total cholesterol. The β-adrenergic receptors are important regulators of lipolysis and interrelationships between the sympathic nervous system and the renin-angiotensin system have been noted.[17] Variation in the β-receptor might therefore affect plasma lipid levels in response to early volume depletion associated with therapy with a thiazide diuretic and activation of the renin-angiotensin system associated with diuretic therapy.

For the change in triglycerides in response to hydrochlorothiazide, the statistically significant predictors were ethnicity, baseline triglycerides, dopamine, and urine sodium excretion. Three polymorphisms were found to predict the change in triglycerides. However, the ethnic effect was much larger than the effect of the polymorphisms. In general, African Americans demonstrate significantly lower triglycerides than their non-Hispanic white counterparts, which was also seen in this study.[18] Non-Hispanic whites had greater triglyceride elevations than African Americans. One of the polymorphisms that predicted the triglyceride response to hydrochlorothiazide was the ENOSA_rs1799983 polymorphism (= Glu298Asp variant). This polymorphism has been found to be positively associated with higher weight, triglycerides, and LDL-cholesterol in a Hispanic population.[15]

Ethnicity was also a statistically significant predictor of the change in glucose. Non-Hispanic whites had larger changes in glucose than African Americans. Other statistically significant predictors were baseline glucose levels, weight, and urine sodium excretion. There were two polymorphisms that predicted the change in glucose. These polymorphisms were in the potassium inwardly rectifying channel, subfamily J, member 1 and in the β_2-adrenergic receptor. The ATP-sensitive potassium channels are an essential component of glucose-dependent insulin secretion in pancreatic islet β-cells. It has been suggested that the adverse effects of thiazide diuretics both on lipid levels and on glucose tolerance are, in part, a consequence of potassium depletion.[11–13,19] Thiazide-induced impairment of glucose tolerance may be a consequence of impaired glucose-stimulated insulin release and peripheral resistance to the action of insulin.[20] Because the initial response of pancreatic β-cells to glucose depends on serum potassium levels, diuretic-induced hypokalemia may cause postprandial hyperglycemia.[20] Therefore a polymorphism in the gene encoding the potassium-rectifying channel is a logical candidate for the prediction of glucose changes during hydrochlorothiazide. In our study the final potassium value (after treatment) was significantly negatively associated with the change in glucose, but the change in potassium (final value [at the end of drug therapy] minus the baseline value [at the end of the washout period]) was

not. In subjects with higher final potassium levels, hydrochlorothiazide had less influence on the glucose levels. This association was still true when the model was adjusted for the use of potassium supplements. Normalizing serum potassium when using hydrochlorothiazide for hypertension might be important to control thiazide-induced hyperglycemia.

Only a small proportion of the glucose and lipid responses to hydrochlorothiazide could be explained by the environmental and genetic factors that were measured in our study. The polymorphisms in this study were chosen because they were candidate genes for prediction of BP response to hydrochlorothiazide, other polymorphisms in genes involved in activity of potassium channels, lipid metabolism, or insulin resistance[21] might be interesting candidates for future studies looking at the metabolic side effects of hydrochlorothiazide.

The risk of developing diabetes mellitus must be weighted against BP control benefits of thiazides (reduction of risk of cardiovascular disease). The ability to predict adverse effects as well as favorable effects would be helpful in choosing the optimal BP-lowering therapy for the individual patient.

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