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SPIRONOLACTONE PREVENTS CHLORTHALIDONE-INDUCED SYMPATHETIC ACTIVATION AND INSULIN RESISTANCE IN HYPERTENSIVE PATIENTS

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Abstract

Recent studies from our laboratory indicate that chlorthalidone triggers persistent activation of the sympathetic nervous system and promotes insulin resistance in hypertensive patients, independent of serum potassium. Mechanisms underlying these adverse effects of chlorthalidone remain unknown but increasing evidence in rodents suggests the role of angiotensin and aldosterone excess in inducing both sympathetic overactivity and insulin resistance. Accordingly, we conducted studies in 17 subjects with untreated stage I hypertension, measuring sympathetic nerve activity (SNA) at baseline, after 12 weeks of chlorthalidone alone (25 mg/day), chlorthalidone plus spironolactone, and chlorthalidone plus irbesartan, using randomized crossover design. We found that chlorthalidone alone decreased 24-hour ambulatory BP (ABP) from 135±3/84±2 to 124±2/78±2 mm Hg and significantly increased SNA from baseline (from 41±3 vs 49±4 bursts/min, $p < 0.01$). Addition of spironolactone to chlorthalidone returned SNA value to baseline (42±3 bursts/min, p = NS) while addition of irbesartan failed to alter the SNA response to chlorthalidone in the same subjects (52±2 bursts/min, $p < 0.01$) despite similar reduction in ABP (121±2/75±2 and 121±2/75±2 mmHg, respectively). Chlorthalidone alone also increased indices of insulin resistance, which was not observed when used in combination with spironolactone. In conclusion, our study demonstrates beneficial effects of spironolactone in attenuating both chlorthalidone-induced sympathetic activation and insulin resistance in humans, independent of BP reduction. Because sympathetic overactivity and insulin resistance contributes to the poor prognosis in patients with cardiovascular disease, combination therapy of chlorthalidone with mineralocorticoid receptor antagonists may constitute a preferable regimen than chlorthalidone alone in hypertensive patients.

Keywords

diuretics; sympathetic nervous system; insulin resistance; hypertension

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Introduction

Chlorthalidone has been proposed as the preferred diuretic for treatment of hypertension, given its superiority in reducing BP and hypertensive target organ complications when compared to other thiazide-type diuretics [1]. Previous studies demonstrated that chlorthalidone-induced BP reduction was accompanied by reflex sympathetic activation [2–4] and detrimental indices of insulin resistance in hypertensive patients [2, 5]. Furthermore, the magnitude of chlorthalidone-induced increase in insulin resistance was found to be correlated with the increase in sympathetic nerve activity (SNA) and independent of serum potassium in our previous study [2]. Despite increasing popularity of chlorthalidone use in the United States [6], mechanisms underlying chlorthalidone-induced sympathetic excitation and insulin resistance remain unknown and effective therapy in preventing these adverse effects of chlorthalidone has not been identified.

Chlorthalidone is known to induce a sustained activation of the renin angiotensin aldosterone system (RAAS) in hypertensive patients [2–4]. In animal experimental models, both angiotensin II (Ang II) and aldosterone cross the blood brain barrier and to directly stimulate central sympathetic outflow to the heart and peripheral circulation [7–9]. In addition, Ang II further triggers aldosterone synthesis in the brain, thereby amplifying central neuronal activation and hypertension even with a small elevation in circulating Ang II [9]. Both Ang II and aldosterone have also been implicated in the pathogenesis of insulin resistance by inhibiting insulin signaling pathway in the adipocytes and skeletal muscle [10, 11], resulting in impaired insulin mediated glucose uptake [12, 13]. Whether addition of angiotensin receptor blockers (ARB) or mineralocorticoid receptor (MR) antagonists prevents chlorthalidone-induced sympathetic activation and insulin resistance has not been previously investigated.

Accordingly, the goal of the present investigation is to determine if addition of MR antagonists or ARBs constitutes an effective strategy in reducing both chlorthalidone-induced sympathetic activation and insulin resistance in hypertensive patients. In untreated hypertensive patients, we performed a randomized crossover trial in which we recorded postganglionic sympathetic action potentials with intraneural microelectrodes and assessed indices of insulin resistance at baseline, after chlorthalidone alone, after chlorthalidone plus spironolactone and after chlorthalidone plus ARB irbesartan. Because Ang II and aldosterone have been shown to impair baroreflex function, which exerts inhibitory influence on the SNA, we also assess baroreflex control of SNA and HR during each treatment arm.

Methods

Seventeen patients with untreated stage 1 hypertension participated in the study after providing written informed consent. The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas. All subjects had BP between 140-159/90-99 mmHg on 3 determinations by oscillometric technique in the seated position. The subjects had no history of heart disease, diabetes mellitus, or evidence of target organ damage such as left ventricular hypertrophy by electrocardiography or chronic kidney disease. The patients had not received antihypertensive drugs for at least 4 weeks before the study.

Experimental protocols

All subjects were randomized to receive 12 weeks of chlorthalidone, 25 mg/day, alone; chlorthalidone, 25 mg daily, plus spironolactone 25 mg daily, and chlorthalidone 25 mg daily plus irbesartan of 150 mg daily, using a single-blind crossover design without washout

between treatments. Each subject was followed every 4 week for measurement of serum potassium (K). All subjects were given oral KCl supplementation to maintain serum K between 4.0–4.5 mmol/L. Ambulatory BP (ABP) monitoring was performed at baseline and after 12 weeks of each treatment phase. Following completion of ABP monitoring, measurement of SNA by peroneal microneurography, casual BP, arterial baroreflex sensitivity, fasting plasma glucose, insulin, plasma renin activity (PRA), and serum aldosterone were performed in the supine position during the morning hours between 8–11 AM (see method detail in the supplement). All subjects were instructed to take study drug 1–2 hours before microneurographic study. Analysis of these variables was performed without the knowledge of treatment each subject had received.

Statistical Analysis

Mixed linear models were used to conduct the repeated measures analysis to assess differences between baseline period, chlorthalidone alone, chlorthalidone plus spironolactone phases and chlorthalidone plus irbesartan. Contrasts from these models were used for pair-wise comparisons. Treatment order was also assessed in the models and no effect of treatment order on any outcome variables was found. Because data sets for insulin, PRA, HOMA-IR, and HOMA-βF data are not normally distributed, the data were analyzed after a natural logarithmic transformation. The 0.05 level of significance was used for model main effects and the 0.02 level of significance was used for pair-wise tests to adjust for multiple testing. Pearson correlation coefficient was used to assess the association between changes in SNA with changes in indices of insulin resistance and other non-metabolic variables. Levels of insulin, PRA, HOMA-IR, and HOMA-βF are expressed as median and the inter-quartile range. Other variables are expressed as mean and SEM. Statistical analysis was performed with SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics of subjects participated in the study are shown in table 1. Chlorthalidone alone caused significant reduction in 24-hr ambulatory BP without affecting 24-hr heart rate (HR, table 1). When spironolactone or irbesartan was added to chlorthalidone, there was a small reduction in ambulatory and casual BP but the reduction did not reach statistical significance when compared to chlorthalidone alone (table 1). Treatment with chlorthalidone plus irbesartan, however, significantly increased the nighttime HR compared to baseline ($p = 0.01$). Chlorthalidone alone caused a significant increase in plasma renin activity and serum aldosterone levels. Addition of spironolactone to chlorthalidone did not alter increase in PRA and serum aldosterone induced by chlorthalidone alone. Addition of irbesartan, however, caused a further increase in PRA compared with chlorthalidone alone without affecting aldosterone responses (table 1). Chlorthalidone alone significantly increased SNA and SNA per 100 RR intervals from baseline (from 41±3 10 49±4 bursts/min and 66±4 to 74±4 bursts/100 RR, $p < 0.01$ vs baseline, fig 1 and 2). Addition of spironolactone to chlorthalidone returned SNA value to baseline (42±3 bursts/min and 67±3 bursts/100 RR, p = NS vs baseline, fig 1 and 2) while addition of irbesartan failed to alter SNA response to chlorthalidone in the same subjects (52±2 bursts/min and 75±3 bursts/100 RR, $p < 0.01$ vs baseline and vs. chlorthalidone plus spironolactone) despite similar reduction in 24-hour ABP (121±2/75±2 and 121±2/75±2 mmHg, respectively, table 1). Baroreflex control of SNA and HR remained unchanged during all phases of treatment (fig 2).

Chlorthalidone alone significantly increased fasting plasma glucose, insulin, and HOMA-IR and reduced QUICKI from baseline (table 1 and fig 3). In contrast, addition of spironolactone returned HOMA-IR and serum insulin levels to baseline in the same subjects, to values significantly lower than chlorthalidone alone (fig 3). HOMA-IR and insulin levels

during irbesartan plus chlorthalidone were not significantly different from during chlorthalidone alone or baseline period. Neither chlorthalidone nor combination of chlorthalidone with spironolactone or irbesartan had any detectable effect on HOMA-βF compared to baseline (111±24 vs 68±19 vs 91±26, vs 72±19%, respectively, $p > 0.05$). With K supplementation, there were no changes in serum K after 12-week of chlorthalidone from baseline (figure 3) or during any treatment period. Percent changes in fasting plasma glucose during chlorthalidone treatment alone from baseline was significantly correlated with percent changes in SNA in both bursts/min ($r = 0.64$, $p = 0.01$) and bursts/ 100 RR interval ($r = 0.76$, $p = 0.001$) which was not observed when chlorthalidone was combined with spironolactone or irbesartan ($p > 0.05$). There were no correlation between changes in insulin, HOMA-IR, QUICKI, serum aldosterone, or PRA with changes in SNA during all treatment phases (data not shown).

Discussion

There are two major new findings of this study. First, addition of spironolactone to chlorthalidone, prevents adverse effects of chlorthalidone on both the sympathetic nervous system and insulin sensitivity in hypertensive patients. Second, these beneficial effects of spironolactone were not observed with the ARB irbesartan despite similar reductions in BP.

Previous work from our laboratory has indicated that chlorthalidone triggers sustained sympathetic activation in hypertensive patients, but the underlying mechanism(s) of this potentially detrimental response remain unknown [2]. Activation of angiotensin receptor subtype I (AT_1R) by Ang II in the central nervous system (CNS) following chlorthalidone-induced volume depletion might be one mechanism. The effects of ARBs on SNA in humans, however, are inconsistent, and studies have found SNA to be unchanged, increased, or decreased after ARB treatment [14, 15]. An increasing body of evidence in rodents suggests that circulating aldosterone penetrates the blood brain barrier and directly stimulates central sympathetic outflow via activation of central mineralocorticoid receptors (MRs) [7, 8, 16]. This central sympathoexcitatory and pressor action of aldosterone is attenuated by intracerebroventricular (ICV) infusion of MR antagonists at doses that had no systemic spillover [17, 18]. Furthermore, aldosterone can be produced locally in the brain upon stimulation by circulating Ang II [9, 19], which may contribute to chlorthalidone-induced sympathetic activation. Inhibition of aldosterone synthesis in the CNS with ICV infusion of aldosterone synthase inhibitor FAD286 has been shown to prevent central neuronal activation and pressor action of Ang II in rats, independent of circulating aldosterone levels [9].

In humans, recent study from our laboratory provided additional support for the animal data as patients with primary aldosteronism (PA) from aldosterone-producing adenomas were found to have sympathetic overactivity which was reversible after surgical resection of the tumor [20]. In contrast, 2 previous studies failed to show elevated SNA in the PA subjects [21, 22]. The difference in the results may be related to more rigorous selection criteria for our subjects which requires demonstration of sustained elevation in plasma aldosterone level or adrenal aldosterone production despite increased sodium intake according to the current Endocrine Society guidelines [20] while the PA subjects in 2 previous studies were identified by only elevated random levels of aldosterone [21, 22].

Despite variability in the SNA data among these cross-sectional studies comparing PA subjects to normal controls, our data from the randomized crossover study provide more definitive evidence for sympathoinhibitory effect of spironolactone when added to chlorthalidone treatment. In our previous study, spironolactone alone was not shown to alter SNA in patients with essential hypertension [2], suggesting that the sympathoinhibitory action

of MR antagonists is more apparent in the setting of renin-angiotensin-aldosterone excess. Furthermore, suppression in SNA during chlorthalidone-spironolactone therapy occurred without any detectable changes in baroreceptor control of SNA or heart rate, suggesting direct effects of spironolactone on the central sympathetic outflow.

In contrast to spironolactone, addition of the ARB irbesartan failed to attenuate the increase in SNA in the same subject, suggesting that Ang II is less important than aldosterone in mediating chlorthalidone-induced increase in SNA. Alternatively, limited oral bioavailability of irbesartan may be responsible for failure of irbesartan to inhibit central AT_1 receptors as suggested by a previous study by Leenen et al in the rat model of Ang II – induced hypertension [23]. Thus, the results of our study may differ with higher dose of irbesartan or other ARBs. Incomplete AT_1R blockade during ARB treatment or failure to suppress aldosterone release, i.e. aldosterone escape or breakthrough phenomenon is another potential mechanisms underlying failure of irbesartan to prevent chlorthalidone-induced increases in sympathetic nerve discharge [24]. Nevertheless, the results of our study are consistent with previous study by Fu et al, which showed markedly increased SNA when hydrochlorothiazide (HCTZ) was administered in combination with losartan [14].

In addition to stimulation of sympathetic nervous system, chlorthalidone is well known to increase plasma glucose and the risk of progression to diabetes mellitus. Although hypokalemia is thought to be the main mechanism of thiazide diuretic-induced dysglycemia, possibly by impairing pancreatic release of insulin [25], previous studies from our group and others demonstrated a component of insulin resistance which is independent of serum potassium [2, 26]. Activation of the renin-angiotensin system is thought to worsen insulin sensitivity, since Ang II has also been shown to both inhibit the insulin signaling pathways in the adipocyte and skeletal muscle and to impair pancreatic beta cell function [27]. Treatment with angiotensin converting enzyme inhibitors (ACEIs) or ARBs has been shown to reduce the development of diabetes mellitus in patients with hypertension or impaired glucose tolerance [28]. In contrast, previous studies have shown variable effects of ACEIs and ARBs on development of thiazide diuretic-induced insulin resistance. While the combination of losartan with HCTZ [29] and combination of captopril with bendrofluazide [30] failed to prevent the detrimental effect of thiazide diuretics on glucose homeostasis, combination of valsartan with HCTZ was shown to prevent the increase in fasting plasma glucose and to restore glucose-induced insulin secretion to pretreatment values in obese patients with hypertension [31]. This variability in study results might derive from variability in the dose and potency of various diuretics, as well as the specific type of ACEIs or ARBs. Nevertheless, the ARB irbesartan failed to prevent the adverse metabolic effects of chlorthalidone in our study.

Like Ang II, aldosterone has been implicated in the pathogenesis of insulin resistance in large populational studies [32] and in patients with primary aldosteronism [33]. In vitro studies demonstrate that aldosterone inhibits insulin signaling pathways both in adipocytes [10] and in vascular smooth muscle cells [11]. In vivo studies have indicated that aldosterone induces dysglycemia in rodents by impairing glucose uptake in the skeletal muscle and liver via inhibition of GLUT2 and GLUT4 gene expression [13]. Treatment with MR antagonists improves insulin sensitivity and skeletal muscle glucose transport in rodents with aldosterone excess [34]; however, there are no previous studies that have addressed the impact of MR blockade during thiazide therapy to insulin sensitivity in humans. Thus, our study represents the first demonstration that spironolactone prevents the chlorthalidone-induced insulin resistance in hypertensive patients. Furthermore, this beneficial effect of spironolactone was not explained by changes in serum potassium, suggesting direct effects of MR blockade.

Our study is limited by lack of a placebo arm but at least the randomized crossover design allows us to compare SNA and indices of insulin resistance during each combination therapy to during chlorthalidone treatment alone in the same subjects. Our study is also limited by the small sample size, which may explain failure to detect significant reduction in the ambulatory or casual BP when irbesartan or spironolactone was added to chlorthalidone. However, the nighttime HR was found to be significantly increased during chlorthalidone plus irbesartan phase compared to baseline, consistent with increased sympathetic drive to the sinus node. Changes in insulin sensitivity were calculated from the HOMA-IR and QUICKI equations rather than directly obtained from the hyperinsulinemic-euglycemic clamp method. Both HOMA-IR and QUICKI have been validated against the hyperinsulinemic glucose clamp and shown to be reliable indices of insulin sensitivity, supporting our findings [35, 36]. Only irbesartan was tested in this study and results may not be applicable for all ARBs. Only SNA targeted to the skeletal muscle vasculature was measured and our study results may not be applicable to other regional sympathetic outflow. Lastly, we cannot ascertain if the ability of spironolactone to improve insulin sensitivity in chlorthalidone-treated subjects is the cause or consequence of sympathoinhibitory effect of spironolactone. Exogenous infusion of insulin has been shown to acutely increase muscle SNA in normotensive subjects during a euglycemic clamp [37]. Conversely, activation of the sympathetic nervous system has been directly implicated in the pathogenesis of insulin resistance by reducing skeletal muscle glucose uptake both by flow-dependent [38, 39] and flow-independent [40, 41] mechanisms. This latter hypothesis is supported by one recent study, wherein catheter-based renal sympathetic denervation improved insulin sensitivity in patients with resistant hypertension [42].

Perspectives

Regardless of the mechanisms underlying the beneficial effects of spironolactone on glucose metabolism and SNA, it is known that both insulin resistance and sympathetic overactivity contribute to the poor prognosis of patients with cardiovascular diseases [43, 44]. Thus, addition of spironolactone might maximize the long-term cardiovascular benefit of chlorthalidone therapy in hypertensive patients by reducing the adverse metabolic consequences and neurohormonal activation. Additional large clinical trials are needed to determine if the combination of chlorthalidone with spironolactone is superior to chlorthalidone alone or other combination therapy in reducing cardiovascular outcomes in hypertensive patients.

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What Is New?

- Chlorthalidone, a thiazide-like diuretic, is known to cause insulin resistance and activation of sympathetic nervous system in hypertensive patients but effective measures to prevent these side effects have not been identified.
- The present study demonstrates that spironolactone, another diuretic which reduces BP by blocking actions of aldosterone hormone, prevents chlorthalidone-induced insulin resistance and sympathetic overactivity.

What Is Relevant?

- Chlorthalidone is widely accepted to be the preferred diuretic for treatment of hypertension but many associated metabolic side effects, particularly increased risk of diabetes mellitus, limits its use in clinical practice.

Summary - of the conclusions of the study

Addition of spironolactone to chlorthalidone may allow hypertensive patients to receive BP lowering benefit from chlorthalidone with minimal metabolic side effects.

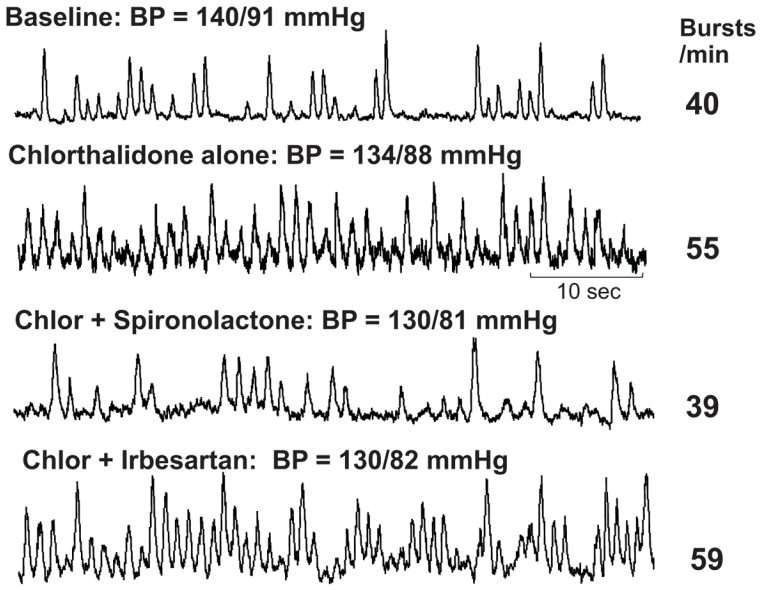

Figure 1.

Original recordings of SNA at baseline, after 12 weeks of chlorthalidone alone, after 12 weeks of chlorthalidone plus spironolactone, and after 12 weeks of chlorthalidone plus irbesartan in one hypertensive subject. In this subject, SNA increased from 40 to 55 bursts/min with chlorthalidone alone but returned to baseline (39 bursts/min) with combination of chlorthalidone plus spironolactone. In contrast, addition of irbesartan failed to alter SNA response to chlorthalidone (59 bursts/min) despite similar reduction in BP.

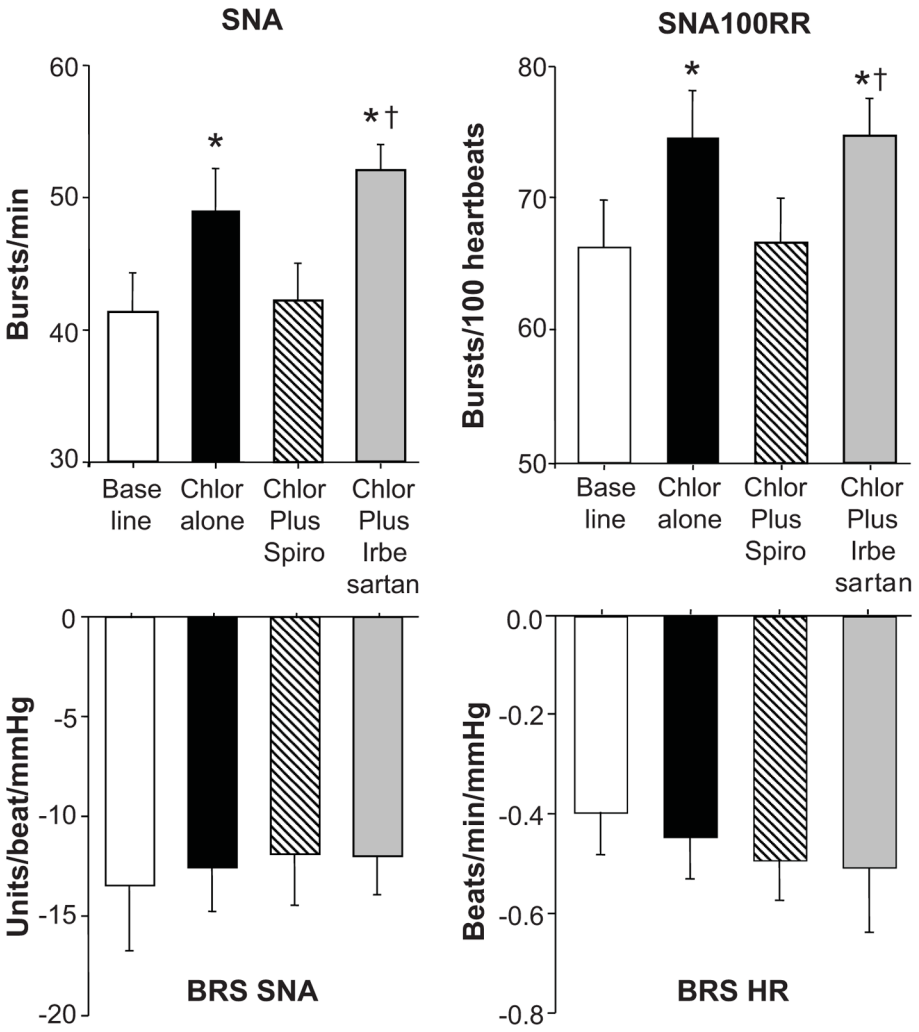

Figure 2.

Summary data showing changes in SNA (top left) and SNA per 100 RR intervals (top right), baroreflex control of SNA (bottom left) and baroreflex control of HR (bottom right) in all subjects after 12 weeks of chlorthalidone (Chlor) alone (solid bars), chlorthalidone plus spironolactone (Spiro, hatched bars), and chlorthalidone plus irbesartan (gray bars) compared with baseline (white bars). Data are mean ± SE. * $p < 0.01$ vs baseline, † $p < 0.01$ vs chlorthalidone plus spironolactone.

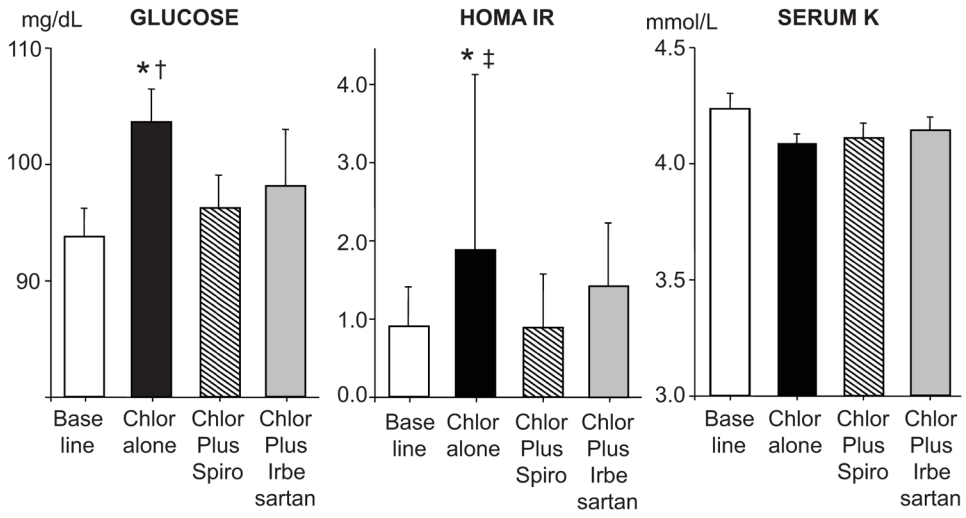

Figure 3.

Summary data showing changes in fasting plasma glucose (left), HOMA-IR (middle), and serum potassium (K), after 12 weeks of chlorthalidone (Chlor) alone (solid bars), chlorthalidone plus spironolactone (Spiro, hatched bars), and chlorthalidone plus irbesartan (gray bars) compared with baseline (white bars). Data are mean ± SE. * $p < 0.01$ vs baseline, † $p < 0.05$ vs chlorthalidone plus spironolactone, ‡ $p < 0.01$ vs chlorthalidone plus spironolactone.

Table 1

Variables	Normal Range	Baseline	Chlorthalidone alone	Chlorthalidone plus Spironolactone	Chlorthalidone plus Irbesartan	ANOVA p
Age, years				50.6±2.3		
BMI, kg/m^2				30.1 ± 1.9		
Female, %				35%		
African Americans, %				35%		
24-hr SBP, mmHg	< 130	135.2±2.6	123.8±2.1*	120.9±2.4*	120.6±2.4*	0.001
24-hr DBP, mmHg	< 80	83.5±2.1	77.6±2.1†	75.3±2.0*	74.9±2.1*	0.003
24-hr HR, beats/min	60–100	75±2	76±2	76±2	80±2	NS
Day SBP, mmHg	< 135	138.5±2.3	126.5±2.5*	124.9±2.9*	124.1±2.7*	0.002
Day DBP, mmHg	< 85	86.6±2.1	79.9±1.7*	78.1±1.5*	76.8±1.9*	0.004
Day HR, beats/min	60–100	77±2	77±2	78±2	81±2	NS
Night SBP, mmHg	< 120	131.1±2.6	119.7±2.1*	117.2±2.4*	114.1±2.4*	0.0003
Night DBP, mmHg	< 80	79.5±2.1	74.1±2.1†	71.7±2.0*	68.7±2.1*	0.0007
Night HR, beats/min	60–100	70±2	71±2	71±3	75±2†	0.049
Casual SBP, mmHg	< 140	149.5±4.2	131.7± 2.3*	132.9± 2.1*	128.9± 3.2*	< 0.0001
Casual DBP, mmHg	< 90	88.0±2.1	80.9±1.3*	81.3±2.1*	80.5±1.8*	0.0014
Casual HR, beats/min	60–100	64±2	64±2	70±2	71±2	NS
PRA, ng/ml/hr	0.05–3.3	0.44	3.27*	5.01*	13.62*§	<0.0001
interquartile range		0.05–1.16	0.84–7.93	2.39–11.50	5.73–17.67	
Aldosterone (ng/dL)	< 21	5.3±1.5	9.2±1.4*	10.8±2.2*	13.3±5.1*	0.013
Insulin, mU/L, median	< 12	3.9	7.6*	4.87‡	6.8	0.024
interquartile range		3.00–6.05	4.08–19.7	3.50–6.78	3.28–10.25	
QUICKI	> 0.31	0.40±0.02	0.35±0.01*	0.39±0.02‡	0.37±0.01	0.023

* $p < 0.01$ vs baseline

† $p < 0.05$ vs baseline

‡ $p = 0.02$ vs chlorthalidone alone

§ $p < 0.01$ vs chlorthalidone alone