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Effects of losartan on whole-body, skeletal muscle, and vascular insulin responses in obesity/insulin resistance without hypertension

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Abstract

Aims—Renin-angiotensin system antagonists have been found to improve glucose metabolism in obese hypertensive and type 2 diabetic subjects. The mechanism of these effects is not well understood. We hypothesized that the angiotensin receptor antagonist losartan would improve insulin-mediated vasodilation, and thereby improve insulin-stimulated glucose uptake in skeletal muscle of insulin resistant subjects.

Materials and Methods—We studied subjects with obesity and insulin resistance but without hypertension, hypercholesterolemia or dysglycemia (age 39.0 ± 9.6 yrs [mean $\pm$ SD], BMI 33.2 ± 5.9 kg/m², BP $115.8 \pm 12.2/70.9 \pm 7.2$ mmHg, LDL 2.1 ± 0.5 mmol/L). Subjects were randomized to 12 weeks' double-blind treatment with losartan 100 mg once daily (n=9) or matching placebo (n=8). Before and after treatment, under hyperinsulinemic euglycemic clamp conditions we measured whole-body insulin stimulated glucose disposal, insulin-mediated vasodilation, and insulin-stimulated leg glucose uptake by the limb balance technique.

Results—Whole-body insulin-stimulated glucose disposal was not significantly increased by losartan. Insulin-mediated vasodilation was augmented following both treatments (increase in leg vascular conductance: pre-treatment 0.7 ± 0.3 L*min⁻¹*mmHg⁻¹ [losartan, mean $\pm$ SEM] and 0.9 ± 0.3 [placebo], post-treatment 1.0 ± 0.4 [losartan] and 1.3 ± 0.6 [placebo]) but not different between treatment groups (p=0.53). Insulin's action to augment NO production and to augment endothelium-dependent vasodilation were also not improved. Leg glucose uptake was not significantly changed by treatments, and not different between groups (p=0.11).

Conclusions—These findings argue against the hypothesis that losartan might improve skeletal muscle glucose metabolism by improving insulin-mediated vasodilation in normotensive insulin resistant obese subjects. The metabolic benefits of angiotensin receptor blockers may require the presence of hypertension in addition to obesity-associated insulin resistance.

Introduction

Improvements in insulin resistance and reductions in the incidence of newly diagnosed type 2 diabetes mellitus have been observed in clinical trials of angiotensin converting enzyme inhibitors (ACEI) and type 1 angiotensin receptor blockers (ARB) (1–3). Many physiological studies using these classes of agents have demonstrated improvements in insulin-stimulated whole body glucose disposal (3–14) but this is not seen in all cases (15–18).

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It is now well recognized that insulin acts in skeletal muscle in part via endothelium-dependent, regulated vasodilator actions to redistribute blood flow (3, 19–21). This effect contributes ~25% of insulin's net actions on glucose uptake in skeletal muscle (22), and impairment in these responses contributes to net metabolic insulin resistance in obesity and type 2 diabetes mellitus. ACEI and ARB class medications improve endothelial dysfunction and nitric oxide production in hypertension (8, 23–25) and in insulin resistant states (26, 27). In this light, it is possible that beneficial effects of ACEI or ARB class medications on the endothelium could improve insulin's endothelium-dependent actions (17, 28). We therefore hypothesized that the type 1 angiotensin receptor antagonist losartan would improve insulin-mediated vasodilation, and thereby improve insulin-stimulated glucose uptake in skeletal muscle, in insulin resistant obese subjects without hypertension.

Methods

Nondiabetic obese subjects were recruited through newspaper advertisement, and classified as obese using body mass index cutpoints of ≥ 35 kg/m² for men or ≥ 30 for women to select for equivalent degrees of obesity across sexes (29). Exclusion criteria included hypertension (SBP $\geq$ 140/DBP $\geq$ 90) or antihypertensive therapy, elevated serum lipids (total cholesterol $\geq$ 5.2 mmol/L, LDL $\geq$ 2.3 mmol/L or TG $\geq$ 2.0 mmol/L), biochemical evidence of renal or hepatic dysfunction, or significant underlying medical conditions. Age below 20 or above 55 years was an exclusion criterion, as were pregnancy and known hypersensitivity to losartan. All subjects underwent a standard 75g oral glucose tolerance test to screen for diabetes mellitus, and had body composition assessed by dual energy X-ray absorptiometry (DEXA) measurement. When originally designed, obesity plus dysglycemia were required enrollment criteria; after the first 6 months of recruitment these criteria were modified to allow normoglycemia but require elevated fasting insulin concentrations ($\geq$ 10.0 mU/mL) in order to focus enrollment of insulin resistant subjects. This study was approved by the local Institutional Review Board, and all subjects gave written informed consent. All procedures were performed in accordance with institutional guidelines. This study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00402194), NCT00402194.

Design

Following screening and enrollment, subjects underwent baseline measurements of insulin's systemic and vascular actions as detailed below. Randomized treatment assignment was done by a third party not involved in study measurements, using a randomly generated assignment sequence. Treatment assignments were masked to the investigator and the participants. Subjects were treated with 50 mg losartan once daily (or matched placebo) for the initial two weeks to document tolerability and a lack of significant change in serum potassium, then increased to 100 mg once daily (or matched placebo) for the remainder of the randomized treatment period. Subjects who failed to complete the study were replaced, with the next enrolled subject assigned to the same treatment as the lost participant in an attempt to maintain balance in treatment assignment. The decision to compare losartan to placebo rather than comparing losartan to a non-RAAS antihypertensive agent was based on an expectation of modest blood pressure effects in this normotensive population, plus a planned correction of endpoints for any changes in blood pressure that did occur (explained in detail below).

Subjects underwent end-of-study measurements following 12 ± 1 weeks of treatment. Subjects did not take their study medication on the morning of the study in order to ensure that any measured changes represented effects of chronic exposure and not the immediately preceding dose. Women with a regular menstrual cycle were studied within the first 11 days of their cycle on both occasions, to minimize the confounding effects of changes in sex steroids on vascular function. Medication compliance was assessed by pill counting.

Procedures and Measurements

Whole leg vascular responses were measured using thermodilution, a highly sensitive technique that has been extensively used to demonstrate vascular effects of insulin (22, 30–32). Before and after treatment, subjects underwent measurements of leg vascular function under basal and insulin-stimulated conditions, to measure insulin's effect to stimulate glucose uptake for the whole body and the leg. Measurements were made under fasting conditions following an overnight fast.

A 6F sheath (Cordis Corp, Miami, FL) was placed into the right femoral vein to allow the insertion of a custom-designed 5F double-lumen thermodilution catheter (Baxter Scientific, Edwards Division, Irvine, CA) to measure leg blood flow (LBF). The right femoral artery was cannulated with a 5.5F double-lumen catheter to allow simultaneous infusion of vasoactive agents and invasive blood pressure monitoring (Spacelabs, Redmond, WA). All hemodynamic measurements were obtained with the subjects in the supine position in a quiet temperature-controlled room. Basal measurements were obtained 30 minutes after the insertion of the catheters. Femoral vein thermodilution was used to measure rates of LBF, calculated by integration of the area under the curve, using a cardiac output computer (model 9520A, American Edwards Laboratories). Reported values are the mean of at least 10 measurements taken at each study stage. Invasively determined MAP was recorded with every other LBF determination.

Endothelium-dependent vasodilation was measured using the cholinergic agonist methacholine chloride, and endothelium-independent vasodilation was measured using sodium nitroprusside, both infused directly into the femoral artery in three sequential doses. Following baseline measurements of vasodilator responses, a hyperinsulinemic euglycemic glucose clamps were performed using an insulin infusion rate of $120 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$. Insulin was administered systemically via an antecubital vein. This insulin dose was used in view of the anticipated insulin resistance in the vasculature, in order to ensure a measureable response. Blood samples from the femoral artery were measured every 5 minutes to ensure maintenance of euglycemia. Once steady state of the insulin infusion was achieved (minimum of 180 minutes from initiation of the procedure) repeat vascular measurements were performed. At the end of each study, L-NMMA (Clinalfa, Basel, Switzerland), a competitive antagonist of L-arginine, was infused at 16 mg/min into the femoral artery to block NO generation by nitric oxide synthase. This is the standard infusion rate used in our laboratory (33), chosen on the basis that it provides near-maximal effect across all populations.

The primary endpoint for this study was insulin-mediated vasodilation, measured at baseline and following 12 weeks of therapy. Because of anticipated changes in blood pressure with the angiotensin receptor blocker, we pre-specified leg vascular conductance (leg blood flow divided by concurrent intra-arterial mean arterial pressure) as the main variable of interest for assessing insulin-mediated vasodilation. Secondary endpoints included insulin's effect to augment methacholine-stimulated vasodilation; vascular responses to nitric oxide synthase inhibition with L-NMMA; skeletal muscle insulin sensitivity for glucose uptake (leg glucose uptake = leg blood flow multiplied by arterio-venous glucose difference at steady state of the insulin infusion); and whole body insulin sensitivity. Nonlinear modeling of the complete clamp datasets was applied to extract steady state rates of whole body glucose disposal and A-V glucose differences (34).

Blood for serum glucose determinations was put in untreated polypropylene tubes, and centrifuged. The glucose concentration of the supernatant was then measured by the glucose oxidase method (Model 2300 Yellow Springs Instruments, Yellow Springs, OH). Blood for determination of plasma insulin was frozen at -20°C . Insulin determinations were made

using a dual-site radioimmunoassay (Millipore, Billerica, MA). Free (nonesterified) fatty acid measurements were performed using a colorimetric assay. Standard methodologies for cholesterol and triglyceride determinations were performed through our local hospital's clinical laboratory.

Power Calculations

Our main endpoint of interest was insulin-mediated vasodilation. We therefore made sample size calculations using this parameter, and estimated demonstrable effects for secondary parameters of interest using the sample size obtained in this way. We reasoned that a correction of the impaired effect of insulin in the skeletal muscle vasculature would convert the response observed in obese subjects into that typically observed in lean subjects. Based on related prior studies, this was estimated as a difference in insulin-stimulated vasodilation (IMV) of $0.11 \text{ L} \cdot \text{min}^{-1}$ (leg blood flow) or $1.2 \times 10^{-4} \text{ L} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ (leg vascular conductance) between the two treatment groups. Effects of this size had been observed with studies using endothelin antagonists in our laboratory (31, 35). We estimated *a priori* that 9 subjects per group would provide 80% power to detect this effect size, recognizing that likelihood of detecting smaller effect sizes is accordingly reduced. This number of subjects was then used to estimate detectable differences (with 80% power) in insulin-stimulated whole body glucose uptake of $2.7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (~35% increase), and differences in insulin-stimulated leg glucose uptake of 41 mg/min (~50% increase). Again, these effect sizes are within the range demonstrated in our laboratory previously (31). With paired studies in our population we have historically seen a 15% noncompletion rate and to allow for this we planned to recruit 11 subjects per group.

Statistics

Chi square or one-way ANOVA were applied for group comparisons at a single time point. Linear mixed modeling was applied to assess repeated measures treatment effects, in order to use all available data. Standard covariance matrices were applied, and data were not transformed.

Results

We screened 32 consecutive volunteer subjects for participation in this protocol. Of these, 22 met inclusion/exclusion criteria and were enrolled in the study. Due to dropouts, we completed the project with 9 subjects in the losartan group and 8 in the placebo group. No losartan-treated subjects withdrew, and no subjects reported medication-related side effects as a reason for withdrawal from the study.

The characteristics of the study population are described in Table 1. Despite randomization, there was a modest difference in the body mass index (BMI) between treatment groups (with a greater mean BMI in the losartan-treated subjects), although the waist circumferences did not differ. This population was normoglycemic but hyperinsulinemic with correspondingly elevated HOMA-IR scores. Baseline cuff blood pressure and lipid parameters were not statistically different between groups, and as designed these parameters were well below current treatment thresholds. Subjects who withdrew from the study were not statistically different from those who completed the study in any of these parameters (not shown). By pill counting, compliance was greater than 95% for both treatment groups. Serum potassium was unaffected by study drug treatment, and no subjects had treatment dose modified or were excluded from the study on this basis.

Vascular outcomes

Cuff blood pressure measurements were not statistically changed by randomized treatments (not shown). Modest reductions in intra-arterial blood pressure were seen (Figure 1), not achieving significance in this normotensive population.

The main study question was whether losartan treatment would augment insulin-mediated vasodilation. Prior to receiving treatment, insulin-induced increases in leg vascular conductance for the combined study population were : baseline $2.74 \pm 0.15 \times 10^{-4} \text{ L} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ (mean $\pm$ SEM) to insulin 3.61 ± 0.23 in the placebo group and baseline 2.40 ± 0.17 to insulin 3.07 ± 0.31 in the losartan group ($p < 0.001$ for insulin effect; $p = 0.31$ comparing pre-treatment data across groups; Figure 2 upper panel). By comparison, unpublished and previously published data from our laboratory show that this insulin exposure caused a larger increase in leg vascular conductance from 2.33 ± 0.37 to 4.81 ± 1.91 in lean subjects ($N = 14$; $p = 0.03$ comparing to this baseline effect in our population). Therefore this pre-treatment effect reflects impaired insulin-mediated vasodilation at baseline, as expected for this obese insulin resistant population.

Following 3 months' treatment, there was no evident change in basal unstimulated leg vascular conductance in either group, and the effect of insulin was essentially unchanged from prior to treatment (placebo: basal LVC $2.34 \pm 0.31 \times 10^{-4}$ to insulin 3.68 ± 0.57 ; losartan: basal 2.67 ± 0.30 to insulin 3.59 ± 1.89 ; $p = 0.51$ for insulin*treatment interaction; Figure 2 middle panel).

A complementary measure of effects of treatment on insulin's vascular effects is provided by the effect of the nitric oxide synthase inhibitor L-NMMA to decrease leg vascular conductance. In these studies this was only measured at steady state of the insulin infusion, and therefore reflects insulin-stimulated nitric oxide bioavailability. The pre-treatment decrements in LVC with L-NMMA were not statistically different between treatment groups (Figure 2 bottom panel). Losartan did not improve insulin-stimulated NO bioavailability (i.e. no increase in magnitude of L-NMMA – induced decrement in LVC following treatment).

Endothelium-dependent vasodilation

We measured endothelium-dependent vasodilation in two ways. First, the direct effects of the endothelium-dependent vasodilator methacholine were evaluated. Second, we measured the effect of insulin to augment methacholine-stimulated vasodilation, an effect that can be additive and depends on insulin's action as an endothelium-dependent vasodilator (36).

Methacholine-stimulated increases in leg blood flow were not statistically different between pre- and post-treatment measurements, nor between treatment groups (Figure 3 upper panel). Endothelium-independent vasodilation, assessed as nitroprusside-stimulated vasodilation, was also not affected by losartan treatment (Figure 3 lower panel).

In the pre-treatment studies there was no evident cross-sectional correlation of insulin sensitivity (whole body insulin-stimulated glucose uptake) with methacholine-induced vasodilation or with insulin-mediated vasodilation. Treatment with losartan did not bring out such relationships (not shown).

Metabolic actions of insulin

Insulin-stimulated whole body glucose uptake was not different between treatment groups at study entry, with an observed range of 3.2 to 9.8 mg/kg/min. There was no apparent effect of losartan treatment to alter whole-body insulin sensitivity ($p = 0.40$; Figure 4 upper panel).

Effects of insulin on skeletal muscle metabolism were measured as insulin-stimulated leg glucose uptake (calculated as leg blood flow*A-V glucose difference, according to the Fick principle). These results are presented in Table 2 and Figure 4 lower panel. Losartan did not significantly augment insulin-stimulated increases in leg blood flow compared with placebo, consistent with the lack of treatment effect on leg vascular conductance described above. Arteriovenous glucose difference (i.e. leg glucose extraction) was not different between treatment groups at baseline, and not different between groups following treatment. There was no significant effect of losartan to increase insulin-stimulated leg glucose uptake compared with placebo ($p=0.11$ for treatment differences across groups).

Planned post-hoc analyses were performed comparing responses in subjects whose baseline insulin sensitivity was above or below the median, in order to consider the possibility of an effect manifesting only in the more insulin-resistant subjects. There was no significant effect of losartan treatment to augment insulin's vascular or metabolic actions in any of the above parameters even within the insulin resistant subset of subjects (not shown). We also repeated the core analyses incorporating blood pressure covariates. Here we observed a significant relationship of baseline blood pressures with whole body glucose uptake, leg A-V glucose difference, insulin-mediated vasodilation and leg glucose uptake (not shown). These relationships were unchanged with treatment. Losartan did not significantly affect BMI (not shown), or beta cell function or adipose insulin sensitivity (Table 3).

Discussion

We evaluated a hypothesized effect of losartan to augment insulin-mediated vasodilation in skeletal muscle, and thereby to augment whole body insulin sensitivity, in obese insulin resistant subjects without hypertension or type 2 diabetes mellitus. We found no evidence for an effect of losartan to improve any parameter of insulin's vascular actions in skeletal muscle in this study population. Insulin-stimulated leg glucose uptake and insulin-stimulated whole body glucose uptake were also not significantly improved by losartan. These findings argue against an effect of losartan to improve whole-body insulin sensitivity by augmenting insulin-mediated vasodilation in obese insulin resistant subjects without hypertension or type 2 diabetes.

Many studies of metabolic effects of ACE inhibitors (ACEI) and angiotensin receptor antagonists (ARBs) have reported significant improvements in whole-body insulin-mediated glucose disposal (3–14) but there have been notable exceptions (15–18). Positive and negative findings have been reported in studies using both ACEI and ARBs. The most important difference between prior positive studies and the current report is that our study included obese subjects without hypertension or diabetes mellitus. A related observation is that subjects with Type 1 diabetes without hypertension and with acceptable glucose control do not receive the same benefits in prevention of microvascular disease with ACEI/ARBs (37, 38). Together with the current results, these observations point to benefits of ACEI/ARB in diabetes that are tied to the presence of hypertension.

The changes in blood pressure, together with the evidence from pill counting, argue against a false negative finding due to poor medication compliance, and the 12 week exposure was chosen to avoid concerns about insufficient treatment duration. We observed slightly greater measurement noise in this study than used in our power calculations, but the unchanged apparent mean responses in insulin-mediated vasodilation (measured either as leg blood flow or leg vascular conductance) support the conclusion of an absent effect. The statistical design was configured to detect clinically relevant effects, namely changes on the order of the difference between lean and obese subjects. The observed effects did not even approach this magnitude of difference, as reflected in the high p values. Further, negative findings

were obtained with 3 different ways of evaluating insulin's vascular actions (direct vasodilation, NO-dependent effects, and augmentation of acetylcholine-induced dilation). Together these findings convincingly argue that the lack of improvement in insulin-mediated vasodilation is a true negative, not limited by statistical power.

Where beneficial effects of ACEI and ARB on glucose metabolism have been observed, data do not consistently support vascular actions as a mediator of these benefits. Paolisso and colleagues (39), studying effects of losartan in hypertensive subjects, and Bonora and colleagues (7), studying effects of lisinopril in type 2 diabetic subjects, reported improvements in non-oxidative glucose disposal with losartan treatment, sufficient to explain the observed augmentation in whole-body insulin resistance (i.e. without invoking effects on insulin's vascular actions). In the former study insulin-induced augmentation of femoral artery blood flow, measured using ultrasound, was concurrently increased by losartan, with a positive correlation between changes in insulin's vascular and metabolic effects (39). Studying obese type 2 diabetic subjects, Hermann and colleagues found that quinapril augmented insulin-induced vasodilation and insulin's effects to augment endothelium-dependent vasodilation in forearm resistance vessels (40). In a LIFE substudy, Olsen and colleagues reported worsening whole-body insulin-stimulated glucose disposal with atenolol but stable values with losartan (17). This was interpreted as preservation of insulin sensitivity with losartan. Similar findings were reported in a large clinical trial using simple measures of insulin sensitivity (13). It is possible that using other techniques, such as microbubble measurement of tissue perfusion effects of insulin (20, 21), could allow demonstration of pertinent vascular effects that contribute to tissue insulin actions without resulting in whole-limb changes in blood flow.

The observed changes in leg glucose uptake did not achieve significance but were directionally consistent with a beneficial losartan effect. This was not a predicted outcome under the current study hypothesis. Since no beneficial effects on insulin's vascular actions were seen, this suggests instead a potential effect on tissue glucose extraction. There is only one published study to compare against our data regarding arteriovenous glucose differences and effects on limb glucose uptake. Galletti and colleagues (8) compared effects of nifedipine and trandolapril on whole-body insulin resistance, and evaluated effects of treatment on insulin-stimulated arm glucose uptake in a manner parallel to the current report. Similar to the current report, they saw no treatment effect on limb blood flow, but did observe a modest increase in A-V glucose difference and a ~70% increase in limb glucose uptake in ACEI-treated subjects. Our losartan-treated subjects exhibited a ~45% increase in leg glucose uptake, not reaching significance. Together these observations, suggest a possible effect of ACEI or ARB on cellular glucose extraction independent of effects on tissue perfusion. This question has been directly evaluated using reverse microdialysis in healthy humans (41). In that report, perfusion of subcutaneous fat with enalaprilat and bradykinin augmented tissue glucose transport, but this was not seen with losartan. This novel hypothesis requires further study.

We measured serum potassium concentrations as a safety parameter before and following 2 weeks' treatment on study medications, and did not observe any clinically important changes. We did not obtain repeat measures at end of study. Similarly, we did not measure treatment effects on other circulating factors of potential relevance such as angiotensin metabolites, aldosterone, catecholamines, endothelin, or natriuretic peptides. These might have been of interest as hypothesis-generating measures to explore potential mediators of an observed benefit, but with the current results we chose not to pursue such measurements.

The mechanism of previously reported beneficial effects of ACEI/ARB on systemic metabolism remains unexplained. We did not observe beneficial effects of losartan treatment

on other aspects of whole-body metabolism, although we did observe a treatment difference in adipose insulin sensitivity that approached significance (Table 3). Other authors have reported improvements in beta cell function (12, 14), including one report where gold-standard measures of first and second phase glucose-stimulated insulin release were improved by valsartan (12). We saw no improvement in the insulinogenic index, but we did not study individuals with baseline defects in beta cell function. Other potential non-vascular mechanisms include improvements in circulating adiponectin (42), reductions in oxidative stress (43), and reductions in circulating inflammatory mediators (44). Further study is required to explore these mechanisms.

In conclusion, 3 months' treatment with losartan in obese normotensive insulin resistant subjects failed to improve insulin-mediated vasodilation, skeletal muscle glucose uptake, or whole-body glucose uptake. This is in contrast to prior studies in hypertensive subjects, suggesting that metabolic benefits of RAS antagonists may require the presence of hypertension.

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Figure 1.

Effects of Losartan on Intra-Arterial Blood Pressure. Upper panel, systolic blood pressure. Lower panel, diastolic blood pressure. Treatment groups were not statistically different at baseline. The principal comparison of interest is treatment effect across groups, designated 'Treatment effect' and reflecting the statistical interaction term of treatment*time.

Figure 2.

Effects of Losartan on Insulin-Stimulated Vascular Response. Upper panel, vascular actions of insulin; middle panel, augmentation of leg vascular conductance at steady state; lower panel, reduction in leg vascular conductance following treatment with L-NMMA at steady state. The principal comparison of interest is treatment effect across groups, designated 'Treatment effect' and reflecting the statistical interaction term of treatment*time.

Figure 3.

Effects of Losartan on Vascular Function. Upper panel, endothelium-dependent vasodilation; lower panel, endothelium-independent vasodilation. Methacholine-induced vasodilation did not differ at baseline between treatment groups, and was not changed in either group following treatment. Nitroprusside-induced vasodilation was reduced in the Losartan-treated group at baseline ($p<0.03$), but treatment did not augment this effect in either group. Bas = baseline conditions; Rx = post-treatment conditions.

Figure 4. Effects of Losartan on Glucose Disposal. Upper panel, whole body glucose disposal at steady state of the insulin infusion; lower panel, leg glucose disposal at steady state of the insulin infusion. Statistical significance is presented for the comparison of treatment effect across groups.

Table 1

Subject Characteristics

Parameter	Placebo	Losartan	P value
Race (C/AA)	4/4	5/4	0.86
Sex (M/F)	3/5	4/5	0.38
Age (yrs)	36.5±10.1	41.0±8.7	0.34
BMI (kg/m ²)	29.3±2.9	36.4±6.6	0.03
Waist (cm)	91.0±26.1	95.2±11.1	0.91
Systolic BP (mmHg)	121±10	122±10	0.60
Diastolic BP (mmHg)	75±7	78±8	0.16
Glucose Fasting (mmol/L)	5.2±0.5	5.2±0.4	0.77
Glucose OGTT 120min (mmol/L)	7.1±1.3	7.1±2.5	0.99
Non-esterified fatty acids Fasting (mmol/L)	0.40±0.18	0.46±0.26	0.50
Insulin Fasting (mU/mL)	17.2±14.3	20.4±10.2	0.48
HOMA-IR (U)	3.4±2.4	4.4±1.7	0.35
Triglycerides (mmol/L)	1.23±0.73	1.18±0.69	0.91
Total Cholesterol (mmol/L)	3.37±0.64	3.69±0.55	0.28
LDL Cholesterol (mmol/L)	2.00±0.46	2.29±0.42	0.19
HDL Cholesterol (mmol/L)	0.92±0.29	0.96±0.27	0.79
Baseline LBF (L/min)	0.26±0.05	0.24±0.05	0.53
Baseline GDR ₁₂₀ (mg/kg/min)	6.8±2.0	5.9±2.2	0.33

Values are presented as mean±sd. P values are presented for comparison of placebo versus losartan by one-way ANOVA.

Table 2

Effect of Losartan on Skeletal Muscle Vascular Responses to Insulin

	Placebo		Losartan		p
	Baseline	Treatment	Baseline	Treatment	
Leg blood flow -Basal (L/min)	0.257±0.016	0.222±0.020	0.243±0.016	0.271±0.016	0.09
Leg blood flow - SS (L/min)	0.356±0.028	0.327±0.049	0.289±0.026	0.353±0.046	0.24
A-V glucose difference-SS (mmol/L)	1.16±0.14	0.96±0.16	1.02±0.13	1.17±0.14	0.21
Leg glucose uptake-SS (mmol/min)	0.41±0.05	0.30±0.09	0.29±0.05	0.42±0.08	0.11

Note: P values represent the effect of treatment across groups. SS indicates steady state of the hyperinsulinemic euglycemic clamp. Values are presented as mean±SEM.

Table 3

Effects of Losartan on Systemic Metabolism

	Placebo		Losartan		P value
	Baseline	Treatment	Baseline	Treatment	
Fasting glucose (mmol/L)	5.7±0.3	5.4±0.3	5.8±0.3	5.6±0.2	0.85
2hr OGTT glucose (mmol/L)	7.7±0.7	7.1±0.3	7.0±0.8	6.9±0.8	0.44
Insulinogenic Index (mU/mmol*100)	3.88±0.65	3.72±1.21	4.37±1.38	3.58±1.04	0.38
Fasting FFA (mmol/L)	0.50±0.07	0.31±0.05	0.46±0.09	0.46±1.0	0.16
Clamp ΔFFA (mmol/L)	0.43±0.04	0.17±0.05	0.37±0.07	0.39±0.09	0.06

Note: P values represent the effect of treatment across groups. Values are presented as mean±SEM. FFA = free fatty acids. Clamp ΔFFA indicates insulin-induced suppression of free fatty acids.