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Research Article

# Systemic and tissue-specific effects of aliskiren on the RAAS and carbohydrate/lipid metabolism in obese patients with hypertension

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## Abstract

Aliskiren penetrates adipose and skeletal muscle in hypertensive patients with abdominal obesity and reduces renin–angiotensin–aldosterone system activity. After discontinuation, blood pressure–lowering effects are observed possibly through drug–tissue binding. We performed microdialysis evaluation of adipose tissue and skeletal muscle before and during an insulin-modified frequently sampled intravenous glucose tolerance test (IM-FSIGT). Aliskiren 300 mg (n = 8) or amlodipine 5 mg (n = 8) once daily were administered during a 12-week randomized treatment period. Aliskiren elicited variable changes in median interstitial angiotensin II (Ang II) in adipose (2.60–1.30 fmol/mL) and skeletal muscle (2.23–0.68 fmol/mL); amlodipine tended to increase adipose and skeletal muscle Ang II ($P = .066$ for skeletal muscle treatment difference). Glucose/insulin increased median plasma Ang II 1 hour after glucose injection (1.04–2.50 fmol/mL; $P = .001$), which was markedly attenuated by aliskiren but not amlodipine. Aliskiren increased glucose disposition index ($P = .012$) and tended to increase acute insulin response to glucose ($P = .067$). Fasting adipose glycerol (−17%; $P = .064$) and fasting muscle glucose dialysate (−17%; $P = .025$) were decreased by aliskiren but not amlodipine. In summary, aliskiren decreased Ang II production in response to glucose/insulin stimulus and elicited metabolic effects in adipose and skeletal muscle suggestive of increased whole-body glucose utilization. J Am Soc Hypertens 2017;■(■):1–10. 

*Keywords:* Adipose tissue; amlodipine; angiotensin II; insulin sensitivity; microdialysis; obesity; plasma renin activity; skeletal muscle.

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## Introduction

All components of the renin–angiotensin–aldosterone system (RAAS) are expressed in human adipose tissue, with upregulation of genes encoding renin, angiotensin-converting enzyme, and AT1 receptors in obese patients with hypertension compared with lean or obese normotensive patients.[1] Weight loss decreased overexpression of these genes in adipose tissue and reduced circulating concentrations of these RAAS components.[2] Preclinical data suggest that the adipose tissue RAAS may control local renin concentrations independently of plasma concentrations.[3] Adipose-generated angiotensin II (Ang II) may contribute to obesity-related hypertension and metabolic abnormalities. Of note, interstitial Ang II modulated adipose and skeletal muscle carbohydrate and lipid metabolism in a tissue-specific fashion in healthy subjects.[4]

We previously showed that the direct renin inhibitor, aliskiren, was distributed to adipose and skeletal muscle tissue at concentrations sufficient to reduce tissue RAAS activity in hypertensive patients with abdominal obesity.[5] Here, we report part 2 of this study, which further explored systemic and tissue-specific effects of the RAAS in regulating lipid and carbohydrate metabolism in patients with hypertension and abdominal obesity. The main objectives were to: (1) assess the effects of aliskiren on Ang II concentrations in interstitial fluid of subcutaneous adipose tissue and skeletal muscle and on RAAS biomarkers in the plasma and (2) compare the effects of aliskiren and amlodipine on lipid and carbohydrate metabolism in subcutaneous adipose tissue and skeletal muscle before and during an insulin-modified frequently sampled intravenous glucose tolerance test (IMFSIGT). Amlodipine was chosen as a comparator[5,6] to control for the blood pressure–lowering effects of aliskiren.

## Methods

### *Patients*

The study population included men and women 18–65 years of age with essential hypertension and abdominal obesity (waist circumference ≥102 cm in men, ≥88 cm in women, and body mass index between 30 and 36 kg/m$^2$). Blood pressure criteria for study entry included: ≥135/85 mm Hg and <160/100 mm Hg at screening, predose, and baseline for newly diagnosed (untreated) hypertension and at baseline only for patients with a history of treated hypertension. Patients had to be nonsmokers or light smokers (urine cotinine concentration <500 ng/mL). The study design was approved by the Institutional Review Board of Hannover Medical School and was conducted in accordance with Good Clinical Practice and in compliance with the Declaration of Helsinki and applicable European Regulations. The study was registered with clinicaltrials.gov (identifier NCT00498433). The experiments were conducted with the understanding and the consent of each participant. All patients provided written informed consent.

Key exclusion criteria included current treatment with ≥3 antihypertensive drugs; type 1 or 2 diabetes mellitus; history of autonomic dysfunction in the recent past; any history of hypertensive encephalopathy or stroke; history of major cardiovascular events (myocardial infarction, unstable angina) during the past 6 months; and any history of acute or chronic bronchospastic disease. Women of child-bearing potential had to be using highly effective contraception; postmenopausal women could not be using hormone replacement therapy.

### *Study Design*

This was a randomized, double-blind, parallel-group, single-center study conducted at the Institute of Clinical Pharmacology, Hannover Medical School, Germany. The study consisted of a screening period of up to 21 days, followed by a washout period of five elimination half-lives of the longest acting drug (1–2 weeks), a 2-week single-blind, placebo run-in period (period 1), and a 12-week double-blind, active treatment period (period 2). Active treatment consisted of 1:1 randomization to once daily aliskiren 300 mg and amlodipine placebo or once daily amlodipine 5 mg and aliskiren placebo. Study drug was administered between 8 AM and 10 AM each day, except on visit days when medication was taken after all visit procedures were completed.

Randomization numbers were assigned in ascending, sequential order and generated in a manner to ensure that treatment assignment was unbiased and concealed from patients and investigator staff. A randomization list was produced by Novartis Drug Supply Management using a validated system that automated the random assignment of treatment arms to randomization numbers in the specified ratio. Patients, investigator staff, persons performing the assessments, and data analysts were blinded to treatment; the identity of treatments was concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration, appearance, taste, and odor. A double-dummy design was used because the identity of the study drug (aliskiren tablet) and active control (amlodipine capsule) could not be disguised due to their different forms.

Pharmacodynamic assessments were performed at baseline (end of placebo run-in period, day 14) and at the end of the active treatment period (day 98). Office sitting blood pressure was measured at all study visits.

### *Adipose Tissue and Skeletal Muscle Microdialysis*

Two microdialysis catheters each (CMA 60, CMA Microdialysis AB, Solna, Sweden) were inserted into the subcutaneous adipose tissue (at the level of the umbilicus)