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Presence of arachidonoyl-carnitine is associated with adverse cardiometabolic responses in hypertensive patients treated with atenolol

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Abstract

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Compliance with ethical standards: Ethical approval and informed consent: The research outlined in this manuscript stems from human subjects research. As indicated, the research protocol was approved by the Institutional Review Board at all of the enrolling sites, and all patients provided written, voluntary informed consent prior to participation in any research procedures.

Introduction—Atenolol, a commonly prescribed β blocker for hypertension, is also associated with adverse cardiometabolic effects such as hyperglycemia and dyslipidemia. Knowledge of the mechanistic underpinnings of these adverse effects of atenolol is incomplete.

Objective—We sought to identify biomarkers associated with risk for these untoward effects of atenolol. We measured baseline blood serum levels of acylcarnitines (ACs) that are involved in a host of different metabolic pathways, to establish associations with adverse cardiometabolic responses after atenolol treatment.

Methods—Serum samples from Caucasian hypertensive patients ($n = 224$) who were treated with atenolol in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study were interrogated using a quantitative LC/MS assay for a large number of unique ACs in serum. For the 23 ACs that were detected in serum from 80 % of all patients, we conducted linear regression for changes in cardiometabolic factors with baseline AC levels, baseline cardiometabolic factors, age, sex, and BMI as covariates. For the 5 ACs that were detected in serum from 20 to 79 % of the patients, we similarly modeled changes in cardiometabolic factors, but with specifying the AC as present/absent in the regression.

Results—Among the 28 ACs, the presence (vs. absence) of arachidonoyl-carnitine (C20:4) was significantly associated with increased glucose ($p = 0.0002$), and was nominally associated with decreased plasma HDL-C ($p = 0.017$) and with less blood pressure (BP) lowering ($p = 0.006$ for systolic BP, $p = 0.002$ for diastolic BP), after adjustment.

Conclusion—Serum level of C20:4 is a promising biomarker to predict adverse cardiometabolic responses including glucose and poor antihypertensive response to atenolol.

Keywords

Acylcarnitine; Arachidonoyl-carnitine; C20:4; Atenolol; Hypertension; Pharmacometabolomics; Cardiometabolic syndrome

1 Introduction

Hypertension (HTN), the most common chronic condition for which medications are prescribed, affects approximately 80 million adult Americans or, one in every three adults in the US (Mozaffarian et al. 2015). Atenolol is an effective, commonly prescribed β -blocker used to treat HTN. However in some individuals, atenolol treatment is also associated with adverse cardiometabolic effects, including dyslipidemia, hyperglycemia and diabetes (Elliott and Meyer 2007; Bangalore et al. 2007), which have negative consequences on health including atherosclerotic cardiovascular disease, myocardial infarction, stroke and death (Girman et al. 2005; Mottillo et al. 2010). The underlying mechanisms responsible for the inter-individual variability associated with the onset of adverse cardiometabolic effects linked to atenolol use are incompletely understood. However, we showed previously that branched chain amino acids in plasma are strongly associated with increased odds of developing impaired fasting glucose following atenolol exposure (Cooper-Dehoff et al. 2014). Elucidating the metabolomic risk factors and important drug-metabolome interactions, in addition to clinical risk factors, could lead to a more personalized treatment approach for HTN management and decrease the frequency of adverse metabolic events.

Acylcarnitines (ACs) are a large class of metabolites that are derived from their cognate acyl-CoAs. Acyl-CoAs play pivotal roles in a host of different metabolic pathways ranging from amino acid catabolism to fatty acid oxidation (FAO). Hence, ACs serve as excellent biomarkers for perturbations of a multitude of different metabolic pathways. More specifically, short chain (Hoppel and Genuth 1980), branched chain amino acid-derived (Newgard et al. 2009), and long chain ACs (Holland et al. 2007; Samuel and Shulman 2012; Mihalik et al. 2010) have been implicated in obesity, insulin resistance and diabetes. Additionally, the Western dietary pattern, which is also implicated in insulin resistance phenotypes, is associated with a specific metabolite signature characterized by branched chain amino acids and short chain ACs (Bouchard-Mercier et al. 2013). We hypothesized that AC profiling in blood serum would yield a biomarker candidate for prospectively identifying patients at increased risk for adverse cardiometabolic effects following atenolol exposure.

2 Methods

2.1 Study cohort

Caucasian HTN patients (n = 224) who were treated with atenolol in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study are included in this analysis. PEAR was undertaken to evaluate the pharmacogenomic determinants of the antihypertensive and adverse metabolic responses to atenolol and hydrochlorothiazide in HTN participants without a history of heart disease or diabetes (Johnson et al. 2009). In PEAR, male or female participants with in-office diastolic blood pressure (BP) ≥ 90 mm Hg, aged from 17 to 65 years of any race, were recruited at the University of Florida (Gainesville, FL, USA), Mayo Clinic (Rochester, MN, USA), and Emory University (Atlanta, GA, USA). Study participants were excluded if they had very elevated blood pressure (systolic BP >180 mm Hg or diastolic BP >110 mmHg), diabetes or documented cardiovascular disease (including history of angina pectoris, heart failure, cardiac pacemaker, myocardial infarction, stroke), or if they had other complications (pregnancy, renal diseases, sleep apnea, etc.). The study protocol was approved by the Institutional Review Board at all study sites and all participants provided written informed consent and the PEAR study was conducted in accordance with the Declaration of Helsinki. Details regarding study design details have been previously published (Johnson et al. 2009) and the PEAR study is registered at clinicaltrials.gov (NCT00246519). Briefly, after an initial 3–8 week washout period, participants were randomized to receive HCTZ 12.5 mg or atenolol 50 mg daily monotherapy for 9 weeks, which included dose titration to HCTZ 25 mg or atenolol 100 mg daily in individuals whose blood pressure remained over 120/70 mmHg. The current study includes only those randomized to receive atenolol.

2.2 Laboratory measurements

At baseline (before atenolol therapy) and after completion of 6–9 weeks atenolol therapy, fasting blood samples were collected for glucose and lipid profile analyses. Changes in laboratory measurements were defined as the difference between the post-atenolol level and the baseline level.

2.3 Biochemical assays

Plasma glucose, triglyceride, and lipids including total cholesterol and high-density lipoprotein cholesterol (HDL-C) concentrations were determined spectrophotometrically by automated enzymatic assays on a Hitachi 911 Chemistry Analyzer (Roche Diagnostics) at the central laboratory at the Mayo Clinic. Low-density lipoprotein cholesterol (LDL) was computed. All of the samples were tested in duplicate, and data reported are the means of the duplicate samples.

2.4 Measurements of blood pressure

BP was rigorously phenotyped in the PEAR study. Participants measured their BP at home using an automated home BP monitor (MicroLife 3 AC1-PC, Minneapolis MN, USA) in a seated position twice daily for the 7 days prior to a study visit. The monitor took readings in triplicate and the average of the three readings was recorded. BP was also measured in the physician's office during a study visit with the same home monitor and protocol. Lastly, ambulatory BP was measured by averaging 24-h ambulatory BP recordings which were obtained at the baseline and post atenolol study visits using Spacelabs (Redmond WA) ambulatory monitors (model 90207A). A composite weighted average of the home, office, and ambulatory BPs was calculated on the basis of row sums of the inverse of the inter-method covariance matrices (Turner et al. 2012). Changes in systolic BP (SBP) and diastolic BP (DBP) were defined as the difference between the post-atenolol measurement and baseline SBP and DBP measurements, respectively.

2.5 Preparation of internal standards and calibration curves for acylcarnitines

The isotopic labeled internal standards used were acetylcarnitine-D3, propionylcarnitine-D3, butyrylcarnitine-D3, isovalerylcarnitine-D9, hexanoylcarnitine-D3, octanoylcarnitine-D3, decanoylcarnitine-D3, dodecanoylcarnitine-D3, tetradecanoylcarnitine-D3, palmitoylcarnitine-D3, octadecanoylcarnitine-D3 (Cambridge Isotope Laboratories, Cambridge MA; CDN Isotopes, Quebec, Canada). Individual stock solutions of these AC internal standards were prepared at a concentration of 10 mM in either water (C2, C3, C4, C5, and C6) or 50 % methanol (C8, C10, C12, C14, C16, and C18). These standard solutions were then combined in 50/50 acetonitrile/0.3 % formic acid to generate a stock mixture of internal standards. This solution contained internal standards at a concentration of 2.5 μ M, except for C2 at 25 μ M, and C10 and C16 at 0.25 μ M. This solution was then diluted tenfold in 50/50 acetonitrile/0.3 % formic acid to generate the working internal standard solution. The resulting solution contained all internal standards at a concentration of 0.25 μ M, except for C2 at 2.5 μ M, and C10 and C16 at 0.025 μ M.

Individual stock solutions of AC powders (Sigma-Aldrich, St. Louis, MO; Toronto Research Chemicals, Toronto, Canada; Larodan, Solna, Sweden; R&D Systems, Minneapolis, MN) were prepared at a concentration of 10 mM in either water (C2, C3, C4, C5, and C6 ACs) or 50 % methanol (C8, C10, C12, C14, C16, and C18 ACs). Aliquots of these solutions were combined to generate a calibrator stock solution, in which C2 AC was present at a concentration of 0.5 mM and all other ACs were present at 0.05 mM. This stock solution was serially diluted in 50/50 acetonitrile/0.3 % formic acid to yield calibrator concentrations

of 0.025, 0.05, 0.1, 0.25, 0.5, 1, 2.5, 5, 10, 25, and 50 μM . However, C2 AC was present in the calibrator stocks at 0.25, 0.5, 1, 2.5, 5, 10, 25, 50, 100, 250, and 500 μM .

To generate the working calibrator curve, a 10 μL aliquot of calibrator stock and 10 μL aliquot of internal standard solution was spiked into 90 μL of 50/50 acetonitrile/0.3 % formic acid. This final calibration curve series resulted in ACs at concentrations of 0.0025, 0.005, 0.01, 0.025, 0.05, 0.1, 0.25, 0.5, 1, 2.5, and 5 μM . C2 acylcarnitine was present at concentrations of 0.025, 0.05, 0.1, 0.25, 0.5, 1, 2.5, 5, 10, 25, and 50 μM .

2.6 Extraction and derivatization of acylcarnitines in human serum

A 100 μL aliquot of human serum was spiked with a 10 μL mixture of AC internal standards. An 800 μL of ice-cold methanol was added to the serum to precipitate proteins. The proteins were pelleted by centrifuging at 10 $^{\circ}\text{C}$ at 18,000 $\times g$. Then, ACs were derivatized for 10 min at room temperature by reconstituting the dried methanolic extract (100 μL) in 100 μL of 0.2 M O-benzylhydroxylamine (Sigma-Aldrich, St. Louis, MO, USA) and 10 μL of 2 M 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (Sigma-Aldrich, St. Louis, MO, USA). This facile chemical derivatization procedure has been optimized and used successfully for the determination of organic acids in a previous study (Tan et al. 2014). After derivatization, the extract was used for LC/MS analysis.

2.7 Liquid chromatography/mass spectrometry of acylcarnitines

Derivatized ACs (2 μL injection) were separated on an Agilent 1290 HPLC (Agilent, Santa Clara, CA, USA) using a 2.1 $\times$ 100 mm, 1.7 μm Waters Acquity UPLC BEH C18 column maintained at 50 $^{\circ}\text{C}$ using a 12.5-min linear gradient with 0.1 % formic acid in water (A) and 0.1 % formic acid in acetonitrile (B) at a flow rate of 0.4 mL/min. The gradient began at 1–20 % B for 0.0–3.0 min., then increased to 30 % B from 3.0 to 5.0 min; followed by an increase to 95 % B from 5.0 to 12.5 min. Column re-equilibration was at 95 % B for 12.6–14.1 min. followed by a decrease to 1 % B from 14.2 to 16.2 min.

The eluent from the HPLC was introduced into the ESI source of an Agilent 6490 triple quadrupole mass spectrometer (Agilent, Santa Clara, CA, USA). The electro-spray voltage was set at 3500 V with a nozzle voltage of 500 V. The nitrogen gas temperature was at 325 $^{\circ}\text{C}$ with a flow of 11 L/min and a nebulizer pressure of 50 psi. The sheath gas temperature was at 325 $^{\circ}\text{C}$ with a sheath gas flow of 10 L/min. The resolution of the first and third quadrupoles was set to give a full-width-half-maximum (FWHM) less than 1 Da. Multiple reaction monitoring was used to quantitate daughter ions generated from each parent ion AC (Supplement Table 1). An example total ion chromatogram of the separation of the high AC calibration sample is provided in Supplement Figure 1. In addition, total ion chromatograms of the ACs of interest are also provided in Supplement Figure 2.

Calibration curves for ACs (μM) in serum were determined by processing the raw data with MassHunter software (Agilent Technologies, Santa Clara, CA, USA). Calibration data was fit with either a linear or quadratic fit with a 1/X or 1/X² weighting with $R^2 = 0.99$ or greater. Inter- and Intraday precision and accuracies of calibration curves were less than ± 20 %. Limits of quantitation (LOQ) ranged from 0.0025 to 0.1 μM (Supplement Table 2). In addition, recoveries of ACs were greater than 80 % with stabilities of 90 % or greater.

2.8 Outcomes

The cardiometabolic outcomes of interest in this analysis were change in SBP, DBP, glucose, and lipid profile following exposure to atenolol, all of which have been shown either individually, or together, to have adverse long-term consequences (Mottillo et al. 2010).

2.9 Statistical methods

The goal of our analysis was to determine whether profiling ACs could identify a novel predictor of the adverse cardiometabolic outcomes associated with atenolol exposure. For the 23 ACs that were quantified in $\geq 80\%$ of the serum samples, ACs were treated as the quantified measure. For the 5 ACs that were quantified in $>20\%$ but $<80\%$ of the serum samples, the presence/absence (1/0) of the AC was used, as determined by the LOQ for that AC (Supplement Tables 2 and 3).

The first step was to look for unadjusted associations with ACs and cardiometabolic outcomes, based on quantitation rate (data not shown). The second step was to determine if any of the ACs were significant predictors of change in cardiometabolic outcomes after accounting for clinical covariates. This is particularly important as some ACs have been shown to be affected by BMI and gender. The composite SBP and DBP measures used in this analysis were already adjusted for baseline BP, age, gender, and BMI (Turner et al. 2012) and so were not further adjusted. A model for the other cardiometabolic outcomes (glucose, triglycerides and cholesterol) that adjusted for covariates including age, gender, BMI, and baseline level of the outcome was fit for each outcome to determine final association with ACs, and the results from the adjusted models are reported in the results section. A Bonferroni corrected alpha of 0.0018 (0.05/28) was used to account for multiple comparisons. ACs with a p value <0.05 were considered as having nominal significance after adjusting for covariates.

3 Results

3.1 Cardiometabolic characteristics before and after exposure to atenolol

A total of 224 Caucasian participants who were treated with atenolol in the PEAR study and with available serum AC and fasting laboratory measurements are included in this analysis. Demographic and baseline characteristics of the study population are summarized in Table 1. Among these middle-aged, overweight, hypertensive participants, 52 % were male, and 50 % had metabolic syndrome at baseline. The changes in cardiometabolic characteristics after 9 weeks of atenolol (100 mg) are summarized in Table 2. Glucose and triglycerides were increased by 1.9 mg/dL and 17.8 mg/dL, on average, respectively, HDL-C was decreased by 2.5 mg/dL on average, while overall BP was lowered $-12.7/-10.4$ mm Hg on average.

3.2 Acylcarnitines and cardiometabolic outcomes

Mean levels, as well as the LOQ for each of the 28 ACs included in this study are summarized in Supplementary Table 3.

By following the two-approach strategy for linear regression modeling (see “Methods” section), the 28 ACs were analyzed with cardiometabolic factors including changes in glucose, HDL-C, LDL-C and triglycerides and BP. There were no ACs associated with changes in LDL-C or triglycerides (data not shown). Results from the adjusted linear regression analyses for glucose, HDL-C, SBP and DBP are summarized in Table 3. Among the 28 ACs, arachidonoyl-carnitine (C20: 4) was statistically significantly associated with change in glucose ($p = 0.0002$) after adjustment for covariates, including gender, age and baseline glucose. C20:4 was also associated with gender ($p = 0.001$), as has been observed by others, but even after inclusion of gender in our model, C20:4 was strongly associated with change in glucose. Because metabolic syndrome is closely linked with gender and glucose, we also tested an association between baseline presence of metabolic syndrome and C20:4, which was not significant ($p = 0.11$). Other long-chain ACs with nominal significance for an association with glucose after adjustment for clinical covariates included C16, C18:1 and C10. C4-DC succinyl was statistically significantly associated with change in HDL-C, while C20:4, C16:1-OH, C14 and C5 2-methylbutyryl were nominally associated with HDL-C change. While none of the 28 ACs were significantly associated with change in SBP or DBP, ACs C20:4, C5:1, C5-OH and C5 2-methylbutyryl had nominal significance.

Only AC C20:4, an AC that was quantified in 53 % of the study population, was consistently associated with or nominally associated with changes in all of our car-diometabolic outcomes. With regard to glucose and HDL-C, participants with measurable “pre-atenolol” serum C20:4 had significantly greater increases of glucose (+3.86 mg/dL, $p = 0.0002$, Fig. 1a) after atenolol and greater reduction of HDL-C (−1.5 mg/dL, $p = 0.017$, Fig. 1b), compared with those subjects with no quantifiable “pre-atenolol” serum C20:4. For those with C20:4 present, BP reduction following treatment with atenolol was poorer (3.15 mmHg less for SBP, $p = 0.006$ and 2.38 mmHg less for DBP, $p = 0.002$) (Fig. 2a, b), as compared with subjects in whom serum C20:4 was not measureable.

4 Discussion

Using a targeted pharmacometabolomic approach, we investigated the relationship between baseline serum AC levels and cardiometabolic responses following exposure to atenolol among a cohort of Caucasians with HTN. We showed that the presence of C20:4, a long chain AC, in serum is significantly associated with increased glucose after treatment with atenolol, and we also observed nominal significance for decreased atenolol BP lowering efficacy and decreased HDL-C, following atenolol treatment. These cardiometabolic outcomes are associated with substantial long-term morbidity and mortality, and in fact, in June of 2014, the Cardiometabolic Think Tank was convened in Washington DC as a “call to action” activity focused on defining new patient care models and approaches to address contemporary issues of cardiometabolic risk and disease (Sperling et al. 2015). Taken together, our findings identify C20:4 as a novel biomarker in serum, with potential utility for personalization of HTN treatment and reduction of cardiometabolic risk linked to atenolol use.

C20:4 is derived from the acyl-CoA adduct of arachidonic acid, a polyunsaturated fatty acid that mediates a panoply of cardiovascular effects (Huang et al. 1997; Roman 2002; Harris et

al. 2009). As depicted in Fig. 3, a dynamic equilibrium exists between C20:4 and arachidonic acid in human cells, with arachidonoyl-CoA serving as an intermediate. By adding a carnitine group to the carboxyl end of arachidonic acid, C20:4 more readily crosses mitochondrial membranes via transporters. C20:4 can then be converted to acetyl-CoA during beta-oxidation (Pignatelli et al. 2003), which eventually is used to fuel tricarboxylic acid cycle during energy metabolism. Arachidonic acid is an abundant omega-6 fatty acid in human cells that originates primarily from cell membrane phospholipids. It is a lipid-derived second messenger involved in multiple cellular signaling pathways (Naor 1991). Furthermore, arachidonic acid is the precursor of many endogenous prostaglandins, leukotrienes and epoxyeicosatrienoic acids (EETs), and hydroxyeicosatetraenoic acids (HETEs) (Needleman et al. 1986). These metabolites play critical roles in regulating BP, glucose and fatty acid metabolism, platelet aggregation and other cardiometabolic conditions. Cognate receptors for the products of arachidonic acid metabolism have been widely shown to regulate the pathways mediating glucose and lipids catabolism and therefore have become the molecular targets of pharmacotherapy against hyperglycemia and dyslipidemia (Olefsky 2000; Murakami et al. 1998). Collectively, the available evidence suggested that C20:4 has a role in glucose metabolism and a large variety of cardiovascular functions in humans.

In addition to C20:4, we identified several other long-chain ACs, including palmitoyl-carnitine (C16) and oleoylcarnitine (C18:1) that had nominal significance for an association with plasma glucose changes after atenolol treatment. Consistent with our findings, certain long-chain ACs have previously been correlated with cardiovascular disease, HTN and type-2 diabetes from multiple independent investigations (Shah et al. 2012; Kalim et al. 2013; Mels et al. 2013; Adams et al. 2009). In animal models, Koves et al. showed that the plasma levels of C16, C18, C18:1 and C18:2 significantly increased in obese rats induced by high-fat feeding, compared to the lean control rats, and also correlated with skeletal muscle insulin resistance (Koves et al. 2005, 2008). In a small clinical trial, Mihalik et al. demonstrated that fasting plasma levels of C16, C18 and C18:1 were significantly higher in groups with obesity and type-2 diabetes (Mihalik et al. 2010). These data suggest that elevated levels of long-chain ACs pose a serious risk for developing cardiovascular diseases and metabolic disorders. Our results extend this notion with an adverse metabolic association following treatment with atenolol.

We also showed succinyl-carnitine (C4-DC succinyl) to be significantly associated with HDL-C changes after atenolol treatment. C4-DC succinyl is derived from acyl-CoAs produced during catabolism of two branched amino acids, (valine and isoleucine). Our prior work showed that the 5 amino acid signature, including valine, leucine, isoleucine and the aromatic amino acids tyrosine and phenylalanine, was associated with impaired fasting glucose after atenolol treatment (Cooper-Dehoff et al. 2014) and with metabolic syndrome among HTN patients (Weng et al. 2015). Since perturbed levels of blood glucose and HDL-C are cardinal features of metabolic syndrome (Grundy et al. 2004), the identification of C4-DC succinyl with HDL-C further highlights the importance of branched amino acids and ACs with regard to the cardiometabolic syndrome.

This study has some limitations worthy of mention. This analysis was restricted to Caucasian participants from PEAR and the generalizability of our findings to other race groups should be assessed in future studies. Additionally, because some of the ACs included in our analysis were present in <80 % of the population, it was necessary to perform analyses using a present/absent approach, including for our top identified signal. This signal should be considered as hypothesis generating, and warrants further investigation and replication in an independent cohort.

5 Concluding remarks

In conclusion, our findings show that patients who exhibit measureable serum levels of C20:4 are at greater risk for atenolol-induced adverse cardiometabolic events and are somewhat resistant to atenolol-mediated BP-lowering efficacy. Other ACs might also contribute to a state of heightened cardiometabolic risk. Note that our work was conducted in a Caucasian cohort and whether these results are generalizable to other race groups needs to be explored. These data suggest that screening for ACs, particularly C20:4, might serve as a tool to allow for more precise prescribing of antihypertensive medications to optimize benefits and minimize risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Association of C20:4 with the changes of glucose and HDL-C after atenolol treatment. **a** Association with the average glucose change (mg/dl, SE); **b** association with the average HDL-C change (mg/dL, SE). p value from logistic regression

Fig. 2. Association of C20:4 with the changes of SBP and DBP after atenolol treatment. **a** Association with the average SBP change (mm Hg, SE); **b** association with the average DBP change (mm Hg, SE). p value is from logistic regression

Fig. 3. Biosynthetic and metabolizing pathway of arachidonic acid

Table 1
Demographic and baseline characteristics of the Caucasian participants (n = 224)
included in this study

Charecteristic	
Age (years, mean $\pm$ SD)	49.7 $\pm$ 9.4
Male sex (n, %)	116, 52
BMI (kg/m ² , mean $\pm$ SD)	30.2 $\pm$ 5.5
Waist circumference (cm, mean $\pm$ SD)	97.7 $\pm$ 12.7
SBP (mmHg, mean $\pm$ SD)	145.1 $\pm$ 9.4
DBP (mmHg, mean $\pm$ SD)	92.9 $\pm$ 5.6
Glucose (mg/dL, mean $\pm$ SD)	91.5 $\pm$ 10.3
Triglyceride (mg/dL, mean $\pm$ SD)	134.5 $\pm$ 70.9
LDL-C (mg/dL, mean $\pm$ SD)	121.2 $\pm$ 29.0
HDL-C (mg/dL, mean $\pm$ SD)	47.0 $\pm$ 12.3

BMI, body mass index; *SD*, standard deviation; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *LDL-C*, low-density lipoprotein cholesterol; *HDL-C*, high-density lipoprotein cholesterol

Table 2
Change in metabolic parameters following 9 weeks of exposure to atenolol 100 mg.
Change is defined as the difference between post atenolol exposure and baseline values

Characteristic	Change (mean $\pm$ SD)
Glucose (mg/dL) (mean $\pm$ SD)	+1.9 $\pm$ 8.8
HDL-C (mg/dL) (mean $\pm$ SD)	-2.5 $\pm$ 5.2
LDL-C (mg/dL) (mean $\pm$ SD)	-1.3 $\pm$ 18.9
Triglyceride (mg/dL) (mean $\pm$ SD)	+17.8 $\pm$ 54.3
SBP (mmHg) (mean $\pm$ SD)	-12.7 $\pm$ 8.6
DBP (mmHg) (mean $\pm$ SD)	-10.4 $\pm$ 5.8

Table 3
Results of linear or logistic regression analysis of the 28 acylcarnitines by cardiometabolic outcome

Acylcarnitine	Glucose		HDL			SBP			DBP			
	Estimate	SE	P value	Estimate	SE	P value	Estimate	SE	P value	Estimate	SE	P value
C20:4	3.86	1.03	0.0002	-1.5	0.62	0.017	3.15	1.14	0.006	2.38	0.76	0.002
C16	39.02	18.9	0.04	-22.18	11.74	0.06	22.1	21.76	0.311	18.6	14.67	0.206
C18:1	15.91	7.89	0.045	-4.66	5.23	0.374	-9.91	9.55	0.301	-3.89	6.45	0.547
C10	16.43	8.4	0.052	-2.31	4.98	0.643	-0.68	8.95	0.94	-1.34	6.04	0.824
C14	109.89	59.26	0.065	-75.26	36.3	0.039	-26.89	67.39	0.69	-9.06	45.45	0.842
C18:2	20.95	11.77	0.077	-13.07	7.24	0.072	7.66	13.44	0.569	2.55	9	0.777
C18	88.86	50.05	0.077	-45.39	29.16	0.121	68.41	54.15	0.208	58.12	36.42	0.112
C12	31.94	19.18	0.097	-10.55	12.05	0.382	8.22	21.99	0.709	6.96	14.82	0.639
C2	0.33	0.23	0.149	0.01	0.14	0.931	-0.2	0.25	0.425	-0.07	0.17	0.666
C4 Isobutyryl	9.4	6.68	0.161	-1.83	4.13	0.658	6.98	7.62	0.361	8.13	5.12	0.114
C5-OH	-111.91	128.51	0.385	-74.7	77.19	0.334	229.72	141.12	0.105	230.12	94.47	0.016
C12:1	44.54	52.13	0.394	-41.89	37.4	0.264	16.09	56.91	0.778	32.73	38.31	0.394
C4-OH	-0.82	1.03	0.428	-0.69	0.63	0.279	-0.23	1.16	0.843	0.11	0.79	0.885
C14:2	16.09	20.29	0.429	-4.51	12.57	0.72	-0.76	23.03	0.974	-3.69	15.52	0.813
C3	-3.13	4.05	0.441	-4.12	2.43	0.091	4.16	4.46	0.352	3.02	3.01	0.316
C14:1	11.73	15.5	0.45	-6.89	9.46	0.467	-20.43	17.24	0.237	-10.69	11.64	0.359
C10-OH	114.25	152.37	0.454	-8.01	94.21	0.932	48.41	173.1	0.78	106.56	116.51	0.361
C8	5.94	8.21	0.47	-2.01	5.09	0.693	1.14	9.33	0.903	-1.85	6.29	0.769
C16:2	57.11	90.35	0.528	-64.15	55.25	0.247	1.84	100.97	0.986	2.4	68.08	0.972
C5:1	-55.84	119.17	0.64	-46.67	81.77	0.569	298.65	122.98	0.016	147.5	82.89	0.077
C16:1-OH	-0.38	1.04	0.719	-1.39	0.64	0.031	0.19	1.19	0.87	0.43	0.8	0.591
C8-OH	15.85	48.65	0.745	-29.49	29.56	0.32	-5.91	54.31	0.913	15.99	36.6	0.663
C5 2-Methylbutyryl	11.38	39	0.771	-46.33	23.14	0.046	80.44	42.01	0.057	63.35	28.24	0.026
C5 Isovaleryl	3.24	20.1	0.872	-12.8	11.34	0.26	27.97	20.41	0.172	23.76	13.74	0.085
C4 Butyryl	1.56	12.91	0.904	-0.41	7.85	0.959	17.12	14.4	0.236	18.05	9.64	0.062
C4-DC Succinyl	-0.07	1.18	0.953	-2.52	0.7	0.0003	1.82	1.31	0.165	1.06	0.88	0.231
C16:1	0.05	1.02	0.961	0.09	0.64	0.889	0.61	1.17	0.603	1.08	0.79	0.17

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Acylcarnitine	Glucose			HDL			SBP			DBP		
	Estimate	SE	P value	Estimate	SE	P value	Estimate	SE	P value	Estimate	SE	P value
C6	1.2	34.58	0.972	-20.14	21.25	0.344	-8.43	39.01	0.829	-16.84	26.28	0.522

ACs are in order of p value for glucose outcome