Hypertension and Its Treatment Influence Changes in Fasting Nonesterified Fatty Acid Concentrations: A Link Between the Sympathetic Nervous System and the Metabolic Syndrome?

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In previous studies, a cross-sectional association has been described between blood pressure (BP) and nonesterified fatty acid (NEFA) concentrations. The direction of causality, and thus, the mechanism explaining this relationship, remains uncertain. Therefore, we analyzed a prospective population-based cohort of 937 subjects who underwent an oral glucose tolerance test (OGTT) on two occasions separated by 4.5 years. In cross-sectional analysis, NEFA measures were correlated with systolic and diastolic BP, both at baseline and at follow-up study. In longitudinal analysis, baseline systolic and diastolic BP predicted changes in fasting NEFA levels (both $P < .01$). However, baseline NEFA levels did not predict change in BP. In multivariate analysis, the relationship between baseline BP and change in fasting NEFA was independent of age and sex. Obesity and its interaction with BP did not explain this association. Absolute changes in NEFA concentrations were greater among subjects who were hypertensive at baseline compared with the normotensive individuals. This change was greater in subjects treated with diuretics compared with those treated with β-adrenergic antagonists ($P < .01$), an observation that provides support for a role of sympathetic nervous system (SNS) activity in explaining the relationship between BP and NEFA concentration.

THE METABOLIC SYNDROME (MS), otherwise known as syndrome X or the insulin resistance syndrome, is a clustering of cardiovascular risk factors (low high-density lipoprotein [HDL] cholesterol and elevated triglyceride concentrations, glucose intolerance, obesity, and hypertension) that are associated with an increased risk of developing type 2 diabetes and coronary heart disease.[1,2] The association between hypertension and other features of the syndrome is relatively weak, and therefore, its inclusion as part of the MS is still debated.[3,4] Insulin resistance has been proposed as the underlying feature of the MS.[1] A relationship between insulin resistance and blood pressure (BP) is possible and may be explained by several mechanisms, including increased sympathetic nervous system (SNS) activity, reduced sodium excretion, vascular smooth muscle cell proliferation, or reduced capillary density of skeletal muscle.[5-9] However, in several studies, hyperinsulinemia, a marker of insulin resistance, and BP were not shown to be linked, particularly in subjects with essential hypertension.[10,11]

Recently, it has been suggested that nonesterified fatty acid (NEFA) metabolism could be a mechanism linking hypertension and the MS.[12-14] The Randle-cycle hypothesis predicts that increased NEFA levels would reduce insulin-mediated glucose uptake, thereby causing insulin resistance.[15] Therefore, a relationship between NEFA and BP would support the inclusion of hypertension as a part of the syndrome. This mechanism is supported by the observation of a higher prevalence of hypertension in individuals with obesity, diabetes, or dyslipidemia, conditions that are associated with increased NEFA levels.[16-19] An association between increased NEFA concentrations and BP has been shown in cross-sectional studies, but the mechanism explaining this association and the direction of causality remain unclear.[13-14] This association could be explained by the hemodynamic, neurohumoral, and microvascular changes linked to BP or by the effect of NEFA on vascular tone.[12,14,20-23] No prospective epidemiological studies have investigated this relationship over time, and therefore, the aim of this study was to investigate the relationship between the change in BP, treated as both a continuous and a categorical variable, and the change in NEFA measures over time.

SUBJECTS AND METHODS

The Ely Study is a prospective population-based cohort established in 1990 and has previously been described in detail.[24,25] Subjects for the study were recruited from a general practice register in Ely, Cambridgeshire. A letter of invitation was sent to a random selection of 1,122 patients not previously known to have diabetes (74% response rate), between the ages of 40 and 65 years at recruitment. A total of 1,071 subjects who participated in phase I of the study from 1990 to 1992 were found to be nondiabetic, and 937 (87%) of these individuals were retested in phase II after a mean interval of 4.5 years. The 134 subjects who were not retested included those who died, who refused to be reexamined, or who moved outside the United Kingdom. The Cambridge Local Research Ethics Committee granted approval for the study, and all subjects provided written consent.

At both baseline and follow-up evaluation, subjects underwent a clinical examination that included dietary and medical questionnaires and anthropometric measurements. The body mass index (BMI) was calculated as the weight in kilograms divided by the height squared in meters. Waist circumference was measured at the midpoint between the inferior border of the costal margin and the anterior superior iliac crest, and hip circumference was measured at the level of the greater trochanter. Diastolic and systolic BP were recorded at rest with the subject seated using an Accutorr automatic sphygmomanometer (Datascope, Cambridge, UK). Three sets of readings were taken in the right arm, 1 minute apart. Hypertension was defined as a diastolic BP of 95 mm Hg or higher.

The oral glucose tolerance test (OGTT) consisted of a 75-g oral glucose challenge with collection of venous blood samples at 0, 30, and 120 minutes. Plasma samples were immediately separated, kept on ice, and stored at −70°C within 4 hours. Serum was separated from the samples kept at room temperature for 30 minutes and was then stored in the same way as the plasma samples. The plasma glucose level was

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measured by the hexokinase method,[26] and the triglyceride level was measured using the RA 1000 instrument (Bayer Diagnostics, Basingstoke, UK) with a standard enzymatic method. Plasma insulin was determined by two-site immunometric assays with either ^{125}I or alkaline phosphatase labels.[27,28] Insulin concentrations were measured at 0, 30, and 120 minutes. The 30-minute insulin incremental response (a measure of first-phase insulin secretion) was included in the analysis, and was calculated by dividing the difference between 30-minute insulin and 0-minute (fasting) insulin concentrations by the 30-minute glucose concentration.[18]

Plasma NEFAs were determined enzymatically based on the activity of acyl-coenzyme A (acyl-CoA) synthetase (Boehringer Mannheim, Lewes, UK). The resultant acyl-CoA was oxidized to yield hydrogen peroxide, which was measured colorimetrically.[29] The assay had a between-assay coefficient of variation of 6% (high NEFA levels) to 10% (low NEFA levels) in phase I and 2.7% (high NEFA levels) to 5.1% (low NEFA levels) in phase II of the study. NEFA concentrations were measured in samples at 0, 30, and 120 minutes during the OGTT in both phases I and II of the study. The NEFA area was defined as the area under the trapezoid described by NEFA measurements at 0, 30, and 120 minutes.[18]

Statistical Analysis

The analysis was restricted to subjects tested at both baseline and follow-up study. Patients were excluded from the first analyses if they used antihypertensive agents either at baseline or at follow-up. To study the effects of β-adrenergic antagonists on NEFAs, subjects treated with any medications of this class alone, without diuretics, at baseline and follow-up study were compared with subjects treated with diuretics alone, without β-blockers, at baseline and follow-up study.

The arithmetic mean ± SEM are presented where the underlying variable was normally distributed. Triglycerides, fasting insulin, the 30-minute insulin incremental response, and NEFAs at fasting and 30 and 120 minutes were normalized by logarithmic transformation and are presented as the geometric mean and 95% confidence interval. *T* tests or Mann-Whitney tests were used to compare means. Changes in NEFAs were defined as the residual of a linear regression model with the NEFA measure at follow-up as the dependent variable and the NEFA measure at baseline as the independent variable. To determine which features predicted change in fasting NEFA levels and measures of NEFA suppression, Pearson correlation coefficients were calculated between the change in NEFA measures and diastolic and systolic BP and factors known to be correlated with NEFAs.[15,18] Each significant feature in univariate analysis and its interaction with BP (if necessary) were included in a multivariate linear regression model with BP to determine whether BP was still an independent factor predicting change in NEFA. For each variable, the β coefficient and its significance are shown. The adjusted R^2 is presented to show the overall variability explained by the model. All features and their interactions that were previously significant were included in the final model. All analyses were conducted using the SPSS (SPSS, Chicago, IL) for Windows package.

RESULTS

Eighty-nine percent of the women initially recruited (543 of 608) and 85% of the men (394 of 463) underwent follow-up testing.[25] Of these individuals, 107 women and 75 men were excluded from the initial analysis because they were being treated with antihypertensives at the baseline and/or follow-up study. The characteristics of the remaining 436 women and 319

Table 1. Characteristics of Subjects at Baseline, at Follow-up, and Differences Between Follow-up and Baseline, by Sex

Characteristic	Women			Men		
	Baseline	Follow-up	Difference	Baseline	Follow-up	Difference
No. of subjects	436	436		319	319	
Age (yr)	52.7 (0.36)	57.1 (0.36)	4.44 (0.02)‡	53.7 (0.44)	58.1 (0.44)	4.46 (0.03)‡
BMI (kg/m²)	25.0 (0.20)	26.0 (0.21)	1.03 (0.10)‡	25.7 (0.16)§	26.5 (0.18)	0.77 (0.08)‡
WHR	0.76 (0.003)	0.80 (0.004)	0.04 (0.003)‡	0.90 (0.003)‖	0.96 (0.004)	0.06 (0.003)‡
Diastolic BP (mm Hg)	75.6 (0.47)	74.2 (0.48)	−1.26 (0.41)†	79.6 (0.55)‖	79.0 (0.59)	−0.45 (0.51)
Systolic BP (mm Hg)	125.0 (0.8)	124.2 (0.8)	−0.78 (0.66)	129.3 (0.8)‖	129.2 (0.9)	0.17 (0.75)
HDL cholesterol (mmol/L)	1.60 (0.02)	1.63 (0.02)	0.02 (0.01)	1.31 (0.02)‖	1.34 (0.02)	0.03 (0.01)*
Fasting insulin (pmol/L)	37.7 (35.6-40.0)	37.7 (35.6-40.0)	1.4 (1.3)	40.0 (37.8-42.5)	42.1 (39.7-44.6)	2.9 (2.3)
Insulin increment	27.1 (25.6-28.8)	32.8 (30.9-34.8)	6.1 (1.1)‡	25.0 (23.1-27.1)	30.3 (28.5-32.1)	6.12 (1.27)‡
Fasting plasma glucose (mmol/L)	5.56 (0.03)	4.85 (0.03)	−0.71 (0.03)‡	5.85 (0.03)‖	5.12 (0.03)	−0.74 (0.05)‡
Plasma glucose 120 min (mmol/L)	6.19 (0.07)	5.83 (0.09)	−0.37 (0.08)‡	6.20 (0.09)	5.84 (0.12)	−0.36 (0.12)†
Triglycerides (mmol/L)	1.07 (1.03-1.11)	0.99 (0.93-1.05)	−0.09 (0.03)†	1.32 (1.25-1.40)‖	1.12 (1.05-1.18)	−0.26 (0.05)‡
Fasting NEFA (mmol/L)	0.45 (0.43-0.48)	0.49 (0.47-0.51)	−0.003 (0.02)	0.36 (0.33-0.39)‖	0.41 (0.39-0.43)	0.03 (0.02)
NEFA 30 min (mmol/L)	0.35 (0.32-0.38)	0.28 (0.26-0.29)	−0.11 (0.14)‡	0.34 (0.31-0.36)	0.27 (0.25-0.29)	−0.11 (0.01)‡
NEFA 120 min (mmol/L)	0.061 (0.057-0.066)	0.058 (0.055-0.061)	−0.01 (0.03)‡	0.071 (0.066-0.077)§	0.065 (0.065-0.071)	−0.01 (0.04)†
NEFA area (mmol · h⁻¹/L)	0.64 (0.02)	0.51 (0.01)	−0.12 (0.02)‡	0.57 (0.02)§	0.47 (0.01)	−0.11 (0.02)‡

NOTE. Data are the arithmetic mean (SEM) and geometric mean (95% confidence interval).
*$P < .05$, †$P < .01$, ‡$P < .001$ (difference *v* 0); §$P < .01$, ‖$P < .001$ (women *v* men).

Table 2. Cross-Sectional Correlation Coefficients Between NEFA Measures and Diastolic and Systolic BP at Baseline and Follow-up Study

Parameter	Fasting NEFA	NEFA Area
Baseline		
Diastolic BP	.09*	.11†
Systolic BP	.16†	.17†
Follow-up		
Diastolic BP	.10†	.17†
Systolic BP	.17†	.24†

NOTE. Data are Pearson correlation coefficients.
*$P < .05$.
†$P < .01$.

men are shown in Table 1. The 30-minute insulin incremental response increased and the NEFA area and NEFA levels at 30 and 120 minutes during the OGTT decreased in men, as well as women. There were no significant changes in BP (except diastolic BP in women) and fasting NEFA concentrations during the follow-up study.

In cross-sectional analysis, fasting NEFA and the NEFA area were all correlated with diastolic and systolic BP both at baseline and at follow-up (Table 2). After adjustment for the baseline NEFA value, both baseline diastolic and systolic BP were associated with fasting NEFA and the NEFA area at follow-up study (Table 3). Baseline BMI was correlated with the change in all NEFA markers, but the waist to hip ratio (WHR) was only correlated with the change in NEFA area. Baseline fasting and 2-hour plasma glucose and fasting insulin, triglyceride, and HDL cholesterol all predicted the change in NEFA.

After stratification by tertiles of baseline BMI (Fig 1), a significant positive association was demonstrated between baseline diastolic and systolic BP and fasting NEFA at follow-up study adjusted for baseline. This association was restricted to subjects in the middle and upper tertiles, ie, those with a BMI of at least 23.5 kg/m^2. No other interaction with BP was found.

To determine the independent factors predicting NEFA measures at follow-up, significant baseline features in univariate analysis and the interaction with BP and BMI were tested in a multivariate linear regression model (Table 4). The 2-hour plasma glucose, rather than fasting glucose, and diastolic rather than systolic BP were chosen for the multivariate analysis because of their reduced variance. In model 1, diastolic BP at baseline independently predicted fasting NEFA concentrations at follow-up study after adjustment for baseline fasting NEFA, age, and sex. Then, the other factors were introduced into the model one by one. Only the 2-hour plasma glucose and fasting insulin were still significant. Finally, these two significant factors were introduced together in model 1, and diastolic BP at baseline independently predicted fasting NEFA concentrations at follow-up after adjustment for baseline fasting NEFA, age, sex, and 2-hour glucose (fasting insulin was no longer significant). Only systolic BP at baseline predicted the NEFA area at follow-up after adjustment for age, sex, 2-hour glucose, fasting insulin, and WHR.

We compared NEFA concentrations during the OGTT in hypertensive subjects (without treatment, n = 28) and normotensive subjects (n = 727) at baseline. Fasting NEFA levels at follow-up study in both sexes and at 30 minutes in men were significantly higher in the hypertensive group (Fig 2). After adjustment for baseline, fasting NEFA and the NEFA area at follow-up were significantly higher in hypertensive subjects compared with normal individuals (both $P < .001$).

In this group of untreated individuals, resting heart rate was correlated both with fasting NEFA ($r = .21$, $P < .01$), and the NEFA area ($r = .23$, $P < .01$). Since the heart rate is related to SNS activity, this raised the possibility that the SNS could be part of the mechanism linking BP and NEFA. We sought to examine this possibility further by investigating the change in NEFA in subjects who were started on antihypertensive therapy during the course of the follow-up study. Antihypertensive agents are known to affect NEFA concentrations,[20,21] but our main comparison was between the sole use of β-blockers and diuretics, since these agents have different effects on SNS activity. At baseline, 113 patients were treated with antihypertensives, 66 with β-blockers, 56 with diuretics, three with ACE inhibitors, and 15 with calcium antagonists. At follow-up, 145 patients were treated with antihypertensives, 66 with β-blockers, 71 with diuretics, 15 with ACE inhibitors, and 22 with calcium antagonists. Thirty-three subjects were treated with β-blockers without diuretics both at baseline and at follow-up. Twenty-eight (85%) of the subjects received β-blockers without intrinsic sympathomimetic activity. Twenty-two subjects were treated with diuretics without β-blockers at baseline and follow-up (55% thiazides, 15% potassium-sparing and thiazides, and 30% loop diuretics). Between baseline and follow-up study, fasting NEFA increased in subjects treated with diuretics and tended to decrease in subjects treated with β-blockers. The difference between β-blockers and diuretics in the fasting NEFA change between baseline and follow-up was significant ($P < .01$). In contrast, the BMI increased more with β-blockers than with diuretics ($P < .05$). No other differences were significant. Figure 3 shows NEFA concentrations at follow-up during

Table 3. Longitudinal Relationship Between Explanatory Variables at Baseline and NEFA Measures at Follow-up

	Baseline Variables									
Follow-up	Age	SBP	DBP	BMI	WHR	PG 0	PG 120	Insulin 0	TG	HDL Cholesterol
Fasting NEFA‡	.19†	.14†	.11†	.08*	−.01	.09*	.20†	.10*	.10*	.00
NEFA area‡	.21†	.18†	.12†	.16†	.09*	.16†	.30†	.18†	.21†	−.10*

NOTE. Data are Pearson correlation coefficients. Fasting NEFA, TG, and insulin 0 (fasting) are normalized by logarithmic transformation.
*$P < .05$.
†$P < .01$.
‡After adjustment for baseline.
Abbreviations: SBP and DBP, systolic and diastolic BP; PG, plasma glucose; TG, triglycerides.

the OGTT. Fasting concentrations were significantly lower in subjects treated with β-blockers versus diuretics, but there was no difference in diastolic and systolic BP at baseline and follow-up. After stratification by sex, there was a trend for lower

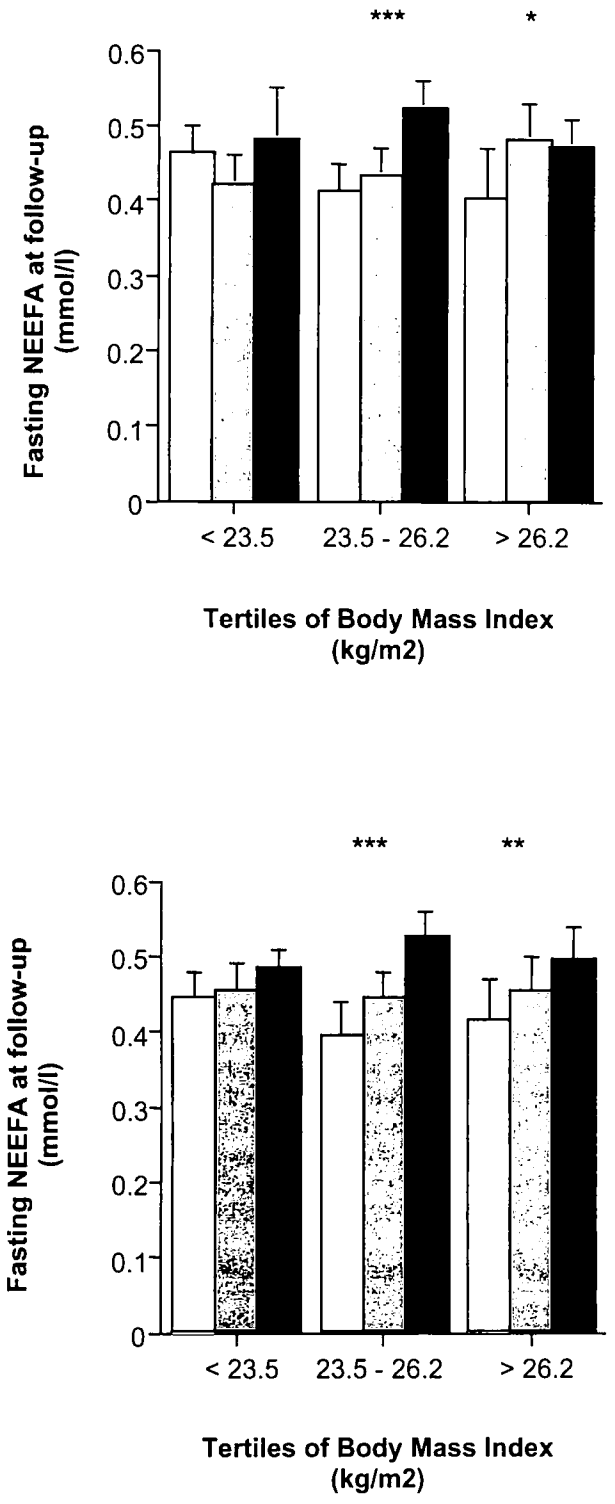

Fig 1. Fasting NEFA at follow-up (adjusted for baseline) according to tertiles of baseline diastolic and systolic BP, by tertiles of baseline BMI: I (□), II (□), III (■). *P = .06, **P = .02, and ***P ≤ .001.

Table 4. Multivariate Linear Regression Analysis With Fasting NEFA Level at Follow-up as Outcome and Baseline Explanatory Variables

	Baseline Fasting NEFA	Age	Sex	DBP	Insulin	R^2 Adjusted
Model 1	.29‡	.18‡	.15‡	.13‡		.19
Model 2	.29‡	.19‡	.15‡	.11†	.08*	.19
Model 3	.25‡	.15‡	.15‡	.11†	.15‡	.20

NOTE. Results are significant standardized β-coefficient.

Abbreviations: DBP, diastolic BP; PG120, 120-minute plasma glucose after OGTT.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

fasting NEFA concentrations with β-blocker treatment ($P = .07$ in women and $P = .06$ in men; data not shown). Furthermore, after adjustment for baseline values, fasting NEFA concentrations at follow-up were still significantly higher in subjects treated with diuretics in comparison to those treated with β-blockers ($P < .01$) and normotensive individuals ($P < .01$), and were not different versus hypertensive patients without treatment. Conversely, subjects treated with β-blockers had lower fasting NEFA levels (after adjustment for baseline) than untreated hypertensive patients ($P < .05$) and were not different versus normotensive individuals.

DISCUSSION

Hypertension is a controversial element of the MS, and its relationship to insulin resistance and diabetes is unclear.[4] It has been postulated that NEFA metabolism could mediate a link between BP and the MS.[13,14] Previous cross-sectional studies have shown that NEFA and BP are correlated, but have not been able to provide evidence about the direction of causality. The present prospective study shows for the first time that BP, treated as a continuous variable or as a category, predicts change in fasting NEFA levels, but the converse is not true. This suggests that either hypertension itself or a phenomenon associated with it is causally linked to changes in NEFA metabolism. There is no support in this study for a mechanism in the opposite direction, ie, elevated NEFA levels causing hypertension. The correlation between heart rate and NEFA levels raises the possibility of SNS activity acting as a common pathway, a hypothesis supported by the intriguing observation of opposite longitudinal effects on NEFA of β-blockers and diuretics in subjects whose hypertension was treated.

In our study, the change in fasting NEFA concentration over 4.5 years was correlated with BP at baseline. After adjustment for age, sex, 2-hour glucose, and fasting NEFA level at baseline, a relationship between diastolic BP at baseline and fasting NEFA at follow-up was observed. This result suggests that BP is associated with the change in the fasting NEFA concentration, a conclusion supported by the observation of greater change in fasting NEFA concentrations over time in hypertensive subjects compared with normotensive individuals. In a small cross-sectional study using a euglycemic-hyperinsulinemic clamp test, Hennes et al[13] compared 10 obese hypertensive and six obese normotensive individuals with seven lean normotensive subjects. They showed that fasting NEFA levels were higher in obese versus lean subjects, but not in obese hypertensive versus

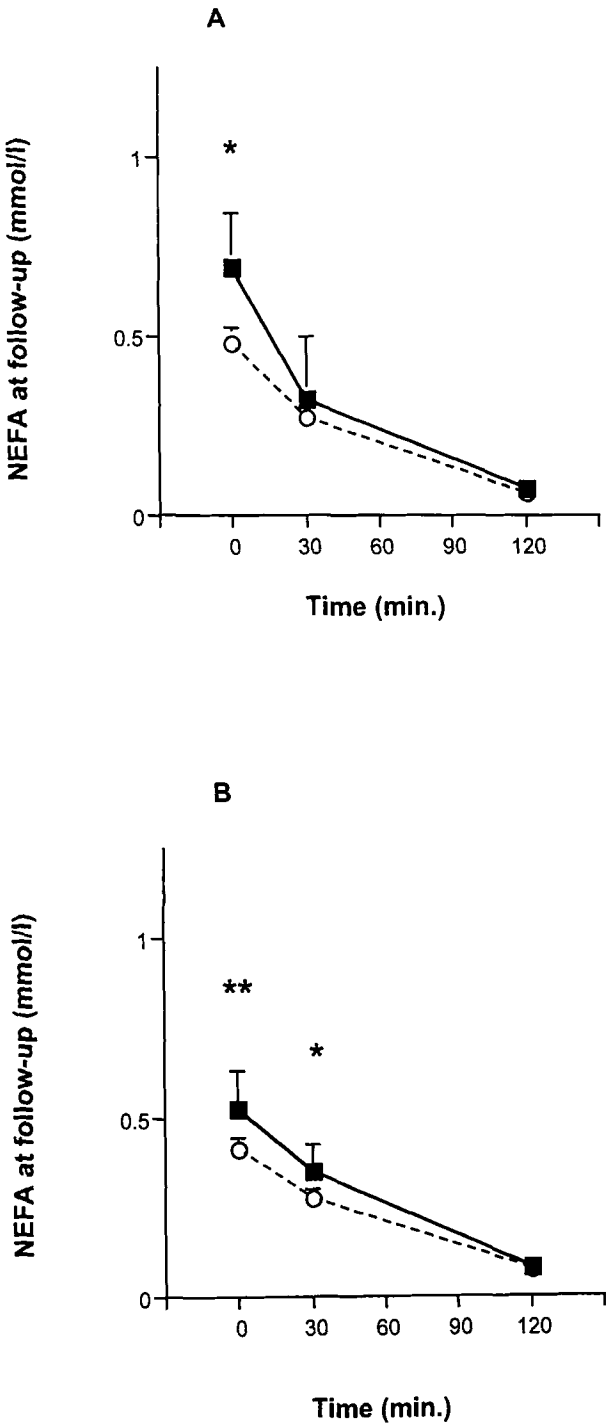

Fig 2. NEFA concentrations at 0, 30, and 120 minutes after OGTT at follow-up in untreated hypertensive (■) and normotensive (○) subjects by gender. *$P < .05$, **$P < .01$. (A) n = 425 normotensive and 11 hypertensive women. (B) n = 302 normotensive and 17 hypertensive men.

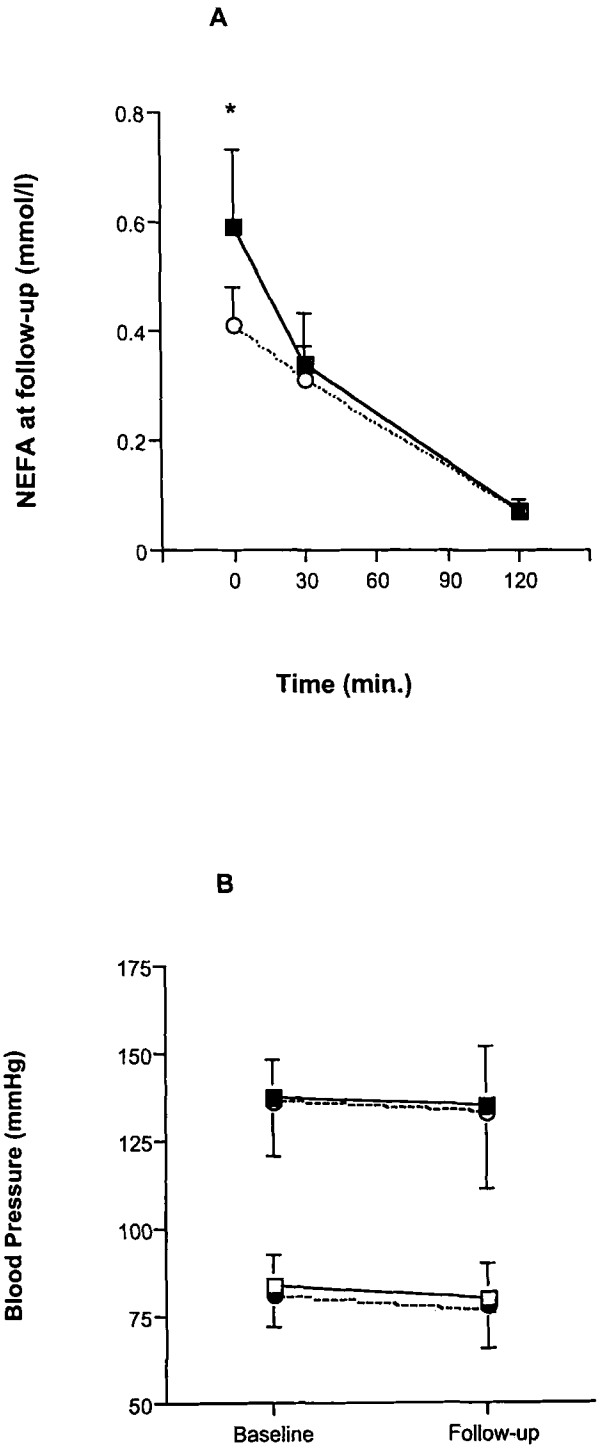

Fig 3. (A) NEFA concentrations at 0, 30, and 120 minutes after OGTT at follow-up in (■) diuretic (n = 22) and (○) β-blocker (n = 33) treatment over 4.5 years. *$P = .003$. (B) Change in diastolic and systolic BP between baseline and follow-up among subjects treated with diuretics (systolic, ■; diastolic, □) and β-blockers (systolic, ○; diastolic, ●).

obese normotensive subjects. Thus, obesity could be a confounding factor in the relation between NEFA levels and BP. Previous data have shown that hypertensive patients have higher fasting NEFA concentrations than BMI-matched control subjects.[30] In our large population, the relationship between BP and fasting NEFA was significant in individuals with a BMI above 26.2, but was stronger in subjects in the middle tertile for BMI (between 23.5 and 26.2 kg/m^2). Furthermore, neither the BMI nor WHR (a marker of abdominal obesity) predicted a change in fasting

NEFA concentration. These data suggest that obesity and its interaction with BP cannot explain the observed association between BP and fasting NEFA.

Since the same difference in the fasting NEFA concentration was found in hypertensive and normotensive subjects with different definitions of hypertension (eg, diastolic BP > 95 and/or systolic BP > 140 mm Hg, or diastolic BP > 95 mm Hg and/or antihypertensive use), it seems unlikely that this difference was due to BP measurement error in our study.

The relationship between BP and fasting NEFA could be explained by the hemodynamic, neurohumoral, and microvascular changes linked to BP. Because it not only regulates BP but also enhances lipolysis, SNS activity may be a confounding factor.[20,23,31-34] SNS and catabolic hormones such as growth hormone and catecholamines regulate lipolysis by stimulating lipoprotein lipase, and they are therefore major determinants of fasting NEFA levels when insulin levels decrease, while in the fed state, the effects of insulin predominate.[35,36] Since BP reflects SNS activity, the predictive effect of BP on the fasting NEFA level may be explained by the SNS. This hypothesis is supported by previous studies showing a cross-sectional relationship between the MS and heart rate used as a marker of SNS activity.[37-39] Therefore, the weaker relationship in subjects with a BMI less than 23.5 g/m^2 in our study suggests that adipose tissue is important for this association and may be explained by decreased SNS activity in lean versus fat individuals.[40]

The opposing effects of β-blockers and diuretics on NEFA levels support this hypothesis. Adrenoreceptors, especially β_1 and β_3, have been found in human fat and may regulate lipolytic activity.[12,41-43] β-Blockers without intrinsic sympathomimetic activity, even those that are β-selective such as atenolol, can reduce lipolysis[21,44] and decrease SNS activity, in contrast to thiazide diuretics.[20,23,45] Both selective and nonselective β-blockers decrease lipoprotein lipase activity,[33] and therefore increase plasma triglyceride levels.[46] Inhibition of lipase may be achieved through the direct inhibitory action of the β-blockers themselves or may be secondary to unopposed α-adrenergic stimulation.[32] Furthermore, since the heart rate is another marker of SNS activity, this hypothesis is consistent with the positive correlations between the heart rate and fasting NEFA or the NEFA area.

In our study, both at baseline and at follow-up study, more than 70% of antihypertensive treatment included diuretics and/or β-blockers, which have different effects on NEFA metabolism. β-Adrenergic antagonists without intrinsic sympathomimetic activity such as atenolol could decrease fasting NEFA concentrations in hypertensive subjects. Other antihypertensive agent also affect NEFA metabolism, as it has been shown that ACE inhibitors may improve insulin-mediated lipolysis.[13] This finding reinforces the importance of considering all features of the MS when choosing antihypertensive treatment.

In conclusion, baseline BP was independently associated with the change in fasting NEFA levels over time. Our results suggest that this relationship may be due to increased SNS activity because, in contrast to diuretic therapy, treatment with β-blockers can prevent an increase in fasting NEFA in hypertension.

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REFERENCES

1. Reaven GM: The role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

2. Haffner SM, Valdez RA, Hazuda HP, et al: Prospective analysis of insulin-resistance syndrome (syndrome X). Diabetes 41:715-722, 1992

3. Taskinen MR: Strategies for the diagnosis of metabolic syndrome. Curr Opin Lipidol 4:434-443, 1993

4. Haffner SM: Insulin and blood pressure: Fact or fantasy? J Clin Endocrinol Metab 76:541-543, 1993

5. Ferrannini E, Buzzigoli G, Bonadonna R, et al: Insulin resistance in essential hypertension. N Engl J Med 317:350-357, 1987

6. Falkner B, Hulman D, Tannebaum J, et al: Insulin resistance and blood pressure in young black men. Hypertension 16:706-711, 1990

7. Weichenhain B, van Kooten HJ, Standl E: Hypertension and insulin resistance. Drugs 46:183-188, 1993 (suppl 2)

8. Julius S, Gudbrandsson T, Jamerson K, et al: The hemodynamic link between insulin resistance and hypertension. J Hypertens 9:983-986, 1991

9. Baron AD, Brechtel-Hook G, Johnson A, et al: Skeletal muscle blood flow. A possible link between insulin resistance and blood pressure. Hypertension 21:129-135, 1993

10. Mbanya JCN, Thomas TH, Wilkinson R, et al: Hypertension and hyperinsulinemia: A relation in diabetes but not in essential hypertension. Lancet 1:733-739, 1988

11. Muller DC, Elahi D, Pratley RE, et al: An epidemiological test of the hyperinsulinemia-hypertension hypothesis. J Clin Endocrinol Metab 76:544-548, 1993

12. Egan BM: Neurohumoral, hemodynamic, and microvascular changes as mechanisms of insulin resistance in hypertension: A provocative but partial picture. Int J Obes 15:30-36, 1991

13. Hennes MMI, O'Shaughnessy IMO, Kelly TM, et al: Insulin-resistant lipolysis in abdominally obese hypertensive individuals. Role of the renin-angiotensin system. Hypertension 28:120-126, 1996

14. Egan BM, Hennes MM, Stepniakowski KT, et al: Obesity hypertension is related more to insulin's fatty acid than glucose action. Hypertension 27:723-728, 1996

15. Randle PJ, Garland PB, Hales CN, et al: The glucose–fatty acid cycle, its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1:785-789, 1963

16. Charles MA, Eschwege E, Thibult N, et al: The role of non-esterified fatty acids in the deterioration of glucose tolerance in caucasian subjects: Results of the Paris Prospective Study. Diabetologia 40:1101-1106, 1997

17. Paolisso G, Tataranni PA, Foley JE, et al: A high concentration of fasting plasma non-esterified fatty acids is a risk factor for the development of NIDDM. Diabetologia 38:1213-1217, 1995

18. Byrne CD, Wareham NJ, Day NE, et al: Decreased nonesterified

fatty acid suppression and features of the insulin resistance syndrome occur in a subgroup of individuals with normal glucose tolerance. Diabetologia 38:1358-1366, 1995

19. Byrne CD, Wareham NJ, Day NE, et al: Hypertriglyceridaemia in subjects with normal and abnormal glucose tolerance: Relative contributions of insulin secretion, insulin resistance and suppression of plasma non-esterified fatty acids. Diabetologia 37:889-896, 1994

20. Tuck ML: The sympathetic nervous system in essential hypertension. Am J Cardiol 112:877-886, 1986

21. Christin L, Ravussin E, Bogardus C, et al: The effect of propranolol on free fatty acid mobilization and resting metabolic rate. Metabolism 38:439-444, 1989

22. Stepniakowski KT, Goodfriend TL, Egan BM: Fatty acids enhance vascular α-adrenergic sensitivity. Hypertension 25:II774-II778, 1995

23. Tuck ML: Obesity, the sympathetic nervous system, and essential hypertension. Hypertension 19:I67-I77, 1992 (suppl)

24. Williams DRR, Wareham NJ, Brown DC, et al: Undiagnosed glucose intolerance in the community: The Isle of Ely Diabetes Project. Diabet Med 12:30-35, 1995

25. Wareham NJ, Byrne CD, Williams DRR, et al: Fasting proinsulin concentrations predict the development of type 2 diabetes. Diabetes Care 22:262-270, 1999

26. Kunst A, Draeger B, Ziegenhorn J: UV-methods with hexokinase and glucose-6-phosphate dehydrogenase, in Bergmeyer HU (ed): Methods of Enzymatic Analysis, vol 4. Weinheim, Germany, Verlag Chemie, 1983, pp 163-172

27. Sobey WJ, Beer SF, Carrington CA, et al: Sensitive and specific two site immunoradiometric assays for human insulin, proinsulin, 65-66 split and 32-33 split proinsulins. Biochem J 260:535-541, 1989

28. Alpha B, Cox L, Crowther N, et al: Sensitive amplified immunoenzymometric assays (IEMA) for human insulin and intact proinsulin. Eur J Clin Chem Biochem 30:27-32, 1992

29. Shimizu S: Enzymatic determination of serum-free fatty acids: A colorimetric method. Anal Biochem 107:193-198, 1980

30. Sheu WH, Jeng CY, Shieh SM, et al: Suppression of non esterified fatty acid concentrations by insulin in patients with hypertension. Chin Med J 56:367-372, 1995

31. Stepniakowski KT, Goodfriend TL, Egan BM: Fatty acids enhance vascular α-adrenergic sensitivity. Hypertension 25:II774-II778, 1995

32. Day JL, Metcalfe J, Simpson CN: Adrenergic mechanisms in control of plasma lipid concentrations. BMJ 284:1145-1148, 1982

33. Lithell H, Pollare T, Vessby B: Metabolic effects of pindolol and propranolol in double-blind cross-over study in essential hypertension. Blood Press 1:92-101, 1992

34. Rebuffe-Scrive M: Neuroregulation of adipose tissue: Molecular and hormonal mechanisms. Int J Obes 15:83-86, 1991

35. Beauville M, Harant I, Crampes F, et al: Effect of long-term rhGH administration in GH-deficient adults on fat cell epinephrine response. Am J Physiol 263:E467-E472, 1992

36. Bianda TL, Hussain MA, Keller A, et al: Insulin-like growth factor-I in man enhances lipid mobilization and oxidation induced by growth hormone pulse. Diabetologia 39:961-969, 1996

37. Palatini P, Casiglia E, Pauletto P, et al: Relationship of tachycardia with high blood pressure and metabolic abnormalities. Hypertension 30:1267-1273, 1997

38. Liao D, Sloan RP, Cascio WE, et al: Multiple metabolic syndrome is associated with lower heart rate variability. Diabetes Care 21:2116-2122, 1998

39. Facchini FS, Stoohs RA, Reaven GM: Enhanced sympathetic nervous system activity. The linchpin between insulin resistance, hyperinsulinemia and heart rate. Am J Hypertens 9:1013-1017, 1996

40. Sowers JR, Whitfield LA, Catania RA, et al: Role of the sympathetic nervous system in blood pressure maintenance in obesity. J Clin Endocrinol Metab 54:1181-1187, 1982

41. Hoffstedt J, Shimizu M, Sjostedt S, et al: Determination of beta 3-adrenoceptor mediated lipolysis in human fat cells. Obes Res 3:447-457, 1995

42. Klein S, Edward JP, Holland OB, et al: Effect of short- and long-term β-adrenergic blockade on lipolysis during fasting in humans. Am J Physiol 257:E65-E73, 1989

43. Lipworth BJ: Clinical pharmacology of beta 3-adrenoceptors. Br J Clin Pharmacol 42:291-300, 1996

44. Pollare T, Lithell H, Selinus I, et al: Sensitivity to insulin during treatment with atenolol and metoprolol: A randomized, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. BMJ 298:1152-1157, 1989

45. Lake CR, Ziegler MG, Coleman MD, et al: Hydrochlorothiazide-induced sympathetic hyperactivity in hypertensive patients. Clin Pharmacol Ther 26:428-432, 1979

46. Leren P: Comparison of effects on lipid metabolism of antihypertensive drugs with alpha- and beta-adrenergic antagonist properties. Am J Med 82:31-35, 1987