Nonalcoholic fatty liver disease, adiponectin and insulin resistance in dipper and nondipper essential hypertensive patients

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Objective **The pathogenesis of nonalcoholic fatty liver disease (NAFLD) is multifactorial, and the presence of insulin resistance is recognized as the pathophysiological hallmark of this condition. Arterial hypertension is referred as an insulin-resistant state, and insulin resistance may substantially contribute to the cardiovascular risk in this disorder. We examined the inter-relationship between insulin sensitivity, adiponectin levels, and NAFLD in hypertensive patients with different circadian blood pressure profiles.**

Methods **Eighty never-treated patients with essential hypertension were selected for having a nocturnal decrement of blood pressure that was at least 10% (dippers, $n = 47$) or less than 10% (nondippers, $n = 33$) of daytime values. No patient had diabetes mellitus, obesity, hyperlipidemia, or other risk factors for hepatic disease. The two groups were similar as to sex, age, and BMI. Abdominal fat distribution and NAFLD were assessed by ultrasonography.**

Results **Hepatic steatosis was detected in 57.5% of all patients. Nondippers showed a higher prevalence of NAFLD than dippers (81.8 vs. 40.4%, $P < 0.005$). Insulin and the homeostasis model of assessment index were higher ($P < 0.001$) and adiponectin was lower ($P < 0.001$) in nondippers than in dippers, whereas no difference was found in regional fat, liver enzymes, and other metabolic parameters. At multivariate analysis, factors independently associated with nondipping were insulin ($P < 0.05$) and adiponectin ($P < 0.01$) with the homeostasis model of assessment index being of borderline significance.**

Conclusion **In the absence of major risk factors for the development of NAFLD, a high prevalence of liver steatosis was associated with insulin resistance and low adiponectin levels in essential hypertensive patients with a nondipping profile.** ***J Hypertens*** **26:2191–2197 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gammaglutamyl transferase; HOMA, homeostasis model assessment; NAFLD, non-alcoholic fatty liver disease; RIA, radioimmunoassay; SFT, subcutaneous fat thickness; VFT, visceral fat thickness

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a major cause of liver morbidity in western countries and is considered as the hepatic manifestation of metabolic syndrome [1–3]. There is evidence that NAFLD is likely also associated with increased cardiovascular risk through insulin resistance-related mechanisms, raising the possibility that it may be not only a marker, but also an early mediator of atherosclerosis [4,5]. The pathogenesis of fatty liver is multifactorial, and the presence of insulin resistance is recognized as an essential requirement for the accumulation of hepatocellular fat [6,7]. Arterial hypertension is referred as an insulin-resistant state, even in the absence of other metabolic abnormalities, and insulin resistance may substantially contribute to the cardiovascular risk in this disorder [8,9]. It has been suggested that NAFLD represents the link in the association of liver enzyme abnormalities with hypertension and other components of metabolic syndrome [10]. Adiponectin is a protein specifically secreted by adipose cells, with positive effects on insulin sensitivity, inflammation, and atherosclerosis [11,12]. Circulating adiponectin levels are inversely correlated with insulin resistance [13,14] and are low in NAFLD [15]. Adiponectin is negatively correlated with blood pressure (BP) [16] and is consistently low in essential hypertension [17,18]. Recently, a direct pathogenetic link between hypoadiponectinemia and hypertension has been hypothesized [19–21].

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Considering that insulin resistance is a common feature in NAFLD and essential hypertension [22], it is likely that both entities frequently coexist in a given patient. In agreement with other studies [23,24], we previously showed that insulin resistance is more prominent and adiponectin level is lower in essential hypertensive patients with BP persistently elevated throughout the 24-h period (i.e. nondippers), than in hypertensive patients with a normal nocturnal BP fall (i.e. dippers) [25]. The aim of the present study was to investigate the inter-relationship between insulin sensitivity, adiponectin levels, and NAFLD in dipper compared with nondipper essential hypertensive patients free from major risk factors for the development of hepatic steatosis.

Methods

Patients

Eighty newly diagnosed never-treated white patients with essential hypertension were prospectively studied. They were consecutively selected, over the past 18 months, from a large essential hypertensive population (more than 900 patients) at our three hospital-based specialized hypertension outpatient clinics.

Patients were first selected according to the following criteria: age 18–65 years; grade 1–2 hypertension according to the criteria of the European Society of Hypertension–European Society of Cardiology guidelines, with clinic BP at least 140/90 mmHg measured by mercury sphygmomanometer in a sitting position in at least three separate casual measurements within the last month [26]; no history or clinical evidence of cardiopulmonary, renal, or hepatic disease. In all patients, the estimated duration of hypertension was less than 1 year.

After the initial screening visit at our clinics, all participants, as outpatients, underwent further selection. Biochemical, hormonal, and instrumental tests excluded those with cardiac and renal disease and those with secondary hypertension. Renal disease was defined as the presence of serum creatinine more than 133 μmol/l in men and more than 120 μmol/l in women. Glomerular filtration rate was estimated by calculating creatinine clearance with the formula of Cockroft–Gault [27]. Conditions known to be associated with fatty liver were specifically ruled out by the following exclusion criteria: diabetes mellitus (i.e. fasting plasma glucose at least 7.0 mmol/l on two separate occasions); moderate-to-severe hyperlipidemia (i.e. serum total cholesterol at least 6.2 mmol/l or triglycerides at least 2.28 mmol/l); obesity (i.e. BMI at least 30 kg/m^2); hepatitis B surface antigen or hepatitis C virus positive serum markers; increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma glutamyl transferase (GGT) due to known causes or history of chronic liver disease (i.e. hemochromatosis, Wilson's disease, etc.); treatment with hepatosteatogenic drugs in the previous year; history of exposure to occupational hepatotoxins; alcohol intake more than 20 g/day; and smoking habit, defined as at least one cigarette daily for 1 year in the past 5 years.

During evaluation, they consumed a normal sodium and potassium diet (i.e. 100–200 mmol/day sodium and 50–70 mmol/day potassium). All individuals followed the diet under the control of hospital staff. The relationship between sodium and potassium intake with sodium and potassium urinary excretion was randomly checked. Patients had been weight stable over the previous 6 months. The waist circumference measurement, taken as the reference measure of abdominal obesity, was made at minimal inspiration to the nearest 0.1 cm, midway between the last rib and the iliac crest.

Within the assessed hypertensive population, 80 patients (48 men and 32 women) met the inclusion criteria and consented to enrol in the study. Each patient provided their informed consent for the study, which was approved by Institutional Ethics Committee.

Blood pressure and heart rate monitoring

All hypertensive patients underwent 24-h ambulatory BP monitoring (Takeda TM2430, Asahi, Japan), which was carried out in a day separate from the follow-up office visit. Recording started between 08:30 and 09:00 h. Patients were instructed to closely report daily activities during the recordings. Recording was programmed for every 15 min over a 24-h period. BP and heart rate (HR) measurements were excluded from the analysis when they were missing or labelled as technically erroneous by the monitor software. If a BP recording had less then 70% successful readings, it was rejected and repeated. During the monitoring, a written diary of physical and mental activities as well as sleep duration was kept. BP readings were discarded in case of a lack of sleep during the night (patients not included in the study). Daytime and nighttime were considered as the intervals from 08:00 to 22:00 h and from midnight to 06:00 h, respectively. BP dipping was defined as a day–night systolic and diastolic fall of at least 10% [25,28]; in accordance with this definition, 47 patients (28 men and 19 women) were dippers and 33 patients (20 men and 13 women) were nondippers.

Liver ultrasonography

Liver ultrasound scanning was carried out in all patients in the morning, after overnight fasting. The diagnosis of fatty liver was performed with a high-resolution ultrasonographic system (AU5, Esaote Biomedica, Genoa, Italy) by using standard criteria [29,30]. A 3.5 MHz transducer was used to obtain the following images: sagittal view of the right lobe of the liver and right kidney, transverse view of the left lateral segment of the liver and spleen, transverse view of the liver and the pancreas, and any focal areas of altered echotexture. The liver steatosis

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was assessed semi-quantitatively on a scale of 0–3 as: grade 0 (absent steatosis), normal echogenicity; grade 1 (mild steatosis), slight, diffuse increase in fine echoes in liver parenchyma with normal visualization of diaphragm and intrahepatic vessel borders and slight exaggeration of liver and kidney echo discrepancy; grade 2 (moderate steatosis), moderate, diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm and, in addition, greater posterior beam attenuation as well as greater discrepancy between hepatic and renal echoes; grade 3 (severe steatosis), marked increase in fine echoes with poor or nonvisualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver and larger discrepancy between hepatic and renal echoes.

For estimation of the prevalence of NAFLD by liver ultrasound, a group of 40 sex-matched, age-matched, and BMI-matched normotensive individuals, selected according to the same exclusion criteria, were used as controls.

Patients were examined on the same day by two experienced operators; each patient was seen in different sessions by each operator, unaware of the ultrasonographic reading of the other. Intra-observer and interobserver variability for different liver ultrasonographic patterns was tested by calculating the Spearman's rank correlation coefficient (i.e., rho). To assess intra-observer variability, each operator, blinded to the patient's clinical and laboratory data, read the ultrasonographic images according to the standard criteria [29,30]; images were reread by the same operator (blinded to the initial reading) 1 month after the initial assessment. Rho values for the two operators were 0.94 and 0.95. To assess interobserver variability, ultrasonographic images of all patients were read by each of the two operators unaware of the other operator's diagnosis; rho value was 0.88. Ultrasound examinations with either intra-observer ($n = 2$) or interobserver ($n = 7$) nonconcordant diagnoses were discarded (patients not included).

Abdominal fat distribution

The abdominal fat distribution was assessed, using ultrasonography [31,32], by the same two operators who performed liver ultrasound. Ultrasound measurements (AU5, Esaote Biomedica, Genoa, Italy) have been shown to be highly correlated to multiscan computed tomography (CT) measurements [33]. Transverse scanning was performed to measure subcutaneous fat thickness using a 7.5 MHz probe and visceral fat thickness using a 3.5 MHz probe, 1 cm above the umbilicus. Subcutaneous fat thickness was defined as the thickness between the skin–fat interface and the linea alba, and visceral fat thickness was defined as the distance between the anterior wall and the internal face of the rectoabdominal muscle perpendicular to the aorta. Intra-observational reproducibility (i.e. coefficients of variation) of the ultrasonographic estimations for each of the two operators was 1.6–2.2% and 1.9–2.6% for visceral fat thickness and subcutaneous fat thickness, respectively. The reproducibility between the two operators was 2.6 and 3.6% for visceral fat thickness and subcutaneous fat thickness, respectively.

Laboratory methods

In all individuals, blood samples for biochemical and metabolic profile were obtained at 08:00 h, after overnight fasting. Insulin sensitivity was calculated according to the formula of the homeostasis model assessment (HOMA index) method: insulin resistance = fasting plasma insulin (μUI/ml) $\times$ fasting plasma glucose (mmol/l)/22.5 [34]. The index is highly correlated with the insulin resistance index assessed by the euglycemic–hyperinsulinemic clamp, which is the gold standard of insulin resistance measurement and is widely adopted in clinical studies for individuals with various degree of insulin sensitivity, including hypertensive patients [35]. Plasma insulin concentration was measured by a chemiluminescence immunoassay using a commercially available kit (Immulite 1 analyzer, Diagnostic Product Corporation, Los Angeles, California, USA): normal range, 6–24 μUI/ml (36–144 pmol/l). Plasma adiponectin was measured by specific radioimmunoassay obtained from Linco Research, Inc. (St Charles, Missouri, USA), with minor modifications, as previously described [18]. Normal values were 29.2 ± 6.4 μg/ml.

For all hormone measurements, intra-assay and interassay coefficients of variation were less than 10%. All other biochemical variables were assayed in plasma or serum using standard methods. The cut-offs for liver enzymes were based on the upper limit of normal in our laboratory. Thus, AST, ALT, and GGT were defined as elevated when more than 35 U/l, more than 35 U/l and more than 45 U/l, respectively.

Statistical analysis

All results are expressed as mean $\pm$ SD for continuous variables and as proportion for categorical variables. Continuous data were subjected to the Kolmogorov–Smirnov test to determine their distribution. Statistical significance between groups was assessed in normally distributed data by Student's t test for independent samples and by Mann–Whitney U-test in nonnormally distributed data. Bonferroni adjustment was applied to multiple comparison tests of continuous data. Categorical variables were analysed by the chi-square analysis or Fisher's exact test when appropriate. Pearson's correlation coefficient was calculated to test for a linear correlation between continuous variables. Potential predictors were evaluated for their ability to distinguish dipper from nondipper hypertensive group of patients. For this purpose, we entered only those variables into the univariate analysis that were significantly different at baseline between

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dipper and nondipper patients (i.e. insulin, HOMA index, and adiponectin). Nocturnal systolic and diastolic BP values were not entered, as they were used *a priori* to define the two groups. Significant predictors of the outcome at univariate analysis were subsequently assessed by multiple logistic regression analysis to find the independent factors associated with a nondipping profile. We tested, in turn, which variables were associated with a higher prevalence of NAFLD at univariate analysis and maintained their association at multivariate analysis. For this purpose, multiple logistic regression analysis was run with NAFLD as dependent variable and age, BMI, and nondipping BP profile as fixed covariates. Potentially confounding metabolic variables were added one at a time, in a forward stepwise fashion, in different models to avoid multicollinearity. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using STATISTICA 6.0 (StatSoft, Tulsa, Oklahoma, USA) for Windows.

Results

Characteristics of patients

Clinical, metabolic, and BP parameters of dipper and nondipper patients are shown in Table 1. The two groups of patients were similar for age, sex, BMI, waist circumference, subcutaneous and visceral fat thickness, clinic, 24-h and diurnal BP, and HR. In addition, the dipper group did not differ from the nondipper group in fasting glucose, liver enzymes, and lipids. Plasma insulin and HOMA index were higher ($P < 0.001$) and adiponectin levels were lower ($P < 0.001$) in nondippers than in dippers. Adiponectin correlated inversely with HOMA index in both dipper and nondipper groups ($r = -0.55$ and $r = -0.80$, respectively, $P < 0.001$). No correlation of HOMA index and adiponectin levels with systolic/diastolic BP levels, either clinic or 24-h ambulatory, was found.

Liver ultrasonography

The liver ultrasonography data are reported in Table 1 and Fig. 1. NAFLD was detected overall in 46 out of 80 (57.5%) of our hypertensive patients; NAFLD was more frequent in nondipper patients (27 out of 33), than in dipper patients (19 out of 47) (81.8% vs. 40.4%, $P < 0.005$) (Table 1). The distribution of ultrasound grading of NAFLD showed a higher prevalence of mild-to-moderate grade in the nondipper than in the dipper group of patients, whereas the severe degree of steatosis was present in two patients of the nondipper group only (Fig. 1).

Among the 40 healthy controls, NAFLD was present in eight individuals (20%), seven having grade 1 and one having grade 2 liver steatosis; none had elevation of serum liver enzymes. Seven out of 47 dipper and 12 out of 33 nondipper patients had AST or ALT or GGT levels or levels of all three exceeding the upper normal range (14.8% vs. 36.3%, respectively, $P < 0.05$). All patients with serum liver enzyme elevation, either dippers or nondippers, had NAFLD grade 1–3 at ultrasonography.

Table 1 Clinic and metabolic characteristics of the study groups

	Dippers ($n = 47$)	Nondippers ($n = 33$)	P
Age (years)	49.7 ± 9.2	47.7 ± 10.0	NS
Sex (men/women)	28/19	20/13	NS
Clinic SBP/DBP (mmHg)	144.9 ± 8.6/92.8 ± 6.9	148.2 ± 7.4/94.0 ± 10.0	NS
Clinic heart rate (bpm)	72.4 ± 9.3	72.8 ± 10.9	NS
24-h SBP/DBP (mmHg)	138.0 ± 7.9/85.7 ± 5.2	141.1 ± 11.2/88.0 ± 6.7	NS
Daytime SBP/DBP (mmHg)	143.5 ± 8.2/89.0 ± 5.7	143.8 ± 8.6/89.2 ± 6.7	NS
Night-time SBP/DBP (mmHg)	120.6 ± 8.6/74.0 ± 5.6	138.2 ± 11.1/85.2 ± 7.9	<0.0001
24-h heart rate (bpm)	73.6 ± 7.4	74.2 ± 9.3	NS
Daytime heart rate (bpm)	76.6 ± 8.0	76.8 ± 9.7	NS
Night-time heart rate (bpm)	63.7 ± 7.7	65.1 ± 9.8	NS
BMI (kg/m^2)	25.3 ± 2.9	26.1 ± 2.9	NS
Waist circumference (cm)	90.3 ± 10.9	95.3 ± 12.1	NS
VFT (mm)	36.2 ± 11.1	41.7 ± 12.8	NS
SFT (mm)	18.3 ± 6.1	19.9 ± 7.2	NS
VFT/SFT	2.1 ± 0.7	2.3 ± 0.9	NS
Total cholesterol (mmol/l)	5.0 ± 0.6	5.2 ± 0.7	NS
LDL cholesterol (mmol/l)	3.2 ± 0.8	3.6 ± 0.6	NS
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.3 ± 0.3	NS
Triglycerides (mmol/l)	1.1 ± 0.4	1.1 ± 0.5	NS
Glucose (mmol/l)	5.0 ± 0.5	4.9 ± 0.8	NS
Insulin (pmol/l)	55.4 ± 27.6	86.5 ± 33.0	<0.001
HOMA index	2.1 ± 1.2	3.1 ± 1.2	<0.001
Adiponectin (μg/ml)	17.7 ± 7.0	10.1 ± 5.8	<0.001
Creatinine clearance (ml/min)	94.9 ± 20.2	99.8 ± 24.3	NS
AST (U/l)	22.1 ± 6.7	24.8 ± 7.3	NS
ALT (U/l)	24.7 ± 12.4	31.1 ± 16.6	NS
GGT (U/l)	23.7 ± 13.3	30.0 ± 18.4	NS
NAFLD prevalence (%)	40.4	81.8	<0.005

Mean values ± SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beats per minute; DBP, diastolic blood pressure; GGT, gamma glutamyl transferase; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; SFT, subcutaneous fat thickness; VFT, visceral fat thickness.

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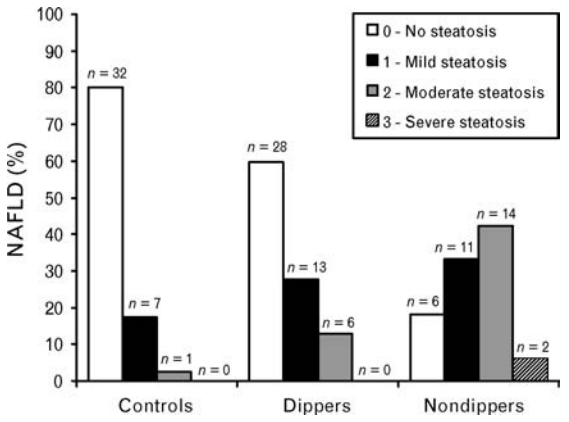
Fig. 1



Nonalcoholic fatty liver disease grading in normotensive controls ($n = 40$), dipper ($n = 47$), and nondipper ($n = 33$) hypertensive patients.

Insulin, HOMA index, and adiponectin ($P < 0.001$) were predictors of nondipping BP profile at univariate analysis. At multivariate analysis, factors independently associated with nondipping again were insulin ($P < 0.05$) and adiponectin ($P < 0.01$), with HOMA index of borderline significance ($0.1 > P > 0.05$).

Intergroup comparison analysis showed a number of variables to be different in hypertensive patients with NAFLD compared with those without NAFLD, including prevalence of nondippers (Table 2). In stepwise multiple logistic regression analysis with NAFLD as a dichotomic dependent variable, nondipping BP profile was a strong predictor of NAFLD ($P < 0.0001$), independent of age and BMI. After addition in the model of HOMA index (Table 3, model 1) and adiponectin (Table 3, model 2), nondipping remained a significant predictor of NAFLD. When other metabolic variables were included, they were rejected by the model partly because of collinearity.

Table 2 Characteristics of hypertensive patients with and without nonalcoholic fatty liver disease

	NAFLD ($n = 46$)	No NAFLD ($n = 34$)	*P*
Age (years)	48.5 ± 9.7	49.5 ± 9.5	NS
Sex (men/women)	28/18	20/14	NS
BMI (kg/m^2)	27.0 ± 2.2	23.9 ± 2.9	<0.001
Waist circumference (cm)	97.4 ± 10.4	85.8 ± 9.9	<0.001
VFT (mm)	42.8 ± 12.0	31.9 ± 9.5	<0.001
SFT (mm)	21.1 ± 6.8	15.9 ± 4.9	<0.001
VFT/SFT	2.2 ± 0.8	2.2 ± 0.9	NS
Total cholesterol (mmol/l)	5.2 ± 0.8	5.1 ± 0.6	NS
LDL cholesterol (mmol/l)	3.6 ± 0.8	3.2 ± 0.7	NS
HDL cholesterol (mmol/l)	1.4 ± 0.3	1.5 ± 0.4	NS
Triglycerides (mmol/l)	1.3 ± 0.5	1.1 ± 0.4	NS
Glucose (mmol/l)	5.2 ± 0.6	4.8 ± 0.5	<0.001
Insulin (pmol/l)	80.4 ± 34.2	52.8 ± 26.4	<0.001
HOMA index	3.1 ± 1.3	1.8 ± 0.9	<0.001
Adiponectin (μg/ml)	11.6 ± 6.0	18.9 ± 8.4	<0.001
Creatinine clearance (ml/min)	100.8 ± 19.4	91.4 ± 25.2	NS
AST (U/l)	24.9 ± 8.2	21.4 ± 4.9	<0.05
ALT (U/l)	31.6 ± 16.5	22.1 ± 9.8	<0.01
GGT (U/l)	29.3 ± 17.4	22.9 ± 13.7	NS
Nondippers, *n* (%)	27 (58.7)	6 (17.7)	<0.01

Mean values ± SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; SFT, subcutaneous fat thickness; VFT, visceral fat thickness.

Discussion

The main finding of the present study was that hypertensive patients with a nondipping BP profile have a higher prevalence of NAFLD than those with a dipping profile. To our knowledge, only one study by Donati *et al.* [36] has previously investigated, using an ultrasonograph methodology similar to ours, the prevalence of NAFLD in nonobese, nondiabetic hypertensive patients. In their population, the prevalence of NAFLD was around 30% in comparison with 12% in healthy controls, and the two major determinants were insulin resistance and BMI. The multivariate analysis performed in our hypertensive population confirms BMI as a strong predictive variable for NAFLD and also shows that nondipping BP profile specifically is a predictor of NAFLD, independent of other metabolic factors. In addition to interobserver variability, the higher prevalence of NAFLD in our study than in that of Donati *et al.* [36], which refers to data obtained from 1999 to 2001, might be not surprising on the basis of the different selection criteria and the general trend of this disease to increase over recent years [2]. Our data overall confirm an elevated prevalence of NAFLD in essential hypertensive patients, being approximately three-fold higher than that found in normotensive controls (20%) or reported in a nonobese general population (16%) recruited from the same geographical area in Italy [37]. When patients were examined in accordance with their circadian BP pattern, nondippers showed a much higher prevalence of NAFLD than dippers. Indeed, liver steatosis was present in the majority of nondippers, with a more severe grading than in dipper patients (Fig. 1). Furthermore, although the difference in the mean values of liver enzymes between the two groups were nonsignificant, a higher percentage of nondippers had AST or ALT or GGT or all three above the normal limits than dippers. Even minor elevation of liver enzymes in individual patients cannot be ignored, as it may reasonably give an indication for the risk of progression of NAFLD to end-stage liver disease [22,38].

Among anthropometric and biochemical parameters investigated in our study, waist circumference and visceral fat thickness were not significantly different between dippers and nondippers. It has been reported that visceral fat (i.e. abdominal adiposity rather than total adiposity) is correlated with arterial BP or the presence of hypertension or both [39,40], but no data are available on the importance of body fat distribution on circadian BP profile. A limitation of our findings could be that the

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Table 3 Multivariable analysis of predictors for nonalcoholic fatty liver disease in hypertensive patients ($n = 80$)

			Model 1		Model 2	
	Std. coeff.	*P*	Std. coeff.	*P*	Std. coeff.	*P*
Age	0.064	0.481	0.018	0.847	−0.008	0.930
BMI	0.488	<0.0001	0.418	<0.0001	0.421	<0.0001
Nondipping BP profile	0.348	<0.0001	0.271	<0.005	0.206	0.047
HOMA index			0.223	0.029	0.125	0.285
Adiponectin					−0.198	0.105

BP, blood pressure; HOMA, homeostasis model assessment; Std. coeff., standardized regression coefficient.

waist circumference as well as the ultrasound technique that we used for measurements of visceral adiposity is considered less accurate than other radiological imaging modalities, that is, CT scan or MRI [30]. However, the amount of visceral fat quantified by ultrasound has been found to reliably predict the risk of cardiovascular and metabolic disease in nonobese individuals [41].

As we previously reported in a smaller hypertensive population [25], insulin resistance was more pronounced and adiponectin level was lower in nondippers than in dippers, further suggesting a role of these metabolic abnormalities in the tendency to induce greater end-organ damage and increased cardiovascular morbidity and mortality of nondippers [42,43]. The association between insulin resistance and nocturnal nondipping pattern in hypertensive patients has been extensively demonstrated [23–25]. Elevated sympathetic nervous activity [44] or increased salt sensitivity of BP [45–47] or both are indicated as the mechanisms underlying this association. An elevated adrenergic tone could also be suggested in our nondipper patients by their low adiponectin levels [25,48]. Interestingly, a recent report found an independent association between low adiponectin levels and increased proximal tubular sodium reabsorption in essential hypertensive men [49], in keeping with experimental evidence that in adiponectin-knockout mice, hypoadiponectinemia causes sodium-dependent hypertension [50]. Although our study was not designed to test BP salt sensitivity, low levels of adiponectin may suggest a primary role of this factor in determining the nondipping phenomenon, either directly or through insulin resistance. Taken together, the observation of higher insulin resistance and lower adiponectin levels, in association with a higher prevalence of NAFLD in nondippers than in dippers, supports the possibility that these two metabolic abnormalities act as concurrent pathogenetic factors of both increased hepatic fat content and nondipping hypertension.

The strength of the present study was that our patients were consecutively selected from a larger population, using a rather narrow range of inclusion criteria with regard to clinical and biochemical variables, in order to minimize the bias of potential risk factors for fatty liver disease. The main limitation of the study was the use of ultrasonography. Ultrasonography is unable to identify fatty infiltration below 30% [30], possibly underestimating the presence of fatty liver; also, ultrasonography cannot detect inflammation and fibrosis and thus, is unable to distinguish between NAFLD, nonalcoholic steatohepatitis, and cryptogenic cirrhosis [1]. The gold standard for the diagnosis of NAFLD remains liver histology. However, because none of our patients had biochemical signs of relevant active disease, liver biopsy was not performed for ethical reasons. Another limitation was that our patients were recruited from a hypertensive population referring to specialist hypertension units and not from a primary care setting; thus, the actual prevalence of NAFLD in an adequate sample of the general population, selected according to criteria adopted in high-quality epidemiological studies, needs to established.

In summary, in the absence of major risk factors for the development of NAFLD, a high prevalence of liver steatosis was associated with insulin resistance and low adiponectin levels in essential hypertensive patients with a nondipping profile. This may suggest an interactive role of these two metabolic variables in the pathogenesis of both fatty liver and altered circadian BP rhythm. Adiponectin has been proposed by recent animal studies as a useful therapy for hypertension as well as for insulin resistance in the context of metabolic syndrome [12,50]. Whether antihypertensive agents, potentially able to correct adiponectin levels or insulin resistance or both [51], could also influence the natural history of NAFLD will be investigated in long-term follow-up studies.

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