Insulin Resistance as a Risk Factor for Hypertensive Patients with Non-Alcoholic Fatty Liver Disease

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RESEARCH

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Abstract

Background: Non-alcoholic fatty liver disease is present in 15–25% of the general population. The aim of this study was to investigate the relationship between insulin resistance and non alcoholic fatty liver disease (NAFLD) in essential hypertensive patients, according to the circadian blood pressure rhythm.

Methods: A prospective pilot study was conducted at the regional outpatient Diagnosis and Treatment Center Cluj-Napoca, Romania. The study included mild to moderate hypertensive patients who had never been previously treated. Patients were divided into two groups according to the circadian (blood pressure) rhythm. Group I included dipper and Group II included hypertensive non-dipper patients. All patients underwent 24 hour ambulatory blood pressure (ABPM) monitoring and abdominal ultrasound, for the diagnosis of fatty liver disease. Plasma insulin and HOMA index (homeostatic model assessment) and the prevalence of NAFLD were measured. Thirty three patients were enrolled in the study, 14 of them in the dipper group and 19 of them in the non-dipper group.

Results: The non-dipper hypertensive patients, showed a statistically higher plasma insulin and HOMA index ($p<0.001$) and also a higher prevalence of the NAFLD when compared to the non-dippers.

Conclusion: The non-dipping BP status of hypertension associated both a higher prevalence of NAFLD and a higher insulin resistance. Although further expansive testing is necessary this study has found that insulin resistance is a pathogenic link between the liver steatosis and non-dipping BP status.

Introduction

Non-alcoholic fatty liver disease is present in 15–25% of the general population [1]. Nonalcoholic fatty liver disease (NAFLD) is now considered the hepatic manifestation of the metabolic syndrome [2-5]. NAFLD has a multifactorial pathogenesis and insulin resistance plays a pathogenic role in its development [8, 9]. Therefore, the NAFLD can be considered as an early mediator of atherosclerosis due to the fact that it is associated with an increased cardiovascular risk. Thus research [10-12] has shown that even in the absence of metabolic abnormalities insulin resistance is often associated with arterial hypertension. Data from a recent study suggests that NAFLD represents the link between patients with liver enzyme abnormalities and with hypertension and other metabolic syndrome components [13].

The aim of the present study was to investigate the relationship between insulin resistance and NAFLD in hypertensive patients according to the circadian blood pressure (BP) rhythm.

Methods

A prospective study was conducted at the regional outpatient Diagnosis and Treatment Center in Cluj-Napoca, Romania.

The study included consecutive eligible adult outpatients of either sex with mild to moderate hypertension with either office sitting systolic BP (SBP) of 140-179 mmHg or office diastolic blood pressure (DBP) 90-109 mmHg. This status was defined according to the international guidelines and was measured by mercury sphygmomanometer in a sitting position in at least three separate casual measurements within the last month [14]. All patients were naive to antihypertensive drug treatment (none had been treated previously as hypertensive patients) and they were enrolled in the study between November 2005 and December 2008.

The patients with seated systolic blood pressure (SBP) > 200 mmHg and known or suspected secondary hypertension were excluded from the study. Seated BP was measured with a standard mercury sphygmomanometer. In addition, patients with clinical or laboratory evidence of cardiovascular, pulmonary, renal, hepatic disease, diabetic mellitus, obesity, chronic alcoholism as well as patients with previous drug induced fatty liver treatment were all excluded from the study.

Before taking part in the present study, all the patients gave written informed consent. Thirty three hypertensive patients completed the inclusion criteria and were

therefore enrolled in the study. All patients underwent 24 hour ambulatory blood pressure (ABPM) monitoring for systolic and diastolic blood pressure evaluation. The ambulatory blood pressure (ABPM) was monitored with ABPM-04, 99/BP411 - Medibase. Before using the ABPM-04, blood pressure was measured with a mercury sphygmomanometer, after the patient had been seating for at least 10 minutes. The arm with higher BP values at sphygmomanometer evaluation was chosen for measurement with the ABPM-04. During the day all patients were asked to ensure that the arm was always parallel to the trunk when the cuff was inflated in order to reduce measurement errors. Readings were obtained automatically at 15 minutes intervals from 6:00 am to 10:00 pm and 30 minutes intervals from 10:00 pm to 6:00 am. All the measurements were performed by the same investigator, using the same equipment, both at the beginning of the study and during the follow up.

Hypertensive patients were divided into two groups: Group I included hypertensive patients defined as dippers and Group II included hypertensive patients defined as non-dippers. Nocturnal dipping was defined as a reduction in average SBP and DBP at night greater than 10% compared with average daytime values [15] and those with normal diurnal BP variation were termed dippers. [16]

For the diagnosis of the fatty liver disease, the noninvasive method of abdominal ultrasound was used. The liver ultrasonography scanning was performed by standard criteria [17-19], by the same investigator, on all patients, in the morning as well as after overnight fasting, using the same equipment (ESAOTE MyLab, with a 3.5-MHz transducer). The presence of liver steatosis was then graded semi-quantitatively according to a previously reported scale [20]: 0 - absent, 1 - mild, 2 - moderate and 3 - severe steatosis.

In order to obtain a biochemical and metabolic profile blood samples were obtained, from all subjects who fasted overnight. Serum triglycerides, total and HDL cholesterol, glucose, insulin, alanine amino transferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) levels were measured, using routine automated assay methods, after an overnight fast. Insulin resistance was calculated by the homeostasis monitoring assessment (HOMA) formula. The HOMA index was calculated as the product of the fasting plasma insulin level (µU/mL) and the fasting plasma glucose level (mmol/L), divided by 22.5. [21-23].

Statistical analysis

Descriptive statistics, including means, standard deviation (SD), ranges and percentages, were used to characterize the study subjects. Statistical significance between groups was assessed by Student's test on normally distributed independent samples and by Mann-Whitney U-test on non-normally distributed data. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 13.

Results

There were no statistically significant differences between the two groups of patients in demographic baseline characteristics. Demographic, clinical and laboratory characteristics of the study population are reported in Table 1 bellow.

Table 1. Baseline Demographic and Clinical Characteristics by Blood Pressure circadian rhythm

Variable	Dippers (n=14)	Non-dippers (n=19)	p-value
Gender: absolute frequency (percentage)			
Male	6 (42.85%)	12 (63.15%)	NS
Female	8 (57.14%)	7 (36.84%)	NS
Age: means±SD			
Male (years)	56.85±12.12	57.04±11.44	NS
Female (years)	52.11±10.92	50.07±12.84	NS
BMI (kg/m²)	27.42±4.91	28.32±4.35	NS
Mean 24h SBP (mmHg)	142.76±15.67	144.57±15.04	NS
Mean 24h DBP (mmHg)	87.86±10.61	85.21±11.42	NS
Triglycerides (mmol/l)	1.2±0.36	1.2±0.47	NS
Total cholesterol (mmol/l)	5.11±0.56	5.21±0.76	NS
LDL cholesterol (mmol/l)	3.5±0.86	3.7±0.62	NS
HDL cholesterol (mmol/l)	1.62±0.36	1.42±0.16	NS
ALT (U/l)	25.22± 9.7	29.78± 10.2	NS
AST (U/l)	21.83± 8.8	25.33± 6.8	NS
GGT (U/l)	24.41± 10.8	27.72± 12.3	NS

SD = standard deviation, SBP= systolic blood pressure,DBP= diastolic blood pressure,
LDL= Low-density lipoprotein, HDL= High-density lipoproteins, ALT= alanine aminotransferase, AST= aspartate aminotransferase, GGT= gamma-glutamyl transferase

In the group of non-dipper hypertensive patients, a statistically significantly higher level of plasma insulin (60.5 ± 28.8 (pmol/l) vs. 87.5 ± 19.4 (pmol/l) and HOMA index (3.5 ± 0.96 vs. 2.3± 0.98) for $p<0.001$ were observed when compared to the dipper group of hypertensive patients. In addition, higher serum levels were observed for AST, ALT and GGT in the non-dipper patients group, but the difference did not achieve a statistical significance. The variation was observed when the mean values of the liver enzymes were compared between the two groups of hypertensive patients.

The non-alcoholic fat liver disease was observed in 57.57 % of hypertensive study subjects. However there was with a significantly higher prevalence of the disease in the dipper patients compared to the non-dipper hypertensive patients ($p<0.05$) as presented in fig 1 and fig.2 (14 out of 19 non-dipper patients vs 6 out of 14 dipper patients for $p<0.05$).

Fig.1. Prevalence of NAFLD in the study hypertensive patients

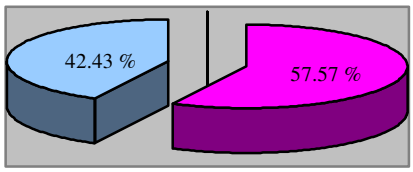
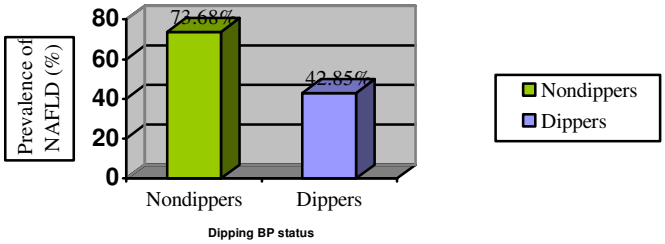
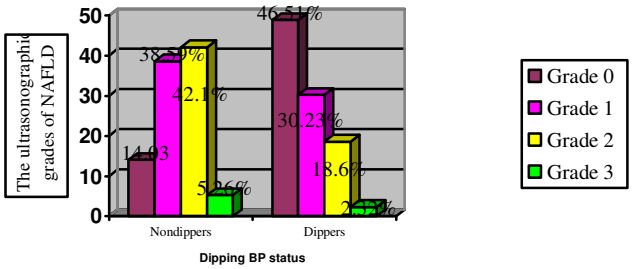


Fig.2.The prevalence of NAFLD by the two hypertensive groups



When the two hypertensive patients groups were compared, in the non dipper group a higher prevalence of mild to moderate liver steatosis grades was observed. In the dipper hypertensive group, there was a higher prevalence of mild liver steatosis or none at all. The liver steatosis grade according to dipping BP status is presented in fig.3 bellow.

Fig.3.The ultrasonographic grades prevalence of NAFLD by the two hypertensive groups



All the patients with elevated serum liver enzyme had grade 1-3 of NAFLD at ultrasonographic examination, regardless of which group they belonged to.

Discussions and Conclusions

This study revealed a significant statistical difference in the prevalence of NAFLD between dipper and non-dipper hypertensive patients. The non-dipper group of patients revealed a higher insulin resistance when compared to dipper group of patients suggesting that insulin resistance could play a role in the tendency of more significant end organ damage in non-dipper hypertensive patients than in dippers [24-27]. The results from the present study are in accordance to the previous studies on this issue [28, 29] confirming the association between the non-dipper status and the level of insulin resistance.

Population-based studies [30, 31] have correlated non-dipping BP status with target organ damage, including cardiovascular morbidity and mortality, progression of preexisting renal disease [32, 33] and cerebrovascular disease [31, 34].

Because the non-dipping BP status of hypertension is associated both with a higher prevalence of NAFLD and with a higher insulin resistance this study concludes that insulin resistance could be the pathogenic link between liver steatosis and non-dipping BP status. Further expansive testing is necessary.

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Both authors were involved in the data collection as well as in its analysis.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.