PRIMARY NON ALCOHOLIC FATTY LIVER DISEASE IN HYPERTENSIVE PATIENTS

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Keywords: essential hypertension, primary non alcoholic fatty liver disease, circadian blood pressure rhythm, insulin resistance

Abstract: The aim of the present study was to investigate the prevalence of NAFLD and the relationship between insulin sensitivity and NAFLD in grade III high and very high cardiovascular additional risk essential hypertensive patients according to the circadian blood pressure (BP) rhythm. This four years prospective study conducted at the Departament of Internal Medicine from the Diagnosis and Treatment Center from Cluj-Napoca. The study included grade III essential hypertensive patients. Hypertensive patients were divided into four groups: dipper(D), non-dipper (ND), reverse-dipper (RD), extreme-dipper (ED) according the diurnal index (DI) from ABPM monitoring. All hypertensive patients underwent 24 hour ambulatory blood pressure monitoring (ABPM) (for systolic and diastolic blood pressure evaluation), blood tests and abdominal ultrasonography for the diagnosis of fatty liver disease. Thirty five hypertensive patients were included in the study, a number of 31.42% ND, 11.43% RD, 8.57% ED and 48.57% D. The prevalence of NAFLD was significantly higher in ND, RD, ED compared to D. When compared to dipper group of hypertensive patients a statistically significantly higher level of plasma insulin was observed in the group of non-dipper (86.3±17.9pmol/l vs. 62.2±203pmol/l, p<0.05), in reverse dipper (88.3±18.6pmol/l vs. 62.2±20.3pmol/l) in extreme-dippers (86.7±16.88pmol/l vs. 62.2±20.3 pmol/l, p<0.05). The altered dipping status (ND, RD, ED) of hypertension associated a higher insulin resistance that could be the pathogenetic link between the NAFLD and altered blood pressure status. Altered blood pressure status could be a marker of NAFLD in hypertensive patients.

Cuvinte cheie: hipertensiune arterială esențială, steatoza hepatică non alcoolică primară, ritmul circadian tensiunii arteriale, rezistența la insulină

Rezumat: Obiectivul acestui studiu a constat în investigarea prevalenței steatozei hepatice non-alcoolice (NAFLD) și relația dintre sensibilitatea la insulină și NAFLD în hipertensiunea arterială (HTA) de grad III risc adițional mare și foarte mare în conformitate cu ritmul circadian al tensiunii arteriale. Acest studiu prospectiv a fost efectuat pe o perioadă de patru ani la Departamentul de Medicină Internă de la Centrul de Diagnostic și Tratament din Cluj-Napoca. Studiul a inclus pacienți cu HTA esențială gradul III. Pacienții hipertensivi au fost împărțiți în patru grupe: dipper (D), non-dipper (ND), reverse-dipper (RD), de extreme dipper (ED), potrivit indexului diurn (DI) de la monitorizarea ambulatorie automată (MATA). Toți pacienții hipertensivi au fost monitorizați MATA timp de 24 de ore pentru presiunea sistolică și diastolică, li s-au efectuat analize de sânge și ecografie abdominală pentru diagnosticarea afectării hepatice. Treizeci și cinci de pacienți hipertensivi au fost incluși în studiu, un număr de 31.42% ND, 11.43% RD, 8.57% ED și 48.57% D. Prevalența NAFLD a fost semnificativ mai mare în ND, RD, ED, comparativ cu D. Când au fost comparați cu grupul cu profil dipper s-a observat un nivel statistic semnificativ mai mare de insulină plasmatică în grupul de non-dipper (86.3 ± 17.9pmol / l vs 62.2 ± 203pmol / l, p <0,05), în reverse dipper (88.3 ± 18.6 pmol / l vs 62.2 ± 20.3pmol / l) în extreme-dippers (86.7 ± 16.88pmol/lvs.62.2±20.3pmol/l,p<0,05). Alterarea statusului dipper (ND, RD, ED) al hipertensiunii arteriale asociază o rezistență la insulină mai mare care ar putea fi legătura dintre patogenetice NAFLD și modificarea statusului tensiunii arteriale. Alterarea statusului tensiunii arteriale ar putea fi un marker al NAFLD la pacienții hipertensivi.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum starting from fatty liver, fatty liver and inflammation to evidence of damage to hepatocytes and can progress to cirrhosis or in the most extreme form of NAFLD can progress to hepatocellular carcinoma or liver failure (1).

Non-alcoholic fatty liver disease is considered the most common liver disease affecting 15–25% of the general population (2). Primary NAFLD results from insulin resistance and NAFLD is considered as part of the metabolic syndrome (3-6).

Essential hypertension is considered an insulin resistant state (7,8) and through the basis of insulin resistance mechanisms recent studies consider NAFLD as an early mediator of atherosclerosis (9,10) and an increased cardiovascular risk factor (11).

The aim of the present study was to investigate the prevalence of NAFLD in grade III high and very high cardiovascular additional risk hypertensive patients according to circadian blood pressure (BP) rhythm and to investigate the relationship between insulin sensitivity and NAFLD in essential hypertensive patients according to the circadian blood pressure (BP) rhythm.

MATERIAL AND METHOD

Study population

From November 2005 to December 2009 a prospective study was conducted. The study included consecutive eligible adult hypertensive patients attending at the Departament of Internal Medicine from the Diagnosis and Treatment Center from Cluj-Napoca.

The study included patients of either sex with grade III essential hypertension and additional high and very high global cardiovascular risk. Essential hypertension was defined according to the ESC/ESH 2007 Guideline European Society of Hypertension (12) as office sitting systolic BP (SBP) of ≥180 mmHg and/or office diastolic blood pressure (DBP) ≥110mmHg measured by mercury sphygmomanometer, at rest in a sitting position in at least three separate casual measurements within the last month.

Patients with mild or moderate essential hypertension or suspected secondary hypertension were excluded. Also patients with chronic alcoholism, diabetic mellitus, evidence of cardiovascular, pulmonary, renal, hepatic disease, patients with previous drug induced fatty liver treatment (corticoids, chronic salicylates, tricyclic antidepressants, tamoxifen, tetracyclines, synthetic oestrogens and amiodarone) (13,14) were excluded from the study.

Thirty five hypertensive patients gave their informed consent before taking part in the study, completed the inclusion criteria and were therefore enrolled in the study.

All hypertensive patients underwent 24 hour ambulatory blood pressure monitoring (ABPM) (for systolic and diastolic blood pressure evaluation), blood tests and abdominal ultrasonography.

The ambulatory blood pressure (ABPM) was monitored with ABPM-04, 99/BP411 - Medibase. Before the beginning of ABPM, blood pressure was measured with a mercury sphygmomanometer, with the patient seating for at least 10 minutes.

The arm with higher BP values at sphygmomanometer evaluation was chosen for ABPM. In order to reduce errors during the day all patients were asked to ensure that the arm was always parallel to the trunk when the cuff was inflated. Readings were obtained automatically at 15 minutes interval from 7:00 am to 22:00 pm and 30 minutes interval from 22:00 pm to 7:00 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 four groups: dipper, non-dipper, reverse-dipper, extreme-dipper according the diurnal index (DI) from ABPM monitoring. Dipper patients were defined as 10%≤DI<20%, non-dipper defined as 0≤DI<10%, extreme-dipper defined as DI≥20%, reverse-dipper defined as DI<0 (15).

The diagnosis of fatty liver, was established using the noninvasive method of abdominal ultrasound followed by the exclusion of the secondary causes of hepatic steatosis: a history of another known liver disease, alcohol intake of 30g/day or more for males and 20g/day or more for females, a positive serology for hepatitis B or C virus or ingestion of drugs known to produce hepatic steatosis.

The liver ultrasonography scanning was performed by standard criteria (16,17) by the same investigator, in all patients in the morning , after overnight fasting, using the same equipment (ESAOTE MyLab, with a 3.5-MHz transducer). The presence of liver steatosis was graded semiquantitatively according to a previously reported scale (18): 0 - absent, 1 - mild, 2 - moderate, and 3 - severe steatosis.

In all hypertensive patients who fasted overnight for biochemical and metabolic profile, blood samples were evaluated by standardised routine laboratory techniques.
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. Reference range of values, are 0–40 IU/l for ALT, 0–37 IU/l for AST, 6–20 mIU/ml for insulinaemia, 0–50 IU/l for cGT, 70–170 mg/dl for triglycerides, 60–110 mg/dl for glucose, and up to 200 mg/dl for total cholesterol.

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. (19,20).

Statistical analysis.

Descriptive statistics, including means, SD, ranges and percentages, were used to characterize the study subjects. Statistical significance between groups was assessed by Student's t test in normally distributed for independent samples. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS and Statistica 8 programe.

RESULTS

NAFLD was present in 14 hypertensive patients (40%) with grade III essential hypertention with high and very high additional cardiovascular risk as reported in figure 1.

Figure no. 1. The prevalence of NAFLD in hypertensive patients
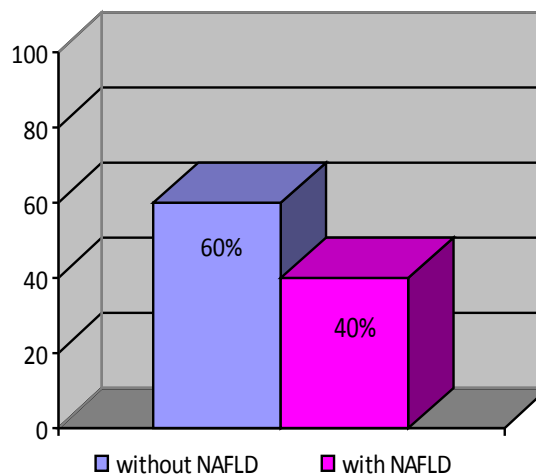
According to diurnal index from ABPM the thirty five hypertensive patients were devided into four groups as following: 48.57% (n=17) patients as dippers, 31.42% (n=11) patients as non-dipper, 11.43% (n=4) pacients as reverse dippers and 8.57% (n=3) patients as extreme dippers.

No statistically significant differences, between the four groups of patients in demographic baseline characteristics (p>0.05) were observed.

Baseline demographic, clinical and laboratory characteristics of the study population are presented in Table 1.

The prevalence of NAFLD was significantly higher in non dipper patients group 54.54% (n=6), reverse dipper hypertensive groups 50% (n=2) and extreme-dipper hypertensive patients 33.33% (n=1) compared to dipper hypertensive patients group 29.41% (n=5)(p<0.05).

The prevalence of liver steatosis grades according to diurnal status of dipper, non dipper, reverse-dipper, extreme dipper was observed as presented in figure 3.

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**Table no. 1. Baseline Demographic and Clinical Characteristics by Blood Pressure circadian rhythm**

Variable	Dippers (n=17)	Nondippers (n=11)	Reverse dippers (n=4)	Extreme dippers (n=3)	p value
Gender: absolute frequency (percentage)					
Male	8 (47.05%)	7 (63.63%)	1(25%)	1(33.33%)	ns
Female	9 (52.95%)	4(36.37%)	3(75%)	2(66.67)	ns
Age: means±SD					
Male (years)	51.6±11.3	53.8±12.22	54.21±12.02	53.87±11.62	ns
Female (years)	50.2±9.78	52.2±10.84	54.66±8.99	52.33±9.79	ns
BMI (kg/m²)	32.42±3.99	35.32±4.55	36.3±7.77	35.5±3.87	ns
Mean 24h SBP (mmHg)	143.5±14.88	143.5±14.75	144.3±17.44	145.8±15.5	ns
Mean 24h DBP (mmHg)	88.7±11.05	86.3±12.06	87.5±12.41	85.3±12.77	ns
Triglycerides (mg/dl)	108.5±33.42	111.5±35.21	110.8±30.77	107.3±32.45	ns
Total cholesterol (mg/dl)	220.3±45.2	205.66±44.31	208.5±41.02	210.8±42.03	ns
HDL cholesterol (mg/dl)	47.5±3.22	46.8±4.04	46.2±3.71	48.3±4.57	ns
ALT (U/l)	19.4±7.77	22.4±8.31	23.9±6.98	24.5±8.87	ns
AST (U/l)	22.8±8.75	20.4±8.53	22.3±7.93	20.6±8.35	ns
GGT (U/l)	23.9±11.1	25.4±12.3	25.5±10.7	20.8±8.33	ns
SD = standard deviation, SBP= systolic blood pressure,DBP= diastolic blood pressure, LDL=low-density lipoprotein, HDL=high-density lipoproteins,ALT=alanine amino transferase, AST=aspartate aminotransferase, GGT= gamma-glutamyl transferase					

Figure no. 2. The prevalence of NAFLD in hypertensive patients
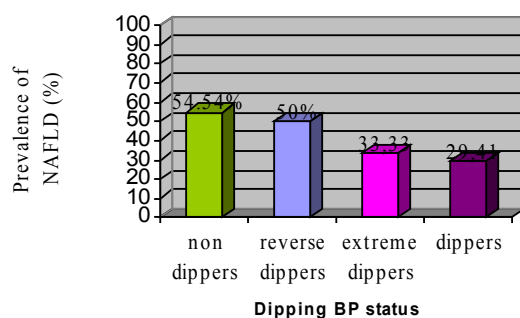
Figure no. 3. The ultrasonographic grades prevalence of NAFLD in hypertensive patients
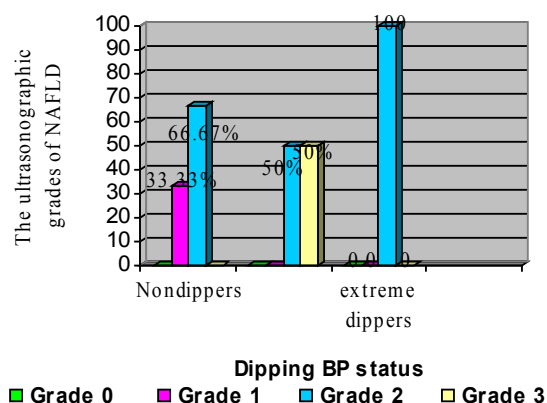
A statistically significantly higher level of plasma insulin was observed in the group of non-dipper when compared to the dipper group of hypertensive patients (86.3±17.9pmol/l vs. 62.2±203pmol/l, p<0.05) in reverse dipper when compared to dipper hypertensive patients (88.3±18.6pmol/l vs.62.2±20.3 pmol/l) in extreme-dippers versus dipper hypertensive patients groups (86.7±16.88pmol/l vs. 62.2±20.3 pmol/l, p<0.05). In the group of non dipper, reverse dipper, extreme-dipper a significantly higher level of HOMA index were observed when compared to the dipper group of hypertensive patients (in non dipper vs. dipper: 3.7±1.03 vs.2.2±0.88, p<0.05), (in reverse dipper vs. dipper 4±0.99 vs. 2.2±0.88,p<0.05) and (in extreme dipper vs. dipper 3.6±0.97 vs.2.2±0.88, p<0.05).

DISCUSSIONS

This study revealed a significantly statistical difference of the NAFLD prevalence, between altered dipping status (non-dipper, reverse-dipper, extreme-dipper) and normal dipping status of hypertensive patients. A higher prevalence of the NAFLD was observed in nondipper hypertensive patients, followed by reverse-dipper and extreme-dipper when compared with dipper hypertensive patients. The liver steatosis grade was more severe in reverse dipper group of hypertensive patients who presented a grade 2 and 3 of NAFLD. All extreme-dipper hypertensive patients presented a grade 2 of disease.

Grade III essential hypertensive patients with altered dipping profile (ND, RD, ED) revealed a statistically significant higher level of plasma insulin when compared to dipper group of hypertensive patients suggesting that insuline resistance could play a role in the tendency of a greater end organe damage in hypertensive patients with an altered circadian rithm (non-dipper, reverse-dipper, extreme-dipper) (21,22).

The association between the nondipper status and insuline resistance, that was observed in the present study has already been demonstrated (23,24).

Altered dipping status (non-dipping, reverse-dipping, extreme-dipping) have been demonstrated in population based studies to correlate with target organe damage, including cardiovascular morbidity and mortality (25-28) progression of preexisting renal disease (29,30) and cerebrovascular disease (31).

Because the altered blood pressure status of hypertension associated both a higher insulin resistance and a higher prevalence of NAFLD brings us to the conclusion that insulin resistance could be the pathogenetic link between the NAFLD and altered blood pressure status. Altered blood pressure status could be a marker of NAFLD in hypertensive patients.

CLINICAL ASPECTS

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