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Paraoxonase and arylesterase activities in untreated dipper and non-dipper hypertensive patients

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Abstract

Objectives: Paraoxonase, a high density lipoprotein (HDL) associated enzyme, was shown to be reduced in patients with cardiovascular diseases. We aimed to examine serum paraoxonase and arylesterase activities, and oxidative stress markers such as lipid hydroperoxide (LOOH) and total antioxidant status (TAS) in dipper and non-dipper hypertensive patients.

Design and methods: Forty-six non-dipper hypertensives (NDH group), 40 dipper hypertensives (DH group) and 28 healthy control subjects were included in the study. Clinical and echocardiographic assessment and ambulatory blood pressure monitoring were performed in all subjects. Serum paraoxonase and arylesterase activities were measured spectrophotometrically. LOOH levels were measured by ferrous oxidation with xylenol orange assay. TAS was determined by using an automated measurement method.

Results: Paraoxonase and arylesterase activities and TAS levels were significantly lower in patients with NDH compared to both DH and control groups ($p<0.001$, for both). Also, LOOH levels were found at high level in patients with NDH compared to control and DH groups. In NDH group, both paraoxonase and arylesterase activities were independently correlated with LDL cholesterol, TAS and LOOH levels. In DH group, both paraoxonase and arylesterase activities were independently correlated with HDL cholesterol and LOOH levels.

Conclusions: Reduced paraoxonase and arylesterase activities in NDH might indicate increased oxidative stress, which plays an important role in the development of cardiovascular diseases. Low serum activities of paraoxonase and arylesterase might be considered as prospective prognostic markers of the development of cardiovascular diseases in dipper and non-dipper hypertensive patients.

Keywords: Antioxidant; Arylesterase; Dipper; High density lipoprotein; Hypertension; Lipid hydroperoxide; Non-dipper; Paraoxonase; Total antioxidant status

Introduction

Ambulatory blood pressure monitoring (ABPM) has shown that blood pressure (BP) is highest during the day and lowest during the night in both normotensives and hypertensives [1]. Patients with essential hypertension (HT) are divided into two groups based on circadian blood pressure patterns: dippers and non-dippers [2]. Dippers manifest a reduction of blood pressure during the night, and non-dippers exhibit persistently elevated blood pressure throughout the 24-hour period. Compared with dippers, non-dippers have higher left ventricular mass [3] and higher cardiovascular morbidity [4]. Non-dipper hypertensives have greater vascular damage in the carotid arteries and higher carotid intima media thickness as well [5,6].

Paraoxonase 1 (PON1) is an enzyme with three activities, which are paraoxonase, arylesterase and diazoxonase [7]. PON1 is a calcium-dependent esterase consisted of 354 amino acids with a molecular mass of approximately 45 kDa, and it is exclusively located on high density lipoprotein (HDL) in serum [8]. PON1 was shown to protect both low density lipoproteins (LDL) and HDL against lipid peroxidation [9,10]. Human serum PON1 activity was shown to be inversely related to the risk of cardiovascular diseases [11], and low PON1 activities

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were observed in atherosclerotic, hypercholesterolemic, hypertensive and diabetic patients [12–15].

PON1 activity was shown at low level in patients with both sustained HT and white coat HT [14]. However, paraoxonase and arylesterase activities were not individually investigated in non-dipper HT (NDH) and dipper HT (DH) groups.

In theory, increased oxidative stress can lead to reduced PON1 activity [16,17]. Since oxidative stress is increased in NDH patients compared with DH patients [18,19], we hypothesized that paraoxonase and arylesterase activities of non-dipper patients are lower than dippers. Therefore, in this study, we aimed to investigate paraoxonase, arylesterase activities, and total antioxidant status (TAS) and lipid hydroperoxide (LOOH) levels in DH and NDH groups.

Materials and methods

Subjects

The overall study population was consisted of 86 consecutive patients: 46 subjects with NDH (NDH group), and 40 patients with DH (DH group). Twenty-eight healthy volunteers were also included in the study as controls (control group). The study group included newly diagnosed patients with HT, without previous antihypertensive medication. Institutional ethics committee approved the study and written informed consent for participation in the study was obtained from all individuals.

Healthy control subjects, from the nonmedical staff of our hospital or their relatives, with BP < 140/90 mmHg in multiple measurements and with same age and gender range with hypertensive patients, were also enrolled in the study. For inclusion into the control group, subjects had to have no known coronary risk factors and cardiac symptoms, normal electrocardiographic and echocardiographic examinations.

Exclusion criteria

Exclusion criteria for entry in the study were smoking, presence of diabetes mellitus, neoplastic diseases, inflammatory diseases such as infections and autoimmune disorders, hypercholesterolemia, hypertriglyceridemia, antihypertensive and lipid-lowering drug use (present or past), antioxidant substance use, known secondary HT, chronic renal failure, cerebrovascular disease, ischemic heart disease, congestive heart failure, and gastrointestinal and liver disease. Cases having ST segment or T wave changes specific for myocardial ischemia, Q waves, and incidental left bundle branch block on ECG were also excluded from the study. Study group was enrolled from the same geographical area (Sanliurfa, Turkey) with similar dietary pattern which was evaluated by a well-trained dietician.

Blood pressure measurement and ambulatory blood pressure monitoring

Blood pressure was measured by using a mechanical sphygmomanometer in office setting. Systolic (SBP) and diastolic blood pressures (DBP) were taken as the first and fifth phases of Korotkoff sounds.

Ambulatory BP device (Tracker NIBP2, Delmar Reynolds, Hertford, UK) was applied to all subjects included into study. Appropriate cuff size was chosen for each subject. All subjects wore an ABPM device for a single 24-hour period. The device was programmed to inflate and record BP at pre-specified intervals (every 15 min during daytime hours and every 30 min during nighttime hours), which provided approximately 80 BP recordings during the 24-hour period. The display of ABPM was inactivated so that viewing each BP reading did not distract subjects. As for analysis of data reports, reports generated from a session of ABPM contained BP recordings for the entire 24 h, heart rate, mean arterial pressure, and BP load as well as summary statistics for the overall 24-hour, daytime and nighttime period. When the readings exceeded at least 80% of the total readings programmed for the testing period, the recording was considered as valid and satisfactory.

Diagnosis of hypertension

In each subject, BP was measured in at least three separate days after 15 min of comfortable sitting and averaged. Then, each subject undertook 24-hour ABPM. Individuals who had systolic BP $\geq$140 mmHg and/or a diastolic BP $\geq$90 mmHg in office setting, and in ABPM, an average 24-hour systolic BP >130 mmHg and/or diastolic BP >80 mmHg, an average daytime systolic BP > 135 mmHg and/or diastolic BP >85 mmHg or an average nighttime systolic BP > 125 mmHg and/or diastolic BP > 75 mmHg were diagnosed as hypertensive [20]. In addition, the subjects who had reduction in BP< 10% change from daytime to nighttime period were defined as NDH, and the subjects who had reduction in BP $\geq$10% change from daytime to nighttime period were considered as DH [2].

Echocardiography

Echocardiographic examination was performed in all study subjects by using a commercially available system (Aloka Prosound SSD 5000 machine with a 3-MHz transducer). Measurements were made during normal breathing at end-expiration. Left atrial diameter, LV end-systolic (LVSd) and end-diastolic diameters (LVDd), end-diastolic interventricular septal thickness (IVSth), and end-diastolic left ventricular posterior wall thickness (PWth) were measured. LV ejection fraction (EF) was determined by Teichholz method [21].

Left ventricular mass (LVM) was calculated using the Devereux formula: $LVM = (1.04[(LVDd + IVSth + PWth)^3 - (LVDd)^3] - 13.6)$ [22]. Then, LV mass index (LVMI) was obtained by the following formula: LVM / body surface area.

Blood sample collection

Blood samples were obtained following an overnight fasting state. Samples were withdrawn from a cubital vein into blood tubes and separated from the cells by centrifugation at 3000 rpm