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# CIRCADIAN RHYTHM OF BLOOD PRESSURE AND URINARY SODIUM EXCRETION IN PATIENTS WITH METABOLIC SYNDROME

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# არტერიული წნევის და ნატრიუმის ექსკრეციის ცირკადული რიტმი მეტაბოლური სინდრომის მქონე პაციენტებში

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## რეზიუმე

მარილმგრძნობიარე ჰიპერტენზია ცნობილია როგორც ყველაზე მძიმე, მკურნალობის მიმართ რეზისტენტული და ფატალური გართულებების მაღალი სიხშირის მქონე ფორმა. ამ ტიპის ჰიპერტენზია უფრო ხშირია მეტაბოლური სინდრომის მქონე პაციენტებში. გაუკუღმართებული ცირკადული რიტმი ე.წ. „non-dippers" („არამყვინთავები") ფენომენი სავარაუდოდ წარმოადგენს კარდიოვასკულური ავადობისა და სიკვდილობის მნიშვნელოვან რისკის ფაქტორს. კვლევის მიზანს წარმოადგენდა არტერიული წნევის ცირკადულ რიტმს, მარილმგრნობიარე ჰიპერტენზიას და მეტაბოლურ სინდრომს შორის ურთიერთკავშირის დადგენა. ჩვენ შევისწავლეთ ესენციური ჰიპერტენზიის I სტადიის (JNC VIII), საშუალო ასაკის 92 ეთნიკურად ქართველი პაციენტი. ყველა პაციენტს ჩაუტარდა ანთროპომეტრია, არტერიული წნევის მონიტორინგი და განესაზღვრა შარდში ნატრიუმის 24 საათიანი ექსკრეცია. ყველა პაციენტს ჩაუტარდა მარილმგრძნობიარობის ტესტი. არტერიული წნევის ცირკადული რიტმი შესწავლილ იქნა წნევის 24 საათიანი მონიტორინგის საფუძველზე. ნატრიუმის თირკმლებით გამოყოფის ცირკადული რიტმი შეფასდა დღის და ღამის ნატრიურეზის შედარებით და მათი თანაფარდობის გამოთვლით. მეტაბოლური სინდრომის დიაგნოზი დაისვა დიაბეტის საერთაშორისო ფედერაციის (IDF9) რეკომენდაციების საფუძველზე. ჩვენმა შედეგებმა გამოავლინა ეთნიკურად ქართველ ჰიპერტენზიით დაავადებულებში სუფრის მარილის მოხმარების მაღალი მაჩვენებელი. ასევე აღმოჩნდა, რომ მარილმგრძნობიარე ჰიპერტენზია ასოცირებულია არტერიული წნევის „არამყვინთავ" ტიპთან და უფრო ხშირია მეტაბოლური სინდრომის მქონე პაციენტებში. ვვარაუდობთ, რომ ნატრიუმის შეზღუდვამ შეიძლება ნაწილობრივ აღადგინოს არტერიული წნევის ნორმალური ცირკადული რიტმი. ნატრიუმის მიღების შემცირება შეიძლება იყოს განსაკუთრებით მნიშვნელოვანი კომპონენტი არტერიული წნევის შესამცირებლად პაციენტებში მეტაბოლური სინდრომის რისკ-ფაქტორებით.

**Introduction.** The metabolic syndrome is characterized by the simultaneous occurrence of metabolic abnormalities including obesity, glucose intolerance, dyslipidemia, and hypertension that result in a marked increase in cardiovascular morbidity and mortality [9]. High blood pressure is a classical feature of the metabolic syndrome (MS), and it has been reported that the metabolic syndrome is present in up to one third of hypertensive patients [17]. The majority of these hypertensive patients suffer from salt-sensitive hypertension. Salt-sensitive essential hypertension is a subset of hypertension characterized by significant blood pressure response to change in dietary salt intake [13]. Cardiovascular events occur more frequently in sodium-sensitive patients with essential hypertension. This type of hypertension is none as most severe, treatment resistance course, with high incidence of fatal complications. Recently, sodium sensitivity was shown to be a cardiovascular risk factor independently of other classic factors [1]. Salt sensitivity of blood pressure, like hypertension, is more prevalent among metabolic syndrome patients [15].

The circadian system is the major regulator of almost every aspect of human health and metabolism. Like other physiological parameters, arterial pressure is characterized by certain circadian rhythm: in healthy subjects blood pressure decreases by 10-20% at night [11]. Substantial part of

hypertensive patients does not show normal nighttime decrease in arterial pressure (so called "non-dippers"). Lack of nocturnal decline in blood pressure, in the form of nocturnal hypertension or 'non-dipping', carries a significant risk of cardiovascular morbidity and mortality which largely exceeds that of office-based hypertension [18]. Moreover, epidemiological data reveal a robust morning increase in adverse CV events, including stroke [14], myocardial infarction, serious ventricular arrhythmias and sudden cardiac death [8,16]. Morning hypertension is elevated in metabolic syndrome patients, probably because of an indirect effect of altered sleep architecture [7]. The prevalence of non-dipping varies between patient populations but is estimated to occur in approximately 50% of hypertensives and more than 80% in at risk salt-sensitive hypertensives [19]. Similar inverted circadian rhythm in "non-dipper" hypertensives was shown regarding renal sodium excretion [4]. Although underlying mechanisms are poorly understood, there is a strong concordance between salt-sensitivity, inverted circadian rhythms of blood pressure and sodium excretion in salt-sensitive hypertensive subjects. Since insulin resistance is thought to be the underlying mechanism for the metabolic syndrome, it is likely that individuals with the metabolic syndrome are more sensitive to a dietary sodium intervention. However, the association between the metabolic syndrome and salt-sensitivity of BP has not been well established [2].

According to some authors, the blood pressure failed to fall during the night in patients with sodium-sensitive hypertension and that sodium restriction shifted the circadian rhythm of the blood pressure from nondipper to dipper in patients with sodium-sensitive hypertension[20]. Some studies confirm that non-dipping hypertension has been associated with insulin resistance, obesity, the Metabolic Syndrome and type 2 diabetes [10] and the presence of the metabolic syndrome may predict the prevalence of a non-dipping (or even inverse dipping) blood pressure phenotype [12].

Thus, the metabolic syndrome is characterized by the aggregation of several risk factors for cardiovascular diseases and type II diabetes. Along with glucose intolerance and dyslipidemias, hypertension and central obesity are important components of the metabolic syndrome. Both hypertension and obesity are associated with salt sensitivity of blood pressure [5,22]. However, the number of human studies reporting the correlation between the metabolic syndrome and the salt sensitivity of blood pressure is still small.

The aim of the study was to determine the relationship between the circadian rhythm of blood pressure, salt-sensitive hypertension and metabolic syndrome.

**Methods**. The study enrolled a total of 92 ethnically Georgian middle-aged (38-62 year old) patients of stage I essential hypertension (JNC VIII). 54 of them where females and 38 males. The administration of any antihypertensive drugs was discontinued at least 2 weeks before the study. Patients were excluded if they had a history of cardiac disease, stroke, hepatic disease, renal disease or diabetes mellitus. No patient showed any evidence of a detectable secondary cause for hypertension. Anthropometry, blood pressure monitoring, and 24-hour urinary sodium excretion were performed. All subjects were volunteers (signed informed consent form) and non-smokers. They were tested for salt-sensitivity: during the first week subjects were on high sodium diet (200 mmol/d per 70 kg) both by adding 100 mmol directly to the food and by administering 100 mmol in capsules ingested 3 times daily with meals. Next week subjects were placed on a low-salt diet aimed at a maximum intake of 40 mmol sodium per day. Compliance with the diet was confirmed by measurement of 24-hour urinary sodium excretion during the last 2 days of both weeks (24-h urinary sodium excretion was used to determine actual levels of salt intake and compliance with sodium diets). Salt sensitivity was assessed by the difference of mean arterial pressure (MAP) on high (200 mmol/day) vs. low (40 mmol/day) salt diet. Salt-sensitivity was considered when difference between MAP exceeded 3 mm Hg.

Blood pressure circadian rhythm was assessed by 24-hour ambulatory blood pressure monitoring with 1-hour intervals. Daytime (from 8:00 AM until 23:00 PM) and night time (from 23:00 PM till 8 AM) mean MAP ratio will be estimated.

Circadian rhythm of renal sodium excretion was assessed by comparison of daytime (from 8:00 AM until 23:00 PM) and nocturnal (from 23:00 PM up to 8:00 AM) natriuresis and calculating their ratio.

MS was classified as recommended by the International Diabetes Federation - IDF9, characterized by abdominal waist circumference ≥ 90 cm in men and ≥ 80 cm in women (at least two of the following

criteria was considered for MS: triglycerides ≥150 mg/dl, HDL-cholesterol <40 for men <50 for women, systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg, and fasting glucose ≥ 100mg/dl). The presence of diabetes mellitus did not exclude the diagnosis of MS. The association of three or more abnormal factors confirmed the diagnosis of MS.

Data obtained are presented as mean ± SEM. The effect of dietary Na intake on measured variables was determined by Student's *t* test and ANOVA. Correlation coefficient was calculated using Pearson method. P<0.05 was considered significant.

**Results and discussion.** Our results have shown that virtually all hypertensive patients consumed very high amount of sodium chloride in excess of 300 mmol sodium. Therefore, we skipped high-salt diet and placed hypertensive subjects on one-week low-salt diet to determine the salt sensitivity.

Salt sensitivity (when difference between MAP exceeded 3 mm Hg) was detected in 57 (62%) of hypertensive patients. MS was detected in 33 (36%) of all hypertensive patients. 25 (76%) of them were salt-sensitive.

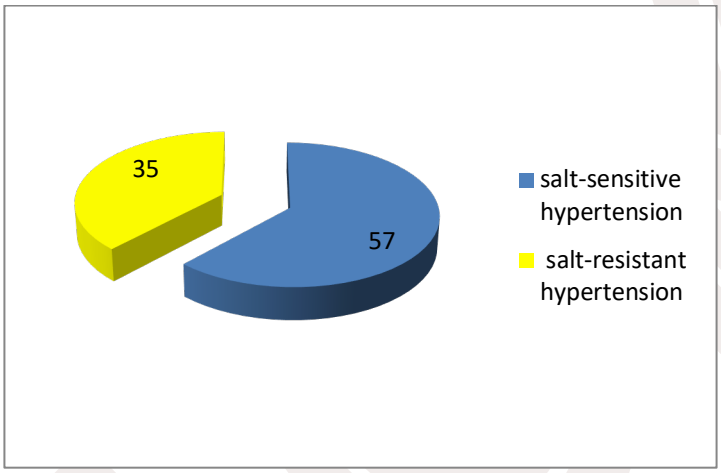


**Fig.1.** Salt sensitivity in hypertensive patients

Our study, as well as some other studies, confirms that salt sensitive hypertension is more prevalent among metabolic syndrome patients [15].

We found that the blood pressure failed to fall during the nighttime in SS patients with essential hypertension. The prevalence of a non-dipper pattern of 24-hour ABP was significantly higher in SS patients than in SR patients. In the high salt diet stage¬the nocturnal declines in both SBP and DBP were detected only in the salt-resistant group (P < 0.01). During the high salt diet, in salt sensitive hypertension, we found elevation of MAP (P< 0.05). The night-time elevation of MAP in the MS group was significantly higher than that in the non-MS group (P<0.01). Salt restriction produced greater BP lowering in MS. In this group both the systolic and diastolic blood pressures failed to fall during night-time under a high-sodium diet but not under a low sodium diet. (Tab.1)

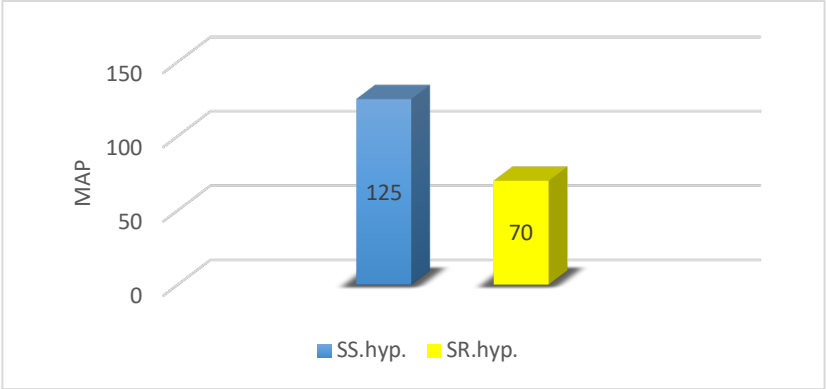


**Fig.2.** Nocturnal declines of MAP in the high salt diet stage

| | High salt diet stage | | Low salt diet stage | |
|---|---|---|---|---|
| | SS. hyp. non MS n=32 | SS. hyp. MS n=25 | SS. hyp. non MS n=32 | SS. hyp. MS n=25 |
| Daytime | | | | |
| SBP mm Hg | 149±9 | 156±8 | 138±8 | 147±7 |
| DBP mm Hg | 93±6 | 96±6 | 89±4 | 92±5 |
| Nighttime | | | | |
| SBP mm Hg | 145±11 | 154±9 | 134±11 | 140±6 |
| DBP mm Hg | 94±5 | 95±5 | 86±6 | 89±4 |

**Tab.1.** The effect of salt intake on the circadian rhythm of blood pressure in SS hypertensives with and without metabolic syndrome

Like some other authors [15], we can assume that during sodium restriction the normal circadian pattern of blood pressure was partially restored, suggesting that the non-dipping phenomenon observed in metabolic syndrome patients is partly caused by increased salt sensitivity of blood pressure.

It has been known that in healthy people, sodium excretion reaches a maximum during the day and a minimum at night during sleep [3]. According to our results in non-dipper hypertensives, placed on the high salt diet, urinary sodium excretion was significantly higher than in dippers, with top levels in MS group ($P<0.001$). This difference was not significant after salt restriction. ($p>0.05$). Therefore, we can assume that patients with sodium sensitive type of hypertension exhibited the lack of nocturnal fall in blood pressure with enhanced natriuresis during night, and in patients with salt-sensitive BP, the circadian rhythms of both BP and urinary sodium excretion were all disturbed. The obtained results coincide with the data of some other studies [6].

On the basis of our research, we can suggest that metabolic syndrome enhances blood pressure response to sodium intake and metabolic syndrome has been more frequently associated with nocturnal non-dipping of blood pressure compared to patients without the syndrome. Salt restriction restored these rhythms from non-dipper to dipper patterns. Normalization of blood pressure circadian profile might be a novel therapeutic goal in the treatment of resistant forms of essential hypertension. Reduction in sodium intake could be particularly important component in reducing blood pressure in patients with multiple risk factors for metabolic syndrome.

**Conclusions:**

1. Prevalence of salt-sensitive hypertension associated with high sodium intake has been detected in Georgian hypertensive subjects.
2. Our findings showed high incidence of salt-sensitive hypertension among patients with metabolic syndrome.
3. Salt-sensitive hypertension is associated with non-dipping pattern of BP (the circadian rhythms of both BP and urinary sodium excretion were all disturbed) and is more common in MS. Salt restriction produced greater BP lowering in patients with MS. Sodium restriction can partially restore the normal circadian pattern of blood pressure. Reduction in sodium intake could be especially important component in reducing blood pressure in patients with risk factors for metabolic syndrome.

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# CIRCADIAN RHYTHM OF BLOOD PRESSURE AND URINARY SODIUM EXCRETION IN PATIENTS WITH METABOLIC SYNDROME

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## SUMMARY

Salt-sensitive hypertension is known as most severe, treatment resistance course, with high incidence of fatal complications. This type of hypertension is more prevalent among metabolic syndrome (MS) patients. Inverted circadian rhythm so called “non-dipper" pattern carries a significant risk of cardiovascular morbidity and mortality. The aim of the study was to determine the relationship between the circadian rhythm of blood pressure, salt-sensitive hypertension and MS. We investigated 92 ethnically Georgian middle-aged patients of stage I essential hypertension (JNC VIII). Anthropometry, blood pressure monitoring, and 24 hr urinary sodium excretion were performed. All subjects were tested for salt-sensitivity. Blood pressure circadian rhythm was assessed by 24 hr ambulatory blood pressure monitoring with 1-hour intervals. Circadian rhythm of renal sodium excretion was assessed by comparison of daytime and nocturnal natriuresis and calculating their ratio. MS was classified as recommended by the International Diabetes Federation - IDF9. Our results have shown that virtually all hypertensive patients of Georgian ethnicity consumed very high amount of sodium chloride. The study revealed high incidence of salt-sensitive hypertension among patients with metabolic syndrome. High salt intake attenuated the circadian rhythm of blood pressure in SS patients; salt-sensitive hypertension is associate with non-dipping pattern of BP and is more common MS. Based on our research we assume that sodium restriction can partially re-establish the normal circadian pattern of blood pressure. Reduction in sodium intake could be an especially important component in reducing blood pressure in patients with risk factors for metabolic syndrome.

**Keywords:** metabolic syndrome; salt-sensitivity of blood pressure; salt-sensitive hypertension, circadian rhythm, renal sodium excretion.