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Creatine kinase increases in adults with uncontrolled hypertension

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ABSTRACT

BACKGROUND
A substantial proportion of uncomplicated, treated primary hypertensive patients have failure of hypertension treatment. The enzyme creatine kinase (CK) regenerates adenosine triphosphate in striated muscle, myocardium and blood vessels. Several studies showed that serum CK was found to be a predictor of blood pressure in the general population. High tissue CK precedes hypertension in populations with high hypertension risk. The hypothesis of this study was to examine that CK increases in uncontrolled hypertension subjects.

METHODS
A cross-sectional study from November until December 2013 was conducted in 82 adult hypertensive patients with mean age of 61.96 ± 10.76 years. Patients' histories were taken and their blood pressure and body mass index were measured. Serum was analyzed for serum CK, random blood glucose and lipid profile. Independent t test and Mann Whitney was used to assess differences in mean CK and other variables between hypertension categories. Chi-square test was also used to assess differences between CK tertiles and status of hypertension.

RESULTS
There was a significant difference in mean CK between controlled hypertension (81.83 ± 29.70 U/L) and uncontrolled hypertension groups (132.17 ± 55.91 U/L). The number of subjects in the high CK tertile (>109.33 U/L) was significantly higher in the uncontrolled hypertension group (81.5%), compared with the controlled hypertension group (18.5%) (p=0.0001).

CONCLUSION
Creatine kinase level increases in adults with uncontrolled hypertension. Measuring serum levels of creatine kinase may help doctors to spot patients whose hypertension will be difficult to treat.

Keywords: Uncontrolled hypertension, creatinine kinase, adult

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Kreatin kinase meningkat pada subjek dewasa dengan hipertensi tidak terkontrol

ABSTRAK

LATAR BELAKANG

Dijumpai banyak pasien hipertensi primer yang berobat dan tanpa komplikasi mengalami kegagalan pengobatan hipertensi. Enzim kreatin kinase (CK) membentuk adenosine triphosphate *pada otot rangka, jantung dan pembuluh darah. Beberapa penelitian menunjukkan CK serum merupakan prediktor tekanan darah pada populasi umum. Kreatin kinase jaringan yang tinggi mencetuskan hipertensi dan dijumpai pada populasi resiko tinggi hipertensi. Hipotesis penelitian ini adalah untuk menguji bahwa CK meningkat pada subjek dengan hipertensi yang tidak terkontrol.*

METODE

Penelitian potong lintang dilakukan antara bulan November hingga Desember 2013 pada 82 pasien hipertensi dewasa usia 61,96 ± 10,76 tahun. Anamnesis, pengukuran tekanan darah dan indeks massa tubuh dikumpulkan dari semua subjek. Serum diambil dan dilakukan pemeriksaan CK, kadar gula darah sewaktu dan profil lipid. Uji t-independen dan Mann-Whitney *menilai perbedaan rerata kadar CK dan variabel lainnya terhadap kategori hipertensi. Uji* chi-square *juga digunakan untuk menilai perbedaan tertile CK dengan status hipertensi.*

HASIL

Jumlah subjek dengan tertil tinggi lebih besar secara bermakna pada kelompok hipertensi tidak terkontrol (81,5%) dibandingkn kelompok hipertensi terkontrol (18,5%) (p=0,0001). Terdapat perbedaan rata-rata CK yang bermakna antara kelompok hipertensi terkontrol (81,83 ± 29,70 U/L) dan hipertensi tidak terkontrol (132,7 ± 55,91 U/L) (p=0,000).

KESIMPULAN

Kadar CK meningkat pada dewasa dengan hipertensi tidak terkontrol. Pemeriksaan kadar CK sangat diperlukan pada subjek dengan hipertensi yang sulit dikendalikan.

Kata kunci: *Tekanan darah, hipertensi, kreatin kinase, dewasa*

INTRODUCTION

Hypertension is a leading risk factor for heart disease, stroke, and kidney failure. Because hypertension is the most common primary diagnosis in the United States, it is not suprising that blood pressure measurement is one of the most common reasons for a visit to the doctor‘s office, and antihypertensive medications are among the most commonly written prescriptions.[1] Blood pressure was controlled only in an estimated 50.1% of all patients with hypertension in The National Health and Nutrition Examination Survey (NHANES) 2007-2008, with most of the improvement since 1988 occurring after 1999-2000. While control of hypertension is on the rise, prevalence of total hypertension continues to increase.[2,3] A substantial proportion of treated hypertensive patients do not achieve blood

pressure control. In general, these patients tend to be obese, older, or have diabetes and end-organ damage. However, many patients have uncomplicated, primary hypertension, and it is not well explained why these patients respond poorly to drug therapy, even when patient's adherence and physician's therapeutic inertia are taken into account.[4-6]

The enzyme creatine kinase (CK) is thought to enhance pressor responses through rapid regeneration of adenosine triphosphate (ATP), as the enzyme catalyzes the reversible transfer of the high-energy phosphate moiety (P) between creatine and adenosine diphosphate (ADP). The rate of transfer of the phosphoryl group by CK is greater than the maximum rate of ATP generation by oxidative phosphorylation and glycolysis together, ensuring rapid resynthesis of ATP. Adenosine triphosphate synthesized by CK is preferentially used to fuel highly energy-demanding processes such as sodium retention, cardiovascular contractility, as well as remodeling of arteries.[7]

A study by Brewster et al.[8] showed that serum CK was a main predictor of blood pressure in the general population, independent of age, sex, BMI, or ethnicity, with a crude systolic blood pressure (BP) increase of 14 mmHg per log CK increase, without evidence of muscle damage. A study by Oudman et al.[9] showed that high tissue CK precedes hypertension and anti-hypertensive therapy lowers high tissue CK in animal models, whereas incubation of human resistance arteries with a CK inhibitor reduces vascular contractility. Another study by Brewster et al.[10] showed that tissue CK is high in population subgroups with high hypertension risk, including in skeletal, cardiac, and vascular muscle.

On the basis of the abovementioned information, considering the high proportion of uncontrolled hypertensive patients and the role of CK in hypertension, we tested the hypothesis that creatinine kinase increases in uncontrolled hypertension among subjects taking anti-hypertensive medications.

METHODS

Research design

A cross-sectional study was conducted at the Department of Internal Medicine of H. Adam Malik Hospital and dr. Pirngadi Hospital, Medan, from November 2013 to December 2013.

Research subjects

The study population comprised hypertensive patients using anti-hypertensive medications. The inclusion criteria of the subjects were males or females ≥18 years of age and taking anti-hypertension drugs for at least 1 month. The exclusion criteria were neuromuscular disease, renal impairment with glomerular filtration rate (GFR) <60 ml/ minute/ 1.73 m^2, and use of statins. The subjects were divided into the controlled and uncontrolled hypertension groups. The controlled hypertension group comprised subjects on anti-hypertensive drugs for more than 1 month with systolic blood pressure (BP) of <140 mmHg (<130 mmHg for subjects with diabetes) and diastolic BP of <90 mmHg (<80 mmHg with diabetes). The uncontrolled hypertension group consisted of subjects on anti-hypertensive drugs for more than 1 month with systolic BP of ≥140 mmHg (≥130 mmHg with diabetes) and/or diastolic BP of ≥90 mmHg (≥80 mmHg with diabetes).[11] The study subjects were selected by consecutive non-random sampling. We used the sample size calculation method for comparing two independent proportions.[12] To calculate the sample size, we used a previous study by Oudman et al.[9] who reported a proportion of hypertension of approximately 0.268 in the low CK population group. The calculated sample size per group was 41, which was estimated to be adequate to detect a 30% difference between the two groups using a two-tailed test, an alpha of 0.05 and power of 80%.

Data collection

All study subjects were interviewed using a questionnaire for age, gender, history of

diabetes, duration of hypertension, use of anti-hypertensive drugs, and levels of medication adherence. The latter was assessed with the Morisky Medication Adherence Scale-8 of 8 questions, in which three levels of adherence were considered (low: scores of 0 to <6; medium: 6 to <8; high: 8).[13] Subjects were measured for height, weight, and body mass index (BMI). The blood pressure was measured in a quiet room with the participant seated. An appropriately adjusted cuff size was used on the non-dominant arm, which was supported at heart level and the blood pressure was calculated as the mean of the first two consecutive readings, with a 15-minute difference in measurement.

Laboratory analysis

Laboratory studies included serum CK, random blood glucose, lipid profile [total cholesterol, low density lipoprotein (LDL) cholesterol, and high density lipoprotein (HDL) cholesterol] measured with the COBAS automated analyzer.

Table 1. Comparison of demographic, clinical and laboratory characteristics of study population

Characteristic	Controlled hypertension (n=41)	Uncontrolled hypertension (n=41)	p value
Gender			
Female	31 (64.6)	17 (35.4)	0.002[a]
Male	10 (29.4)	24 (70.6)	
Age (years)	61.49 ± 12.42	62.24 ± 8.79	0.930[b]
History of diabetes			
Yes	4 (28.6)	10 (71.4)	0.078[a]
No	37 (54.4)	31 (45.6)	
Duration of hypertension (years)	7.41 (5.91)	8.62 (6.86)	0.468[b]
Number of anti-hypertensives used			
1	10 (76.9)	3 (23.1)	0.015[a]
2	30 (50.0)	30 (50.0)	
3	1 (11.1)	8 (88.9)	
Anti-hypertensive drug categories			
ARB	8 (80.0)	2 (20.0)	0.181[a]
CCB	2 (66.7)	1 (33.3)	
ARB + Beta blocker	2 (66.7)	1 (2.4)	
ARB + CCB	24 (49.0)	25 (51.0)	
ARB + Diuretic	1 (100.0)	0 (0.0)	
ACE inhibitor + Diuretic	1 (33.3)	2 (66.7)	
ACE inhibitor + CCB	2 (50.0)	2 (50.0)	
ARB + CCB + Diuretic	0 (0.0)	5 (100.0)	
ARB + CCB + Beta blocker	1 (50.0)	1 (50.0)	
ACE inhibitor + CCB + Diuretic	0 (0.0)	2 (100.0)	
Medication adherence			
Low	3 (42.8)	4 (57.2)	0.538[a]
Medium	21 (56.8)	16 (43.2)	
High	17 (44.7)	21 (55.3)	
BMI (kg/m^2)	27.46 ± 3.95	27.20 ± 3.47	0.751[c]
CK (U/L)	81.83 ± 29.70	132.17 ± 55.91	0.0001[b]
Blood glucose (mg/dL)	117.88 ± 72.70	127.66 ± 64.30	0.174[b]
Total cholesterol (mg/dL)	194.02 ± 40.52	187.51 ± 37.68	0.663[b]
LDL (mg/dL)	121.07 ± 32.11	119.17 ± 33.21	0.795[b]
HDL (mg/dL)	44.17 ± 12.08	41.02 ± 9.36	0.191[c]

[a]Chi square; [b] Mann Whitney; [c] independent t test; *Values represent mean ± SD, and numbers (%)

ACE inhibitor= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; BMI= body mass index; CCB= calcium channel blocker; CK= creatine kinase; HDL= high density lipoprotein; LDL= low density lipoprotein

Table 2. Creatine kinase levels in controlled and uncontrolled hypertension groups

	Controlled hypertension (n,%)	Uncontrolled hypertension (n,%)	p value
Creatine Kinase (U/L)			
< 78	22 (84.6)	4 (15.4)	0.0001
78 – 109.33	14 (48.3)	15 (51.7)	
> 109.33	5 (18.5)	22 (81.5)	

Statistical analysis

Kolmogorov-Smirnov normality test was used to assess normal distribution of the data. The independent t-test was used to establish differences in mean CK and other variables between hypertension categories for normally distributed data, and the Mann-Whitney test for non-normally distributed data. The chi-square test was used to assess differences between CK tertiles and status of hypertension. Statistical analyses were performed with the SPSS statistical package for Windows, version 17.0, and a p-value of <0.05 was considered statistically significant.

Ethical clearance

The study protocol was approved by the Health Research Ethical Committee, Faculty of Medicine, University of Sumatera Utara. All study subjects signed written informed consent after having been informed about the aims and benefits of the study.

RESULTS

During the study period 41 study subjects for each group were obtained. By using the Kolmogorov Smirnov test, we found that the data for age, duration of hypertension, CK level, random blood glucose, total cholesterol, and LDL cholesterol were non-normally distributed, while BMI and HDL cholesterol were normally distributed.

Using the chi-square test, based on the status of hypertension categories, we found a significant difference for gender (p=0.002) and number of anti-hypertensives used (p=0.015) versus status of hypertension. The Mann Whitney test showed a significant difference in mean CK between controlled and uncontrolled hypertension groups (p=0.0001) (Table 1).

By using the chi square test, we found significant differences between CK tertiles with status of hypertension. The number of subjects in the high CK tertile (>109.33 U/L) was significantly higher (81.5%) in the uncontrolled hypertension group, compared with the controlled hypertension group (18.5%) (p=0.0001) (Table 2).

DISCUSSION

In this study involving 82 subjects we found that CK level increases significantly in subjects with uncontrolled hypertension. A similar result was found by Oudman et al.[9] in that elevated levels of CK increase the incidence risk of hypertension and that subjects with uncontrolled hypertension have higher CK levels compared with normotensive subjects and those with controlled hypertension.

In one of their studies, Brewster et al.[14] found that subjects with idiopathic hyperCKemia showed greater hypertension risk than controls. A contrary result from the study by Johnsen et al.[15] did not find differences in CK levels between those with controlled and uncontrolled hypertension; however, the study objective of these investigators was to analyze associations between CK levels and blood pressure in a normal population, not in a hypertensive population.

In the study by Brewster et al.[8] it was found that serum CK activity was independently

associated with blood pressure in a multiethnic population. A linear regression analysis found an increase in systolic BP and diastolic BP, respectively, of 8.0 mmHg (95% CI 3.3-12.7) and 4.7 mmHg (95% CI 1.9-7.5) per log CK increase after adjustment for age, sex, BMI, and ethnicity. The study by Johnsen et al.[15] showed similar results, i.e. that serum CK activity in a Caucasian normal population was independently associated with blood pressure, where a one unit increase in log CK was associated with a 3.3 mmHg (95% CI 1.4-5.2) increase in systolic BP and a 1.3 mmHg (95% CI 0.3-2.3) increase in diastolic BP. In an another study, Brewster et al.[16] showed that low CK was associated with a 73% higher incidence of fainting in a random population sample. Our study showed similar results to another study, where serum CK was significantly higher in the uncontrolled hypertension group and systolic BP and diastolic BP were significantly correlated with CK levels.

A number of physiological mechanisms are involved in the maintenance of normal blood pressure, and their derangement may play a part in the development of essential hypertension. It is probable that a great many interrelated factors contribute to the raised blood pressure in hypertensive patients, and their relative roles may differ between individuals. Among the factors that have been intensively studied are salt intake, obesity, insulin resistance, the renin-angiotensin system, the sympathetic nervous system, genetics, endothelial dysfunction, low birth weight and intrauterine nutrition, and neurovascular anomalies.[17]

The CK system is of particular importance in tissues that display high and variable rates of ATP turnover, including skeletal muscle, the cardiovascular system, brain, and the kidney. In these tissues the enzyme provides ATP for muscle contraction and ion transport.[10] High serum CK activity was previously postulated as a genetic factor that could explain the higher blood pressures found in black people, a population subgroup with a greater prevalence of hypertension and its complications. Pressor responses were proposed to be enhanced via increased ATP availability for cardiovascular contractility, renal sodium retention, and capillary rarefaction of skeletal muscle.[18]

The enzyme CK is abundantly expressed in both the mitochondrion and the cytosol. At the mitochondrial site, it facilitates the formation of creatine phosphate, which is transported by CK to subcellular locations of high-energy demands. Here, CK is tightly bound in the immediate proximity of ATP-utilizing enzymes, such as Na^+/K^+-ATPase and Ca^{2+}-ATPase at membranes, and myosin light-chain kinase and myosin ATPase at the contractile proteins, where it rapidly provides ATP to these enzymes. Creatine kinase thus fuels highly energy-demanding processes such as sodium retention, cardiovascular contractility, and remodeling of arteries. Relatively high activity of the enzyme, particularly in resistance arteries, is thought to enhance pressure responses and lead to higher blood pressure levels.[8]

A limitation of this study was the small size of the study population, being restricted to two central hospitals. As a follow-up to this study, a cohort study should be performed to determine causal relationships of CK level increments with control of blood pressure in hypertension. Measuring serum levels of CK may help doctors to spot patients whose hypertension will be difficult to treat.

CONCLUSION

Creatine kinase level increases in adults with uncontrolled hypertension. It is hoped that scientific interest will explain the possible involvement of the CK in the pathophysiology of the hypertension.

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