



SDI Review Form 1.6

Journal Name:	British Journal of Medicine and Medical Research
Manuscript Number:	Ms_BJMMR_27559
Title of the Manuscript:	Interrelationship of serum uric acid levels and cardiovascular disease risk factors in Bangladeshi patients treated with antihypertensive drugs
Type of the Article	Original Research Article

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This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<u>Compulsory</u> REVISION comments	<p>**The major weakness of the present study is actually the study groups which were not managed well.</p> <p>① There were "hypertensive subjects" who took BP and lipid-lowering medications, and cardiovascular subjects" without taking those medications. There certainly are patients with cardiovascular diseases without high BP and lipid disorder. However, this is unusual. Are those "cardiovascular subjects" patients with cardiovascular diseases?, because it was not shown in the text. Please clearly characterize the studied subjects, including the diseases and the medications, etc.</p>	<p>Answer: Rather referring them to cardiovascular subjects (CVDs), we have corrected the groupings of the subjects as Controls, Hypertensive subjects without drugs (WOD) and hypertensive subjects with drugs (WD). Characteristics have been provided as yellow-shaded lines. Please see the Abstract</p>
	<p>② In the abstract, "hypertensive subjects" and "cardiovascular subjects" are two group, but in the Research design and Methods, two groups were "cardiovascular subjects". Which one is correct?</p>	<p>Answer: Rather referring them to cardiovascular subjects (CVDs), we have corrected them as Hypertensive subjects without drugs (WOD) and hypertensive subjects with drugs (WD). Please see the Abstract</p>
	<p>③ Several important parameters were missing in the tables. One is renal function that authors has mentioned. The other one is cigarette smoking acknowledged to be an critical cardiovascular risk factors, probably more important than uric acid level. Results from analysis excluding critical factors would be basically not reliable.</p>	<p>Answer: Thank you for your concern. Yes, renal dysfunctions and smoking are important risk factors for CVDs. Other than these two factors, our intention was here to evaluate whether uric acid could act as an independent risk factor for the hypertension/ cardiovascular diseases (CVDs).</p>



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	<p>④ UA and TC levels among groups are too different from our common medical practice. The TC/LDL/HDL level in WOD group is especially weird and different from the other two groups. Was the LDL level measured, or calculated? The calculated LDL level would be seriously disturbed by high VLDL level, reflected by high TG.</p>	<p>Answer: Recently, attention is being paid to uric acid (UA) whether it could act as a risk factor to cardiovascular patients. Yes, we completely agree with you. However, if you now look at our 'case' definition, I hope it would be perceivable: The participants WOD were asked for whether they had already started 'taking' of lipid-lowering- and anti-hypertensive drugs. Responders with 'no' were included and assigned as hypertensive subjects without drugs (WOD). This might be the reason as why their TC/LDL levels were very high (this is also the reason why they visited the doctor with self-reporting complaints of hypertension). Yes, LDL-C was calculated.</p>
	<p>⑤ Also noted is the zinc level. The difference between control and disease groups is five-fold (with small numbers of SEM), and this makes the study groups very specific, but not representative. Please explain how they were distributed.</p>	<p>Answer: In our case, the mean zinc levels in normal subjects were $51.0 \pm 2.1 \mu\text{g/dL}$ in men and $55.2 \pm 2.8 \mu\text{g/dL}$ in women. We agree with you. Our sample size was small, and larger sample size is necessary for a generalization of zinc levels in our population. Still, why the levels of zinc in the hypertensive subjects dropped to one fifth of those of the control subjects remains to be known clearly. A variety of ranges for serum zinc levels have been noted in the literature:</p> <ul style="list-style-type: none"> i) The mean level of Zn in serum was $116.6 \pm 55.2 \mu\text{g/dL}$ and $105.2 \pm 66.9 \mu\text{g/dL}$ in males and females, respectively in <i>Rev Esp Fisiol.</i> 1985 Dec;41(4):463-70; ii) 73 $\mu\text{g/dL}$ in <i>Polish Journal of Environmental Studies</i>: vol. 12 (3), 375-379, 2003; iii) 70-100 $\mu\text{mol/L}$ in (http://emedicine.medscape.com/article/2172316-overview) iv) 109-130 $\mu\text{g/dL}$ in <i>Comprehensive Reviews in Food Sciences and Food Safety</i> v) 75 -0.95 $\mu\text{g/dL}$ in <i>British Journal of Ophthalmology</i>: 71, 212-214, 1987



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	<p>⑥ BMI and BW. All three groups had almost the same BW, but the control group had much lower BMI--that means they are taller, 1.75 m versus 1.53 m. I imagine that the appropriate control group should be easy to find.</p>	<p>Answer: We agree with you.</p>
<p><u>Minor</u> REVISION comments</p>	<p>1. Authors spent large volume of text in explaining the clinical implication of their finding, However, a cross-sectional study can only provide limited information, even in well-demarcated study groups. Authors might consider to revise and shorten the discussion, and try not to confuse the reader by writing "With our experimental data limit, we are not sure as why serum uric acid was independently correlated with LDL-C only."</p>	<p>Answer: We agree with you. One of the most important matters that we wanted to highlight as how an increased LDL-C level was independently correlated with uric acid. Thus we referred to xanthine oxidase, which, when produces uric acid, can also produce free radical as one of the byproducts. As you know, free radical can oxidize LDL-C, and oxidized LDL-C is associated with atherosclerotic plaques (such references are available in the literature). In addition, we explained the status of Na, Cl and K in our hypertensive subjects. Thus the discussion was lengthy. We have deleted, the words "With our experimental data limit" Finally, we have shortened the discussion (strikethrough red lines). Please see Our Discussion section</p>



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	<p>2.In the Discussion, authors stated that patients with higher zinc level had higher CV risk factors. However, the role of zinc in cardiovascular diseases is not characterized yet. Authors also wrote" Therefore, zinc can slow down the progression of atherosclerosis [39, 40]." These two references are cell and animal studies. Authors should refrain from excessive extrapolation.</p>	<p>Answer: We have changed the previous expression as follows:</p> <p>Therefore, zinc can slow down the progression of atherosclerosis [39, 40]. The hypertensive subjects had zinc value of $11.8 \pm 0.10 \sim 10.2 \pm 0.17 \mu\text{g/dL}$ (in WOD and WD subjects) compared to $52.4 \pm 1.7 \mu\text{g/dL}$ in the control subjects. There was a big difference between the values of the control versus hypertensive subjects of WD and WOD groups. Subjects with serum zinc concentration ($11.8 \pm 0.10 \sim 10.2 \pm 0.17 \mu\text{g/dL}$) lower than the baseline of the controls ($52.4.2 \pm 1.7 \mu\text{g/dL}$) had a higher risk for cardiovascular risk factors.</p> <p>We have shortened the discussion (strikethrough red sentences) Please see Page8, lines 290-296</p>
<p><u>Optional/General</u> comments</p>		