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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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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)
Compulsory REVISION comments	<p>1) A rationale for measuring uric acid should be stated in the Introduction.</p>	<p>1. a rationale for measuring uric acid has been described in the 'Introduction'. In the yellow shade, we have added the following sentences-----</p> <p>Since uric acid has been considered an indicator of other CVD risk factors such as hypertension, dyslipidemia, obesity, glucose intolerance, and renal disease [16-19], and multiple studies provide strong evidence that an elevated uric acid may also bear independent risk factor association with total and/or CV mortality [20-23]. Therefore,</p> <p>An addition the following lines in the Introduction, says about the rationality of the measurements of uric acid in the present investigation.....</p> <p>Lines 29-32 Hyperuricemia is closely related to obesity, hypertension [4] and dyslipidaemia [5]. Previous studies have demonstrated a strong relationship between serum uric acid levels and coronary heart disease (CHD), with some studies suggesting that uric acid may be an independent risk factor for cardiovascular diseases [4,6-8].</p> <p>Lines 34-35 However, the nature of the relationship between uric acid and cardiovascular disease remains a subject of debate [10-12].</p> <p>Lines 46-47 In the present investigation on the Bangladeshi population, we have examined whether the serum uric acid could act as an independent risk factor for CVDs.</p>



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	<p>2) Are Zn levels in CVD Bangladeshi subjects different than in CVD subjects from other countries?</p>	<p>The population size was small in our investigation. Thus it is not possible to generalize about the normal zinc level in Bangladeshi subjects and those in other countries.</p> <p>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.</p> <p>A variety of ranges for the 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. 1985 Dec;41(4):463-70;</i> ii) $73 \mu\text{g/dL}$ in <i>Polish Journal of Environmental Studies: vol. 12 (3), 375-379, 2003;</i> 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) $75-109.5 \mu\text{g/dL}$ in <i>British Journal of Ophthalmology: 71, 212-214, 1987</i>
	<p>3) Line 58: What was the medical reasoning behind not treating CVD patients with the available anti-CVD-drugs? Cost? Access?</p>	<p>The subjects without drugs (WOD) means, these subjects yet did not start 'taking' drugs. Sampling was done at their first visit to the doctors with self-reporting complaints of hypertension. Besides anti-lipidemic drugs, diuretics and angiotensin-II receptor blockers were the most prevalent drugs as medication. Please see, page 7, lines 215-216.</p>
	<p>4) What role did BMI play in this analysis? From the BMI measurements it appeared that the CVD patients were obese?</p>	<p>The subjects who were already under treatment, i.e. the subjects with drugs (WD), and also without drugs (WOD) were with higher BMI. Thus their overweight may expose them to the risk of CVDs.</p>



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		<p>If the patients are overweight or obese, they are at increased risk of having abnormal levels of blood lipids. These include high levels of TG and LDL-C and low levels of HDL-C. Abnormal levels of these blood fats are a risk factor for CVDs, including coronary heart disease. The chances of having high blood pressure are greater if one is overweight or obese. The risk of having a stroke rises as BMI increases. The correlations analyses (Table 3) between BMI vs. LDL-C or systolic blood pressure (SBP) were positive and revealed that the patients were at the risk of cardiovascular diseases (CVDs).</p>
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	<p>5) It is Intriguing that the patients had low Zn levels whether or not they were on anti-CVD drugs? Can this be further explained?</p>	<p>We have added these sentences in place: Please see yellow shaded areas: The correlation of CVDs with zinc deficiency is still not clear. Hsieh et al. (2011) [43] have reported reduced serum zinc levels among the patients of Coronary Artery Disease. Other investigators have found zinc deficiency as a risk factor for ischaemic heart disease and its various clinical manifestations (Olsén et al., 2012) [44]. Zinc deficiency also leads to reduced survival in the patients of coronary artery disease (Pilz et al, 2009) [45]. The results of our investigation are thus consistent with these reports.</p>
	<p>6) Lines 257-259. The limitations of the study design should be clearly stated.</p>	<p>We have added the following sentences: However, such a conclusion should be drawn on a large number of population sizes.</p>
	<p>7) Of all the parameters considered, uric acid levels was statistically related only with LDL-C levels. The author's should delve into this relationship in more detail. Why only LDL-C?</p>	<p>Our Table 3 shows that uric acid (UA) level had an excellent correlation ($r \geq 0.75$, $P < 0.05$) individually with BMI, SBP, LDL-C and Zn, while moderate or good correlation ($r = \pm 0.50 \pm 0.75$, $P < 0.05$) with Age, DBP, TC and K. We did not tell that uric acid had correlation with only LDL-C. Rather we mentioned that the correlation LDL-C with UA was independent of other confounding factors (e.g., other parameters such as BMI, SBP, Zn, Age, DBP, TC and K). The independent correlation was evaluated by the multiple regression analysis. This also seems fascinating to us, as why LDL-C only was independently correlated with UA. Finally we have added the following sentences as follows: lipid-lowering drugs. This suggests that the relationship between LDL-C and uric acid is not simple as it anticipated.</p>