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Interactive roles of monovalent and divalent cations in pathogenesis of hypertension caused by alcohol

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SUMMARY Subjects whose daily alcohol intake varied from less than 22 g to over 88 g were studied. They differed in their mean systolic and diastolic blood pressures compared with those of controls who were teetotallers. The association between alcohol consumption and blood pressure was independent of age. Ex-alcohol users who were much older than current alcohol users had lower systolic and diastolic blood pressures. The association of body mass index with sustained raised blood pressure was apparent. When body mass index was eliminated as a variable there was an appreciable residual effect on mean arterial pressure.

Alcohol users and controls did not differ in mean plasma sodium concentration. Red blood cell intracellular sodium concentration, however, was higher in beer drinkers than in controls. On the other hand, red blood cell intracellular concentration of magnesium in beer drinkers was decreased. It is suggested that definite interactions between sodium, magnesium, and calcium ions may have some vital roles in the sustained rise in blood pressure in alcohol users.

Coronary heart diseases are common in Nigeria.[1-3] Although it is now well established that there are a multiplicity of risk factors for development of coronary heart disease such as hypertension, hyperlipidaemia, obesity, physical inactivity and stressful living,[4] the interactive roles of dietary monovalent and divalent metals have not been emphasised until relatively recently.[5] Several reports from other countries have suggested a relation between alcohol consumption, dietary sodium and potassium, and essential hypertension.[6-8] There are still conflicting data, however, about the roles of dietary sodium and potassium as major factors in the pathogenesis of essential hypertension.[8-9]

Chronic alcoholism has long been known to be associated with a net body loss of magnesium, evidenced by low serum and myocardial tissue magnesium.[10] In addition, 40–80% of chronic alcoholics develop high blood pressure.[11-12] In Nigeria lager beer is a favourite alcoholic beverage. The raw materials used in beer production in Nigeria—barley and yeast—are imported mainly from Europe, but the brewing of the beer is done entirely locally. The quality of the finished product, however, is said to conform to international standards for lager beers. The alcoholic content of Nigerian beer ranges from 3·0–3·5%, but no data are available about the inorganic content. In a previous study in this laboratory, however, it was observed that lager beer contains almost five times as much the sodium content of local drinking water (1·75 (0·48) (mEq/l) *v* 0·38 (0·13) mmol/l) (mEq/l).[13]

In view of the widespread consumption of lager beers in Nigeria due to the increase in disposable income of urban wage earners, it was thought valid to investigate the interactive roles of some inorganic metals in the development of high blood pressure in beer drinkers.

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Material and methods

Adiposity in all subjects selected for this study was assessed using Quetelet's body mass index weight (kg)/height^2 (m): systolic and diastolic (phase V of the Korotkov sounds) blood pressures were measured using a standard mercury sphygmomanometer with regular cuffs. Readings were taken in the seated position after 20 minutes of rest. Mean arterial pressure (MAP) was calculated by the addition of diastolic pressure and one third of the pulse pressure (diastolic blood pressure plus one third (systolic blood pressure—diastolic blood pressure)). Subjects were classified as having raised blood pressure if they had a diastolic blood pressure of greater than 90 mm Hg or a systolic blood pressure of greater than 150 mm Hg, or both.

After all subjects had rested for a further 10 minutes, to allow for haemodynamic equilibration, 10

ml venous blood samples were drawn from an antecubital vein using sterile, non-toxic pyrogen free plastic syringes. The blood was carefully emptied into heparinised tubes, gently mixed, and then centrifuged. The plasma was separated into plain plastic tubes and the buffy coat retained for some other studies. The fresh cells were next washed using the procedure that has been standardised by Lijnen and others.[14] The cells were washed three times with ice cold choline chloride (140 mM). The cells were then haemolysed with double distilled water, and intracellular sodium and magnesium were measured by flame photometry (Elvi, Milano). Plasma sodium and magnesium were also measured by flame photometry using the same instrument.

The significance of differences was assessed using the student's t test for unpaired observations and the χ^2 test and correlation coefficient and regression tests for association.

The selected subjects for the study, all men, fell into three categories:

CATEGORY 1

Eighty eight beer drinkers comprising 39 blood donors, 32 members of Ibadan University community, and 17 men who were attending the general outpatients' clinic of a government hospital for routine medical examinations were included in this category.

Table 1 *Graded alcohol consumption of healthy male beer drinkers*

No of subjects	*Alcohol consumption (g/day)*
14	11–22
16	22–44
35	44–66
13	66–88
10	88 and above

The mean age of the men was 32·2 (SD 6·1, range 21–46) years. They were selected using the following criteria:

(i) Every volunteer had to have at least a one year history of continuous alcohol (lager beer) consumption.
(ii) No volunteer was intoxicated at the time of blood collection.
(iii) The last beer was taken less than 24 hours before blood collection.
(iv) There was a history of at least seven days of daily beer consumption before blood collection.
(v) There was no clinical evidence of either overhydration or dehydration.
(vi) No volunteer had a medical history of cardiovascular, renal, hepatic, or any other metabolic disease.
(vii) No volunteer was receiving any form of medication.

Five groups of alcohol consumers were investigated (table 1). In Nigeria lager beer is sold in bottles each with a fluid capacity of 6·2 m/dl. One litre of Nigerian beer therefore contains 35·5 g of alcohol and 1·75 mmol (mEq/l) of sodium.[13]

The mean body mass index for this group of volunteers was 20·3 (SD 2·5, range 16·3–27·8). Their mean systolic and diastolic blood pressures were 154 (SD 23, range 110–190) mm Hg and 92 (SD 12, range 70–110) mm Hg, respectively (table 2).

CATEGORY 2

The second group of volunteers comprised 20 ex-beer drinkers. They were selected from the University of Ibadan staff community. The mean period of abstinence of these subjects was 8·1 (2·3) range 5–12 years. Twelve used to be heavy drinkers (88 g alcohol/day) and had stopped drinking on medical advice. The

Table 2 *Mean (SD) ages, body mass indexes, blood pressures, plasma and red blood cell intracellular sodium and magnesium concentrations in beer drinkers, ex-beer drinkers, and teetotallers*

	No of subjects	*Age (years)*	*Body mass index*	*Systolic blood pressure (mm Hg)*	*Diastolic blood pressure (mm Hg)*	*Plasma*		*Erythrocytes*	
						Sodium (mmol/l)	*Magnesium (mmol/l)*	*Sodium (mmol/l cells)*	*Magnesium (mmol/l cells)*
Beer drinkers	88	32·2 (6·1)[a]	20·3 (2·5)[c]	154 (23)[d]	92 (12)[e]	134 (7)[f]	0·3 (0·2)[g]	8·4 (1·3)	2·1 (0·6)[i]
Ex-beer drinkers	22	39·1 (4·0)[b]	19·2 (3·8)	136 (32)	80 (13)	135 (7)	0·9 (0·3)	7·9 (1·1)[h]	3·4 (0·8)
Teetotallers	92	34·0 (5·7)	18·9 (3·0)	132 (20)	81 (11)	138 (6)	0·8 (0·3)	6·5 (1·5)	3·2 (0·8)

a Compared with that of teetotallers, value not significantly different; $p > 0.10$.
b Compared with that of beer-drinkers and teetotallers, value significantly increased; $p < 0.001$.
c Compared with those of teetotallers, values significantly higher; $0.01 < p < 0.005$.
d Compared with those of teetotallers, values significantly higher; $p < 0.001$; Compared with that of ex-beer drinkers, value significantly higher; $p < 0.005$.
e Compared with that of teetotallers and ex-beer drinkers, values significantly higher; $p < 0.001$.
f Compared with that of teetotallers and ex-beer drinkers, values not significantly different; $p > 0.70$.
g Compared with that of teetotallers and ex-beer drinkers, values significantly lower; $p < 0.001$.
h Compared with that of beer drinkers, values not significantly different; $p > 0.10$; Compared with that of teetotallers, value significantly higher; $p < 0.0125$.
i Compared with that of ex-beer drinkers and teetotallers, values significantly lower; $p < 0.005$.

remaining eight subjects used to drink lightly (22 g alcohol/day) and had stopped drinking on their own initiative. The mean age of this group of subjects was 39·1 (4·0) range 30–49 years and their mean body mass index was 19·2 (3·8) range 14·0–22·5 years. The mean values for systolic and diastolic blood pressures were 136 (32) range 105–180 mm Hg and 80 (13) range 65–100 mm Hg.

CATEGORY 3

In the third group were 92 healthy men who were total abstainers. They comprised 18 blood donors, 11 members of Ibadan University staff clinic, and 63 muslims who were at an epidemiological clinic of a government hospital to obtain the mandatory inoculations preparatory to pilgrimage trips to the Middle East. Their average age was 34·0 (5·7) range 20–48 years and their average body mass index was 18·9 (3·0) range 14·0–25·2. Mean systolic and diastolic blood pressures were 132 (20) range 100–180 mm Hg and 81 (11) range 60–110 mm Hg, respectively.

Results

GENERAL CHARACTERISTICS OF THE SUBJECTS

The beer drinkers and the teetotallers who used neither alcohol nor tobacco did not differ in their mean age but they differed in their mean body mass index (table 2). Although the ex-beer drinkers were older, they did not have a higher mean body mass index than the two other groups of subjects (table 2). Systolic and diastolic blood pressures were higher in beer drinkers than in ex-beer drinkers and in teetotallers (table 2). There was also a significant degree of positive correlation between body mass index and mean arterial pressure in beer drinkers (figure). When 20 teetotallers who had a comparable mean body mass index with 14 subjects who were consuming 11–22 g alcohol per day (the least amount of alcohol consumption), however, were compared, using the χ^2 test, there was a significant association between alcohol consumption and raised mean arterial pressure (table 3). Mean arterial pressure was also higher in subjects consuming 66 g of alcohol/day than in those who were consuming less than 22 g of alcohol/day. Both groups of subjects also had comparable body mass indices (table 4).

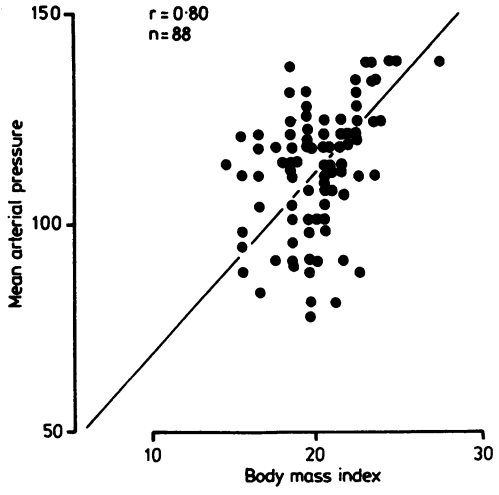

Figure *Correlation between body mass index and mean arterial pressure in beer drinkers.*

Table 2 shows the extracellular and red blood cell intracellular concentrations of sodium and magnesium in all three categories of subjects investigated. The mean plasma sodium did not differ greatly in all the subjects. Plasma magnesium, however, was lower in beer drinkers than in teetotallers and ex-beer drinkers. The mean red blood cell intracellular sodium concentration was higher in beer drinkers than in teetotallers, but there was no change when compared with the intracellular sodium in ex-beer drinkers. The red blood cell intracellular magnesium concentration was also lower in beer drinkers than in teetotallers and ex-beer drinkers.

Table 4 *Mean arterial blood pressure in subjects consuming different quantities of alcohol*

	Body mass index	*Mean arterial pressure*
11–22 g/per day	19·6 (4·1)	98·3 (13·4)
66 g/per day	19·4 (4·0)	114 (16·6)
p value	> 0·70	< 0·001

All values are means (± 1 SD).

Table 3 *Association between raised mean arterial pressure and lager beer consumption*

	*Body mass index**	*No with raised mean arterial pressure*	*No with normal mean arterial pressure*	*χ^2 test*	*p value*
Beer drinkers (11–22 g alcohol/day)	19·6 (4·1)	8	6	5·15	0·02 < p < 0·05
Teetotallers	19·2 (4·3)	4	16		

*Values are means ± 1SD.
Mean arterial pressure = diastolic BP + ⅓ (pulse pressure).

Discussion

Many studies have reported the correlation between alcohol consumption and blood pressure independent of the effects of both age and weight.[15-17] The extent of the influence of these factors on the prevalence of hypertension is not clear, and the true mechanism of hypertension caused by alcohol is also presently unknown. In this study consumers of alcohol and teetotallers did not differ in their mean age but they did differ in their mean systolic and diastolic blood pressures. This suggests that age is not likely to be an important contributory factor in the development of hypertension, as has been reported by various groups. This suggestion is further corroborated by the finding of appreciably lower systolic and diastolic blood pressures in ex-beer drinkers who are much older than current alcohol users. There seems to be an association between body mass index and alcohol consumption, evidenced by a higher mean body mass index in beer drinkers compared with that of teetotallers. There was also a high degree of positive correlation between body mass index and increased mean arterial pressure. When the effect of body mass index was eliminated as a variable, however, it was again clear that both alcohol consumption on its own and the relative quantity of ingested alcohol have direct associations with increased mean arterial pressure. There is substantive evidence to show that either alcohol alone or other factors in the composition of lager beers are directly responsible for increased blood pressures in alcohol consumers.

Among the probable mechanisms that have been suggested for the sustained high blood pressure in alcohol users are increased sympathetic activity,[18] Cushing's syndrome, induced by alcohol[19] and activation of the renin-angiotensin system.[20] None of these listed mechanisms, however, has been unequivocally established in most alcohol consumers. Indeed, Cushing's syndrome induced by alcohol with increased plasma cortisol concentration is comparatively rare. Alcohol has also not been generally shown to ensure the hyperactivity of the renin-angiotensin-aldosterone system.

The hypomagnesemia, the increased intracellular concentration of sodium, and the decreased intracellular concentration of magnesium that have been established in the course of this study in beer drinkers have not been previously reported in this field. Apart from the universal causative effect of salt in the pathogenesis of essential hypertension in man, it seems that the increased sodium content, aside from the alcohol effect, in locally brewed Nigerian lager beers may be part of the explanation for the increased blood pressure that has been observed in this group of alcohol users. It has been established in a previous study that the locally brewed Nigerian lager beer contains five times as much as the sodium content of local drinking water.[13]

The hypomagnesemia and the decreased intracellular concentration of magnesium found in these beer drinkers may be related to the increase in the degree of basal tension of some small and large coronary arteries that has been observed after the experimental withdrawal of extracellular magnesium.[21]

A changed intracellular concentration of sodium has also been suggested as being able to change the transport of calcium ions by sodium-calcium exchange and thereby increasing the calcium concentration in the cells and tension in vascular smooth muscle.[22] This mechanism may lead to the decreased intracellular concentration of magnesium in these alcohol consumers, resulting in increased basal tension and raised blood pressure.

Beer drinkers and ex-beer drinkers do not differ in their mean intracellular concentration of sodium (table 2). The increased intracellular magnesium concentration in ex-beer drinkers, however, may probably counteract the effect of ion accumulation via the sodium-calcium exchange mechanism. This may be part of the explanation for the normal blood pressure in this category of subjects in spite of the increased intracellular sodium concentration. Magnesium ions have been known to act as a regulatory cofactor in the cascade of events initiated by cell stimulation, which proceed through ion fluxes, enzymatic induction, energy dependent metabolic responses and return of the vascular cell to its basal state.[23-26]

The findings of this study suggest that definite interactions between sodium, magnesium, and calcium ions have some vital roles in the sustained increase of blood pressure seen in alcohol users.

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