Comparison of Endogenous Antioxidant levels in Hypertensive Patients and Non-hypertensive subjects

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Abstract

Background: Reactive oxygen species (ROS) participate in normal cell signaling as mediators that regulate vascular function. Free radicals play important roles in various conditions, including Atherosclerosis, Ischemia reperfusion injury, Arrhythmias, Cardiomyopathy, Congestive Cardiac Failure, and hypertension. The present study was undertaken to assess the status of some endogenous antioxidants viz. ferric reducing ability of plasma, serum uric acid, serum bilirubin and serum albumin in hypertensive patients and to compare these with the same in non-hypertensive subjects.

Methods: The study was conducted on 220 hypertensive patients taking anti-hypertensive medication and 220 age- and sex-matched non-hypertensive subjects. Ferric Reducing Ability of Plasma (FRAP), Serum albumin, Serum uric acid and Serum total bilirubin were measured. Comparison of data in the two groups was done by Student's unpaired t-test.

Results: The FRAP (and hence anti-oxidant capacity) was significantly lower in hypertensive patients as compared to non-hypertensive subjects. The values of serum albumin were significantly lower and values of serum uric acid significantly higher in hypertensive patients as compared to non-hypertensive subjects.

Conclusion: Total anti-oxidant capacity as estimated by FRAP was significantly lower in hypertensive patients as compared to non-hypertensive subjects.

Key words: hypertension; antioxidants; endogenous

Introduction

Hypertension is the most vital risk factor for cardiovascular morbidity and mortality. Globally, hypertension prevalence was said to be 25% in men and 20% in women in 2015.[1] Hypertension is consistently associated with the development of heart failure, stroke, and chronic kidney disease; an estimated 57% and 24% of stroke and coronary artery disease related deaths respectively are because of hypertension.[2] Ramakrishnan et al. estimated the prevalence to be 30.7% in India.[3]

Reactive oxygen species (ROS) participate in normal cell signaling as mediators that regulate vascular function.[4] Within the vascular wall, ROS are produced by all layers, including endothelium, smooth muscle, and adventitia.[5] ROS includes superoxide ion (O_2-), hydrogen peroxide (H_2O_2), hydroxyl ion (OH), nitric oxide (NO), and peroxynitrite (ONOO). Under physiological conditions, ROS are produced in low concentrations and act as a signaling molecule that can regulate vascular smooth muscle cell (VSMC) contraction and relaxation, and help in VSMC growth[6].

Under pathophysiological conditions, these free radicals play important roles in various conditions, including Atherosclerosis, Ischemia reperfusion injury, Arrhythmias, Cardiomyopathy, Congestive Cardiac Failure, and Diabetes.[7] Increased levels of bilirubin could prevent the actions of Angiotensin II through scavenging of superoxide anions in the vasculature and also inhibit NADPH oxidase and protein kinase C activity, both of which can mediate Angiotensin II induced vascular injury.[8] Lanone et al demonstrated that bilirubin can counteract hypotension elicited by endotoxin through a mechanism mediated by direct

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inhibition of NAD(P)H oxidase, involved in inducible NO synthase (iNOS) induction, that consequently ends up in a decrease of iNOS expression and activity[9]. Levine et al. observed that preferential oxidation of exposed methionine residues in enzymes like glutamine synthase, had little effect on their biological function. Oxidation and reduction cycle of methionine residues in biological systems can function as ROS scavenging system that may help in protection of proteins from extensive modifications.[10]

One of the most important sites where the anti-oxidant effects of uric acid are seen is the central nervous system, especially in multiple sclerosis, Parkinson's disease, and acute stroke.[11] While chronic elevations in uric acid are associated with increased stroke risk[12] Kuzkaya et al. showed that uric acid could be a scavenger of peroxynitrite in the extracellular space. However, it cannot scavenge superoxide (O^-_2), and the presence of ascorbic acid and thiols is important for complete scavenging of peroxynitrite.[13]

The present study was undertaken to assess the status of some endogenous antioxidants viz. ferric reducing ability of plasma, serum uric acid, serum bilirubin and serum albumin in hypertensive patients and to compare these with the same in non-hypertensive subjects.

Material and Methods

After obtaining prior IRB permission, the present study was conducted in National Institute of Medical Sciences and Research, Jaipur. The study was conducted on 220 hypertensive patients taking anti-hypertensive medication and 220 age- and sex-matched non-hypertensive subjects, all of whom were taken from Pacific Institute of Medical Sciences, Udaipur. The following were measured in their blood samples:

- Ferric Reducing Ability of Plasma (FRAP)[14]
- Serum albumin[15]
- Serum uric acid[16]
- Serum total bilirubin[17]

Comparison of data obtained in hypertensive patients and non-hypertensive subjects was done by Student's unpaired t-test.

Results

Table1 and Figure 1 show the total anti-oxidant capacity in hypertensive patients and non-hypertensive subjects in terms of Ferric Reducing Ability of Plasma (FRAP) assay. The mean ± SD of FRAP in hypertensive patients was 507.5 ± 66.47μmoles/L. The same in non-hypertensive subjects was 823.0 ±102.3 μmoles/L. The FRAP (and hence anti-oxidant capacity) was significantly lower in hypertensive patients as compared to non-hypertensive subjects.

Table 1: Total anti-oxidant capacity in Hypertensive Patients and Non-hypertensive Subjectsas measured by Ferric Reducing Ability of Plasma (the values are mean ± SD)

Parameter	Hypertensive Patients (n=220)	Non-hypertensive Subjects (n=220)
Ferric Reducing Ability of Plasma (μmoles/L)	507.5 ± 66.47	823.0 ± 102.3*

*p < 0.001

Fig 1: Comparison of total anti-oxidant capacity in Hypertensive Patients and Non-hypertensive Subjects

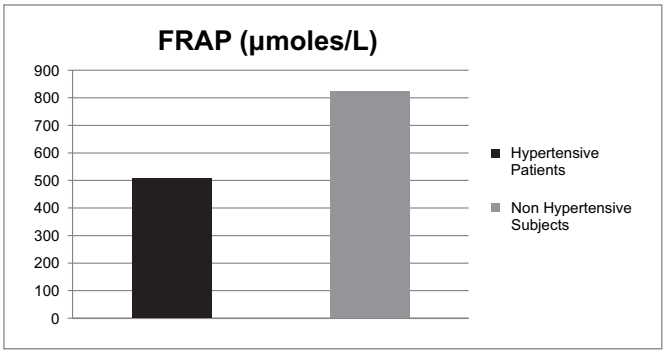


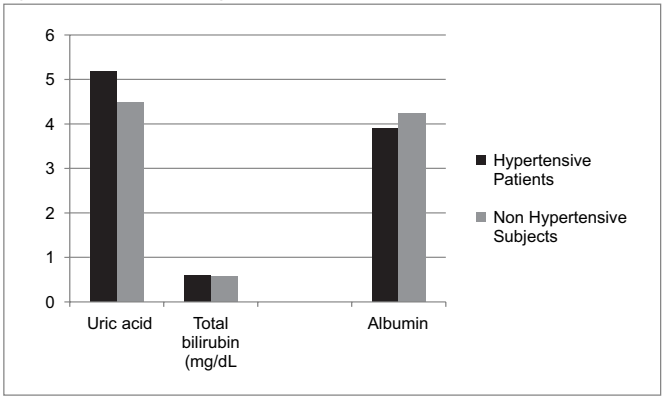
Table 2 and Figure 2 show the levels of endogenous antioxidants viz. serum albumin, serum uric acid and serum bilirubin in hypertensive patients and in non-hypertensive subjects. The mean ± SD uric acid (mg/dL), total bilirubin (mg/dL) and albumin (g/dL) in hypertensive patients were 5.18±1.01, 0.59±0.21 and 3.89±0.44 respectively. The same in non-hypertensive subjects were 4.49±0.76, 0.58±0.18 and 4.24±0.44 respectively. The values of serum albumin were significantly lower and values of serum uric acid significantly higher in hypertensive patients as compared to non-hypertensive subjects. The difference in serum bilirubin was not significant.

Table 2: Comparison of three endogenous antioxidants in Hypertensive Patients and Non-hypertensive Subjects(the values are mean ± SD)

Parameters	Hypertensive Patients (n=220)	Non-hypertensive Subjects (n=220)
Serum uric acid (mg/dL)	5.18±1.01	4.49 ±0.76*
Serum total bilirubin (mg/dL)	0.59 ± 0.21	0.58± 0.18NS
Serum albumin (g/dL)	3.89± 0.44	4.24 ± 0.44*

*p <0.001 NS p> 0.05

Figure 2: Comparison of some Endogenous Antioxidants in Hypertensive Patients and Non-hypertensive Subjects



Discussion

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and the ability of a biological system to detoxify the reactive species. This could be considered to be the pathogenesis of high blood pressure, a major factor for heart disease mortality.[18] Verma et al. found serum FRAP level to be decreased in hypertensive patients in comparison to healthy controls which indicated that decreased FRAP level has a role in lipid peroxidation and in the pathogenesis of hypertension[19]. Kashyap et al. also found a significant decrease in the level of FRAP in essential hypertension. They suggested that increase in Fe^{3+} can initiate lipid peroxidation and aggravate free radical-induced cellular damage[20]. Padhy et al. found an observable decrease in total antioxidant status in hypertensive cases, which suggested the importance of serum antioxidant status in blood pressure modulation.[21] Benzie et al. observed that FRAP assay offers a highly reliable index of antioxidant in biological fluids that are deployed to prevent generation of ROS, destroy potential oxidants, and to scavenge ROS which minimizes oxidative stress-induced tissue damage, and may play a protective role in cardiovascular diseases.[22] Redon et al. showed that oxidative stress is increased in hypertensive subjects in vascular cells and also in extravascular cells.[23] Our results are in conformity with these observations and confirm that plasma FRAP was significantly decreased in hypertensive patients.

Decreased serum albumin was a common explanatory factor for three microvascular complications i.e. retinopathy, nephropathy and neuropathy in hypertensive patients with Type II diabetes mellitus, thus showing that a positive significance in the begining of microvascular complications.[24] Høstmark et al. found a positive association between serum albumin and blood pressure in a cross-sectional study.[25] Our results support the former report because serum albumin was significantly lower in our hypertensive patients.

Elevated urate levels in circulation are one of the major antioxidants that protect cells from oxidative damage.[26] Kellogg and Fridovich described the ability of urate to scavenge oxygen radicals and protect the erythrocyte membrane from lipid oxidation.[27] Perlsteinet al. concluded that the baseline serum uric acid level is a marker for hypertension risk development.[28] Kuwabara et al. have also shown a relationship between hyperuricemia and hypertension in adults.[29] In a study on general adult population in Bangladesh, a positive association was found between elevated serum uric acid and hypertension[30]. Our results support the view that serum uric acid and blood pressure are positively correlated which is contradictory to the report of Forman who found no association between elevated serum uric acid and hypertension.[31]

Stojanov et al. have reported that bilirubin has antioxidant and anti-inflammatory activity and is inversely correlated with the risk of Ischemic heart disease, hypertension, Type II Diabetes mellitus and obesity.[32] Chin et al. observed a negative association of Hyperbilirubinemia and incidence of Hypertension[33]. Wang et al. showed that Hyperbilirubinemia decrease the risk of hypertension by inactivating and inhibiting the synthesis of reactive oxygen species in vascular cells.[34] We found serum bilirubin to be within the normal range and comparable in hypertensive and non-hypertensive subjects thereby showing a lack of relationship between serum bilirubin and hypertension.

Conclusion:

Total anti-oxidant capacity as estimated by FRAP was significantly lower in hypertensive patients as compared to non-hypertensive subjects. Serum

albumin was significantly lower and serum uric acid significantly higher in hypertensive patients as compared to non-hypertensive subjects. Serum bilirubin level was comparable in hypertensive patients and non-hypertensive subjects.

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