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Oxidative stress in hypertension induced epistaxis - Evaluation of biomarkers in male patients

KEYWORDS: Antioxidant Enzymes, Electrolytes, Hypertension, Oxidative stress

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ABSTRACT *Oxidative stress results from an imbalance between reducing agents and enzymes involved in the removal of free radicals and/or reactive oxygen species. Hypertension is a most common cardiovascular disease in the world. Development of hypertension requires a sub-stained absolute or relative over expansion of blood volume or reduction of the capacitance of the cardiovascular system. Hypertension is associated with epistaxis. The present study comprised 82 hypertensive male patients with epistaxis attended Otorhinolaryngology Department, Gandhi Memorial Hospital, S. S. Medical College, Rewa (Study Group) and 81 ages matched male healthy volunteers (Control Group). The age range was taken from 20-80 years. Antihypertensive drugs effects were observed under supervision of Pharmacology Department, S. S. Medical College, Rewa (M. P.). Blood samples were collected from the patients at the time of admission as well as from individuals of male healthy control groups. Biochemical parameters such as electrolytes, glucose, protein (Total), creatinine, urea, superoxide dismutase (SOD), glutathione reductase (GSH-R), glutathione peroxidase (GSH-Px), catalase and plasma malondialdehyde (P-MDA) were varying significantly in hypertensive patients with epistaxis. Oxidative stress contributes to development of hypertension.*

INTRODUCTION

Oxidative stress results from an imbalance between reducing agents and enzymes involved in the removal of free radicals and/or reactive oxygen species. Oxidative stress affects a complex array of genes involved in inflammation, coagulation, fibrinolysis, cell cycle, signal transduction and programmed cell death.[1] Free radicals are generated during normal physiological processes but increased production of free radicals can cause alteration of biomolecules such as lipid peroxidation.[2] The cells have evolved a number of antioxidant defence mechanisms that neutralize free radicals. These antioxidant defence mechanisms can be categorized in to two types - free radical scavenging and chain breaking antioxidants. The free radical scavenging mechanisms include enzymatic antioxidant like Superoxide dismutase (SOD), Glutathione peroxidase (GSH-Px) and catalase, which limit the cellular concentration of free radicals and prevent excessive oxidative damage.[3] There exists a balance between the pro oxidant process/free radical generation and the antioxidant mechanisms of the cell. Under certain condition, this balance is disturbed there occurs a shift towards the oxidative processes resulting in increased level of oxidative stress.[4]

Hypertension is a most common cardiovascular disease in the world. Hypertension is directly due to over expansion of actual or effective blood volume compartment. In volume dependent hypertension, the physiologic mechanism fail to respond appropriately to intravascular expansion or some pathophysiologic process causes excess production of sodium retaining factors that stimulates the kidney to conserve sodium.[5,6]

Other main category of hypertension is initiated by excess vasoconstrictor influences that directly increase peripheral resistance or decrease cardiovascular capacitance (or both). Importantly, for vasoconstrictor hypertension to be sustained there must also be significant sodium retaining effects on the kidney. In the absence of a concomitant renal effect, the elevated arterial pressure causes pressure natriuresis volume; thus, the hypertension is ameliorated.[7,8] Derangements encompassing activation of a vasoconstrictor system that also has direct sodium retaining effects such as the rennin angiotensin aldosterone system lead to an even more powerful hypertensive stimulus that is not easily counteracted.[9]

It is estimated that 60% of the population will have at least one episode of epistaxis in their lifetime and 6% of them will seek medical attention. A slight male preponderance with 55% male and 45% female has been reported. Epistaxis is rare in neonates but common among children and young adults and peaks in the sixth decade giving a bi-modal age presentation.[10] The etiologic role of hypertension in epistaxis is not certain. It is possible that hypertension causes arteriolosclerotic nasal vascular changes that predispose hypertensives to increased susceptibility to epistaxis.[11]

Objectives of this study to find out electrolyte imbalance, variation in biochemical parameters, antioxidant enzymes and oxidant product in hypertension induced epistaxis in male patients.

MATERIALS AND METHODS

The present study comprised 82 hypertensive male patients with epistaxis attended Otorhinolaryngology Department, Gandhi Memorial Hospital, S. S. Medical College, Rewa (Study Group) and 81 ages matched male healthy volunteers (Control Group). The age range was taken from 20-80 years. Antihypertensive drugs effects were observed under supervision of Pharmacology Department, S. S. Medical College, Rewa (M. P.). Blood samples were collected from the patients at the time of admission as well

Volume : 6 | Issue : 2 | FEBRUARY 2016 | ISSN - 2249-555X

as from individuals of male healthy control groups. Clinical investigations were performed in the Clinical Biochemistry Section, Central Pathology Laboratory, Department of Biochemistry, S. S. Medical College, Rewa (M.P.). Serum glucose, protein (Total), creatinine, urea, and superoxide dismutase were estimated by GOD-POD, biuret, jaffe's, diacetyl monoxime and misra H P et al methods respectively. Plasma malondialdehyde, haemolysate glutathione reductase, glutathione peroxidase and catalase were estimated by Jean C D et al method (1983), Horn H D (1963), Hafeman D G method (1974) and Asror K sinha method (1972) respectively. Serum electrolytes were estimated by electrolyte analyzer. Obtained data were analyzed statistically by using student 't' test.

OBSERVATIONS

Table 1: Mean±SD value and significant test between control group and study group (age group 20-30 years)

S. No.	Particulars	Mean±SD		t-test	P-value
		Control Group (n=21)	Study Group (n=22)		
Electrolyte:					
1	Serum Sodium (mEq/L)	137.69 ± 1.99	130.98 ± 1.30	13.150	< 0.001
2	Serum Potassium (mEq/L)	4.05 ± 0.28	5.99 ± 0.17	27.610	< 0.001
Biochemical Parameters:					
3	Serum Glucose (mg/dl)	79.54 ± 4.87	116.43 ± 2.13	32.441	< 0.001
4	Serum Protein (Total) (gm/dl)	6.68 ± 0.30	6.26 ± 0.12	6.080	< 0.001
5	Serum Creatinine (mg/dl)	0.81 ± 0.09	1.09 ± 0.15	7.378	< 0.001
6	Serum Urea (mg/dl)	24.31 ± 2.06	41.48 ± 2.29	25.807	< 0.001
Antioxidant / Oxidant product:					
7	Superoxide dismutase (EU/mg protein/ml)	12.36 ± 1.86	9.91 ± 0.26	6.119	< 0.001
8	Glutathione reductase (EU/gm protein)	20.54 ± 0.14	17.59 ± 0.11	77.028	< 0.001
9	Glutathione peroxidase (EU/mg % Hb)	11.06 ± 0.58	6.82 ± 0.27	30.966	< 0.001
10	Catalase (EU/mg protein/ml)	6.36 ± 0.10	4.42 ± 0.12	57.445	< 0.001
11	Plasma Malondialdehyde(nano mol/ml)	2.94 ± 0.48	5.20 ± 0.30	18.608	< 0.001
Blood pressure:					
12	Systolic blood Pressure (mm Hg)	123.33 ± 2.48	146.91 ± 2.11	33.635	< 0.001
13	Diastolic blood Pressure (mm Hg)	82.67 ± 1.33	98 ± 2.47	7.450	< 0.001

Table 2: Mean±SD value and significant test between control group and study group (age group 31-50 years)

S. No.	Particulars	Mean ± SD		t-test	P-value
		Control Group (n=30)	Study Group (n=30)		
Electrolyte:					
1	Serum Sodium (mEq/L)	140.48 ± 1.30	128.53 ± 2.06	26.870	< 0.001
2	Serum Potassium (mEq/L)	4.44 ± 0.36	6.02 ± 0.17	21.737	< 0.001
Biochemical Parameters:					
3	Serum Glucose (mg/dl)	89.55 ± 2.81	118.7 ± 2.02	46.135	< 0.001
4	Serum Protein (Total) (gm/dl)	7.17 ± 0.30	6.44 ± 0.16	11.760	< 0.001
5	Serum Creatinine (mg/dl)	0.89 ± 0.07	1.90 ± 0.16	31.676	< 0.001
6	Serum Urea (mg/dl)	27.71 ± 2.89	44.4 ± 1.94	26.263	< 0.001
Antioxidant / Oxidant product					
7	Superoxide dismutase (EU/mg protein/ml)	13.38 ± 1.05	9.73 ± 0.38	17.903	< 0.001
8	Glutathione reductase (EU/gm protein)	19.95 ± 0.16	16.92 ± 0.18	68.911	< 0.001
9	Glutathione peroxidase (EU/mg % Hb)	9.86 ± 0.15	6.09 ± 0.13	104.029	< 0.001
10	Catalase (EU/mg protein/ml)	5.85 ± 0.15	3.9 ± 0.06	66.111	< 0.001
11	Plasma Malondialdehyde (nano mol/ml)	3.47 ± 0.48	8.74 ± 0.45	43.871	< 0.001
Blood pressure					
12	Systolic blood Pressure (mm Hg)	123.33 ± 2.84	146.8 ± 3.66	27.749	< 0.001
13	Diastolic blood Pressure (mm Hg)	82.47 ± 2.08	97.4 ± 1.67	30.657	< 0.001

Volume : 6 | Issue : 2 | FEBRUARY 2016 | ISSN - 2249-555X

Table 3: Mean±SD value and significant test between control group and study group (age group 51-80 years)

S. No.	Particulars	Mean ± SD		t-test	P-value
		Control Group (n=30)	Study Group (n=30)		
Electrolyte					
1	Serum Sodium (mEq/L)	142.46 ± 1.35	127.67 ± 2.09	32.558	< 0.001
2	Serum Potassium (mEq/L)	5.16 ± 0.25	6.50 ± 0.22	22.039	< 0.001
Biochemical Parameters					
3	Serum Glucose (mg/dl)	99.33 ± 3.46	127.27 ± 4.17	26.243	< 0.001
4	Serum Protein (Total) (gm/dl)	7.52 ± 0.40	6.35 ± 0.12	15.345	< 0.001
5	Serum Creatinine (mg/dl)	0.94 ± 0.10	2.39 ± 0.26	28.510	< 0.001
6	Serum Urea (mg/dl)	35.42 ± 4.16	48.47 ± 2.05	15.412	< 0.001
Antioxidant / Oxidant product					
7	Superoxide dismutase (EU/mg protein/ml)	12.62 ± 1.70	9.08 ± 0.50	10.942	< 0.001
8	Glutathione reductase (EU/gm protein)	19.29 ± 0.12	16 ± 0.13	101.855	< 0.001
9	Glutathione peroxidase (EU/mg % Hb)	9.25 ± 0.09	5.55 ± 0.09	159.223	< 0.001
10	Catalase (EU/mg protein/ml)	5.24 ± 0.09	3.55 ± 0.06	85.576	< 0.001
11	Plasma Malondialdehyde (nano mol/ml)	3.69 ± 0.26	8.94 ± 0.37	63.588	< 0.001
Blood pressure					
12	Systolic Blood Pressure (mm Hg)	130.53 ± 3.10	148.53 ± 3.96	19.604	< 0.001
13	Diastolic Blood Pressure (mm Hg)	85.33 ± 1.69	99.47 ± 3.67	19.168	< 0.001

Table 4: Mean±SD value and significant test between study group (20–30 years) and study group (31–50 years)

S. No.	Particulars	Mean ± SD		t-test	P-value
		Study Group (20–30 yrs) (n = 22)	Study Group (31–50 yrs) (n = 30)		
Electrolyte					
1	Serum Sodium (mEq / L)	130.98 ± 1.30	128.53 ± 2.06	4.902	< 0.001
2	Serum Potassium (mEq / L)	5.99 ± 0.17	6.02 ± 0.17	0.629	0.532
Biochemical Parameters					
3	Serum Glucose (mg/dl)	116.42 ± 2.13	118.7 ± 2.02	3.930	< 0.001
4	Serum Protein (Total) (gm/dl)	6.26 ± 0.12	6.44 ± 0.16	4.436	< 0.001
5	Serum Creatinine (mg/dl)	1.09 ± 0.15	1.90 ± 0.16	18.513	< 0.001
6	Serum Urea (mg/dl)	41.48 ± 2.29	44.4 ± 1.94	4.968	< 0.001
Antioxidant / Oxidant product					
7	S- Superoxide dismutase (EU/mg protein/ml)	9.91 ± 0.26	9.73 ± 0.38	1.915	0.061
8	Glutathione reductase (EU/gm protein)	17.59 ± 0.11	16.92 ± 0.18	15.448	< 0.001
9	Glutathione peroxidase (EU/mg % Hb)	6.82 ± 0.27	6.09 ± 0.13	12.936	< 0.001
10	Catalase (EU/mg protein/ml)	4.42 ± 0.12	3.9 ± 0.06	20.538	< 0.001
11	Plasma Malondialdehyde (nano mol/ml)	5.20 ± 0.30	8.74 ± 0.45	32.008	< 0.001
Blood Pressure					
12	Systolic blood Pressure (mm Hg)	146.91 ± 2.11	146.8 ± 3.66	0.126	0.900
13	Diastolic blood Pressure (mm Hg)	98 ± 2.47	97.4 ± 1.67	1.046	0.301

Table 5: Mean±SD value and significant test between study group (31–50 years) and study group (51–80 years)

S. No.	Particulars	Mean ± SD		t-test	P-value
		Study Group (31–50 yrs) (n=30)	Study Group (51–80 yrs) (n=30)		
Electrolytes					
1	Serum Sodium (mEq/L)	128.53 ± 2.06	127.67 ± 2.09	1.605	0.114
2	Serum Potassium (mEq/L)	6.02 ± 0.17	6.50 ± 0.22	9.456	< 0.001
Biochemical Parameters					
3	Serum Glucose (mg/dl)	118.7 ± 2.02	127.27 ± 4.17	10.131	< 0.001
4	Serum Protein (Total) (gm/dl)	6.44 ± 0.16	6.35 ± 0.12	2.465	< 0.05
5	Serum Creatinine (mg/dl)	1.90 ± 0.16	2.39 ± 0.26	8.791	< 0.001
6	Serum Urea (mg/dl)	44.4 ± 1.94	48.47 ± 2.05	7.898	< 0.001
Antioxidant / Oxidant product					
7	Superoxide dismutase (EU/mg protein/ml)	9.73 ± 0.38	9.08 ± 0.50	5.669	< 0.001
8	Glutathione reductase (EU/gm protein)	16.92 ± 0.18	16 ± 0.13	22.695	< 0.001
9	Glutathione peroxidase (EU/mg % Hb)	6.09 ± 0.13	5.55 ± 0.09	18.706	< 0.001
10	Catalase (EU/mg protein/ml)	3.9 ± 0.06	3.55 ± 0.06	22.592	< 0.001
11	Plasma Malondialdehyde(nano mol/ml)	8.74 ± 0.45	8.94 ± 0.37	1.880	0.065
Blood Pressure					
12	Systolic blood Pressure (mm Hg)	146.8 ± 3.66	148.53 ± 3.96	1.757	0.084
13	Diastolic blood Pressure (mm Hg)	97.4 ± 1.67	99.47 ± 3.67	2.812	<0.0001

Volume : 6 | Issue : 2 | FEBRUARY 2016 | ISSN - 2249-555X

RESULTS

Table 1 - 3 revealed that systolic / diastolic blood pressure, potassium ions, glucose, creatinine, urea and P-MDA increased significantly (P<0.001) in study group. Sodium ions, protein (T), SOD, GSH-R, GSH-Px and catalase were deceased significantly (P<0.001) in study groups.

Table 4 revealed that serum glucose, protein (T), creatinine, urea and P-MDA increased significantly (P<0.001) in the age group of 31–50 years of male hypertensive patients. Sodium ions, GSH-R, GSH-Px and catalase were decreased significantly (P<0.001) in the age group of 31–50 years of male hypertensive patients.

Table 5 revealed that diastolic blood pressure, potassium, glucose, creatinine and urea were increased significantly (P<0.001) in the age group of 51–80 years of male hypertensive patients. Serum protein (T) was decreased significantly (P < 0.05) in the age group of 51–80 years of male hypertensive patients. SOD, GSH-R, GSH-Px and catalase were decreased significantly (P<0.001) in the age group of 51–80 years of male hypertensive patients.

DISCUSSION AND CONCLUSION

The seventh report of the United States Joint National Committee for Detection, Evaluation and Treatment of high blood pressure recommended a new classification system for hypertension.[12] Hypertension: stage-1 (mild), stage-2 (moderate), stage-3 (sever), and stage-4 (very severe). Present study, the level of systolic and diastolic blood pressure are increased significantly (P < 0.001) in the age range of 20–30, 31–50, and 51–80 years of male hypertension with epistaxis patients as compared to male healthy control groups (Table 1 to 3). With the exception of a low relatively isolated society, average blood pressure tends to rise progressively with increasing in all most every population.[13]

Hyperglycemia is a known cause of enhanced plasma free radicals concentration. These are many ways by which *hyperglycemia* may increase the generation of free radicals. The term "autoxidation glycosylation" described the capability of glucose to analyze, there by reducing molecular oxygen and yielding oxidizing intermediates.[14] Higher systolic and diastolic blood pressures and older age were all associated with higher serum creatinine levels.[15] We found elevated significant (P<0.001) results in male hypertension with epistaxis patients for serum potassium, glucose, creatinine, urea and plasma malondialdehyde as compared to the male healthy control groups. Same significant higher values have been showed by other studies.[16-18]

The oxidative status during hypertension was evaluated by analyzing pro-oxidant and antioxidant in blood. The RBC was selected for the estimation of these enzymes because they are easily accessible; rich in thiol and are potentially involved in attack from and protection against free radicals. Malondialdehyde a secondary breakdown product of fatty acid peroxide, is a highly reactive substance and even in physiological concentration can react with erythrocyte membrane phospholipids, cross-linking their polar heads.[19] When modified malondialdehyde, red blood cells (RBC) lose their normal cationic gradient and show reduced deformability in vitro, in addition to a significantly shortened life span in vivo.[20] In our study level of serum sodium, protein (Total), superoxide dismutase, glutathione reductase, glutathione peroxidase, and catalase are decreased significantly (P< 0.001) in male hypertension with epistaxis patients as compared to control group. Similar results have been represented by other authors.[21-25]

Age–related increases in hypertension prevalence have also been reported in numerous other national survey conducted in different countries at various stages of economic development.[26-27] Emerging evidence indicated that hypertension is a vascular disease associated with inflammation, induced through redox-sensitive mechanisms that are regulated by ang-II. High blood pressure is linked to vascular damage, oxidative stress and inflammation. Of the many factors implicated in hypertensive vascular disease, ang-II appears to be one of the most important.[28] We found significant (P<0.001) elevated values of serum glucose, protein (T), creatinine, urea and plasma MDA in the age range (31–50 years) of male hypertension with epistaxis patients when compared to healthy male (20–30 years). Anne-Sofie Furberg and Inger Thune (2001) reported that hyperglycemia is significant factor for development of hypertension.[29] Angiotensin II has direct and indirect effects on insulin and its signaling pathways, providing support for the biologic mechanism underlying the benefits of renin–angiotensin system, which causes hyperglycemia.[30] An increase in serum creatinine above normal or the presence of proteinurea could constitute the most potent predictor for the future development of cardiovascular death in essential hypertension.[31]

Values of sodium, glutathione reductase, glutathione peroxidase and catalase are decreased significantly (P<0.001) in study group (31–50 years) compared to another study group (20–30 years). Nicotine can be a potent stimulus to ADH release in humans and this may have contributed to the development of hyponatremia. It is likely, therefore, that smoking was central to the pathophysiology of the hyponatremic hypertensive syndrome in many patients.[32-33]

The present result appears to first explaination that significantly (P<0.001) increased diastolic blood pressure and serum potassium, glucose, creatinine and urea of male hypertensive patients with epistaxis (51–80 years) when compared to male cases (31–50 years). **D**ata from third National Health and Nutrition Examination Survey (NHANES-III) showed that 24% of United States adult population has high blood pressure.[34] Familial hyperkalemia and hypertension is an autosomal dominant disorder characterized by hyperkalemia, hypertension, and low renin.[35-36] This abnormality in membrane Na^+-K^+-$2Cl^-$ co-transport could be responsible for the hyperkalemia.[37]

We found significantly (P<0.05) lower level of serum protein and observed significant (P<0.001) decreased values of SOD, GSH R, GSH Px and catalase and these results have supported by other author.[38] There is growing evidence that increased oxidative stress and associated oxidative damage are mediators of vascular injury in cardiovascular stress is intensified with the process of aging and in the elderly, this is accompanied by a more common occurrence of primary hypertension.[39-40] The main novel findings of this study are that oxidative stress contributes to development hypertension.

Hypertension being the third commonest cause in this report shows epistaxis as evidence of poor blood pressure control. This collaborates with an earlier report also from Lagos in Nigeria of some patients who had epistaxis when their hypertension was not controlled due to cessation of antihypertensive drug therapy. The need for regular blood pressure check and compliance to antihypertensive medications must be emphasized. Varsney and Saxena in Deh-

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radun India recorded hypertension as the second commonest cause of epistaxis after idiopathic causes while Chaiyasate et al reported hypertension to be the commonest cause of epistaxis followed by idiopathic causes in the Chiang Mai University Hospital Thailand.[41,42]

It can be concluded that oxidative stresses are associated with hypertension. Hypertension is associated with epistaxis. Antioxidant enzymes and biochemical parameters varies with diseases.

REFERENCE

1. Buonocore G & Perrone S. "Biomarkers of oxidative stress in the fetus and newborn". Haematologica reports. 2(10), pp 103-107, 2006. 2. Cheesman KH & Slater TF. "An introduction to free radical biochemistry". Br Medical Bulletin. 49(3), pp 481-493, 1993. 3. Scott Walsh. "Lipid Peroxidation in Pregnancy". Hypertension in Pregnancy. 13(1), pp1-32, 1994. 4. Halliwell B & Gutteridge JMC. "Oxidative stress and antioxidant protection: some special cases". Free Radicals in Biology and Medicine". Oxford Science Publications: Oxford, pp 485–543, 2000. 5. Hamlyn J M & Blaustein M P. "Sodium chloride, extracellular fluid volume and blood pressure regulation". Am J Physiol. 251(4 Pt 2), pp 563-575, 1986. 6. De Wardener H E. "The primary role of the kidney and salt intake in the aetiology of essential hypertension". Clin Sci. 79, pp 289-292, 1990. 7. Cowley A W Jr. "Long–term control of arterial blood pressure". Physiol Rev. 72, pp 231-236, 1992. 8. Guyton A C, Hall J E, Coleman T G, et al. "The dominant role of the kidney in long–term arterial pressure regulation in normal and hypertensive status". In Laragh J H, Brenner B M (eds.): Hypertension, Pathophysiology, Diagnosis, and Management. 2nd ed. New York. Reven Press, pp1311, 1995. 9. Mitchell K D, Braam B, Navar L G. "Hypertensiogenic mechanism mediated by renal action of renin–angiotensi system". Hypertension. 19 (suppl I), pp 1-18, 1992. 10. S Varshney, R K Saxena. "Epistaxis: a retrospective clinical study". Indian J Otolaryngol Head Neck Surg. 57 (2), pp 125-129, 2005. 11. S A Isezuo, S Segun-Busari, E Ezunu, A Yakubu, K Iseh, J Legbo et. al. "Relationship between epistaxis and hypertension: a study of patients seen in the emergency units of two tertiary health institutions in Nigeria". Niger J Clin Pract. 11 (4), pp 379-382, 2008. 12. Joint National Committee on Detection, Evaluation, Treatment of High Blood Pressure. "The Fifth Report of Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure (JNCV-V)". Arch Intern Med. 153, pp 154-183, 1993. 13. Whelton P K, He J, Klaz M J. "Blood pressure in westernized population; Swales j D (ed.): Text book of hypertension". Oxford, Black Well Scientific Publication. pp 11-21, 1994. 14. Hant J V, Dean R T, et al. "Hydroxyl radicals production and autoxidative glycosylation. Glucose autoxidation as the cause of protein damage in experimental glycation model of diabetes mellitus and aging". Biochem J. 256, pp 205-212, 1988. 15. Josef Coresh, Laura Wei, Geraldine Mc Quillan, et al. "Prevalence of high blood pressure and elevated serum creatinine level in the United States". Arch Intern Med. 161, pp 1207-1216, 2001. 16. Amir P Golbang, Meena Murthy, Abbas Hamad, et al. "A new kindred with pseudohypoaldosteronism type II and a novel mutation (564 > H) in the acidic motif of the WNK 4 gene". Hypertension. 46, pp 295-300, 2005. 17. Maria L Mansego, Sebastian Biesa, Veronica Gonzalez-Albert, et al. "Discordant response of glutathione and thioredoxin system in human hypertension"? Antioxidants & Redox Signaling. 9 (4), pp 1-8, 2007. 18. M I Pikilidou, A N Lasaridis, P A Sarafidis, et al. "Blood pressure and serum potassium levels in hypertensive patients receving". Clin Exp Hypertens. 29, pp 563-573, 2007. 19. Shohet S B, Jain S K. Vitamin E and blood cell function". Ann N Y Acad Sci. 393, pp 229-236, 1982. 20. Jain S K, Mohandas N, Clark M R, et al. "The effect of malondialdehyde, a product of lipid peroxidation, on the deformability, dehydration and 53Cr-Survival of erythrocytes". Br J Haemate. 53, pp 247-255, 1983. 21. Pedro-Botet J, Cavas M I, Martin S, et al. "Decreased endogenous antioxidant enzymatic status in essential hypertension". J Hum Hypertens. 14 (6), pp 343-345, 2000. 22. Djamil Knouf, Malika Bouchenak, Bachir Mohmmed. "Changes in serum lipid and antioxidant status in West Algerian patients with essential hypertension treated with acebutolol compared to healthy subjects". Med Sci Monti. 9 (8), pp 109-115, 2003. 23. Thomos Abraham Vurgese, S B Radhakishan. "Frequency and etiology of hyponatremia in adult hospitalized patients in medical ward of a general hospital in Kuwait". Kuwait Med J. 38 (3), pp 211-213, 2006. 24. H Nandeesha, V Sathiyapriya, Zachariach Bobby, et al. "Altered oxidant-antioxidant status in non-obese men with moderate essential hypertension". Indian J Med Sci. 61 (6), pp 326-331, 2007. 25. H D Khanna, M K Sinha, S Khanna, et al. "Oxidative stress in hypertension: Association with antihypertensive treatment". Indian J Physiol Pharmacol. 52 (3), pp 283-287, 2008. 26. Ibrahim M M, et al. "Hypertension prevalence, awareness, treatment, and control in Egypt. Result from the Eygyption National Hypertension Project, NHP investigation team". Hypertension. 26 (6 pt 1), pp 886-890, 1995. 27. Tao S, Wu X, Duan X et al. "Hypertension prevalence and status of awareness, treatment, and control in China". Chin Med J. pp 108, pp 483-489, 1995. 28. Touyz R M. "Molecular and cellular mechanisms in vascular injury in hypertension: Role of angiotensin-II". Curr Opin Nephrol Hypertens. 14 (2), pp 125-131, 2005. 29. Anne-Safie Furberg, Inger Thune. "Metabolic abnormalities (hypertension, hyperglycemic and overweight) lifestyle (high-energy intake and physical inactivity) and endometrial cancer risk in a Norwegian Cohort". Inter J Can. 104(6), pp 669-676, 2003. 30. Vivian A Fonseca, Fonseca. "Insulin resistance, diabetes hypertension, and renin-angiotensine system inhibition: reducing risk for cardiovascular disease". J Clin Hypertens. 8(10), pp 713-720, 2006. 31. Sarkar D, Latif S A, Uddin MM. "Studies on serum creatinine and creatinine clearance in hypertensive patients". J Bangaladesh Soc Physio. 1, pp 19-26, 2006. 32. Mamta Agrawal, Relvin L Linn, Mark Richards, M Gary Nicholls. "Hyponatremia-hypertensive syndrome with renal ischemia". Hypertension. 33, pp 1020-1024, 1999. 33. Hussain M K, Frantz A G, Ciarochi F, Robinson A G. "Nicotine-stimulated release of neurophysin and vasopressin in human". J Clin Endocrinol Metab. 41, pp 1113-1117, 1975. 34. Burt V L, Whelton P, Roccella E J et al. "Prevalence of hypertension in the U S adult population: Result from the Third National Health and Nutrition Examination Survey, 1988 – 1991". Hypertension. 35, pp 305-313, 1995. 35. E Soppi, J Viikari, P Seppala, et al. "Unusual association of hyperkalemia and hypertension". Hypertension. 8 pp 174-177, 1986. 36. Haim Mayan, Gabriel Munter, et al. "Hypercalceuria in familial hyperkalemia and hypertension accompanies hyperkalemia and precedes hypertension: description of a large family with the Q 565 E WNK4 mutation". The J Clin Endo and Metab. 89 (8), pp 4025-4030, 2004. 37. Stiefel Pablo, Gareia-Morillo Savador, Miranda Maria Luisa, et al. "Gordon's syndrome: Increased maximal rate of the Na-K-Cl contrasport and erythrocyte membrane replacement of sphingomyelin by phosphatilylethanolamine". J Hypertension. 18 (9), pp 1327-1330, 2000. 38. Eugenia Hopps, Rosalia Lo Presti, Gregorio Caimi. "Pathophysiology of polymorphonuclear leukocyte in arterial hypertension". Clin Hemato Microcirculation. 41 (3), pp 209-218, 2009. 39. Harman D. "Aging: A theory based on free radical and radiation chemistry". J Gerontol. 11, pp 298-300, 1956. 40. Zalba G, Jse G S, Mareno M U, et al. "Oxidative stress in arterial hypertension: Role of NAD(P) H oxidase". Hypertension. 38, pp 1395-1399, 2001. 41. Chaiyasate S, Roongrotwattanasiri K, Fooanan S, Sumitsawan Y. "Epistaxis in Chiang Mai university". J Med Assoc Thai. 88, pp 1282-1286, 2005. 42. Varshney S, Saxena R K. "Epistaxis: a retrospective clinical study". Indian Journal of Otolaryngology, Head Neck Surgery. 57, pp 125-129, 2005.