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Hypertensive Patients With and Without Microalbuminuria: A Comparison of Serum Arginine and Nitric Oxide Reactive Species

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Abstract:
Taking into account the controversial nature of data pertaining to plasma arginine levels in hypertension, the fact that humans only synthesize NO from this amino acid, the crucial role that NO plays in preserving endothelial function, and the significance of microalbuminuria early identification.

Aim: Thus, this study set out to determine if hypertension patients with microalbuminuria had elevated levels of nitric oxide reactive species (NOS) and serum arginine, and if so, whether or not there was a link between these two variables and urine microalbumin.

Materials & methods: The S.C.B. medical inpatient and outpatient departments will be closed from October 2018 until September 2019. Thirty-one hypertension patients without microalbuminuria attended the Medical College in Cuttack, Odisha, India; the patients' count was fifty-one. Thirty-one healthy volunteers, matched for age and sex, made up the control group. This research was carried out in collaboration with the departments of medicine and biochemistry at the S.C.B. Medical College in Cuttack, which is located in the central Indian state of Odisha.

Results: The study examined the Pearson's association between NO (µmol/L) and arginine (ng/ml) in individuals with hypertension. The results showed a substantial positive connection ($p = 0.014$, $r = 0.612$). In hypertensive individuals, the Pearson's correlation between urine albumin (mg/dl) and arginine (ng/ml) was examined. With an r-value of -0.364 and a p-value of 0.001, it was discovered that there was a significant inverse association occurring.

Conclusion: In this part of India, hardly much research has been done on arginine. The results of the present study indicated that arginine and nitric levels were positively correlated with critical hypertension. Nevertheless, larger-scale, multicenter studies may be worthwhile to investigate arginine's therapeutic potential in the setting of hypertension.

Key words: Hypertension, Nitric Oxide, Renin Angiotensin Aldosterone System, Insulin, Angiotensin Converting Enzyme, Blood pressure.

Introduction:

Within the Southeast Asian region, hypertension (HTN) is considered to be the third most significant risk factor that has an impact on the sickness burden that may be linked to human activities [1]. An analysis of the data pertaining to the prevalence of hypertension throughout the world in 2012 found that twenty-six percent of Indian males and twenty-nine percent of Indian women were affected by the condition. The percentage of Indian men and women who suffer from hypertension is expected to increase to 22.9 and 23.6 percent, respectively, by the year 2025, according to projections [1].

Under normal physiological conditions, vascular homeostasis is maintained by a complex biochemical network that includes the renin-angiotensin-aldosterone system (RAAS), insulin, and the nicotinic oxide (NO) route. Any alteration to one element may have an impact on others, leading to impaired blood pressure management and hypertension [2]. Although there is a wealth of data linking endothelial dysfunction to hypertension, the precise nature of this association is still unclear. Because NO has a vasodilatory effect, it has been observed that it can reduce Angiotensin II-induced peripheral vasoconstriction and decrease RAAS activation [3]. Reduced NO bioavailability has been shown to increase oxidative stress, improve sympathetic blood outflow, and amplify the pro-hypertensive actions of the sympathetic nervous system ([3].

Nitric Oxide Synthase undergoes an enzymatic conversion to create arginine, the building component of NO. Endothelial nitric oxide synthase (eNOS) is one enzyme that aids in the production of NO from endothelial cells [2]. The precursor of NO, arginine, is a necessary part of physiological processes that support the maintenance of vascular health and homeostasis [1,2]. In addition to its other advantages, arginine lowers levels of angiotensin II and its effects via decreasing the activity of the enzyme known as angiotensin-converting enzyme (ACE). Increased blood pressure and endothelial dysfunction can be brought on by alterations in the metabolism of arginine, as well as by a lack of or an insufficient amount of this amino acid [2]. There have been a few research that have evaluated plasma arginine levels in hypertension patients, and the conclusions of those studies have been the subject of debate. The results of a research [4] showed that plasma arginine levels were not significantly different between individuals with essential hypertension and those without the condition. Patients with EH had greater plasma arginine concentrations, according to another research [5]. This claim contradicts the widely held notion that lower NO levels are suggestive of endothelial dysfunction, which is one possible cause of essential hypertension. However, it has been proposed that other variables like oxidative stress or changes in the RAAS may mask the beneficial effects of arginine's increased NO generation [2].

Five to fifteen percent of those who have essential hypertension will experience clinical proteinuria and a severe decline in their renal function as a result of their condition. When albumin excretion in the urine varies from 30 to 300 mg/24 h, microalbuminuria is detected. Microalbuminuria may stand alone as a predictor of cardiovascular mortality and morbidity in patients with essential hypertension [6]. The risk of peripheral artery disease, ischemic and hemorrhagic stroke, and renal failure is doubled in the presence of microalbuminuria. This might be explained by increased renal endothelial permeability and diffuse endothelial dysfunction [6]. Therefore, preventing the onset of chronic kidney disease and enabling adequate care of individuals with hypertension depend on the early diagnosis of microalbuminuria.

The current study was conducted to measure plasma arginine levels in hypertensive patients, ascertain their correlation with serum NO and microalbuminuria, and assess the therapeutic potential of arginine in essential hypertension. The controversial reports on plasma arginine

levels in hypertension, the importance of early detection of microalbuminuria, the crucial role of NO in endothelial function, and the fact that this amino acid is the sole source of NO synthesis in humans all contributed to these findings. Thus, this study set out to determine if hypertension patients with microalbuminuria had elevated levels of nitric oxide reactive species (NOS) and serum arginine, and if so, whether or not there was a link between these two variables and urine microalbumin.

Materials & methods:

The S.C.B. Medical College in Cuttack, Odisha, has an institutional ethics committee that has given its blessing to the research for it to proceed. It is because of the Drugs and Cosmetics Rules, 1945, Rule 122DD, Registration No. ECR/84/Inst/OR/2013 (710/18.09.18) that this problem has arisen. Written informed permission was acquired for each subject. This inquiry was a case-control research project. The 102 hypertensive patients in the case group were split into two groups according to the presence of microalbuminuria. The S.C.B. medical inpatient and outpatient departments will be closed from October 2018 until September 2019. Thirty-one hypertension patients without microalbuminuria attended the Medical College in Cuttack, Odisha, India; the patients' count was fifty-one. Thirty-one healthy volunteers, matched for age and sex, made up the control group. This study was carried out in cooperation with the S.C.B. Medical College's departments of medicine and biochemistry in Cuttack, Odisha, India.

Patients between the ages of 30 and 65 who had a clinical diagnosis of hypertension, with or without microalbuminuria, met the study's inclusion requirements. A study-specific informed consent form that the patient must sign and understand should serve as documentation of their agreement to participate in the research.

Exclusion criteria included known cases of complications, endocrine abnormalities, cardiovascular illnesses, or diabetes mellitus. a CKD case that has been documented. Examples of known autoimmune diseases. those who drink booze and smoke.

All healthy patients and volunteers provided written consent. Blood pressure readings were regularly taken while the subjects were sitting. The patient was told to wait at least 10 minutes after engaging in any vigorous exercise before having their blood pressure taken. The right arm was used for measurements. The measurements were taken with sphygmomanometers. During a single visit, two measures were taken, and the average was determined.

Five milliliters of urine collected in a sterile container were used to quantify the urine albumin content spectrophotometrically at the Department of Biochemistry's Post Graduate Laboratory using the Pyrogallol Red technique. Five milliliters (mL) of fasting venous blood were drawn; four milliliters were preserved in regular vials for the serum's biochemical examination, and one milliliter was put in vials containing oxo-fluoride to estimate plasma glucose. Serum urea, serum creatinine, serum lipid profile, and fasting plasma glucose were measured at the Regional Diagnostic Center, S. C. B. Medical College, Cuttack, using commercially available standard assays that were adjusted for use with an auto-analyzer.

The GOD-POD technique and a Benesphere device were used to determine the glucose concentration. serum urea level estimation utilizing the GLDH/kinetic approach. Justification for using enzymatic reagents to estimate serum creatinine. Using AGAPPE Limited reagent, the CHOD-PAP (cholesterol oxidase-peroxidase technique) was used to measure serum cholesterol. Serum triglyceride levels were determined using the Glycerol-3-Phosphate-Oxidase/Peroxidase technique (GPO-TOPS). The serum HDL-C level was determined by selective inhibition. The Friedewald formula was used to estimate the serum LDL values. Equational measurement of serum arginine levels was performed with an enzyme-linked immunosorbent test reagent. The

Griess technique was used to assess the amounts of serum nitrite. Using Pyrogallol Red, the amount of protein and albumin discharged in the urine was measured.

Analytical statistics:

The dataset was entered and saved as Excel files in its entirety. The statistical analysis was carried out using SPSS (Statistical Package for the Social Sciences) version 20.0. This table shows the results along with the mean and standard deviation values. The Unpaired Student's T test, post-hoc Tukey HSD, and a one-way ANOVA were utilized to see if the parameter means showed any significant relationships. A scatter plot was then made after that. We utilized Pearson's correlation test to see whether there were any correlations between the various biological indicators. When the p-value was less than 0.05, the results were considered statistically significant; when it was less than 0.01; they were considered extremely significant.

Results:

The age and gender distribution of both healthy persons and hypertension patients is shown in Table 1. Twenty-one females and thirty males comprised the participants who were assigned to the control group. Each of the 102 hypertensive patients who were included in the case group had a microalbuminuric (hypertensive with microalbuminuria) instance and a normoalbuminuric (hypertensive without microalbuminuria) occurrence. In the group with microalbuminuria, there were twenty-two females and thirty males, while in the group with normoalbuminuria, there were twenty females and thirty males. The age range of 40–59 accounted for the majority of instances with microalbuminuria and normoalbuminuria.

Table 1: Age and gender distribution of healthy volunteers and hypertensive patients

Age Group(in years)	Control Group(n=51)			Hypertensive(n=102)					
				Normoalbuminuric(n=51)			Microalbuminuria(n=51)		
	M	F	Total	M	F	Total	M	F	Total
30-39	1	1	2	4	2	6	4	3	7
40-49	13	10	23	17	13	30	14	9	23
50-59	15	9	24	8	5	13	11	7	18
60-69	1	1	2	0	2	2	2	1	3
TOTAL	30	21	51	29	22	51	31	20	51

The blood pressure, renal function, and lipid profile of hypertensive patients and healthy volunteers are compared in Table 2. The individuals with hypertension had noticeably greater SBP and DBP. Compared to Case Group I and controls, Case Group II's mean blood urea level was considerably higher (p=0.000). Furthermore, Case Group II's value was greater than Case Group I's (p=0.013). Compared to controls, Case Group II's mean creatinine value was substantially higher (p=0.016) than Case Group I's (p=0.998). In comparison to the control group, the levels of total cholesterol, triglycerides, LDL-C, and VLDL-C were considerably higher in the two case groups. Nevertheless, compared to Case Group II, total cholesterol and triglyceride levels were significantly higher in Case Group I.

Table 2: Comparison of blood pressure, renal function tests and lipid profile in healthy volunteers and hypertensive patients

Parameter	Controls Mean ± SD (n=51)	Cases	
		Case Group I Mean ± SD (n=51)	Case Group II Mean ± SD (n=51)
SBP (mmHg)	129.8±5.04	158.03±7.2[a, c]	165.7±7.5[b, c]
DBP (mmHg)	82.17±4.29	98.6±7.9[a]	99.4±9.5[b]
Urea (mg/dl)	20.84±5.02	20.4±4.4[c]	23.0±6.2[b, c]
Creatinine (mg/dl)	1.14±0.3	1.19±0.4[c]	1.49±0.7[b, c]
Total Cholesterol	185.6±35.8	213.17±27.87[a, c]	234.31±23.53[b, c]
Triglycerides	126.6±58.49	217.74±41.19[a, c]	229.17±59.04[b, c]
HDL-C	51.35±8.19	51.60±8.07[a]	50.70±7.09
LDL-C	110.56±31.72	140.31±34.82[a]	143.35±35.26[b]

Note: *a–significant between group I and control, b–significant between group II and control, c–significant between group I and group II.

The average serum concentrations of NO, arginine, and urine microalbumin for each of the three research groups are shown in Table 3. Compared to both case groups, controls had greater serum arginine concentrations (p=0.014). Furthermore, it was shown that case group I had a greater serum arginine value than case group II (p=0.016). Additionally, the mean serum NO concentration was greater in the controls than in the two case groups (p=0.025), with case group I show a higher value than case group II (p=0.019). Statistical significance was seen in the values between the control group and case group II (p = 0.006), despite the fact that case group II had a higher value than both case group I and the controls. However, a statistically significant difference (p = 0.623) was not found between the values found in case group I. Moreover, there was a significant difference (p = 0.008) between the two case groups.

Table 3: Serum arginine, nitric oxide (NO), and urine microalbumin concentrations in healthy volunteers and hypertensive patients.

Parameter	Controls Mean ± SD (n=51)	Cases	
		Case Group I Mean ± SD (n=51)	Case Group II Mean ± SD (n=51)
Arginine (ng/ml)	101.31±81.28	22.24±10.30[a, c]	17.25±6.24[b, c]
NO (µmol/L)	20.65±5.78	8.46±3.7[a, c]	5.26±2.21[b, c]
Urine albumin (mg/dl)	10.61 ± 7.33	14.71 ± 8.52[c]	164.74 ± 55.46[b, c]

Note: *a–significant between group I and control, b–significant between group II and control, c–significant between group I and group II

The study examined the Pearson's association between NO (µmol/L) and arginine (ng/ml) in individuals with hypertension. The results showed a substantial positive connection (p = 0.014, r = 0.612). In hypertensive individuals, the Pearson's correlation between urine albumin (mg/dl) and arginine (ng/ml) was examined. A noteworthy inverse relationship was noted, with an r-value of -0.364 and a p-value of 0.001.

Discussion:

Primary or essential hypertension has unknown causal reasons. Essential HTN is present in almost 90% of individuals with HTN [1]. Clinical proteinuria and significant decline in renal

function are hallmarks of essential hypertension. Microalbuminuria in the urine is an indicator of kidney function. There is evidence that in essential hypertension patients, microalbuminuria independently predicts cardiovascular morbidity and death. Microalbuminuria increases the risk of peripheral vascular disease, ischemic and hemorrhagic stroke, and renal failure [6].

Under normal physiological settings, a complex biochemical network consisting of insulin, the NO pathway, and RAAS maintains vascular homeostasis. Changes in any one of these reasons may cause harm to the body's capacity to control HTN and blood pressure [5]. During the process of the enzyme NOS producing nitric oxide (NO), the semi-essential amino acid L-arginine is utilized as a catalyst. These three isoforms of NOS are referred to as nNOS, iNOS, and eNOS respectively. One type of cell or tissue is responsible for the expression of each of these. Vasodilatation, inflammation, cell communication, neuronal protection, immunological defense, and actions that are particular to tissues are some of the well-established functions of nitric oxide (NO) [7]. Through its vasodilatation action, NO has the ability to reduce the activation of RAAS and to function as a buffer against the peripheral vasoconstriction that is caused by Angiotensin II itself. New evidence suggests that reducing NO bioavailability might increase sympathetic output, worsen oxidative stress, and improve the SNS's prohypertensive actions [8]. The endothelium's nitric oxide synthase (NOS) produces endothelial-derived relaxing factor (EDRF), a specific kind of NO. Its job is to regulate the blood vessel tone. An increase in blood flow and dilatation of the arteries are caused by NO's relaxing impact on the smooth muscle of the vascular system [9]. The production of cGMP occurs when nitric oxide (NO) interacts to soluble guanylyl cyclase (sGC). Cyclic GMP is a second messenger that plays a role in a variety of signaling cascades, such as the control of ion channels and the phosphorylation of proteins. This leads to the relaxation and vasodilation of vascular smooth muscles [10].

The body's interior environment and blood vessel health are maintained by a multitude of physiological processes, of which arginine is a crucial component. Since arginine inhibits ACE action, it lowers angiotensin II levels and its effects. Changes in arginine metabolism as well as an arginine deficiency or shortage can lead to endothelial dysfunction and hypertension [11].

Food intake and the body's natural production both contribute to the requirement for arginine. If an aberration prevents arginine from being produced or diverts it to a non-hemodynamic route, there may be a complete lack of arginine [12]. The patients in Case Group I had stage I HTN (when albumin excretion was within physiological limits), while the patients in Case Group II had stage 2 HTN (microalbuminuria, when albumin excretion was within 30-300 mg/dl). These conclusions are based on the findings. As a result, when HTN severity increases, so does albumin excretion in urine. Bhowmick et al. [13] also reported a similar outcome. The findings demonstrated a substantial correlation between blood pressure and microalbuminuria. Even in those with high blood pressure that is within normal range, microalbuminuria is far more prevalent.

Serum creatinine and urea levels in the case and control groups were compared, and the results showed statistically significant differences ($p = 0.016$ and 0.000, respectively). Table 8 demonstrates that there was a statistically significant difference ($p = 0.013$ and $p = 0.000$, respectively) in the mean blood creatinine and urea levels of the two case groups. Normoalbuminuric HTN patients showed lower mean urea and creatinine levels compared to macroalbuminuric HTN patients.

In this study, the lipid profile parameters of the control and case groups were evaluated. Table 9 demonstrates that for every lipid profile marker, the case group's levels were significantly greater than those of the control group. Our study's findings support those of Eguchi et al. [14], who

found a connection between hypercholesterolemia and both HTN and endothelial dysfunction. The renin-angiotensinogen-aldosterone system (RAAS) is activated, and vascular tone is raised when elevated cholesterol levels promote angiotensinogen. Another mechanism that was revealed by Feron and colleagues provide an explanation of the process by which hypercholesterolemia prevents vascular endothelial cells from producing nitric oxide (NO). They discovered that increased levels of low-density lipoprotein (LDL) cholesterol boost caveolin's inhibitory interaction with endothelial nitric oxide synthase (eNOS), which raises caveolin levels. The structure of caveolin is significantly impacted by caveolin, a protein. The output of NO is thus decreased [15].

Case group mean serum arginine concentration was significantly lower than control group mean serum arginine concentration (P = 0.000). When Groups I and II's data were compared, a statistically significant difference (p = 0.000) was found. Endothelial dysfunction and hypotension may result from reduced arginine levels. According to Perticone et al. [16], similar outcomes have been seen.

The concentration of nitric oxide in the blood was significantly lower in cases I and II compared to the control group (p = 0.000 and p = 0.000, respectively). When Groups I and II's data were compared, a statistically significant difference (p = 0.000) was found. Findings from the study of MacAllister et al. [17] also showed similar outcomes. Considering this, it's possible that low NO levels cause hypotension. The following mechanisms, according to the authors' theories, might account for the decrease in NO levels that happens at a little lower concentration of the substrate (L-arginine). When nitric oxide synthase and arginase are out of whack, not only does ornithine production rise, but nitric oxide from arginine production falls as well [18].

The group with hypertension had a higher mean amount of albumin in their urine compared to the group that served as the control. A similar set of observations was also discovered by Mattei and colleagues [19]. People who suffer from cardiovascular disease, renal illness, and general vascular dysfunction are thought to be more likely to experience adverse consequences as a result of this manifestation. In a clinical context, microalbuminuria is usually the first sign of renal impairment. With treatments that stop or decrease the growth of microalbuminuria and any other actions taken to minimize it, end-organ damage can be avoided or postponed. All individuals with diabetes or HTN should get the test at least once a year. Measuring the albumin excretion rate is one of the most accurate methods to detect nephropathy early [20]. An R-value of 0.612 and a p-value of 0.014 indicated a significant positive correlation between serum arginine and blood NO. It was discovered that this association was substantial. Similar to Monique Moss and her associates [21], we arrived at the same decision.

An increased amount of arginine is associated with a greater quantity of NO. Since arginine is the only substrate for the enzyme nitric oxide synthase (NOS), arginine levels increase NO levels through this method. Moreover, elevated arginine levels prevent NO from being converted to peroxynitrite, which in turn slows down the uncoupling of NOS enzymes [22]. Our results show that there is a statistically significant negative correlation (r=-0.417, p=0.001) between the levels of microalbumin and serum NO. As a result, there is an inverse relationship between the levels of microalbumin and NO in those with hypertension. Another item that we noticed was something that was comparable to what Earle et al. [23] found.

Studies have demonstrated that NO metabolites, such nitrite/nitrate (NOx), can function as health status monitors for patients with CVDs and as biomarkers for hypertension (HTN) and cardiovascular disease (CVD) in clinical settings. Therefore, HTN causes microalbuminuria as a result of a decrease in NO levels [24]. With an R-value of -0.364 and a p-value of 0.001, we

investigated the relationship between microalbumin levels and serum arginine and discovered that it was statistically significant to have an inverse relationship. Our findings are in agreement with those of Martynyuk and colleagues [25]. Because of this, the levels of arginine in individuals with hypertension are lower than the levels of microalbumin. In light of these data, it appears that arginine is an effective marker for these individuals. Since arginine is a substrate for nitric oxide synthase (NOS), an increase in arginine levels will result in an increase in NO levels. This is because NO levels are directly tied to arginine levels. As serum arginine levels rise, blood pressure decreases, which in turn lowers microalbumin levels [26].

Conclusion:

It was determined that arginine metabolism is altered, and nitric oxide bioavailability is reduced in hypertensive people with microalbuminuria. These findings emphasize the importance of keeping an eye on these biomarkers in people with hypertension since they may serve as early warning signs of endothelial dysfunction and increased cardiovascular risk. To elucidate the molecular relationships among arginine, nitric oxide, and microalbuminuria, more research is needed. This will make it easier to create focused therapies and improved methods of managing hypertensive individuals. Understanding these correlations may lead to better results and lower rates of cardiovascular morbidity and death in this patient population. In this part of India, hardly much research has been done on arginine. The results of the present study indicated that arginine and nitric levels were positively correlated with critical hypertension. However, larger-scale, multicenter research would be valuable to explore the therapeutic potential of arginine in the context of hypertension.

Conflict of interest:

The authors declare that they have no conflict of interest.

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