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A Study of Renin-Angiotensin-Aldosterone System (RAAS) Changes in Hypertension

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Abstract
Aim: To evaluate Renin-Angiotensin-Aldosterone system (RAAS) changes in Hypertension.
Material and Methods: This cross-sectional study was conducted in Department of General Medicine, Sharda hospital and Central Research Lab of SMS & R, Sharda University, Greater Noida during the period 2022-2024 after obtaining clearance from Institutional Ethics Committee. 75 hypertensive patients (both male and female) diagnosed according to the ISH 2020 criteria aged 35-70 years were recruited for the present study. Investigations included serum renin, ACE-II, aldosterone, cortisol, IL-6 and TNF-α through ELISA technique.
Results: Most common age group of presentation was 50-60 years. There were 52 non-smokers (69.3%) and 23 smokers (30.7%). The mean ACE-II levels observed in this study were 4.72 ± 9.98 at the first visit and 8.48 ± 5.85 at the second visit. A significant difference was found in all the values with statistical significance. The diagnostic accuracy of ACE-II is 55.17% with a confidence interval of (0.39, 0.72).
Conclusion: This study discovered that there is a significant increase in levels of all the components of RAAS and also in the proinflammatory markers in the patients of Hypertension. This study revealed the a statistically significant correlation was established in the values of Renin, Aldosterone, ACE-II, Cortisol, IL-6 and TNF-α. It was established from this study that RAAS affects both diagnosis and prognosis of Hypertension. This study also found a correlation between proinflammatory markers like IL-6 an TNF-α with RAAS. Hypertensive patients should be regularly monitored for changes in components of RAAS and should be advised adequate diet and lifestyle modification.
Keywords: Hypertension, Renin, Aldosterone, ACE-II, Cortisol, IL-6, TNF-α

Introduction

The risk of developing hypertension starts as early as the fetal stage and persists throughout a person's life, presenting various indicators and opportunities for preventive measures along the way. The exact mechanisms that trigger the onset of chronic hypertension in any given individual remain uncertain and elusive. Blood pressure regulation involves several intricate systems, each with its own complexity and interdependence. These systems include the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the kidneys, among others. Factors such as genetics, diet, lifestyle, and environmental influences all play roles in

this multifaceted process. As individuals age, the cumulative effects of untreated hypertension can be severe. Over a lifetime, untreated hypertension can result in a significantly higher risk of early disability or death due to cardiovascular diseases, including heart attack, stroke, and heart failure. [1]

Recent studies in India have reported a prevalence of hypertension at 25% among urban populations and 10% among rural populations. According to WHO estimates from 2008, the prevalence of elevated BP in India was 32.5%, with 33.2% of men and 31.7% of women affected. This rising prevalence underscores the urgent need for public health interventions aimed at prevention, early detection, and management of hypertension to mitigate its impact on the population's health and the healthcare infrastructure. Efforts to address lifestyle factors, increase awareness, and provide accessible healthcare services are crucial in combating this growing epidemic.[2]

The renin-angiotensin system (RAS) has become a crucial element in understanding the pathophysiology of vascular diseases. Angiotensin (Ang) II, the primary peptide of the RAS, was initially regarded as merely a vasoactive hormone. However, recent perspectives have redefined Ang II as a growth factor that influences cell proliferation, apoptosis, and fibrosis. More recently, this role has expanded to include its function as a proinflammatory mediator. Ang II promotes the production of chemokines, cytokines, and adhesion molecules in resident vascular cells, which facilitate the migration of inflammatory cells to sites of tissue injury. Additionally, Ang II acts as a chemotactic and mitogenic agent for mononuclear cells. The vascular damage induced by Ang II is mediated through the activation of transcription factors, redox signaling pathways, and the production of endogenous growth factors. Furthermore, other components of the RAS may also play a role in the development of cardiovascular diseases.[3]

The changes in RAS help in the early diagnosis and also affect the prognosis of hypertensive patients. Not many studies have been done to elicit the changes the values of RAS in Indian population. There is also little data available on the proinflammatory effects of RAS which was addressed in this study. This study aims to address the changes observed in RAS system to increase the diagnostic accuracy and predict the outcome of patients affected with hypertension and decrease the morbidity associated with it. The objectives of the study are as follows:

Primary Objective: To study the changes in levels of Serum Renin, Serum Aldosterone, Serum ACE-II, Serum Cortisol, Serum IL-6 and Serum TNF-α in hypertensive patients.
Secondary Objective: To determine ACE-II as a potential diagnostic and prognostic biomarker in hypertension.

Materials and Methods

This cross-sectional study has been conducted on patients attending the OPD or admitted in General Medicine department of School of Medical Sciences and Research, Sharda University, Greater Noida. After getting permission from ethical committee, research work was initiated on the above protocol. Complete confidentiality regarding the subject's information has been maintained through all phases of the study.

Sample Size: 75
Study duration: One and Half Year, August 2022 to March 2024
Study population: All Hypertensive patients visiting OPD or admitted to Sharda Hospital.
Sample Size Calculation
The following simple Cochran formula can be used -:
$n = Z^2 P (1-P)/d^2$

where:
n= sample size
Z = Z statistic for a level of confidence
P= expected prevalence or proportion (in proportion of one; if 20%, P= 0.2)
d = precision(in proportion of one; if 5 %, d = 0.05)
Value of Z = 1.96
Prevalence of Hypertension in India= 29.8 %
Precision = 6%
d= 0.11
By using this formula, sample size is = 75

Inclusion Criteria
All Hypertensive patients (both male and female) diagnosed according to the ISH 2020 criteria. All eligible patients aged 35-70 years who have been diagnosed with Hypertension.

Category	Systolic (mmHg)		Diastolic (mmHg)
Normal BP	<130	and	<85
High-normal BP	130–139	and/or	85–89
Grade 1 Hypertension	140–159	and/or	90–99
Grade 2 Hypertension	≥160	and/or	≥100

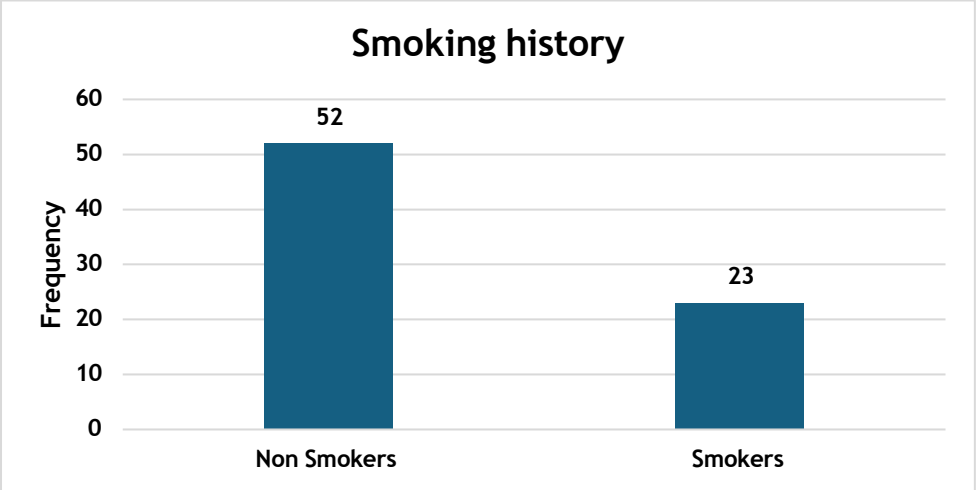
Exclusion criteria
1. Not consenting to participate in the study
2. k/c/o Chronic Kidney disease
3. k/c/o Cushing's Syndrome
4. k/c/o Congenital Heart Disease
5. k/c/o Uncontrolled diabetes
6. k/c/o Thyroid disease
7. k/c/o Haematological disease
8. k/c/o Liver disease
9. H/O drug, substance or alcohol abuse
10. Pregnancy

Study of parameters: Serum renin, ACE-II, aldosterone, cortisol, IL-6 and TNF-α through ELISA technique.

Statistical analysis
All the data obtained was entered in Microsoft excel and analysed using SPSS version 21. The statistical difference between the categorical variable was analysed using the analysis of variance (Anova)/chi-square test. A p-value less than 0.05 has been considered statistically significant.

Results

The mean age was 54.71 years (SD = 10.906 years). There were 32 female participants (42.7%) and 43 male participants (57.3%). This study consisted of more males than females, with a ratio of 1.3:1. There were 52 non-smokers (69.3%) and 23 smokers (30.7%) as shown in graph 1.



Graph 1: Smoking history

The mean cortisol level at 1st visit was 10.227 µg/dl (SD = 8.4078 µg/dl), with a median of 7.200 µg/dl, 25th percentile of 5.100 µg/dl, and 75th percentile of 9.600 µg/dl. The mean cortisol level at 2nd visit was 28.991 µg/dl (SD = 27.9086 µg/dl), with a median of 18.600 µg/dl, 25th percentile of 10.800 µg/dl, and 75th percentile of 37.200 µg/dl. The mean IL-6 level at 1st visit was 7.295 pg/mL (SD = 7.9800 pg/mL), with a median of 5.000 pg/mL, 25th percentile of 3.100 pg/mL, and 75th percentile of 6.500 pg/mL. The mean IL-6 level at 2nd visit was 11.4261 pg/mL (SD = 12.05350 pg/mL), with a median of 9.3000 pg/mL, 25th percentile of 6.0300 pg/mL, and 75th percentile of 12.3000 pg/mL. The mean renin level at 1st visit was 1.9836 ng/mL (SD = 1.06640 ng/mL), with a median of 1.9500 ng/mL, 25th percentile of 0.9100 ng/mL, and 75th percentile of 3.0200 ng/mL. The mean renin level at 2nd visit was 3.6304 ng/mL (SD = 4.06830 ng/mL), with a median of 2.2600 ng/mL, 25th percentile of 0.7300 ng/mL, and 75th percentile of 4.6100 ng/mL. The mean ACE-2 level at 1st visit was 8.47880 ng/mL (SD = 5.851309 ng/mL), with a median of 7.89000 ng/mL, 25th percentile of 3.21000 ng/mL, and 75th percentile of 13.45600 ng/mL. The mean ACE-2 level at 2nd visit was 4.72595 ng/mL (SD = 9.986541 ng/mL), with a median of 0.21400 ng/mL, 25th percentile of 0.10700 ng/mL, and 75th percentile of 0.98100 ng/mL (table 1).

Table 1: Mean of the parameters among the participants

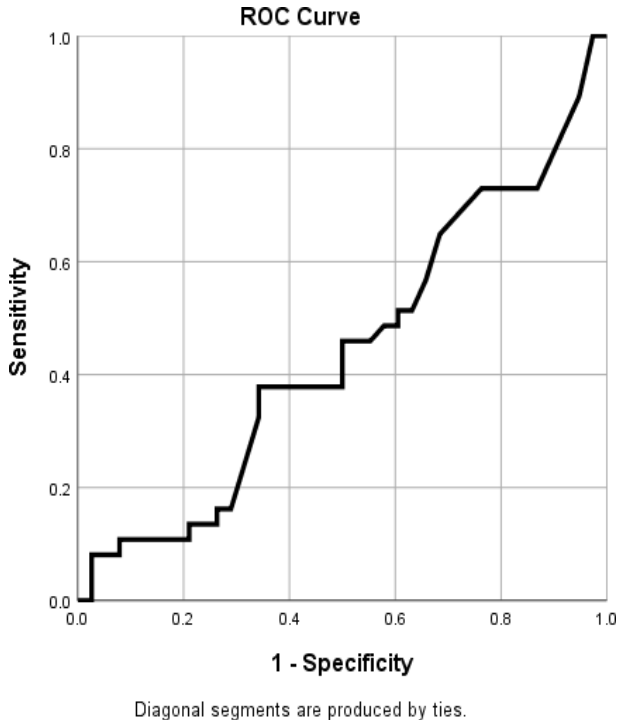
	Mean	Median	SD	Percentiles	
				25	75
Cortisol 1st visit (µg/dl)	10.227	7.200	8.4078	5.100	9.600
Cortisol 2nd visit (µg/dl)	28.991	18.600	27.9086	10.800	37.200
Aldosterone 1st visit (pg/ml)	13.832	11.500	9.2187	6.500	19.800
Aldosterone 2nd visit (pg/ml)	44.9903	23.5000	46.65423	14.5000	64.0000
IL-6 1st visit (pg/mL)	7.295	5.000	7.9800	3.100	6.500
IL-6 2nd visit (pg/mL)	11.4261	9.3000	12.05350	6.0300	12.3000
TNF-α 1st visit (pg/mL)	9.512	9.200	5.7742	4.500	14.600
TNF-α 2nd visit (pg/mL)	6.3285	6.4000	3.15310	4.1000	9.0000

RENIN 1st visit (ng/mL)	1.9836	1.9500	1.06640	.9100	3.0200
RENIN 2nd visit (ng/mL)	3.6304	2.2600	4.06830	.7300	4.6100
ACE-2 1st visit (ng/mL)	8.47880	7.89000	5.851309	3.21000	13.45600
ACE-2 2nd visit (ng/mL)	4.72595	.21400	9.986541	.10700	.98100

The mean renin level at 2nd visit was 3.6304 ng/mL (SD = 4.06830 ng/mL), and the mean renin level at 1st visit was 1.9836 ng/mL (SD = 1.06640 ng/mL), with a p-value of 0.001. The mean cortisol level at 2nd visit was 28.991 µg/dl (SD = 27.9086 µg/dl), and the mean cortisol level at 1st visit was 10.227 µg/dl (SD = 8.4078 µg/dl), with a p-value of <0.001. The mean ACE-2 level at 2nd visit was 4.72595 ng/mL (SD = 9.986541 ng/mL), and the mean ACE-2 level at 1st visit was 8.47880 ng/mL (SD = 5.851309 ng/mL), with a p-value of 0.007. The mean IL-6 level at 2nd visit was 11.4261 pg/mL (SD = 12.05350 pg/mL), and the mean IL-6 level at 1st visit was 7.295 pg/mL (SD = 7.9800 pg/mL), with a p-value of 0.013. The mean TNF-α level at 2nd visit was 6.3285 pg/mL (SD = 3.15310 pg/mL), and the mean TNF-α level at 1st visit was 9.512 pg/mL (SD = 5.7742 pg/mL), with a p-value of <0.001. The mean aldosterone level at 2nd visit was 44.9903 pg/mL (SD = 46.65423 pg/mL), and the mean aldosterone level at 1st visit was 13.832 pg/mL (SD = 9.2187 pg/mL), with a p-value of <0.001 (table 2).

Table 2: Mean pair of the participants

		Mean	N	Std. Deviation	Std. Error Mean	P value
PAIR 1	RENIN 1st visit (ng/mL)	1.9836	75	1.06640	.12314	0.001
	RENIN 2nd visit (ng/mL)	3.6304	75	4.06830	.46977	
PAIR 2	CORTISOL 1st visit (µg/dl)	10.227	75	8.4078	.9709	<0.001
	CORTISOL 2nd visit(µg/dl)	28.991	75	27.9086	3.2226	
PAIR 3	ACE-2 1st visit (ng/mL)	8.47880	75	5.851309	.675651	0.007
	ACE-2 2nd visit (ng/mL)	4.72595	75	9.986541	1.153146	
PAIR 4	IL-6 1st visit (pg/mL)	7.295	75	7.9800	.9214	0.013
	IL-6 2nd visit (pg/mL)	11.4261	75	12.05350	1.39182	
PAIR 5	TNF-α 1st visit (pg/mL)	9.512	75	5.7742	.6668	<0.001
	TNF-α 2nd visit (pg/mL)	6.3285	75	3.15310	.36409	
PAIR 6	ALDOSTERONE 1st visit (pg/mL)	13.832	75	9.2187	1.0645	<0.001
	ALDOSTERONE 2nd visit (pg/mL)	44.9903	75	46.65423	5.38717	



Graph 2: ROC curve

The sensitivity is 16.22% with a confidence interval of (0.0, 0.33). This indicates that ACE-2 levels correctly identify only 16.22% of patients with Grade 1 Hypertension. The specificity is 100% with a confidence interval of (0.89, 1.0). This means that ACE-2 levels perfectly identify patients who do not have Grade 1 Hypertension. The diagnostic accuracy is 55.17% with a confidence interval of (0.39, 0.72). This means that the ACE-2 classification matches the actual grade in 55.17% of the cases. The p-value is 0.000000252, indicating a statistically significant association between ACE-2 levels and Grade 1 Hypertension. Given these findings, ACE-2 levels alone are not a highly reliable indicator for detecting Grade 1 Hypertension, despite the perfect specificity and PPV. The low sensitivity and moderate overall accuracy suggest that other diagnostic methods should complement ACE-2 level assessments (graph 2, table 3).

Table 3: Area under the curve

Metric	Value	95% Confidence Interval
Sensitivity	0.16	(0.0, 0.33)
Specificity	1.0	(0.89, 1.0)
Positive Predictive Value (PPV)	1.0	(0.89, 1.0)
Negative Predictive Value (NPV)	0.5	(0.31, 0.69)
Positive Likelihood Ratio (PLR)	∞	-
Negative Likelihood Ratio (NLR)	0.83	-
Diagnostic Accuracy	0.55	(0.39, 0.72)
P-value	<0.001	-

Area Under the Curve, Test Result Variable(s): ACE-2 (ng/mL)				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.442	.067	.388	.311	.573

Discussion

This study was conducted involving 75 hypertensive individuals within an outpatient department to investigate their physiological parameters across two distinct time points spaced one month apart. The study aimed to assess variations in renin, angiotensin, aldosterone, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF alpha), and angiotensin-converting enzyme 2 (ACE2) levels within this cohort. Through meticulous examination, we sought to discern any potential fluctuations or patterns in these biomarkers over time, shedding light on the dynamic nature of hypertensive physiology. By conducting comprehensive analyses at multiple intervals, the study aimed to contribute valuable insights into the intricate mechanisms underlying hypertension and its potential implications for clinical management.

The mean age of the study population was 54.71 +/- 10.91 years, which corroborates with the JNC 8 statistics for hypertensive patients. The mean age in a study Syed et al [4] was 37.5 ± 8.54 in the controls, while it was 39.2 ± 7.73 in pre-hypertensive patients, 46.2 ± 12.1 in grade I hypertensives and 47.5 ± 11.6 in grade II hypertensives. This was higher than the findings in our study.

This study consisted of more males than females (43 vs 32 years), with a ratio of 1.3:1. In the study by Syed et al [4], in their study subjects (n = 276), the gender distribution was almost equal with respect to sex (male: 49.6%; female 50.4%). This ratio is reversed as compared to the present study. In a study by Alderman et al [5], on renin levels in hypertensive patients, 63% were males, which is much higher than the distribution noted in the current study.

Even though cortisol-induced high blood pressure typically involves retaining sodium and expanding volume, research involving synthetic glucocorticoids or sodium limitation implies that hypertension may largely occur regardless of sodium levels and volume status. While an elevation in cardiac output isn't necessary for the increase in blood pressure associated with cortisol, the specific contribution of heightened total or regional peripheral resistance as a primary mechanism remains uncertain.

In the present study, the mean cortisol at first visit was found to be 10.23 +/- 8.4 µg/dl. The mean cortisol at second visit was found to be 28.99 +/- 27.91 µg/dl. The difference between the two groups was found to be statistically significant. There is a weak positive correlation, however, the correlation was statistically significant. In a study by Syed et al [4], the serum cortisol level in four groups was 7.61 ± 4.15, 9.36 ± 3.25, 9.08 ± 3.97, and 9.99 ± 4.85, respectively. The difference between the groups was found to be statistically significant. Comparing with this study the serum cortisol levels were found to higher in the present study.

A study conducted within a community setting revealed that even slight elevations in plasma aldosterone concentration, falling within the physiological range, could predispose individuals to hypertension (HTN) development. However, sustained increases over the long term are believed to result from the complex interplay of unidentified genetic factors and known environmental influences such as high-fat and high-salt diets, reduced physical activity, stress, and caffeine intake. These factors collectively contribute to the phenotype of aldosterone-associated HTN and cardiovascular (CV) damage, particularly manifesting in middle age and beyond. Given the significant role of aldosterone in these processes, there is growing consideration for including it as a primary screening target to prevent CV events.

The mean aldosterone level at the time of first visit was 13.83 +/- 9.22 while it was 44.99+/- 46.65 pg/mL at the time of second visit. The difference between the two groups is found to be statistically significant. There is a weak positive correlation, and the correlation is statistically significant. In a study by Syed et al [4], the mean aldosterone level was the highest in, HTN stage I (12.41 ± 5.72) as compared to control group (9.17 ± 3.49), pre-HTN (8.76 ± 3.31), and stage II HTN (12.05 ± 6.84). The mean aldosterone level in this study was in high normal range and was found to have positive correlation with BMI and WC in controls, and to TC

and LDL in pre-HTN group. Comparing with this study the mean aldosterone levels were found to be higher in the present study at both the visits.

Association of aldosterone with obesity, lipid levels, and IR had been confirmed by studies as adipokines and insulin stimulates aldosterone production, which in turn causes fluid retention, endothelial cell dysfunction, atherosclerosis, and HTN.

In the present study, the mean renin value at second visit was found to be 1.98 +/- 1.06 ng/mL the mean renin value at second visit was found to be 3.63 +/- 4.07 ng/mL. The difference between the two groups was found to be statistically significant. There is a weak positive correlation and, the correlation was statistically significant. In a study by Alderman et al [5], they observed that 1.40 (0.5, 2.7), with 0.3 (0.2, 0.5) in the low renin group, 1.8 (1.2, 2.7) in the medium group and 6.2 (5.3, 7.7) in the high renin group. The difference between the 3 groups was observed to be statistically significant < .001.

Roughly one-third of hypertension patients are diagnosed with "low-renin hypertension," a condition where the renin levels are notably low. Individuals with this type of hypertension tend to exhibit salt sensitivity and may show improved responses to diuretic treatment. The category of low-renin hypertension encompasses patients with normokalemic primary hyperaldosteronism, primarily idiopathic in nature, which is found in around 15% of hypertensive individuals and may signify an advanced stage in the progression of neurohormonal alterations in what is termed "essential" hypertension. While early studies suggested that patients with low renin levels might experience a relatively positive prognosis, more recent epidemiological research indicates that those with low-renin and/or salt-sensitive hypertension face a heightened risk of organ damage, cardiovascular incidents, and mortality when compared to other hypertensive cohorts.

ACE2 exhibits elevated expression specifically within the endothelial cells lining the arteries, arterioles, and venules of the heart and kidneys. This has positioned ACE2 as a promising target for therapeutic interventions aimed at managing hypertension and cardiac issues. Numerous animal studies, conducted on rat models with diet-induced hypertension, have revealed a correlation between heightened blood pressure and decreased mRNA expression and protein levels of ACE2. These findings indicate that diminished ACE2 levels may result in increased levels of Angiotensin II, consequently leading to hypertension.

The mean ACE-II levels observed in this study were 4.72 ± 9.98 at the first visit and 8.48 ± 5.85 at the second visit, with the difference between the two measurements being statistically significant. There was a weak positive correlation, which was also statistically significant. The diagnostic accuracy was 55.17%, with a confidence interval of 0.39 to 0.72, indicating that the ACE-2 classification correctly identified the actual grade in 55.17% of cases. Despite perfect specificity and positive predictive value (PPV), ACE-2 levels alone are not highly reliable for detecting Grade 1 Hypertension. The low sensitivity and moderate overall accuracy suggest the need for additional diagnostic methods to supplement ACE-2 level assessments. The mean ACE-II levels in the present study is 5.16 in grade I hypertensives, while it was 4.3 in grade II hypertensives. There was no significant difference between the two groups.

In a study by Jung Kyun Oh et al [6], the S-ACE activity was significantly elevated in 15 hypertensive diabetics (14.29± 7.10 Unit) as compared with that in 23 normotensive diabetics (6.24±3.68 Unit) ($p<0.005$). The S-ACE activity was directly correlated to the mean arterial pressure ($r=0.54$) ($p<0.005$). In a study by Elrayess et al [7], the ACE-2 enzyme levels in the total population of hypertensive patients with COVID 19 was 2784.8 +/-1471.2 pg/ml. Angiotensin II levels were lowest in the CCB treated group (2266.8 ng/ml, ±1061.2), whereas ACE2 levels were highest in this group (630.2 ng/ml, ±947.3). The count was highest in ACEi treated group (1.8 10^3/mL ± 1.1) compared to ARB treated group which had the lowest count (1.3 10^3/mL ± 0.69).

It is interesting to note that several immune cells, including T lymphocytes, dendritic cells, and macrophages, have angiotensin 1 receptors (AT1R). When angiotensin II binds to AT1R, it influences the differentiation of these immune cells and stimulates the production of proinflammatory cytokines like IL-6, IFN-γ, and TNF-α. Additionally, angiotensin II promotes the adhesion and migration of leukocytes by acting on P-selectins and adhesion molecules. This interaction affects the immune system even without causing vasoconstriction, which highlights the role of the renin-angiotensin-aldosterone system (RAAS) in the inflammatory aspects of hypertension (HTN). Angiotensin II not only contributes to the onset of HTN but also to the associated organ damage. Furthermore, proinflammatory cytokines such as TNF-α can increase the production of angiotensin-converting enzyme (ACE), which further promotes inflammation-mediated hypertension.

In this study, IL6 mean value is 7.29 +/- 7.98 and 11.43+/- 12.05 at first and second visit respectively. Whereas TNF-α is 9.512 +/- 5.77 and 6.33 +/- 3.15 at first and second visit respectively. The difference between the two groups was found to be statistically significant. There is a weak positive correlation and, the correlation was statistically significant. In a study by Bautista et al [8], the IL6 in hypertensives was significantly higher than [10.0(7.9,12.6) vs 5.0(3.5,6.9); p value- 0.005)]. Similarly, TNF-α(pg/dl) was higher in hypertensives than those without hypertension [7.9(4.2,15.0) vs 1.8(0.8,4.0) p value 0.015). Thus, comparing these two studies suggest that higher levels of IL-6 and TNF-α are associated with hypertension. This shows that IL6 and TNF are potential markers for severity of hypertension.

Limitations

The study population is small as compared to the studies taken for reference. Age and sex propensity matching necessary in larger sample sizes.

Conclusion

This study discovered that there is a significant increase in levels of all the components of RAAS and also in the proinflammatory markers in the patients of Hypertension. The patents were identified as hypertensive according to ISH 2020 criteria for Hypertension and were included in study after informed consent. The mean values of all the individual components of RAAS were calculated at two separate visits and a difference between these values was studied. This study revealed the a statistically significant correlation was established in the values of Renin, Aldosterone, ACE-II, Cortisol, IL-6 and TNF-α. It was established from this study that RAAS affects both diagnosis and prognosis of Hypertension. This study also found a correlation between proinflammatory markers like IL-6 an TNF-α with RAAS. The sample size taken in this study was less compared to previous studies which demands the need for bigger cohort in the future studies to establish significance of RAAS changes as potential diagnostic markers for hypertension.

Regular follow up of hypertensive patients and lifestyle modifications should be advised to all hypertensive papulation. RAAS system changes can be considered for study of early diagnostic workup of all patients with cardiometabolic syndrome and thus preventing morbidity and mortality. The progression to chronic kidney disease for all the Hypertensive patients can be stopped by using RAAS modifiers such as ACE inhibitors and ARBs. Hypertensive patients should be regularly monitored for changes in components of RAAS and should be advised adequate diet and lifestyle modification.

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