Spectrum of renin angiotensin aldosterone system disorders in young hypertensives of Pakistan

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Abstract

The study was a cross sectional study conducted at the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology (AFIP) Rawalpindi from Jan 2016 to Dec 2016. One hundred and sixty-five young hypertensive subjects, aged 17-40 years of either gender presenting in the outpatient department (OPD) were recruited from local population of Rawalpindi. All subjects were having blood pressure more than 140/90 mm of Hg and were not on any anti-hypertensive medicine. Patients with renal dysfunction, heart failure, pregnancy and secondary hypertension were excluded from the study. Blood sample was taken from each patient to analyze arterial blood gases, plasma renin, serum aldosterone and electrolytes. Sandwich chemiluminescence immunoassay and ELISA techniques were used to analyze plasma renin and serum aldosterone level. Arterial blood gases and electrolytes like sodium and potassium were measured by potentiometry, while bicarbonate was calculated. Normally distributed continuous variables were presented as mean+SD and others as median. Multiple regression analysis was performed to compute association of age, electrolytes, systolic and diastolic blood pressure in OPD and Endocrine Clinic AFIP with essential hypertension and primary hyperaldosteronism. $P<0.05$ was considered statistically significant. Out of 80 subjects, 72 were diagnosed with essential hypertension and 8 with primary hyperaldosteronism. None of the patients had Liddle syndrome, apparent mineralocorticoid excess or Gordon syndrome. Mean age of patients having essential hypertension was 30.97+7.13 years, whereas those with primary hyperaldosteronism was 29.25+7.1 years. Mean serum sodium was 137.8+6.5 mmol/l and potassium was 4.23+0.6 mmol/l. Mean systolic blood pressure of patients measured in OPD was 172.7+19.2 mm of Hg whereas diastolic blood pressure was 100.0+8.3 mm of Hg. Mean systolic blood pressure measured in Endocrine Clinic AFIP was 142.7+10.5 mm of Hg and diastolic blood pressure was 90.3+6.5 mm of Hg. Diastolic blood pressure was significantly higher ($p=0.001$) among all the patients reported in OPD. No statistically significant association was found between age, systolic and diastolic blood pressure ($p<0.05$) in either OPD or endocrine clinic. Therefore, it was concluded that hypertension is not uncommon in young population of Pakistan. Primary hyperaldosteronism as compared to other RAAS disorders, remains the leading cause of hypertension in young population.

Introduction:

Hypertension and chronic kidney disease are highly prevalent diseases around the world. The WHO indicate that one in four men and one in five women have hypertension. CKD affects up to ten percent of the world's population. Hypertension and CKD are closely interlinked, such that CKD is one of the most common causes of secondary hypertension and hypertension is an important factor related to CKD progression. The best-known example is renal artery stenosis, which is characterized by both hypertension and progressive loss of renal function. It was recognized as the prototype of angiotensin-dependent hypertension, contributing to the discovery of the renin–angiotensin-aldosterone system (RAAS). A growing body of evidence suggests that both hypertension and kidney disease may have their origins in early life. During kidney development, an exposure to a suboptimal intrauterine environment results in lifelong negative influences on renal structure and function and on renal compensatory mechanisms by so-called renal programming. The developing kidney can be programmed by a diversity of early-life insults, leading to hypertension and kidney disease in adulthood. The concept that adverse conditions during organogenesis increase the vulnerability for developing adult diseases is called fetal origins hypothesis, more recently named "Developmental Origins of Health and Disease" (DOHaD). On the other hand, this concept leads to a theoretical shift of therapeutic approach from adult life to earlier stage, namely reprogramming, to potentially reverse disease processes before clinical disease becomes evident. Blood pressure is tightly controlled by very complex networks, including the RAAS, endothelial function, sympathetic nervous system, natriuretic peptides, inflammation and the immune system. The RAAS serves a counter-regulatory role in the pathogenesis and development of hypertension. Several potential molecular mechanisms involved in developmental programming of hypertension and kidney disease have been addressed, including aberrant RAAS, oxidative stress, nitric oxide deficiency, gut microbiota dysbiosis, dysregulated nutrient-sensing signals, epigenetic regulation, and reduced nephron number. Among them, the RAAS not only plays a vital role in the regulation of BP but also closely interacts with other mechanisms. The RAAS is a major hormone cascade composed of different angiotensin peptides with a variety of biological functions mediated by distinct receptors. There are two major pathways in the RAAS: classical and non-classical pathways. The classical RAAS is mainly made up of angiotensin-converting enzyme , angiotensin II, and angiotensin II type 1 receptor . Under pathophysiological conditions, the classical RAAS can be activated to trigger vasoconstriction and inflammation, thus promoting hypertension and kidney damage. Conversely, the non-classical RAAS composed of the ACE2-ANG-(1-7)-MAS receptor axis counterbalances the detrimental effects of ANG II signaling. Of note is that both axes of the RAAS have been linked to fetal programming. Although blockade of the

classical RAAS provides the rationale for current antihypertensive and renoprotective therapies, there is limited data on whether early targeting on the RAAS can prevent hypertension and kidney disease of developmental origins. In the review, therefore, we present a contemporary update of the RAAS, explaining its role on hypertension and kidney disease of developmental origins and emphasizing its links to other mechanisms. We also highlight the potential reprogramming interventions that target the RAAS for prevention of developmental programming of hypertension and kidney disease. We retrieved related literature from all articles indexed in PubMed/MEDLINE. We used the following keywords and their combinations: "renin", "angiotensin", "chronic kidney disease", "developmental programming", "DOHaD", "offspring", "mother", "nephrogenesis", "nephron", "prorenin receptor", "aldosterone", "mineralocorticoid receptor", "pregnancy", "progeny", "reprogramming", "angiotensinogen", "angiotensin-converting enzyme", and "hypertension". Additional studies were then selected and evaluated based on appropriate references in eligible papers.

Methods:

This cross-sectional study was conducted at the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan, from January to December, 2016. It comprised hypertensive subjects aged 17-40 years of either gender presenting in the outpatient department. All subjects were having blood pressure more than 140/90mmHg and were not on any anti-hypertensive medicine. Blood sample was taken from each patient to analyse arterial blood gases, plasma renin, serum aldosterone and electrolytes. Association of qualitative variables like age, systolic and diastolic blood pressure with essential hypertension and primary hyperaldosteronism was explored.

Results:

Of the 80 patients, 72(90%) were diagnosed with essential hypertension and 8(10%) with primary hyperaldosteronism. None of the patients had Liddle syndrome, apparent mineralocorticoid excess or Gordon syndrome. Mean age of patients having essential hypertension was 30.97±7.1 years, whereas, for those with primary hyperaldosteronism it was 29.25±7.1 years. Systolic blood pressure was significantly higher ($p = 0.000$) among all patients. No statistically significant association was found between age, systolic and diastolic blood pressure ($p<0.05$).

Conclusion:

Current evidence has provided vigorous but incomplete data in regard to the potential therapeutic role of RAAS-based interventions in hypertension and kidney disease of developmental origins. This review affords a brief overview on the various RAAS-based therapies that shows benefits on renal programming, including renin inhibitor, ACEI, ARB, AT1R antisense, and ACE2 activator. So far, one major unsolved problem is that almost no studies have taken a holistic approach to simultaneous quantify the expression/activity of the entire repertoire of the RAAS components in an experiment. Due to the complex nature of RAAS signaling, the reprogramming effect in response to early-life RAAS-based interventions, either individually or in combination, are incomplete and difficult to predict. Therefore, future work in developing ideal methodology is needed to get a more holistic view of the RAAS and ensure RAAS-based therapy would only apply in the right direction. Moreover, attention will need to be paid to decide the optimal dosage in a sex-dependent manner to maximize the benefit without increasing toxicity prior to clinical translation. Despite significant progress being made in the availability of a broad range of RAASbased drugs, less attention has been paid to investigate their reprogramming effects on hypertension and kidney disease. Another challenge is that specific developmental windows for different RAAS-based therapies to reprogram the processes driving hypertension and kidney disease still await further clarification. For now, our review has taken a step forward by linking RAAS to hypertension and kidney disease of developmental origins, which may yield insights into new RAAS-based interventions for preventing renal programming-related disorders in a clinical setting.