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ORIGINAL ARTICLE

A comparative study of plasma renin activity, aldosterone and atrial natriuretic hormone between normotensive and hypertensive people living at below sea level altitude (Jordan Valley) and those residing at moderate altitude above sea level (Irbid City)

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Abstract

A cross-sectional study was designed to investigate the association of the levels of plasma renin activity (PRA) and aldosterone (ALDO) and atrial natriuretic hormone (ANH) with the rates of hypertension prevalence in people living at 340 meters below sea level, the Jordan Valley (JV) and those residing at 620 meters above sea level, Irbid City. 1072 natives from the JV and 1402 natives from Irbid City were covered by a questionnaire to estimate hypertension prevalence in the JV and Irbid city (population age: 35–65 years). Male subjects were selected from the JV (24 hypertensives, 46±15 years old, and 93 normotensives, 33±13 years old) and from Irbid City (31 hypertensives, 47±12 years old, and 89 normotensives, 40±13 years old) to evaluate the levels of PRA, ALDO and ANH. Hypertension was less common in the JV than in Irbid City (9.9% vs. 13.6%). The levels of PRA in the hypertensive subjects compared to the normotensive subjects were lower in the JV (1.7±1.0 vs. 2.6±1.4 ng/ml/hr) but were similar in Irbid City (2.9±2.7 vs. 3.2±2.7). The levels of ALDO in the hypertensive subjects compared to the normotensive subjects were similar in the JV (119±58 vs. 139±66 pg/ml) but were higher in Irbid City (199±112 vs. 146±84). The levels of ANH in the hypertensive subjects compared to the normotensive subjects were lower in the JV (13.9±9.3 vs. 28.0±12.7 ng/ml) and were also lower in Irbid City (21.0±12.2 vs. 26.7±11.6).

INTRODUCTION AND BACKGROUND

Background

Hypertension is one of the major medical problems of the world. It affects more than 15% of the population in western countries, and it is one of the major risk factors for coronary heart disease, cerebrovascular accident, chronic renal failure, and congestive heart failure (Hauston, *et al.,* 1999). Hypertension includes all individuals with a sustained elevation of arterial BP of more than 90 mm Hg diastolic and/or more than 140 mm systolic.

Etiology of hypertension and hormonal aspects

The majority of hypertensive subjects (>90%) have no defined organ defect responsible for the elevated BP (*essential hypertension*). A small minority of hypertensive patients (<10%) has a specific organ defect, which with its correction, hypertension may be cured (*secondary hypertension*) (Tuck, 1990, Kaplan, 1998).

Hormonal factors are clearly involved in the pathophysiology of most forms of secondary hypertension, renin-angiotensin (renal hypertension); ALDO (primary aldosteronism); glucocorticiods (Cushing's syndrome); catecholamines (pheochromocytoma); estrogen (oral contraceptives) and growth hormone (acromegaly) (Williams and Moore, 1995, Kaplan, 1998).

The role of hormonal factors in the pathophysiology of patients with essential hypertension is less well understood. Essential hypertension is unlikely to represent a homogeneous group of patients. The reported hypothesis of the pathophysiological mechanisms of essential hypertension have been based on the concept that the elevation in blood pressure (BP) is mediated by overactivity of systems that tend to elevate BP (pressor systems) and / or by a deficiency in systems that tend to lower BP (depressor systems) (Kaufmann *et al.,* 1986).

The renin-angiotensin system (a pressor) has been considered to be the essential endocrine mechanism involved in devolping and sustaining arterial hypertension (Kaufmann *et al.,* 1986). Evidence for a possible role of ALDO (a pressor) in the genesis of essential hypertension has also been addressed (Fraser and Padfield, 1985). The pathophysiological significance of the ANH (a depressor) is not yet clear (Hofbauer and Bonner, 1985)

Regulation of renin-angiotensin system

The major regulatory event in the renin-angiotensin cascade, in absence of alterations of angiotensinogen concentration, is the renin secretion. Changes in renin secretion are reflected on the enzymatic activity of renin and, in turn, on the concentration of A-II, the biologically active component of renin-angiotensin system (Hsueh and Tuck, 1990).

The major mechanisms that stimulate renin release from the JG cells, include:

1) Decreased blood perfusion (volume) in the renal afferent arterioles (which is probably mediated by a cellular stretch mechanism).
2) Decreased sodium chloride load at the macula densa (specialized group of renal distal tubular cells in approximation to the JG apparatus).
3) Sympathetic nervous system stimulation of B1-adrenergic receptors at the JG cells (mediated by norepinephrine).
4) Local effectors such as dopamine, prostaglandins and kinins (Hsueh and Tuck, 1990, Siragy and Carey, 1998).

The major mechanisms that inhibit renin release, include:

1) Negative-feedback inhibition by A-II at the JG cells.
2) Inhibition by hormonal factors, ADH and ANH.
3) Inhibition by local effectors such as nitric oxide and adenosine (Hsueh and Tuck 1990, Siragy and Carey, 1998).

Renin measurement

The most commonly used assay for renin measurements measures the *plasma renin activity* (PRA). This consists of two steps. First, plasma is incubated at 37 c for specific period of time, allowing the renin in the sample to cleave angiotensin-I from angiotensinogen. The second step is to measure the angiotensin-I formed by radioimmunoassay (RIA). Results of these assays are generally reported as nanograms of angiotensin-I generated per milliliter of plasma per hour of incubation (ng/ml/hr). Some laboratories prefer to add an excess of angiotensinogen to the sample. This allows the renin activity measurement to be independent of the endogenous angiotensinogen concentration (Williams and Moore, 1995).

Factors affecting PRA

Physiologic stimulation of renin release (and hence PRA) occurs in the presence of hypotension, decreased sodium intake, dehydration, and upright posture as well as with changes in the time of day (morning) or menstrual cycle. Increased potassium intake or serum potassium concentration can also stimulate renin release. Nearly all diuretics and antihypertensive agents affect renin release; if the renin-angiotensin system is to be clinically evaluated, these agents should be tapered and discontinued three weeks before evaluation, if possible (Siragy and Carey, 1998). In addition, age and race affect renin activity. Renin levels decline with age. Black patients have higher prevalence of low-renin hypertension (Williams and Moore, 1995)

One of the fundamental observations in patients with essential hypertension is the variation in PRA values, which range from low to high levels. Approximately, 10–15% of patients with essential hypertension has elevated levels of PRA, and around 60% of patients with essential hypertension have normal PRA levels (Williams, 1991, Laragh and Sealey, 1991, Kaufmann *et al.,* 1986,

Kaplan, 1988). The high and the normal plasma renin values in hypertension may indicate a renin-mediated hypertension. This is supported by observations that these patients respond favorably to anti-renin system treatments including angiotensin-converting enzyme inhibitors and β-blockers (Laragh and Sealey, 1991).

The normal renin value in any hypertensive person is considered abnormally high in the context of the elevated BP (Laragh and Sealey, 1991). A hypothesis explaining the normal-renin essential hypertension supposes the presence of two functionally abnormal nephrons, a minor subgroup of hypofiltering nephrons with impaired sodium excretion and renin hypersecretion, and a larger subgroup of normal nephrons that adaptly react to the increased blood pressure by suppressing renin secretion, and increasing glomerular filtration rate. Renin suppression in the normal nephrons compensates the excess production in the impaired nephrons, producing a net output equal to that seen in normotensive individuals, however, the interference with overall sodium excretion results in increased blood pressure (Laragh and Sealey, 1991).

ALDO role in essential hypertension

A major feature of mineralocorticoid excess syndrome is the suppression of plasma renin (In hypertension due to primary aldosteronism, PRA levels are suppressed and respond sluggishly to sodium depletion (Laragh and Sealey, 1991, Laidlaw, 1979)). The observation therefore that approximately 20–30% of patients with essential hypertension having low levels of renin was taken as indicating the presence of excess mineralocorticoid activity in this subgroup of essential hypertension. In addition, patients with low-renin hypertension (as a group) have long been shown to be more sensitive to the hypotensive effect of diuretics, suggesting at least a more marked dependency upon sodium rather than other forms of essential hypertension (Fraser and Padfield, 1985).

It has been shown, however, that hypokalemia and the expansion of the exchangeable sodium state or plasma volume are absent in low-renin essential hypertension. Nevertheless, this does not automatically exclude the possibility of mineralocorticoid excess. Among 80 patients with proven primary aldosteronism, persistent normokalemia was demonstrated in 27.5%. Also, in some individuals expanded plasma volume and exchangeable sodium cannot be demonstrated and thus it may not be reasonable to dismiss the possibility of mineralocorticoid excess in the absence of these indices (Fraser and Padfield, 1985).

In low-renin essential hypertension, ALDO levels are normal, but are considered to be inappropriately high in view of the suppressed levels of renin. This dissociation between renin and ALDO levels may be explained by an enhanced sensitivity of ALDO Aldosterone secretion to A-II (Hsueh and Tuck, 1990).

Patients with normal-renin essential hypertension, show a higher than normal ALDO: renin or ALDO: A-II ratio (Collins *et al.,* 1970) p165 green There is some evidence of mild ALDO excess in essential hypertension. (Fraser and Padfield, 1995).

The percentage of cases of low-renin essential hypertension increases progressively with age of the population (Kaplan, 1988).). Among hypertensive subjects, the prevalence of low-renin hypertension was 37% in those over age 50 compared with 12% in those younger than 40 years of age (Tuck, 1990).

Low-renin essential hypertension prevalence is affected by race. There is a higher prevalence of low-renin hypertension among black patients. In a study on 100 unselected hypertensives, low renin levels were found in 26% of the white subjects and 51% of black subjects (Williams, 1995).

Atrial natriuretic hormone

ANH represents a family of peptides synthesized and stored mainly in the myocytes of the right and left atria of the heart. The biologically significant circulating form of ANH is a 28 amino acid structure derived from a 126 amino prohormone (Tuck, 1990).

Physiological Roles and mechanisms of action of ANH

ANH is one of the most powerful molecules known to produce natriuresis (sodium excretion) and diuresis (increased urinary volume). Also it has vasorelaxant properties (Tuck, 1990). All these actions tend to lower the BP. ANH exerts its action by the following mechanisms:

1) ANH increases directly the renal glomerular filtration rate.
2) ANH inhibits indirectly renal reabsorption of sodium and water by inhibiting renin secretion and ALDO biosynthesis.
3) ANH has direct vasorelaxant properties mainly at the renal and aortic vascular beds and it acts as an antagonist to the vasoconstrictive activity induced by A-II, catecholeamines, and ADH.
4) ANH decreases cardiac output in hypertensive humans and animals. However, in states of congestive heart failure, it increases cardiac output (Tuck, 1990).

Regulation of ANH secretion

ANH secretion is stimulated by the following factors:

1) Elevated right atrial pressure.
2) Fluid redistribution to the cardiac pulmonary area such as by head-out water immersion.
3) High sodium intake.
4) Volume overload.
5) Supine position (Tuck, 1990).

Role of ANH in the essential hypertension

Natriuretic hormone deficiency can increase sodium reabsorption and expand extracellular fluid volume, leading to hypertension (Siragy, 1998).

There is no gross abnormalities in ANH levels in human hypertension, and very little is known of possible involvement in the pathophysiolgy of hypertension (Hsueh and Tuck, 1990).

Some researchers have reported mild to moderate elevations of mean serum ANH levels in patients with essential hypertension. Others have reported levels that are equivalent to those in the normotensive population. The wide range of ANH levels in essential hypertension may be a reflection of variable increases in atrial pressure in these patients rather than a primary underlying pathophysiological factor (Hsueh and Tuck, 1990).

Biological effects of altitude

The reported biological effects of altitude residency include growth patterns, lung function, blood values, and blood pressure. At high altitudes, Children grow more slowly but their growth period is longer to compensate. Lung capacity and chest size are greater in persons living at high altitudes due to the altitude-hypoxic stress. Hematocrits, hemoglobin levels and red blood cell counts increase as altitude increases the blood volume increases minimally, consequently, the blood is more viscous. The polycythemia puts some strain on the heart that helps explain the higher pulse rate that occurs during the first weeks of acclimatization to high altitude.

Altitude and Hypertension

There is some controversy about whether BP is lower and hypertension decreases at high altitudes. Some studies say yes (Khalid, 1995) others say no (Ruiz and Penaloza, 1979). Because the socioeconomic factors are involved in blood pressure and hypertension, studies that control for such factors are needed before the controversy can be settled.

Altitude and hormonal levels

Altitude variation between the below sea level and above sea level seems to be associated with differences in some hormonal levels. Serum levels of adrenocorticotropic hormone (ACTH) and cortisol were higher in people living in JV, 340m below sea level than those in people residing in Ramtha, 600m above sea level (El-Migdadi *et al.,* 1999). In males and females of the JV, serum levels of the leutinizing hormone (LH), follicular stimulating hormone (FSH), testosterone (T), and progesterone (P) were all higher than those of Irbid City (El-Migdadi *et al.,* 2000).

Several studies have reported effects of exercise at different altitudes on the levels of some BP-regulating hormones such as PRA, ALDO and ANH (Colice and Ramirez, 1986, Tunny *et al.*, 1989, Milledge, 1992), however, studies are scarce regarding the effect of altitude on the mean levels of these hormones in normotensive or hypertensive variants of resident people.

Recent data strongly suggest that essential hypertension is a syndrome with several different causes. Reported pathophysiological mechanisms of hypertension have been based on the concept that the elevation in blood pressure (BP) is mediated by overactivity of systems that tend to elevate BP (pressor systems) and/or by deficiency of systems tending to lower BP (depressor systems) (Kaufmann, 1986, Siragy, 1998).

The influence of altitude upon hypertension prevalence has been reported (Khalid, 1995, Mirrakhimov, 1985, Ruiz, 1977). These studies have dealt with environments with altitudes above the sea level but not with altitudes below the see level. Also, residing at altitude below the sea level has been reported to affect the levels of some hormones (El-Migdadi, *et al.,* 2000). However, there are no available data regarding the effect of environments located below the sea level on the levels of BP-regulating hormones or on the rate of hypertension prevalence in the resident people of these environments.

The study herein was designed to investigate the hypothesis of a possible association of the levels of two pressor hormones, plasma renin activity (PRA) and aldosterone (ALDO), and a depressor hormone, atrial natriuretic hormone (ANH) with the rates of hypertension prevalence in people living at different altitude-environments relative to the sea level (below, the Jordan Valley and above, Irbid City). First, hypertension prevalence in people living in the Jordan valley (JV), 340 meters below sea level, and those residing in Irbid City, 620 meters above sea level was estimated. Then the levels of plasma renin activity (PRA), aldosterone (ALDO), and atrial natriuretic hormone (ANH) in people living in the Jordan Valley and those residing in Irbid City was investigated using normotensive and hypertensive variants.

MATERIALS AND METHODS

Description of research areas

Irbid City is located in Northwestern Jordan. Its altitude is about 620 meters above sea level. Summer temperatures in Irbid City are between 20 °C and 35 °C. Winter temperatures fluctuate between 10 °C and 25 °C. Jordan valley (JV), the valley of Jordan river, has an altitude of about 209 m below sea level in the area of lake Tebria and 408 m below sea level at the dead sea, the lowest point on earth. Its climate is mild in winter and hot and dry in summer. Summer temperature in JV may reach 49 °C in August, the hottest month in the year.

Study design and populations

The study is a cross-sectional that was carried out in Irbid City and the JV during June–July 1999. It is composed of two parts. The first part was to estimate hypertension prevalence in the people living in the JV and in Irbid City. The second was to evaluate the mean levels of BP-regulating hormones, PRA, ALDO and ANH, in the hypertensive and normotensive people of the JV and Irbid City.

Sample groups, sampling and examination procedures

1 402 adult residents from Irbid City and 1 072 adult residents from the JV were scanned in an investigation

for estimating hypertension prevalence in the Jordan Valley and Irbid City. Seven secondary schools in Irbid city and fife secondary schools in JV were chosen. All the 11th grade classes were visited. Each student was interviewed by a structured questionnaire in which he was asked if his/her father or mother had a history of hypertension. Therefore, the sampling frame in this part of the study included the adult residents of Irbid City and JV with age of 35 years or more.

Male subjects from Irbid City (89 normotensives and 31 hypertensives) and from the JV (93 normotensives and 24 hypertensives) were used for evaluating the mean levels of PRA, ALDO and ANH in the JV and Irbid City according to the hypertensive and normotensive variants. Visits were made to the main public hospitals, Princess Basma Teaching Hospital in Irbid City and Abu-Obeidah Hospital in the JV. Permissions were taken from the directors of hospital laboratories. Systematic random samples were selected at the blood collection room where every third male person was included into the sample after taking his permission.

Each subject was interviewed by a structured format that included the subject name, residence, history of hypertension, anti-hypertensive treatment, histories of other diseases (diabetes mellitus, renal problems and cardiovascular problems), diet-salt content, smoking, weight, and height. BP Measurements were done to decide if the patient was hypertensive or normotensive. Blood samples were taken to measure the levels of PRA, ALDO and ANH. Table 1 shows the proportions of the participated subjects according to several criteria.

Blood pressure measurement and criteria for diagnosing hypertension

Blood pressure measurements were done at the quiet surroundings of the blood banking room using a well-calibrated sphygmomanometer and a stethoscope. Measurements were taken at the upright (sitting) position after the subject has rested for 5 minutes. A subject was considered hypertensive when his measured blood pressure was more than 140 mm Hg systolic and/or more than 90 mm Hg diastolic, or when he was on anti-hypertensive medication. Otherwise, the subject was considered normotensive. Whenever it was possible, blood pressure measurements were done twice on two separate occasions to assure repeatability of blood pressure measurements. This possibility was available for 12% of the subjects. There was high consistency in the blood pressure values that were measured in two occasions and the diagnosis of hypertension was the same in the two occasions.

Blood sample collection and handling

Venous blood samples were collected in the morning between 7:45–9:00 AM (PRA and ALDO are highest in the morning because of diurnal variation). EDTA-containing vacutainer tubes (5 ml) and plain vacutainer tubes (10 ml) were used for obtaining plasma and serum samples, respectively. Blood in the plain tubes was set at room temperature for 15 minutes to allow blood clotting. Plasma and serum samples were separated by centrifugation at 3 000 rpm for 90 seconds. Quantitative tests for glucose, urea, creatinine, sodium, and potassium, triacylglycerol (TAG), cholesterol HDL and LDL were done immediately after separating serum samples (data and results are not listed). Portions of the plasma and serum samples had been distributed into plastic eppindorff tubes and stored at –70 °C before they were used for the quantitative determination of PRA, ALDO and ANH 3–5 weeks later.

Biochemical measurements

Plasma renin activity (PRA) was determined using "Diasorin" Gamma Coot PRA ^{125}I-radioimmunoassay of

Table 1. Subject Proportions of the Hypertensive and Normotensive Sample Groups used for evaluating the mean levels of PRA, ALDO and ANH levels in the Jordan Valley and Irbid City

	Jordan Valley		Irbid City	
	Hypertensives	*Normotensives*	*Hypertensives*	*Normotensives*
Sample Size	34 (28%)	86	24 (21%)	93
Gender	Males	Males	Males	Males
Age (M±SD) y	47±12	40±13	46±15	33±13
Anti-hypertensive medication	26 (76%)	0	5 (21%)	0
Renal Problems	10 (29%)	9 (11%)	0	1 (1%)
Diabetes Mellitus	10 (29%)	23 (27%)	4 (17%)	3 (3%)
Cardiovascular Problems	3 (9%)	8 (13%)	2 (8%)	4 (4%)
Obesity	6 (18%)	19 (22%)	14 (58%)	21 (23%)
High-Salt Diet	3 (9%)	19 (22%)	5 (21%)	13 (14%)

generated angiotensin-I kit (Minnesota, USA). The PRA assay consisted of two steps. First, plasma was incubated at 37 °C, pH 6.0 for three hours, allowing the renin in the sample to cleave angiotensin-I from angiotensinogen. The second step was to measure the angiotensin-I by competitive binding radioimmunoassay (RIA). Results of these assays are reported as nanograms of angiotensin-I generated per milliliter of plasma per hour of incubation (ng/ml/hr). Some laboratories prefer to add an excess of angiotensinogen to the sample. This allows the renin activity measurement to be independent of the endogenous angiotensinogen concentration.

- Serum level of aldosterone (ALDO) was determined using "Diasorin s.r.l." Aldoctk-2 ^{125}I-radioimmunoassay kit (Saluggia, Italy). The method adopted for separation is based on the use of antibody-coated tubes.
- Plasma level of Atrial natriuretic hormone (ANH) was determined using "Incstar" ANP ^{125}I-radioimmunoassay kit (Minnesota, USA). Cartridge extraction method have been used on plasma to purify the samples from nonspecific substances prior to being assayed.

Data processing and statistical analysis

Data were frequency distributed and cross-tabulated. The rates of hypertension prevalence, and the means and standard deviations of tested parameters were calculated by the researcher. Student t-test was used to test the significance of differences between the means where applicable. The level of significance was set at $\alpha = 0.05$

Ethical considerations

- Permission was asked from each subject before blood sample was collected and a signed consent was taken from all participants.
- Disposable needles and aseptic procedures were used in blood collection.
- Every subject was given his results upon his request.

RESULTS

Table 2 shows the results of a questionnaire carried out to estimate the rates of hypertension prevalence in people living in the JV and Irbid City. Hypertension was less common in the JV than in Irbid City (9.9% vs. 13.6%). Women had higher hypertension prevalence than men for both the JV (11.6% vs. 8.2%) and Irbid City (14.7% vs. 12.6%). These results are diagrammed in Figure 1.

Table 3 shows the results of a comparative study (t-test, $p<0.05$) applied on the mean levels of PRA, ALDO and ANH of the hypertensive and normotensive subjects of the JV. In the JV, the levels of PRA in the hypertensive subjects were lower than those in the normotensives (1.7 vs. 2.6 ng/ml/hr); the levels of ALDO in the hypertensives were similar to those in the normotensives (119 vs. 139 pg/ml) and the levels of ANH in the hypertensives were lower than those in the normotensives (13.9 vs. 28.0 ng/ml). These results are diagrammed in Figure 2.

Table 4 shows the results of a comparative study (t-test, $p<0.05$) applied on the mean levels of PRA, ALDO and ANH of the hypertensive and normotensive subjects of Irbid City. In Irbid city, the levels of PRA in the hypertensives (2.9) were similar to those in the normotensives (3.2); the levels of ALDO in the hypertensives (199) were higher than those in the normotensives (146); and the levels of ANH in the hypertensives (21.0) were lower than those in the normotensives (26.7). These results are diagrammed in Figure 3.

Table 5 shows the results of a comparative study (t-test, $p<0.05$) applied on the mean levels of PRA, ALDO and ANH of the normotensive subjects of the JV and the normotensive subjects of Irbid City. The levels of PRA, ALDO and ANH in the normotensive subjects of the JV (2.6, 139 and 28.0 respectively) were similar to those of the normotensive subjects of Irbid City (3.2, 147 and 26.7 respectively). These results are diagrammed in Figure 4.

Table 2. The rates of hypertension prevalence in people living in the Jordan Valley and Irbid City (population age >35 years)

	Jordan Valley			Irbid City		
	Total	*Male*	*Female*	*Total*	*Male*	*Female*
Sample Size	1072	536	536	1402	701	701
Hypertension Prevalence %	9.9%	8.2%	11.6%	13.6%	12.6%	14.7%

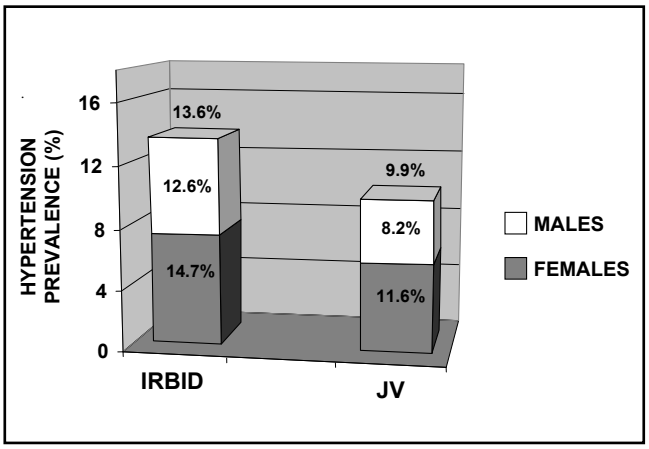

Figure 1. The rates of hypertension prevalence in the Jordan Valley and Irbid City (Population age <35 years).

Table 3. A Comparative study of the levels (Mean±SD) of Plasma Renin Activity (PRA), Aldosterone (ALDO) and Atrial Natriuretic Hormone (ANH) between the Hypertensive and Normotensive subjects of the Jordan Valley ($p<0.05$).

	PRA (ng/ml/hr)	ALDO) (pg/ml)	ANH) (ng/ml)
Hypertensives (n=24)	1.7 ± 1.0	119 ± 58	13.9 ± 9.3
Normotensives (n=92)	2.6 ± 1.4	139 ± 66	28.0 ±12.7
t-test	3.07	1.33	5.06

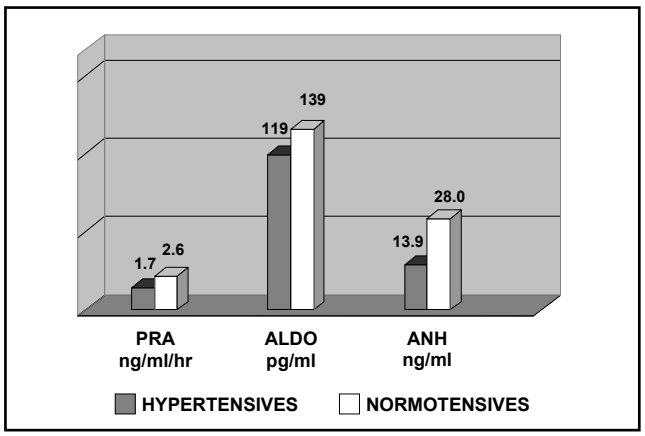

Figure 2. Mean levels of Plasma Renin Aactivity (PRA), Aldosterone (ALDO), and Atrial Natriuretic Hormone (ANH) in the Hypertensive and Normotensive subjects of the Jordan Valley.

Table 4. A Comparative study of the levels (Mean±SD) of Plasma Renin Activity (PRA), Aldosterone (ALDO) and Atrial Natriuretic Hormone (ANH) between the Hypertensive and Normotensive subjects of Irbid City ($p<0.05$)

	PRA (ng/ml/hr)	ALDO) (pg/ml)	ANH) (ng/ml)
Hypertensives (n=31)	2.9 ± 2.7	199 ± 112	21.0 ± 12.2
Normotensives (n=89)	3.2 ± 2.7	147 ± 84	26.7 ± 11.6
t-test	0.90	2.75	2.30

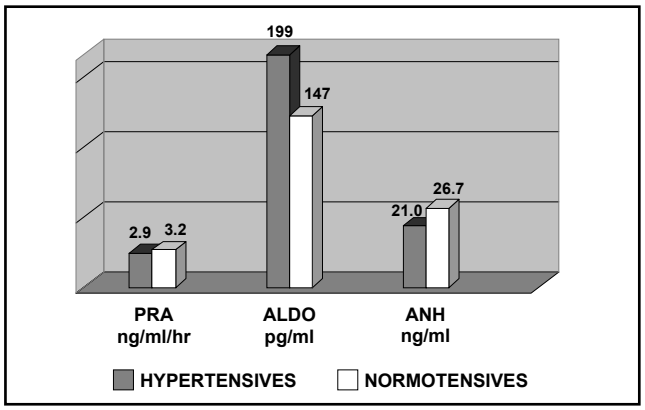

Figure 3. Mean levels of Plasma Renin Aactivity (PRA), Aldosterone (ALDO), and Atrial Natriuretic Hormone (ANH) in the Hypertensive and Normotensive subjects of the Irbid City.

Table 5. A Comparative study of the levels (Mean±SD) of Plasma Renin Activity (PPA), Aldosterone (ALDO) and Atrial Natriuretic Hormone (ANH) between the normotensive subjects of the Jordan Valley and Irbid City ($p<0.05$)

	PRA (ng/ml/hr)	ALDO) (pg/ml)	ANH) (ng/ml)
Jordan Valley (n=92)	2.6 ± 1.4	139 ± 66	28.0 ± 12.7
Irbid City (n=89)	3.2 ± 2.7	147 ± 84	26.7 ± 11.6
t- test	1.92	0.58	0.70

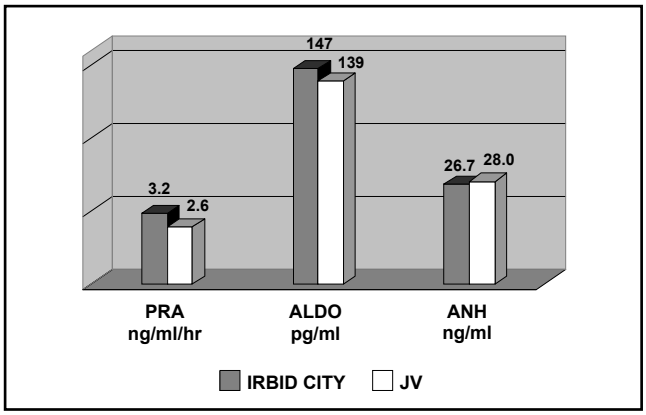

Figure 4. Effect of altitude-area (Irbid City and Jordan Valley) on means of Plasma Renin Activity (PRA), Aldosterone (ALDO), and Atrial Natriuretic Hormone (ANH) in Normotensive residents.

DISCUSSION

The study reported herein was designed to investigate the possible association of the levels of two pressor hormones, plasma renin activity (PRA) and aldosterone (ALDO), and a depressor hormone, atrial natriuretic hormone (ANH) with the rates of hypertension prevalence in people living at different altitude-environments relative to the sea level (below, the Jordan Valley and above, Irbid City) using normotensive and hypertensive variants. Table 6 (deduced from Tables 2, 3 and 4) is a summary of the major results of the present study. Figure 5 also diagrams these results.

Hypertension is less common in people living at the below sea level altitude in the JV compared to those residing at the above sea level altitude in Irbid City

Table 6. The Effects Of Altitude-Environment (the Jordan Valley and Irbid City) on the rate of Hypertension Prevalence, and on the levels of Plasma Renin Activity (PRA), Aldosterone (ALDO), and Atrial Natriuretic Hormone (ANH) in Hypertension (Deduced from Tables 2, 3, and 4)

	Hypertension Prevalence %	Hormonal Levels in Hypertension (compared to those of the normotensives)		
		PRA	ALDO	ANH
Jordan Valley	9.9%	Low	Normal	Low
Irbid City	13.6%	Normal	High	Low

(Table 1, Table 6 and Figure 5). These data agree with what is reported by Khalid (1995) that lowlanders have lower hypertension prevalence than highlanders. However, several other studies have reported higher rates of hypertension prevalence among people living at low altitudes compared to high altitudes (Ruiz and Penzaloza, 1979, Mirrakhimov, 1992). This discrepancy in data may be based on the suggested involvement of genetics and other environmental factors (such as the dietary customs, physical activity, and socio-economic conditions) in the genesis of essential hypertension. Nevertheless, there is a possibility that hypertension prevalence may be elevated at the altitude of the sea level and be lower at the altitudes below or above the sea level. A study investigating hypertension prevalence among people living at the sea level altitude and at the above and the below sea level altitudes is suggested for future research.

The levels of PRA and ALDO are lower in the hypertensive subjects of the JV (low and normal, respectively) compared to those in the hypertensive subjects of Irbid City (normal and high, respectively) (Table 3, Figure 2, Table 4, Figure 3, Table 6 and Figure 5). Therefore, there is a correlation between the decreased levels of PRA and ALDO in the hypertensives of the JV and the decreased rate of hypertension prevalence in the JV. On the other hand, data for ANH suggest that there is no correlation between the levels of ANH (low at both locations) and hypertension prevalence.

In Irbid City, the levels of PRA in hypertensives are similar to those in normotensives (Table 4, Figure 3, Table 6 and Figure 5). These data are in agreement with what is reported in the literature that normal levels of PRA are present in the majority (60%) of patients with essential hypertension (Kaplan, 1988, Laragh, 1991, Hsueh, 1990).

In the JV, on the other hand, there are lower levels of PRA in the hypertensives compared to those in normotensives (Table 3, Figure 2, Table 6 and Figure 5). Black hypertensives are reported to have higher prevalence of low-renin hypertension than white patients do (Williams, 1995). Role of genetics in the development of hypertension is based on the fact that there are differences in the genetic background of the peoples of the JV and those living in Irbid City and the higher rate of consanguineous marriages in the JV. An experiment investigating PRA levels in subjects living in the JV before and after transfer and adaptation to higher altitude in Irbid city is suggested for future studies.

ALDO may play a role in the development of hypertension in Irbid City. This is based on the fact that there is elevated serum level of this pressor hormone in hypertensives of Irbid City compared to those in normotensives (Table 3, Figure 2, Table 4, Figure 3, Table 6 and Figure 5). However, in the JV there is comparable levels of aldosterone in both hypertensives and normotensives suggesting that ALDO is not a major contributing factor in the development of hypertension in the below sea level environment. In addition, the role of ALDO in hyperten-

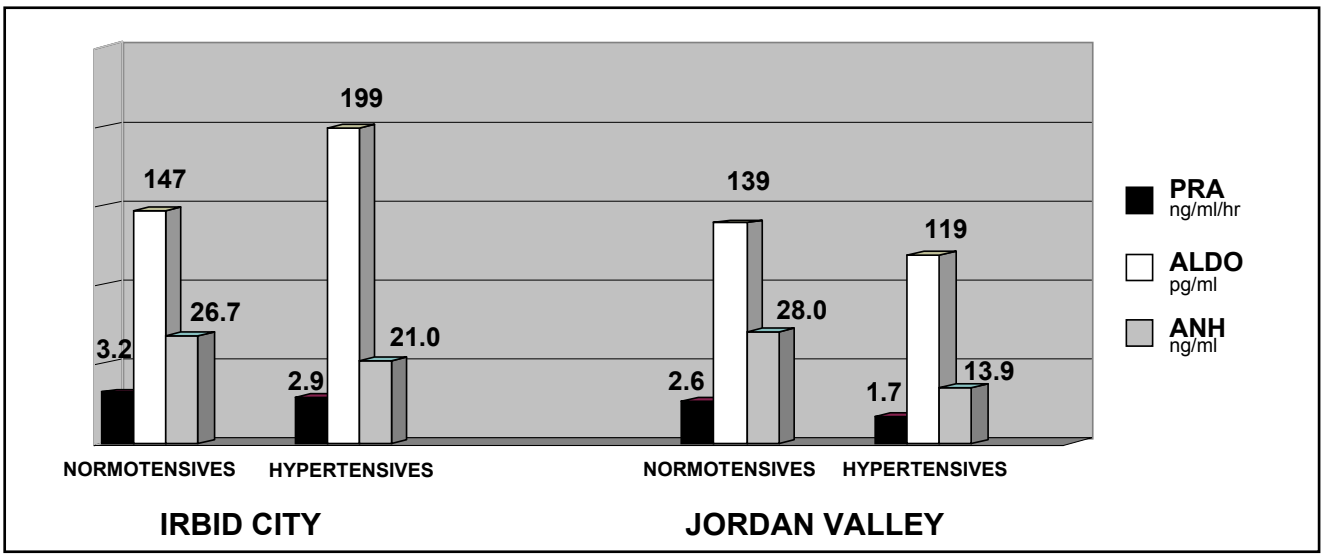

Figure 5. Mean levels of Plasma Renin Activity (PRA), Aldosterone (ALDO), and Atrial Natriuretic Hormone (ANH) in Normotensives and Hypertensives of Irbid City and Jordan Valley.

sion at above sea level in Irbid city, but not at the below sea level in the JV, is proposed here to be an important factor associated with higher hypertension prevalence in Irbid city compared to the JV.

Plasma levels of ANH in hypertensive subjects are low compared to those in normotensives at both locations, supporting the notion that the decreased level of this depressor hormone in hypertensives seems to be a factor in the pathogenicity of hypertension. Additionally, living at different altitudes does not control ANH.

In normotensive people, there is no difference in serum levels of PRA, ALDO and ANH between Irbid City and the JV (Table 5, Figure 4, Table 6 and Figure 5). Altitude seems to have no whatsoever effect on serum levels of PRA, ALDO and ANH in normotensives.

Study limitation

PRA and ALDO levels are reported to rise due to treatment with diuretics or low diet-salt content and therefore it is recommended to stop hypotensive drugs, if possible, three weeks prior to measuring these hormones. Table 1 shows different subject proportions with these variables in the hypertensive groups since the control of these variables with adequate sample sizes of was not applicable.

CONCLUSIONS

1) Higher levels of PRA and ALDO correlates with increased hypertension prevalence in Irbid City compared to the JV.
2) ANH levels are low in hypertension, and are not altitude-dependent.

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