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Original Article

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The Relationship Between Urotensin-II Level and Carotid Intima Media Thickness in Dialysis Patients

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ABSTRACT

Objective: The most important cause of mortality in patients with chronic kidney disease is cardiovascular disease. Despite traditional risk factors being controlled, the lack of desired reduction in mortality rates has led to an investigation of new treatment strategies. In experimental studies, urotension-II has been shown to increase foam cell formation, reactive oxygen radicals, oxide-Low Density Lipoprotein (LDL) levels, and matrix metalloproteinase expression and thus contributing to the development of atherosclerosis. The aim of the study was to investigate the relationship between urotension-II and carotid intima media thickness in dialysis patients.

Methods: This study included 33 hemodialysis patients, 35 peritoneal dialysis patients, and 15 healthy individuals. Patients with traditional risk factors for the development of cardiovascular disease, such as diabetes mellitus, familial hypercholesterolemia, and a family history of early cardiac disease, were not included in the study. Furthermore, all individuals with active infection and malignancy were excluded. All laboratory data and urotension-II levels were analyzed. To prevent interobserver errors, carotid intima media thickness measurements were performed by a single radiologist

Results: There was no difference between the groups in terms of age, gender, smoking, and dialysis duration. Urotension-II levels were significantly higher only in hemodialysis group compared to peritoneal dialysis and control groups. Carotid intima media thickness was significantly higher in both dialysis groups. Factors affecting carotid intima media thickness were age in peritoneal dialysis patients, as well as glucose, albumin, phosphorus, parathormone, interleukin-6, C-reactive protein, and uric acid in hemodialysis patients.

Conclusion: Although the role of urotension-II in the development of atherosclerosis was demonstrated in experimental studies, no positive correlation was found between urotension-II and carotid intima media thickness in current study.

Keywords: Atherosclerosis, carotid intima media thickness, hemodialysis, inflammation, peritoneal dialysis, urotensin-II

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INTRODUCTION

Urotensin-II (U-II) is a cyclic peptide with 11 amino acids found in many tissues such as heart, kidney, and central nervous system, especially in the vascular area.[1] Its effect on the vascular environment can be both vasodilation and vasoconstriction. The reason it has 2 opposing effects is due to the differential expression of the U-II receptor in the vascular beds. These specific receptors can affect different intracellular and extracellular pathways based on its localization within the cell or nuclear membrane.[2]

It has been shown in experimental studies that U-II increases foam cell formation, reactive oxygen radicals, oxide LDL level, and matrix metalloproteinase expression, thus contributing to the development of atherosclerosis.[3,4] In addition, studies have reported that U-II antagonists provide plaque stabilization and reduce mortality in mice with congestive heart failure.[5,6]

Cardiovascular diseases are the most important cause of mortality in chronic kidney disease (CKD). In addition to traditional risk factors, CKD-related factors such as malnutrition, secondary hyperparathyroidism, and inflammation also contribute to the accelerated atherosclerotic process. Carotid intima media thickness (CIMT) measurement is an important radiological method for detecting atherosclerosis early before plaques develop. The aim of our study was to investigate the relationship between U-II and CIMT in dialysis patients.

METHODS

Patients and Study Design

The study included 33 hemodialysis (HD), and 35 peritoneal dialysis (PD), who had been on dialysis for at least 6 months, as well as 15 controls aged 18-75, and whose neck region can be comfortably positioned. Patients with traditional risk factors for the development of cardiovascular disease, such as diabetes mellitus, familial hypercholesterolemia**,** and a family history of early cardiac disease, were not included in the study. Demographic characteristics of the all group patients, (age, gender, dialysis time, smoking) were recorded. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m2). Each participant's blood pressure was measured by a nurse or trained staff in the health check-up for control group, before the start of hemodialysis for HD group, and at the time of no peritoneal dialysis solution in the abdomen for PD group. A standard mercury sphygmomanometer or an automated blood pressure measurement monitor was used. Furthermore, all individuals with active infection and malignancy were excluded. Ethical approval of the study was obtained from our Hospital Ethics Committee (Date: July 09, Desicion no: 285).

Laboratory Analyses

Blood samples were obtained from an arterial line before the start of HD. Glucose, urea, creatinine, calcium, phosphorus, intact parathormone (PTH), albumin, uric acid, C-reactive protein (CRP), interleukin (IL)-6, sedimentation rate, complete blood count, total cholesterol, High Density Lipoprotein (HDL), LDL, and triglyceride levels were measured after 12 hours of fasting in all patients. Blood which was taken from the patients in an Ethylene Diamine Tetra Acetic Acid (EDTA) tube for U-II measurement was centrifuged at 2500 rpm for 10 minutes and then stored in a −80°C freezer. After blood collection from all patients, an U-II ELISA was performed based on the manufacture's protocol (U-II (human); EIA kit, Phoenix Pharmaceuticals, Belmont, Calif, USA).

Radiological Evaluation

Carotid artery examinations of all patients were performed using SDU-2200 Shimadzu Doppler US device and 10 MHz linear probe. The patients were examined in the supine position, with their neck slightly extended, and their head facing the opposite side of the carotid artery being evaluated. All measurements were made by a single radiologist in order to prevent interobserver errors. Both sides of the common carotid artery and the proximal internal carotid artery were evaluated morphologically in the longitudinal and transverse planes along their entire length in B-mode. Intima media thickness was calculated by measuring the distance between the intimal-luminal interface and the medial-adventitial interface on a frozen longitudinal image from 1 cm proximal to the bifurcation. The morphology and size of the existing plaque structures in the common carotid artery and proximal internal carotid artery were recorded.

Statistical Analyses

Statistical Package for the Social Sciences version 22 (IBM SPSS Corp.; Armonk, NY, USA) was used for the statistical analysis. The Kolmogorov–Smirnov and Shapirov-Wilk normality test were used to verify data distribution normality. Parametric variables are presented as mean and standard deviation, non-parametric variables are presented as median values with interquartile ranges (IQR) One-way ANOVA, analysis of variance test, was used for variables with normal distribution and Kruskall–Wallis test was used for variables without normal distribution. Post hoc analysis (Tamhane's-T2) was performed for parameters that were found to be significant. A spearman correlation analysis was used to examine the relationship between CIMT, urotensin-II, and all laboratory data. Since the sample size in the groups was small, multivariate cox regression analysis was evaluated together in all patients to determine the factors affecting the presence of plaque. Chi-square test was used to compare the categorical data. A *P*-value of less than .05 was considered significant. Dialysis patients were divided into 2 subgroups as those with and without cardiovascular disease (CVD). Independent samples *t* test was used to compare parametric continuous variables between groups. Mann–Whitney *U* was employed for the comparison of non-parametric variables.

MAIN POINTS

- Urotensin-II (U-II) is a cyclic peptide with 11 amino acids found in many tissues such as heart, kidney, and central nervous system, especially in the vascular area. In experimental studies, U-II has been shown to contribute to the development of atherosclerosis. It was emphasized that U-II antagonists could be a cardioprotective molecule.
- Urotensin-II levels were significantly higher only in hemodialysis group compared to peritoneal dialysis and control groups. It was observed that there was no effect of U-II on carotid intima media thickness (CIMT) and the presence of plaque.
- Factors affecting CIMT and the presence of plaque were inflammation and secondary hyperparathyroidism.

RESULTS

The mean age of the patients included in the study was 42 (40) years for HD, 42 (15) for PD, and 48 (19) years for the

Table 1. Comparison of Basic Characteristics and Laboratory Parameters Between the 3 Groups

Parameters	Hemodialysis (n = 33)	Peritoneal Dialysis (n = 35)	Control (n = 15)	*P*
Gender, female (%)	35.7	42.9	21.4	NS
Age (year)	42 (40) (min:18; max:84)	42 (15) (min:25; max:78)	48 (19) (min:34; max:65)	NS
Smoking (%)	51.9	29.6	18.5	NS
Presence of plaque (%)	58.1	38.7	3.2	.006
Dialysis time (month)	15 (36) (min:6; max:180)	24 (36) (min:6; max:84)	-	NS
BMI (kg/m^2)	21.49 ± 2.93 (min:16; max:31)	25.54 ± 4.61 (min:17.5; max:33.5)	25.49 ± 4.48 (min:18.7; max:32.25)	<.001[c];.015[a]
Systolic BP (mmHg)	116.6 ± 13.8 (min:90; max:150)	128.2 ± 22.2 (min:90; max:170)	119 ± 16.6 (min:100; max:140)	.035[c]
Diastolic BP (mmHg)	75 (10) (min:70; max:95)	80 (20) (min:60; max:105)	75 (10) (min:60; max:88)	.034[b];.023[c]
Glucose (mg/dL)	89.1 ± 17.4 (min:55; max:122)	88.4 ± 14.7 (min:63; max:123)	81.8 ± 14.5 (min:55; max:104)	NS
Urea (mg/dL)	121.03 ± 45.87 (min:67; max:249)	122.64 ± 46.72 (min:53; max:232)	27.98 ± 8.52 (min:14; max:46)	<.001[a,b]
Creatinine (mg/dL)	7.1 (4.6) (min:3.3; max:17.6)	8.8 (3.7) (min:3.97; max:15.4)	0.8 (0.1) (min:0.7; max:1)	<.001[a,b]
Albumin (g/dL)	3.8 (0.8) (min:2.1; max:4.5)	3.6 (0.9) (min:2.3; max:4.2)	4.5 (0.5) (min:3.6; max:5.1)	<.001[a]
Uric acid (mg/dL)	5.2 (1.35) (min:2.9; max:8.2)	5.5 (1.3) (min:3.8; max:8.1)	3.9 (0.7) (min:2.8; max:5.6)	.003[a]; <.001[b]
Calcium (mg/dL)	9 (1.2) (min:7.6; max:12.2)	9.2 (1.3) (min:7.7; max:12.8)	9.7 (0.9) (min:8.8; max:10.7)	.025[b]
Phosphorus (mg/dL)	4.5 (2.9) (min:3.3; max:9.8)	4.4 (1.6) (min:3; max:9.4)	3.1 (0.9) (min:2.1; max:4)	<.001[a,b]
Magnesium (mmol/L)	1 (0.35) (min:0.7 max:2.2)	1 (0.22) (min:0.6; max:1.67)	0.88 (0.05) (min:0.8 max:1)	.043[a]
PTH (ng/L)	332 (446) (min:150 max:1520)	333 (270) (min:126; max:1060)	55 (25)	<.001[a,b]
Total cholesterol (mg/dL)	168.2 ± 55.5 (min:80; max:310)	196.5 ± 39.3 (min:117; max:284)	186.7 ± 37.5 (min:123; max:265)	.047[c]
HDL (mg/dL)	34 (14.5) (min:23; max:61)	38 (11) (min:25; max:72)	46 (11) (min:31; max:76)	.023[a]
LDL (mg/dL)	82 (66.5) (min:28; max:205)	125 (51) (min:53; max:188)	108 (51) (min:61; max:174)	.05[c]
Triglyceride (mg/dL)	165 (96.5) (min:62; max:341)	174 (87) (min:63; max:508)	122 (65) (min:48; max:417)	NS
WBC ($10^6/L$)	6800 (3150) (min:3700; max:10 300)	7600 (3400) (min:4200; max:13 800)	7600 (4900) (min:5100; max:12 300)	NS
Hgb (g/dL)	11.1 (1.8) (min:8.1; max:13.9)	11.2 (1.8) (min:8.9 max:15.1)	14.2 (2) (min:10 max:16.1)	<.001[a,b]
Platelet ($10^6/L$)	213 000 (147 000) (min:183 000; max:586 000)	279 000 (115 000) (min:97 000; max:587 000)	278 000 (90 000) (min:194 000; max:866 000)	.048[c]

(*Continued*)

Table 1. Comparison of Basic Characteristics and Laboratory Parameters Between the 3 Groups (*Continued*)

Parameters	Hemodialysis (n = 33)	Peritoneal Dialysis (n = 35)	Control (n = 15)	*P*
ESR (mm/h)	31 (42) (min:2; max:98)	47 (52) (min:7; max:118)	12 (11) (min:3; max:44)	.005[a]; <.001[b]
CRP (mg/L)	0.73 (0.75) (min:0.1; max:1.69)	0.87 (0.81) (min:0.21; max:4.22)	0.4 (0.39) (min:0.2; max:1.2)	002[b]
IL-6 (pg/mL)	21.43 (41.54) (min:1.3; max:70)	15 (31.95) (min:0.64; max:51.8)	4.49 (3.23) (min:0.49; max:44.7)	.002[a]; .012[b]
CIMT (mm)	0.8 (0.3) (min:0.4; max:1.25)	0.7 (0.2) (min:0.4; max:1.18)	0.68 (0.22) (min:0.4; max:0.86)	.029[a]; .005[b]
Urotensin II (ng/mL)	6.3 (4.1) (min:3.16; max:37.4)	4.4 (3.1) (min:2.56; max:34.3)	5.5 (2:3) (min:2.4; max:8.12)	.014[c]

[a]Hemodialysis control group; [b]Peritoneal dialysis control group; [c]Hemodialysis peritoneal dialysis group. BP, blood pressure; WBC, white blood cell; CRP, C-reactive protein; BMI, body mass index; CIMT, carotis intima media thickness; ESR, erythrocyte sedimentation rate; PTH, parathormone; NS, not significant.

control group. The duration of dialysis was 15 (36) months in HD patients and 24 (36) months in the PD patients. The underlying etiologies of CKD are unknown group (30.88%), hypertension (29.42%), chronic glomerulonephritis (23.53%), amyloidosis (11.76%), stones (2.94%), and polycystic kidney disease (1.47%). There was no difference between the groups in terms of gender, age, and smoking. Body mass index was found to be significantly lower in HD patients compared to both the PD group and the control group (P = .015; P < .001, respectively). Both systolic and diastolic blood pressures were significantly higher in the PD group compared to the HD group (P = .035; P = .032, respectively).

A significant difference was found between the groups in terms of U-II levels, CIMT, IL-6, and CRP levels (Table 1). Carotid intima media thickness and IL-6 levels were higher in hemodialysis and peritoneal dialysis groups compared to control group (P = .029, P =.005). There was no difference between hemodialysis and peritoneal dialysis groups in terms of CIMT. Urotension-II was higher only in HD group compared to PD and control groups.

Table 2. Correlation Analysis Between Carotid Intima Media Thickness and Parameters in Dialysis Patients

	Parameters	*r*	*P*
Hemodialysis	Age	0.857	<.001
	Albumin	−0.365	.018
	PTH	0.359	.02
	Phosphorus	0.549	<.001
	Uric acid	0.358	.02
	Glucose	0.392	.012
	CRP	0.308	.041
	IL-6	0.328	.031
Peritoneal dialysis	Age	0.671	<.001

CRP, C-reactive protein; IL-6, interleukin-6; PTH, parathormone.

Table 3. Correlation Analysis Between Urotensin II and Parameters in Dialysis Patient

	Parameters	*r*	*P*
Peritoneal dialysis	Total cholesterol	0.325	.029
	LDL	0.290	.046
	Triglyceride	0.316	.032
	Age	0.288	.047
Hemodialysis	Uric acid	0.316	.037

Factors affecting CIMT were age in HD and PD patients and glucose, albumin, phosphorus, PTH, IL-6, CRP, and uric acid in HD patients (Table 2). There was no correlation between U-II and CIMT. In the correlation analysis performed to understand how U-II affects, we found a correlation between U-II and LDL, total cholesterol, and triglyceride in the PD group and uric acid in the HD group (Table 3).

The presence of plaque was higher in dialysis patients compared to the control group (P = .006). In the regression analysis,

Table 4. Multivariate Cox Regression Analysis of the Parameters Affecting the Presence of Plaque

Parameters	*β*	HR	95% CI	*P*
Urotensin-II	0.026	0.974	0.916-1.036	.405
Age	0.041	1.041	1.017-1.067	.001
HDL	0.022	0.978	0.943-1.014	.233
PTH	0.003	0.997	0.995-0.999	.002
Smoking	1.158	3.182	1.425-7.108	.048
CRP	0.063	1.065	0.591-1.919	.834
Systolic BP	0.025	1.025	0.993-1.059	.132
Diastolic BP	0.039	0.962	0.918-1.007	.099

BP, blood pressure; CRP, C-reactive protein; PTH, parathormone.

Table 5. Comparison of Basic Characteristics and Laboratory Parameters Between the Subgroups of Dialysis Patients

Parameters	Group With CVD (n = 11)	Group Without CVD (n = 57)	*P*
Gender, female (%)	52.6	27.3	.123
Age (year)	64 (22)	40 (20)	<.001
Smoking (%)	81.8	18.2	<.001
Presence of plaque (%)	81.8	49.1	.046
Dialysis time (month)	24 (36)	12 (12)	.02
BMI (kg/m^2)	22.6 ± 3.69	23.7 ± 4.5	.527
Systolic BP (mmHg)	118 ± 16	120 ± 20	.428
Diastolic BP (mmHg)	75.4 ± 11.2	78.85 ± 14.9	.492
Glucose (mg/dL)	96 (18)	88 (28)	.481
Urea (mg/dL)	119 (64)	121 (67)	.647
Creatinine (mg/dL)	7.1 (5)	8.6 (4.1)	.216
Albumin (g/dL)	3.6 (0.6)	3.7 (0.9)	.628
Uric acid (mg/dL)	4.9 (1.8)	5.5 (1.2)	.571
Calcium (mg/dL)	9.35 ± 1.66	9.2 ± 0.91	.751
Phosphorus (mg/dL)	4.6 (1.8)	4.4 (2.5)	.233
Magnesium (mmol/L)	1 (0.3)	1 (0.24)	.465
PTH (ng/L)	367 (363)	196 (209)	.036
Total cholesterol (mg/dL)	159 (36)	194 (75.5)	.457
HDL (mg/dL)	45 (29)	36 (11)	.076
LDL (mg/dL)	81 (38)	115 (63)	.200
Triglyceride (mg/dL)	174 (121)	167 (92.5)	.614
WBC (10^6/L)	7500 (3300)	7400 (3550)	.738
Hgb (g/dL)	11.4 (2.4)	11.1(1.85)	.405
Platelet (10^6/L)	246 000 (131 000)	250 000 (136 000)	.713
CRP (mg/L)	0.95 ± 0.29	0.86 ± 0.66	.286
IL-6 (pg/mL)	41.58 (29.1)	15.7 (30.6)	.926
Urotensin-II	5.16 (6.84)	5.48 (3.83)	.913
CIMT (mm)	0.9 (0.38)	0.65 (0.2)	.003

BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CIMT, carotis intima media thickness; CVD, cardiovascular disease; IL-6, interleukin-6; PTH, parathormone; WBC, white blood cell.

age (hazard ratio (HR):1.041, *P* < .001), PTH (HR:0.997, *P* = .02), and smoking (HR:3.182, *P* =.048) were found to be independent risk factors for plaque development (Table 4). It was observed that there was no effect of U-II on the presence of plaque.

Dialysis patients were divided into 2 subgroups as those with and without CVD. Carotis intima media thickness and the presence of plaque were higher in the group with CVD compared to the group without CVD. Furthermore, patients were older, dialysis times were longer, smoking was more, and PTH levels were higher. There was no difference between 2 groups in terms of U-II levels (Table 5).

DISCUSSION

Cardiovascular diseases are the most important cause of mortality in patients with CKD. Despite the traditional risk factors are under control, the lack of desired reduction in mortality rates has led to an investigation of new treatment strategies.

In the current study, the relationship of urotension-II with CIMT, as a predictor of atherosclerosis, was investigated. Patients with traditional risk factors for the development of cardiovascular disease, such as diabetes mellitus, familial hypercholesterolemia, and a family history of early cardiac disease, were not included in the study. Another reason why diabetic patients were not included in the study was the decrease in lymphocyte count in diabetic patients.[7,8] The main source of U-II is endothelial cells and lymphocytes.[9,10]

Urotension-II is the peptide detected in endothelial and vascular smooth muscle cells. Intercellular cell adhesion molecule (ICAM) plays a very important role in the development of atherosclerosis by increasing the expression of vascular cell adhesion molecule adhesion molecules. Vascular cell adhesion molecule acts as a chemotactic factor and provides leukocyte infiltration, acts synergistically with oxide LDL, causes vascular smooth muscle cell proliferation, and induces the transformation of macrophages into foam cells.[11-13] In experimental studies, U-II has been reported to antagonize and stabilize plaques by reducing foam cell formation,[5] which prevents and even treats atherosclerosis-related kidney diseases by inhibiting the JAK pathway.[14] However, there are conflicting results regarding the U-II levels in clinical studies. In the studies performed by Zoccali[15] and Mallamac[16]i, the U-II levels were reported to be higher in HD patients compared to controls. However, Mosenkis et al[17] found U-II to be low in HD patients compared to controls in their study. Unlike these studies, in the current study, there was no significant difference between dialysis groups and the control group in terms of U-II levels. However, U-II was significantly higher in HD patients compared to PD patients. The main source of U-II is endothelial cells and lymphocytes.[9,10] The encounter of the blood with a foreign surface (dialyzer) during HD is a condition that activates lymphocytes. This might be the reason for the high U-II levels in HD patients. Mosenkis et al[17] also reported that the U-II levels were higher following hemodialysis in HD patients in their study.

It is known from the experimental studies that U-II level plays a role in the pathogenesis of atherosclerosis. In our study, although CIMT was found to be higher in both HD and PD patients compared to the control group, no relationship was found between CIMT and U-II. There are studies in the literature that demonstrate a relationship between CIMT and U-II.

However, these studies are not conducted in patients with kidney failure.[18] In studies conducted on patients with kidney failure, the relationship between echocardiography findings, hypertension status, laboratory markers of atherosclerosis, and U-II wasexamined. Mallamaci et al[16] have found a negative correlation between U-II and fibrinogen, ICAM, and asymmetrical dimethyl arginine (ADMA) and it was emphasized that U-II could be a cardioprotective molecule. In another study, a positive correlation was found between U-II and left ventricular systolic function.[19] In a study conducted on 191 hemodialysis patients, patients were followed up for an average time of 3.6 years. During the follow-up period, 94 patients died and 88 had incident fatal and non-fatal cardiovascular events. In Kaplan–Meier analysis, high U-II was strongly and inversely associated with incident cardiovascular events ($P < .001$).[15] A study conducted in patients with acute coronary syndrome (ACS) without CKD reported that decreased plasma U-II concentration in patients with ACS could be associated with more injury to myocardium.[20]

Urotension-II levels were found to be higher in hypertensive patients compared to normotensive patients[21] and in non-dipper hypertension patients compared to dipper HT patients.[22] It has been indicated that Spock2 (urotensin gene product) protein reacts with angiotensin 2 receptors and has an effect on signal pathways functioning in the regulation of BP.[23] In our study, although both systolic and diastolic blood pressures were found to be higher in PD patients compared to HD patients, no correlation was found between them and U-II. In fact, the U-II levels were lower in PD patients. In a study on PD patients conducted by Bai et al[24], blood pressure was shown to be high in the group with low U-II levels, although there was no volume load. This was interpreted as the cause of volume-resistant HT in PD patients.

In the current study, the presence of plaque was also evaluated in addition to CIMT. The factors affecting the presence of plaque were age, high PTH, and smoking, excluding U-II. The factors affecting CIMT were also age, albumin, phosphorus, PTH, CRP, uric acid, and glucose.

The limitations of our study were that the number of patients was low, ECHO findings of patients were missing, and U-II levels were not measured in the urine and tissue.

CONCLUSION

CVD is the most important cause of mortality in CKD patients. In experimental studies, it has been shown that U-II plays a role in the development of atherosclerosis. However, clinical studies have found confusing results. In the current clinical study, no positive correlation was found between U-2 and CIMT.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ankara Training and Research Hospital (Date: July 9, 2008, Decision No: 0285).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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RefereNCES

1. Jégou S, Cartier D, Dubessy C, et al. Loca-lization of the urotensin II receptor in the rat central nervous system. *J Comp Neurol*. 2006;495(1):21-36. [CrossRef]
2. Chatenet D, Nguyen TT, Létourneau M, Fournier A. Update on the urotensiner-gic system: new trends in receptor localization, activation, and drug design. *Front Endocrinol (Lausanne)*. 2012;3:174. [CrossRef]
3. Li Y, Zhao S, Wang Y, et al. Urotensin II promotes atherosclerosis in cholesterol-fed rabbits. *PLOS ONE*. 2014;9(4):e95089. [CrossRef]
4. Shiraishi Y, Watanabe T, Suguro T, et al. Chronic urotensin II infusion enhances macrophage foam cell formation and atherosclerosis in apolipoprotein E-knockout mice. *J Hypertens*. 2008;26(10): 1955-1965. [CrossRef]
5. Yu Q-Q, Cheng D-X, Xu L-R, et al. Urotensin II and urantide exert opposite effects on the cellular components of atherosclerotic plaque in hypercholesterolemic rabbits. *Acta Pharmol Sin*. 2019; 0:1-8.
6. Nishi M, Tagawa H, Ueno M, Marumoto S, Nagayama T. The urotensin II receptor antagonist DS37001789 ameliorates mortality in pressure-overload mice with heart failure. *Heliyon*. 2020;6(2): e03352. [CrossRef]
7. Nekoua MP, Fachinan R, Atchamou AK, et al. Modulation of immune cells and Th1/Th2 cytokines in insulin-treated type 2 diabetes mellitus. *Afr Health Sci*. 2016;16(3):712-724. [CrossRef]
8. Muller YD, Golshayan D, Ehirchiou D, et al. Immunosuppressive effects of streptozotocin-induced diabetes result in absolute lymphopenia and a relative increase of T regulatory cells. *Diabetes*. 2011;60(9):2331-2340. [CrossRef]
9. Totsune K, Takahashi K, Arihara Z, Sone M, Ito S, Murakami O. Increased plasma urotensin II levels in patients with diabetes mellitus. *Clin Sci (Lond)*. 2003;104(1):1-5.
10. Bousette N, Patel L, Douglas SA, Ohlstein EH, Giaid A. Increased expression of urotensin II and its cognate receptor GPR14 in atherosclerotic lesions of the human aorta. *Atherosclerosis*. 2004; 176(1):117-123. [CrossRef]
11. Cirillo P, De Rosa S, Pacileo M, et al. Human urotensin II induces tissue factor and cellular adhesion molecules expression in human coronary endothelial cells: an emerging role for urotensin II in cardiovascular disease. *J Thromb Haemost*. 2008;6(5):726-736. [CrossRef]
12. Watanabe T, Takahashi K, Kanome T, et al. Human urotensin-II potentiates the mitogenic effect of mildly oxidized low-density

lipoprotein on vascular smooth muscle cells: comparison with other vasoactive agents and hydrogen peroxide. *Hypertens Res*. 2006;29(10):821-831. [CrossRef]
13. Watanabe T, Suguro T, Kanome T, et al. Human urotensin II accelerates foam cell formation in human monocyte-derived macrophages. *Hypertension*. 2005;46(4):738-744. [CrossRef]
14. Wang T, Xie YQ, Miao GX, et al. urotensin receptor antagonist urantide improves athrosclerosis-related kidney injury by inhibiting JAK2/STAT3 signaling patways in rats. *Life Sci*. 2020;247:117421. [CrossRef]
15. Zoccali C, Mallamaci F, Tripepi G, Cutrupi S, Pizzini P, Malatino L. Urotensin II is an inverse predictor of incident cardiovascular events in end stage renal disease. *Kidney Int*. 2006;69(7):1253-1258. [CrossRef]
16. Mallamaci F, Cutrupi S, Pizzini P, Tripepi G, Zoccali C. Urotensin II and biomarkers of endothelial activation and atherosclerosis in end stage renal disease. *Am J Hypertens*. 2006;19(5):505-510. [CrossRef]
17. Mosenkis A, Kallem RR, Danoff TM, Aiyar N, Bazeley J, Townsend RR. Renal impairment, hypertension and plasma urotensin II. *Nephrol Dial Transplant*. 2011;26(2):609-614. [CrossRef]
18. Demirpence M, Guler A, Yılmaz H, et al. ıs elevated urotensin II level a predictor for increased cardiovascular risk in subjects with acromegaly? *J Endocrinol Invest*. 2019;42(2):207-215. [CrossRef]
19. Zoccali C, Mallamaci F, Benedetto FA, et al. Urotensın II and cardiomyopathy in end-stage renal disease.*Hypertension*. 2008;51(2): 326-333. [CrossRef]
20. Babińska M, Holecki M, Prochaczek F, et al. Is plasma urotensin II concentration an indicator of myocardial damage in patients with acute coronary syndrome? *Arch Med Sci*. 2012;8(3):449-454. [CrossRef]
21. Cheung BM, Leung R, Man YB, Wong LY. Plasma concentration of urotensin II is raised in hypertension. *J Hypertens*. 2004;22(7): 1341-1344. [CrossRef]
22. Erbay AR, Meric M, Alacam H, et al. Serum uro-tensin II levels in patients with non-dipper hypertension. *Clin Exp Hypertens*. 2013;35(7):506-511. [CrossRef]
23. Ashenagar MS, Tabuchi M, Kinoshita K, et al. Gene expression in the adrenal glands of three spontaneously hypertensive rat substrains. *Mol Med Rep*. 2010;3(2):213-222. [CrossRef]
24. Bai Q, Zhang J, Zhang AH, et al. Roles of human urotensin II in volume resistance hypertension in peritoneal dialysis patients. *Ren Fail*. 2012;34(6):713-717. [CrossRef]