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Androgenic Markers as Indicators of Early Renal Impairment in Hypertensive patients

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Abstract

Hypertension is a major cause of premature renal failure and is often associated with metabolic and hormonal abnormalities in men.

The growing body of evidence indicates that testosterone deficiency can increase renal susceptibility through mechanisms involving endothelial dysfunction. The purpose of the present study was to determine the association between total testosterone, free testosterone, sex hormone-binding globulin (SHBG), and early renal impairment in hypertensive men.

The study included 100 male patients diagnosed with essential hypertension (cases) and 60 male volunteers (control group). Participants were selected from internal medicine outpatient clinics at AL-Numan hospital; venous blood was centrifuged at 3000 rpm for 10 minutes to obtain serum.

Hypertensive individuals had significantly lower total testosterone (10.81 ± 2.92 nmol/L) and free testosterone levels (175.11 ± 48.24 pool/L), along with high levels of SHBG. These hormonal derangements were associated with a decrease in estimated Glomerular Filtration Rate (eGFR) and significant changes in Albumin-to-Creatinine Ratio (ACR), uric acid, and bicarbonate imbalances.

The current study shows significant differences in serum levels of androgenic markers between patients and controls. Quantitative analysis of serum parameters in hypertensive men found that free testosterone and SHBG showed a high correlation with renal dysfunction.

Keywords: Hypertension; Total testosterone; Free testosterone; SHBG; Renal biomarkers; eGFR; ACR.

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Introduction

One of the most common chronic ailments worldwide and a significant cause of renal and cardiovascular morbidity is hypertension, which progressively affects vascular and metabolic pathways (1). There is a growing body of evidence that it involves more than merely elevated blood pressure, with endocrine changes that can contribute to clinically insidious kidney dysfunction occurring early (2). Androgen status is an endocrine parameter recognized for its potential to increase men's sensitivity to renal issues. Testosterone, particularly in its free and physiologically active form, plays a crucial role in maintaining endothelial integrity, facilitating nitric oxide signaling, regulating oxidative stress, and overseeing metabolic processes (3). Even though total testosterone levels may remain within the normal range, significant changes in free testosterone can occur due to alterations in sex hormone-binding globulin (SHBG), which are typical in individuals with high blood pressure and metabolic issues (4,5). These disturbances in androgen bioavailability could support microvasculopathy, glomerular inflammation, and low-grade inflammation - pathways that accelerate the progression of renal dysfunction (6). Recent clinical data indicate that decreased androgen concentrations are associated with early signs of kidney dysfunction, including reduced eGFR and increased albuminuria (7,8).

This paper focuses on how androgenic hormones are associated with early renal impairment in hypertensive patients; however, most studies have primarily examined total testosterone measurements without considering the importance of free testosterone and SHBG in men with hypertension. Furthermore, limited research has been conducted on hormone levels in conjunction with significant kidney health indicators, such as the ACR, eGFR, creatinine, and other biochemical markers. This study seeks to determine how total testosterone, free testosterone, and SHBG can help predict early renal impairment in hypertensive patients, deepen understanding of the issue, and enhance clinical evaluations.

Materials &Methods

Subjects and methods:

The study included 100 male patients diagnosed with essential hypertension and 60 healthy male volunteers without a history of hypertension, diabetes mellitus, or known renal disease (controls). Participants were recruited from internal medicine outpatient clinics at AL-Numan hospital, and the research was conducted 1 day per week from September 2025 to December 2025.

Inclusion and exclusion criteria: males aged ≥18 years with hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) were included.

Patients with diabetes mellitus, liver or thyroid diseases, other chronic conditions, or medications that may cause hypertension were excluded from this study.

Demographic criteria, medical history (hypertension duration, medication), smoking status, anthropometrics (height, weight, BMI, waist circumference), and blood pressure measurements (average of 2 seated readings) were recorded.

Participants collected blood samples in the morning after a 10–12-hour overnight fast. Five milliliters of venous blood were drawn from

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both patients and healthy individuals. The blood was transferred to anticoagulant-free tubes and incubated at room temperature for 15 minutes. The samples were then centrifuged at 3000 revolutions per minute for 10 minutes to extract serum, after which they were stored in Obendorf tubes at -20 degrees for future use.

The tests conducted included Total Testosterone, Free Testosterone, and sex hormone-binding globulin (SHBG), measured via Chemiluminescent Immunoassay Cobas e411. A urine sample was used to assess the albumin/creatinine ratio (ACR). Additional biochemical assays for creatinine, urea, uric acid, and bicarbonate were performed using a colorimetric kit and measured with an automated chemistry analyzer from China.

Statistical Analysis

Statistical analysis of the data was conducted using SPSS version 26; a t-test was applied to assess the means of the variables. A significance level of $P \leq 0.05$ was used to determine statistical significance. The ANOVA test was used to compare groups at a significant level ($P \leq 0.05$), and the variable values were presented as mean ± standard deviation.

Results:

Table 1 shows that individuals with hypertension were slightly older (44.33 ± 9.52 years) than the control group (42.21 ± 7.09 years), and hypertensive men had a slightly higher BMI (25.66 ± 3.72 kg/m²). Central obesity, markedly higher in hypertensive men, measured 103.04 ± 9.44 cm ($p < 0.001$). Systolic and diastolic BP were significantly higher in hypertensive men ($p < 0.001$). The hypertensive group had a mean disease duration of 8.7 ± 4.2 years.

Table 2 shows notable distinctions between the hypertensive cohort and healthy controls across all assessed renal and hormonal metrics ($p < 0.001$). Hypertensive individuals exhibited elevated creatinine (1.37 ± 0.24 vs. 0.86 ± 0.11 mg/dL), urea (43.81 ± 9.54 vs. 28.46 ± 5.63 mg/dL), and uric acid (6.03 ± 1.12 vs. 4.18 ± 0.94 mg/dL), along with lower bicarbonate (21.29 ± 2.44 vs. 24.46 ± 2.51 mmol/L). These changes were associated with a significant decline in eGFR (65.06 ± 14.22 vs. 104.96 ± 11.51 mL/min/1.73 m²) and considerable increases in ACR (89.68 ± 34.70 vs. 11.81 ± 4.16 mg/g). Furthermore, hypertensive individuals had lower total testosterone (10.81 ± 2.92 vs. 18.67 ± 3.31 nmol/L) and free testosterone (175.11 ± 48.24 vs. 320.02 ± 55.45 pool/L), whereas SHBG levels were elevated (48.06 ± 8.94 vs. 34.21 ± 7.31 nmol/L).

Table 3 illustrates the relationship between hormonal markers and kidney function measures. Lower testosterone levels are associated with reduced kidney function and higher renal damage markers, as shown by a modest positive association between total testosterone and eGFR ($r = 0.42$) and a negative correlation with ACR ($r = –0.39$). Free testosterone showed stronger correlations than total testosterone, indicating a more robust positive relationship with eGFR ($r = 0.47$) and a notable negative correlation with ACR ($r = –0.44$). SHBG showed a markedly significant positive correlation with ACR ($r = 0.38$, $p < 0.001$) and a notable negative correlation with eGFR ($r = –0.33$, $p < 0.01$).

Table 4 presents the multivariable regression model used to identify independent predictors of eGFR in men with hypertension. Age significantly reduced eGFR ($\beta = –0.41$, $p < 0.001$). BMI showed a notable negative association ($\beta =$

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–0.29, p = 0.020), suggesting that a higher BMI reduces the kidneys' ability to filter blood. Systolic blood pressure was another key predictor (β = –0.26, p = 0.012). Free testosterone was the key hormone influencing eGFR (β = +0.89, p < 0.001). Conversely, SHBG had a significant negative effect on eGFR (β = –0.24, p = 0.031). ACR was a notable predictor (β = –0.20, p = 0.036), suggesting that higher albuminuria and changes in the urinary creatinine ratio are independently associated with decreased kidney function.

Table 1: Demographic and Clinical Characteristics of the Study Population

Variable	Controls (n=60)	Hypertensive (n=100)	P-value
Age (years)	42.21 ± 7.09	44.33 ± 9.52	NS
BMI (kg/m²)	24.61 ± 2.73	25.66 ± 3.72	NS
Waist circumference (cm)	86.04 ± 7.92	103.04 ± 9.44	**<0.001**
Systolic BP (mmHg)	118.20 ± 7.56	154.64 ± 12.89	**<0.001**
Diastolic BP (mmHg)	75.78 ± 6.21	92.09 ± 8.19	**<0.001**
Smokers, n (%)	14 (23.3%)	46 (46.0%)	**0.004**
Family history of hypertension, n (%)	10 (16.7%)	44 (44.0%)	**<0.001**
Physical inactivity, n (%)	12 (20.0%)	57 (57.0%)	**<0.001**
Central obesity, n (%)	15 (25.0%)	69 (69.0%)	**<0.001**
Dyslipidemia, n (%)	13 (21.7%)	61 (61.0%)	**<0.001**
Duration of hypertension (years)	—	8.73 ± 4.26	—

"Values of p<0.05 were considered to be significant."

Table 2 Comparison of Biomarkers Between the Hypertensive Group and the Control Group.

Parameters	Controls (mean ± SD)	Hypertensive (mean ± SD)	P- value
Creatinine (mg/dL)	0.86 ± 0.11	1.37 ± 0.24	**<0.001**
Urea (mg/dL)	28.46 ± 5.63	43.81 ± 9.54	**<0.001**
Uric Acid (mg/dL)	4.18 ± 0.94	6.03 ± 1.12	**<0.001**
Bicarbonate (mmol/L)	24.46 ± 2.51	21.29 ± 2.44	**<0.001**
eGFR (mL/min/1.73m²)	104.96 ± 11.51	65.06 ± 14.22	**<0.001**
ACR (mg/g)	11.81 ± 4.16	89.68 ± 34.70	**<0.001**
Total Testosterone (nmol/L)	18.67 ± 3.31	10.81 ± 2.92	**<0.001**
Free Testosterone (pmol/L)	320.02 ± 55.45	175.11 ± 48.24	**<0.001**
SHBG (nmol/L)	34.21 ± 7.31	48.06 ± 8.94	**<0.001**

"Values of p<0.05 were considered to be significant."

ACR; albumin/creatinine ratio, SHBG; sex hormone-binding protein.

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Table 3. Correlation Between Hormonal Parameters and Renal Functions Among the Study Group.

Parameter	eGFR (r)	ACR (r)	Bicarbonate (r)	P-value
Total Testosterone	+0.42	–0.39	+0.28	**<0.001**
Free Testosterone	**+0.47**	**–0.44**	**+0.31**	**<0.001**
SHBG	**–0.33**	**+0.38**	**–0.22**	**<0.01**

"Values of p<0.05 were considered to be significant."

SHBG: sex hormone-binding protein.

Table 4 Multivariable Linear Regression Analysis for Predictors of eGFR in Hypertensive Patients

Predictor	β Coefficient	P-value
Age	–0.41	**<0.001**
BMI	–0.29	**0.020**
Systolic BP	–0.26	**0.012**
Free Testosterone (pmol/L)	**+0.89**	**<0.001**
SHBG (nmol/L)	**–0.24**	**0.031**
ACR	–0.20	**0.036**

Discussion

Hypertension is a major long-term contributor to early kidney dysfunction, leading to hormonal and metabolic disturbances that may increase the risk of kidney damage. Recent studies indicate that waist circumference in individuals with hypertension may be a more sensitive indicator of renal dysfunction than BMI alone. WC is a body measurement used to assess the distribution of fat in the abdominal area, which is addressed in the present research (9,10). Dyslipidemia, characterized by elevated lipid levels in the bloodstream, is commonly observed in individuals with hypertension, central obesity (especially excess fat around the waist), and ectopic fat accumulation within and outside the kidneys and along blood vessels (11). Genetic factors, lifestyle choices, duration, and environmental elements may have influenced this observation. Consequently, hypertension is considered a multifactorial condition (12,13).

Routine testing reveals elevated levels of creatinine, urea, and uric acid, accompanied by a significant decline in estimated eGFR (14). Moreover, bicarbonate concentrations were decreased in these patients, indicating they might be experiencing metabolic acidosis, an early sign that their kidneys are having difficulty maintaining the appropriate acid-base balance, potentially worsening their kidney issues that can arise when the kidney fails to uphold its homeostasis (15, 16). Hypertension reduces blood flow by constricting renal blood vessels. Consequently, the kidneys cannot eliminate all waste materials and excess fluid from the body. Blood pressure rises when there is excess fluid in the

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blood vessels (17). The hypertensive group exhibited early signs of dysfunction and notable alterations in ACR. These results align with recent studies that uncovered hypertension, disturbances in renal microvascular stability, and increased early glomerular leakage occurring before the clear emergence of advanced kidney disease (18). Androgens play a crucial role in regulating blood pressure (BP). Moreover, several studies have confirmed that hormonal dysfunction exacerbates kidney injury (19). The protein sex hormone-binding globulin (SHBG) binds testosterone. Free testosterone, an active component of the hormone, is recognized as a more reliable indicator of metabolic and cardiovascular outcomes and shows a stronger relationship with renal function than total testosterone does (20, 21).

Nonetheless, prior studies indicate that imbalances in androgen levels are prevalent among individuals with hypertension, potentially affecting vascular tone, oxidative balance, and inflammatory pathways (8). Testosterone might bind to the aldosterone receptor, affecting blood pressure and fluid regulation. Consequently, it could be linked to arterial hypertension by activating the RAAS system and enhancing sodium reabsorption. These processes might result in renal damage due to arterial hypertension (22, 23). An inverse correlation between testosterone levels and hypertension reinforces the idea that hypertension arises with decreased androgen production, independent of age or body mass index.

The correlation analysis indicated that total and free testosterone were positively correlated with eGFR and bicarbonate levels, and inversely correlated with ACR results. Conversely, SHBG showed an opposite correlation, suggesting that reduced androgen bioavailability contributes to early kidney injury in individuals with hypertension.

These findings underscore the clinical significance of using both free testosterone and SHBG in hormone disturbance for hypertensive patients to determine androgen deficiency and its possible effects on kidney function.

LIMITATIONS:

The study's sample size is limited. Second, serum sex hormone levels were measured only once, so the potential to detect temporal variations in hormone levels and to establish an individual's long-term status correctly was lost. Consequently, future studies should consider average outcomes across multiple evaluations of sex hormone levels.

Conclusion

The link between reduced testosterone levels and kidney function markers supports the notion that hormonal deficiency plays a crucial role in the progression of renal failure in hypertensive patients. The evidence suggests that low testosterone may contribute to the progression of renal failure rather than merely being a symptom, and addressing it could lead to improved clinical outcomes. Nevertheless, these benefits must be weighed against potential risks, such as fluid retention or worsening heart failure.

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Conflicts of interest: nil

Ethical statement

Patients provided verbal consent, and information was collected using a questionnaire for this study.

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Ethical approval for this study was obtained from the Ethics Committee at the College of Medicine, Al-Iraqia University (FM.SA/2-1/2/2026).

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