

Reduced Urinary Endothelin-1 Levels Are Associated with Elevated Blood Pressure in Young Adults: A Cross-Sectional Study

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ABSTRACT

INTRODUCTION: Urinary biomarkers offer practical and non-invasive advantages for clinical screening, including early cardiovascular risk assessment. While endothelin-1 (ET-1) is a recognised serum biomarker for hypertension, its role in urine, particularly among young adults, has not been fully explored. Therefore, this study aimed to evaluate the association between urinary ET-1 levels and elevated blood pressure (BP) among young adults. **MATERIALS AND METHODS:** In this cross-sectional study, 117 adults aged 18-45 years were recruited: normotensive (n=44; systolic blood pressure (SBP) <120 and diastolic blood pressure (DBP) <80 mmHg), prehypertensive (n=40; SBP 120-139 and/or DBP 80-89 mmHg), and newly diagnosed hypertensive (n=33; SBP≥140 and/or DBP≥90 mmHg). Pregnant women, individuals who were receiving antihypertensive therapy, or those diagnosed with underlying renal disease were excluded from the study. Plasma and urinary ET-1 levels were measured via enzyme-linked immunosorbent assay (ELISA). Urinary ET-1 was normalised to urinary creatinine to adjust for hydration status. **RESULTS:** Creatinine-normalised urinary ET-1 concentrations decreased progressively across the normotensive, prehypertensive, and hypertensive groups; median (25th-75th percentile) 26.39 (22.19-48.82) pg/mmol, 20.61 (14.72-38.55) pg/mmol and 13.49 (9.69-27.27) pg/mmol, respectively ($p=0.002$). Hypertensive participants exhibited significantly lower normalised urinary ET-1 levels compared to normotensive controls ($p=0.001$). In contrast, plasma ET-1 levels showed neither significant intergroup differences nor a significant correlation with urinary ET-1 levels. **CONCLUSION:** Reduced urinary ET-1 levels are significantly associated with elevated BP in young adults. However, prospective longitudinal studies are required to establish causality and clarify its mechanistic role in the development of young-onset hypertension.

Keywords

Young Adults, Hypertension, Prehypertension, Creatinine-normalised Urinary Biomarker, Cross-sectional Study

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INTRODUCTION

Hypertension remains the strongest modifiable risk factor for global premature mortality and morbidity, causing approximately 10.8 million avoidable deaths annually.¹⁻³ Crucially, emerging evidence suggests that

cardiovascular risk begins to accumulate well before the formal clinical threshold for hypertension is met.⁴⁻⁸ Individuals classified as prehypertensive, defined by a systolic blood pressure (SBP) of 120-139 mmHg or a

diastolic blood pressure (DBP) of 80–89 mmHg, exhibit a significantly higher predisposition toward progressing to clinical hypertension, developing overt cardiovascular disease, and suffering premature death.^{9–11} This prehypertensive phase represents a pivotal transitional state in blood pressure (BP) regulation.⁹ If left unaddressed, this persistent elevation may trigger metabolic and vascular derangements that facilitate adverse myocardial remodelling.⁹

Additionally, elevated BP during early adulthood also substantially contributes to long-term cardiovascular morbidity and mortality.^{12–15} The rising incidence of both hypertension and prehypertension in the younger population underscores the need for timely identification of early BP abnormalities.¹⁵ However, despite this urgency, early detection efforts remain challenging and often inadequate. In Malaysia, for instance, the highest proportion of undiagnosed hypertension cases (80.4%) occurs among young adults aged 18–29, highlighting a critical gap in current screening and preventive strategies.¹⁶

Several factors contribute to this gap, including poor health awareness and a lack of engagement with preventive services among the young, alongside the inherent limitations of traditional diagnostics.^{12,17} Conventional office-based BP measurements using sphygmomanometers are inadequate as the sole diagnostic tool, given that hypertension is a multifactorial and heterogeneous condition shaped by the complex interplay of genetic, environmental, and behavioural factors.¹⁸ Furthermore, office measurements are susceptible to confounding by natural BP variability, white-coat and masked hypertension, and potential measurement errors, which may hinder accurate detection in younger populations.^{18–22}

Consequently, identifying and utilising early-stage biomarkers that can reflect the initial pathophysiological changes associated with young-onset hypertension are critically important. While various plasma and serum

biomarkers show promise, their utility is often hampered by the invasive nature of venepuncture. This can induce procedure-related anxiety, potentially deterring young adults from participating in screening programmes.²³ Conversely, urine, once considered a waste product, is gaining increasing interest in clinical applications for early detection, risk stratification, and disease monitoring, particularly in cardiovascular and renal conditions.^{24–26} Urinary biomarkers offer further advantages in young populations, in which the absence of polypharmacy, pre-existing renal diseases, or other comorbidities such as chronic diseases minimises confounding influences.²⁷

Among the potential urinary biomarkers for the early development of hypertension in young adults is endothelin-1 (ET-1). Plasma ET-1 is a potent vasoconstrictor peptide, and its levels have been shown to be strongly associated with SBP in young adults.²⁸ Meanwhile, urinary ET-1, predominantly produced locally by renal cells, contributes to the regulation of fluid balance by promoting the renal excretion of sodium and water.^{29–30} Previous studies investigating urinary ET-1 in hypertension have primarily focused on older populations and cohorts with secondary hypertension, such as patients with chronic kidney disease or diabetes mellitus. These studies have yielded inconsistent findings, with some reporting elevated levels, others lower levels, and some showing no significant difference.^{31–35}

Furthermore, prior studies investigating urinary ET-1 have primarily compared established hypertension with normotension, largely overlooking the prehypertensive stage.^{31–35} Evaluating ET-1 during prehypertension is critical, as subclinical pathophysiological changes during this window offer a vital target for early intervention, particularly in young adults.⁹ To address this gap, this study investigated urinary ET-1 levels among normotensive, prehypertensive, and hypertensive young adults to determine the relationship between urinary ET-1 levels and early BP elevation.

MATERIALS AND METHODS

Calculation of Sample Size

The required sample size was determined based on a mean difference analysis using OpenEpi software (Version 3.01), following the parameters described by Raina et al.²⁹ With a two-sided confidence level of 95% and a statistical power of 95%, a 1:2 allocation ratio was applied. This calculation indicated a minimum requirement of 32 participants per group to ensure sufficient power to detect significant differences in biomarker concentrations.

Study Design and Subject Recruitment

This was a comparative cross-sectional study comprising 117 young adults aged 18–45 years: 44 participants in the normotensive group, 40 participants in the prehypertensive group, and 33 participants in the hypertensive group. All participants, including hypertensive participants, were recruited from a health-screening programme conducted at a local tertiary education institution. BP was measured across two separate visits. During the initial health screening, three BP readings were taken and averaged. Eligible subjects were then invited to participate in the study and scheduled for a sample collection visit. During the second visit, another three BP measurements were obtained and averaged. Participants were classified as hypertensive only if they consistently met the diagnostic criteria for hypertension across both visits.

Pregnant women, participants with chronic illnesses, including diabetes mellitus, previously diagnosed hypertension, neoplasm, an infection during the preceding four weeks, autoimmune diseases, and anxiety disorders, and/or on long-term medications, such as antihypertensive medications, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX-2) inhibitors, and combined oral contraceptive pills (COCP), were excluded from the study to minimise confounding factors. Prior to the sample collection appointment, participants were instructed to fast for at least eight hours specifically for the fasting blood investigations. They were also advised to refrain from

physical exercise, smoking, and caffeine consumption for at least 30 minutes before BP measurement.

Upon arrival at the appointment, all participants were given at least 10 minutes to rest in a seated position in a quiet room before BP was measured. BP was measured using an automated upper-arm oscillometric monitor (HEM-7120; Omron Healthcare Co., Ltd., Japan). An appropriately sized cuff was selected such that the bladder length encircled at least 80% of the arm circumference and the bladder width was at least 40% of the arm circumference. A standard cuff (HEM-CR24, Type B; 22–32 cm) was used for participants with arm circumferences of 22–32 cm, whereas a wide-range cuff (HEM-RML31, Type B; 22–42 cm) was used for those with arm circumferences greater than 32 cm and up to 42 cm. The device was factory-calibrated by the manufacturer and has been clinically validated for accuracy in accordance with the European Society of Hypertension International Protocol (ESH-IP / ISO 81060-2). Three BP measurements were performed at 10-minute intervals for all participants in a sitting position, with their arms and backs supported. Participants were categorised as normotensive, prehypertensive, or hypertensive based on the average of three BP measurements, adhering to the Joint National Committee (JNC) guidelines on BP categories.³⁶ Normotensive participants were defined as healthy individuals with an average SBP of less than 120 mmHg and DBP of less than 80 mmHg. Prehypertensive participants were defined as individuals with an average SBP of 120–139 mmHg and/or a DBP of 80–89 mmHg. Hypertensive participants were defined as individuals with an average SBP $\geq$ 140 mmHg and/or a DBP $\geq$ 90 mmHg in both screening and sample collection visits.

Urine and Blood Samples Collection

Data and sample collection were standardised between 8:00 a.m. and 10:00 a.m. Each participant was provided with a urine container and instructed to collect approximately 30 mL of midstream urine. The collected urine samples were centrifuged at $10,000 \times g$ for 15 minutes at 4°C. The supernatant was collected and

stored at -80°C for further analysis. For blood collection, approximately 10 mL of venous blood was drawn from the antecubital vein of each participant. Then, 8 mL of blood was dispatched for biochemical profile analysis, including full blood count (FBC), renal profile (RP), liver function test (LFT), fasting lipid profile (FLP), and fasting blood sugar (FBS) at Innoquest Pathology Sdn. Bhd. The remaining 2 mL of blood was centrifuged for 10 minutes at $1,000 \times g$ at 4°C , and the plasma sample was collected and stored at -80°C for future analysis. To prevent observer bias, urine and plasma samples were anonymised with unique code numbers prior to analysis. Consequently, laboratory personnel remained strictly blinded to the participants' BP classifications during ELISA testing.

Enzyme-linked Immunosorbent Assays (ELISA) Analysis

An ELISA kit (Elabscience, United States) with Catalogue Number: E-EL-H0064 for human ET-1 (sensitivity: 0.75 pg/mL; detection range: 1.25–80 pg/mL) was used to quantify the concentrations of ET-1 in urine and plasma samples. The microplate was pre-coated with an antibody (Ab) specific to the target protein, ET-1. First, 100 μL of standards or samples were added to the microplate wells, where the target proteins were bound to the antibody. The protein-antibody complex was detected using a biotinylated detection antibody specific to the target protein and was further recognised by an Avidin-Horseradish Peroxidase (HRP) conjugate. The optical density (OD) of the enzyme-substrate reaction was measured using a microplate reader Infinite 200 PRO (TECAN, Switzerland) at a wavelength of 450 nm. Standard curves for urinary and plasma ET-1 levels were constructed, and the actual protein concentration for each sample was determined using the corresponding standard curve equations.

Prior to processing the study cohort, pilot optimisation experiments were performed to determine the optimal sample dilution and evaluate potential matrix interference. The OD values for neat (undiluted) urine (OD=0.186) and plasma (OD=0.328) fell within the

dynamic linear range of the standard curve (Lowest Standard OD=0.133; Highest Standard OD=1.171). Meanwhile, a two-fold dilution of urine resulted in an OD of 0.148, approaching the lower boundary of detection. Therefore, neat (undiluted) samples were selected for downstream clinical analyses to maintain maximum quantitative accuracy and analytical sensitivity. Samples were analysed in duplicate, adhering to a strict duplicate acceptance criterion of coefficient of variation (CV) less than 10%. The assay demonstrated a mean intra-assay %CV of 0.33% (range: 0.1%–1.38%) across all samples analysed.

To account for variations in urine dilution and hydration status, absolute urinary ET-1 concentrations (pg/mL) were normalised to urinary creatinine concentrations. Urinary creatinine was first converted from $\mu\text{mol/L}$ to mmol/L, and normalised ET-1 values were calculated by dividing absolute ET-1 (pg/mL) by creatinine (mmol/L), expressed as pg/mmol. Urinary creatinine concentrations were determined by an accredited central diagnostic laboratory at Innoquest Pathology Sdn. Bhd.

Statistical Analysis

Baseline sociodemographic characteristics and cardiovascular risk factor profiles were analysed using appropriate statistical tests based on the data distribution. Categorical variables were expressed as numbers and percentages. Normally distributed continuous variables were analysed using standard one-way analysis of variance (ANOVA), followed by Games–Howell post-hoc tests for pairwise comparisons when equal variance was not assumed. Data are presented as mean (standard deviation [SD]). Non-normally distributed continuous variables and ordinal data were evaluated across the three independent groups using the Kruskal–Wallis test, with post-hoc pairwise comparisons conducted via the Mann–Whitney U test. Non-parametric data are presented as median (interquartile range [IQR]) or (25th–75th percentile). Correlations between plasma and urinary concentrations of ET-1 in prehypertension and hypertension were

assessed using Spearman's rank-order correlation analysis.

RESULTS

Sociodemographic and Risk Factor Profiles

The baseline sociodemographic characteristics and cardiovascular risk profiles of the participants are presented in Table I. Participant age, gender distribution, and smoking status did not differ significantly across the normotensive, prehypertensive, and hypertensive groups. As expected, mean systolic and diastolic BP demonstrated significant progressive increases across the clinical categories ($p < 0.001$). Meanwhile, post-hoc pairwise analyses indicated that both hypertensive and prehypertensive participants had significantly higher mean arterial pressure and body mass index (BMI) than normotensive participants ($p < 0.005$). Additionally, hypertensive participants exhibited significantly higher waist circumference and pulse rate compared to normotensive controls ($p < 0.01$). Interestingly, the fasting blood glucose levels were significantly highest in the prehypertensive group compared to other cohorts ($p = 0.032$).

Table I: Sociodemographic characteristics and cardiovascular risk factor profiles of all participants.

Variables	Normotensive (n=44)	Prehypertensive (n=40)	Hypertensive (n=33)	p-value
Age (years)	35.2 ± 5	35.1 ± 6	37.0 ± 6	0.204 [#]
Male, n (%)	19 (43)	21 (52)	22 (67)	0.123 [‡]
Female, n (%)	25 (57)	19 (48)	11 (33)	
Smoking status, n (%)				
Active smoker	7 (15)	11 (28)	5 (15)	0.305 [‡]
Non-smoker	37 (85)	29 (72)	28 (85)	
Systolic blood pressure (mmHg)	109 ± 7.25	^a 127 ± 6.18	^{a, b} 142 ± 13.24	<0.001[#]
Diastolic blood pressure (mmHg)	74 ± 5.7	^a 83 ± 6.4	^{a, b} 97 ± 9.9	<0.001[#]
Mean arterial pressure (mmHg)	84 ± 7.7	^a 95 ± 6.1	^a 106 ± 12.9	<0.001[#]
Body mass index (kg/m ²)	25.1 ± 5.2	^a 29.9 ± 6.8	^a 31.5 ± 8.1	0.020[#]
Waist circumference (cm)	88.3 ± 13.8	95.3 ± 16.1	^a 99.0 ± 14.7	0.008[#]
Pulse rate (beats per minute)	72 ± 12	78 ± 12	^a 81 ± 13	0.007[#]
Fasting blood sugar* (mmol/L)	4.69 (0.41)	[‡] 5.01 (0.55)	4.93 (0.73)	0.032[‡]
Total cholesterol (mmol/L)	5.39 ± 0.77	5.61 ± 0.78	5.42 ± 0.83	0.429 [#]

Notes: Data are expressed as n (%), Mean ± Standard Deviation (SD), or

[‡]Median (Interquartile Range, IQR).

[#]Analysed using One-Way ANOVA across groups.

^{*}Analysed using Kruskal-Wallis test across groups.

[‡]Analysed using Pearson Chi-Square test across groups (for categorical variables).

^a $p < 0.05$ when compared to the Normotensive group using Games-Howell post-hoc pairwise comparison.

^b $p < 0.05$ when compared to the Prehypertensive group using Games-Howell post-hoc pairwise comparison.

^c $p < 0.05$ when compared to the Normotensive group using Mann-Whitney U post-hoc test.

Urinary and Plasma Concentrations of Endothelin-1

The concentrations of absolute and creatinine-normalised urinary ET-1, urinary creatinine, and plasma ET-1 among the normotensive, prehypertensive, and hypertensive groups are summarised in Table II. Absolute urinary ET-1 levels decreased across the groups, with the highest median concentration observed in the normotensive group [2.51 (1.48–6.01) pg/mL], followed by the prehypertensive group [1.81 (1.08–3.09) pg/mL], and the lowest in the hypertensive group [1.28 (0.75–2.46) pg/mL, $p = 0.023$]. Post-hoc pairwise analysis revealed that absolute urinary ET-1 levels were significantly lower in the hypertensive group than in the normotensive group ($p = 0.011$). Similarly, creatinine-normalised urinary ET-1 levels demonstrated a significant progressive reduction across the groups: [26.39 (22.19–48.82)] pg/mmol in the normotensive group, [20.61 (14.72–38.55)] pg/mmol in the prehypertensive group, and [13.49 (9.69–27.27)] pg/mmol in the hypertensive group ($p = 0.002$). Furthermore, creatinine-normalised ET-1 levels were significantly lower in the hypertensive group than in the normotensive group ($p = 0.001$). In contrast, no statistically significant differences were observed across the three groups for urinary creatinine or plasma ET-1 levels.

Table II: Absolute and creatinine-normalised urinary endothelin-1 (ET-1), urinary creatinine, and plasma ET-1 concentrations in normotensive, prehypertensive and hypertensive groups.

Biomarker	Normotensive (n=44)	Prehypertensive (n=40)	Hypertensive (n=33)	p-value
Absolute urinary ET-1 (pg/mL)	2.51 (1.48-6.01)	1.81 (1.08-3.09)	1.28 (0.75-2.46) ^a	0.023[*]
Urinary creatinine (μmol/L)	70.34 ± 15.07	74.98 ± 17.17	74.36 ± 16.68	0.372 [#]
Creatinine-normalised ET-1 (pg/mmol)	26.39 (22.19-48.82)	20.61 (14.72-38.55)	13.49 (9.69-27.27) ^b	0.002[*]
Plasma ET-1 (pg/mL)	2.86 (1.70-4.24)	2.89 (2.00-10.17)	2.36 (1.75-6.01)	0.513 [*]

Notes: Data are expressed as Median (25th–75th percentile) or Mean ± Standard Deviation (SD).

[#]Analysed using One-Way ANOVA across groups.

^{*}Analysed using Kruskal-Wallis test across groups.

^aPairwise difference between Normotension and Hypertension is statistically significant via Mann-Whitney U post-hoc test, $p = 0.011$

^bPairwise difference between Normotension and Hypertension is statistically significant via Mann-Whitney U post-hoc test, $p = 0.001$

Correlations Between Plasma and Urinary Endothelin-1 Levels

Correlation analysis revealed no significant association between plasma and urinary ET-1 concentrations in either the prehypertensive or hypertensive groups (Table III). In the prehypertensive group, there was no

meaningful correlation between plasma and urinary ET-1 levels ($r=0.040$, $p=0.788$). Similarly, although a weak inverse correlation was observed in the hypertensive group, it did not reach statistical significance ($r=-0.244$, $p=0.201$).

Table III: Correlation between plasma and urinary endothelin-1 in prehypertensive and hypertensive groups.

Subject groups	Spearman's rho	p-value
Prehypertensive	0.04	0.788
Hypertensive	-0.244	0.201

Note: $p<0.05$ was considered statistically significant.

DISCUSSION

In the present study, both absolute and creatinine-normalised urinary ET-1 levels demonstrated a progressive decline from normotensive to hypertensive in young adults, with significantly lower concentrations observed in the hypertensive group than in their normotensive counterparts. This finding is consistent with previous reports suggesting that reduced renal ET-1 synthesis or excretion may contribute to sodium and water retention, thereby increasing the blood volume and promoting the development of hypertension, particularly in salt-sensitive individuals.^{32,34} Urinary ET-1 primarily reflects local intrarenal synthesis rather than filtration from systemic circulation.^{29,37-38} In this study, to account for variations in urine hydration status and volume, urinary ET-1 concentrations were normalised to urinary creatinine. This ratio ensures that differences in ET-1 excretion are not due to the concentration of the urine itself.³²

Renally derived ET-1 primarily acts through local autocrine and paracrine mechanisms, exerting diuretic effects by inhibiting vasopressin-induced cyclic adenosine monophosphate (cAMP) accumulation in the collecting ducts, which leads to reduced aquaporin-2 channel insertion into the apical membrane and thus diminished water reabsorption.³⁰ Moreover, reduced renal ET-1 levels can impair sodium excretion by attenuating several natriuretic pathways within the nephron.³⁰ Under physiological conditions, intrarenal ET-1 production is upregulated in response to high sodium intake and acts via endothelin receptor subtype

B (ETB) receptors in the thick ascending limb and collecting duct to enhance nitric oxide (NO) production, inhibit chloride transport, and reduce epithelial sodium channel activity, thereby suppressing sodium reabsorption.³⁰

Renal ET-1 also induces vasodilation of the vasa recta, thereby augmenting medullary blood flow and promoting natriuresis.³⁰ Additional actions include suppression of sodium-potassium adenosine triphosphatase (Na^+/K^+ -ATPase) activity in the proximal tubule and inhibition of renin secretion from the juxtaglomerular apparatus.³⁰ Consequently, a decline in renal ET-1 synthesis can diminish the diuretic and natriuretic effects, leading to sodium and water retention, volume expansion, and elevated BP.³⁰

In contrast, the plasma ET-1 concentrations in this study did not differ significantly among the three groups. This finding contradicts a previous study that reported significantly higher mean serum ET-1 levels in patients with essential hypertension than in the control group.³⁹ However, other studies have found normal plasma ET-1 concentrations in individuals with essential hypertension, while noting elevated local ET-1 expression within the vascular wall.⁴⁰⁻⁴²

The inconsistencies in reported plasma ET-1 levels among patients with hypertension may be attributed to several factors. First, ET-1 has an extremely short plasma half-life of approximately 1-2 minutes, resulting in rapid clearance from circulation.⁴³ Second, ET-1 secretion by endothelial cells is predominantly directed towards adjacent vascular smooth muscle cells (VSMCs), resulting in minimal increases in measurable plasma ET-1 concentrations.⁴³ Additional factors that may account for these discrepancies include variability in assay antibody specificity, the degree of cardiovascular damage, salt intake, obesity, diabetes, and ethnic background.⁴³

This study showed that the correlation between plasma and urinary ET-1 concentrations was negligible in the

prehypertensive group and weakly negative in the hypertensive group, with no statistical significance. These results indicate that urinary ET-1 levels do not directly reflect plasma concentrations in young adults with elevated BP, suggesting that urinary ET-1 may be regulated by independent renal mechanisms. The absence of a significant correlation between urinary and plasma ET-1 levels observed in this study is consistent with the findings of previous studies, supporting the notion that urinary ET-1 is predominantly derived from local renal synthesis rather than from systemic filtration, with less than 1.0% of urinary ET-1 originating from filtered plasma load.^{29, 33, 35} Consequently, urinary ET-1 concentrations may not reliably reflect plasma ET-1 levels.

Our study showed that hypertensive young adults demonstrated elevated levels of key cardiometabolic risk indicators, including BMI, waist circumference, total cholesterol, mean arterial pressure, and pulse rate, compared to their normotensive counterparts. These findings align with previous local studies in Malaysia reporting that hypertension in young adults frequently co-occurs with features of metabolic syndrome.⁴⁴⁻⁴⁵ Metabolic syndrome is defined by the Harmonised Joint Interim Statement of 2009 as a constellation of central obesity, dyslipidaemia, insulin resistance, and elevated BP.⁴⁶

Nevertheless, the observed clustering of these cardiometabolic risk factors introduces potential residual confounding that could influence urinary ET-1 levels. While multivariable regression analysis to adjust for these cardiometabolic covariates would ideally isolate the independent association between hypertension and urinary ET-1, formal statistical adjustment was not conducted in the present study. Given our modest sample size across sub-groups, fitting a complex multivariable model with multiple interrelated covariates risked severe model over-fitting, loss of statistical power, and unstable parameter estimates. Consequently, these findings should be interpreted with caution as unadjusted associations, and future larger-scale cohort

studies with sufficient statistical power are warranted to perform multivariable-adjusted analyses to confirm whether urinary ET-1 serves as an independent marker or an unadjusted surrogate of cardiometabolic dysfunction.

Several other limitations of this study warrant consideration. First, the cross-sectional design and modest sample size preclude causal inferences, requiring larger longitudinal cohorts to track young-onset hypertension. Second, BP was measured in a clinic setting, raising the potential for white-coat or masked hypertension. Future studies incorporating 24-hour ambulatory blood pressure monitoring (ABPM) would provide a more precise characterisation of BP phenotypes. Third, salt sensitivity was not formally evaluated using controlled sodium-loading protocols, which is pertinent given renal ET-1's role in natriuresis. Lastly, a single-centre recruitment from a university health screening and the exclusion of comorbidities may introduce selection bias, limiting generalisability to broader young-adult populations.

CONCLUSION

In summary, these findings demonstrate that reduced urinary ET-1 excretion is associated with early BP elevation in young adults, potentially reflecting subclinical renal endothelin signalling dysregulation. Although these observations elucidate early pathophysiological mechanisms, urinary ET-1 should be conceptualised as a novel candidate biomarker rather than a definitive diagnostic tool. Translating these insights into clinical practice will require rigorous validation in larger, longitudinal, multi-centre cohorts to establish the predictive and clinical utility of urinary ET-1.

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INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

Written informed consent was obtained from all participants prior to recruitment. Ethical approval for this study was granted by the IIUM Research Ethics Committee (IREC 2024-339).

CONFLICT OF INTEREST

There is no conflict of interest.

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