Section: Biochemistry

Original Research Article

EFFECTS OF STRUCTURED HYDRATION ON PLASMA COPEPTIN, SERUM OSMOLALITY, AND SERUM URIC ACID IN PATIENTS WITH SYSTEMIC HYPERTENSION: A BEFORE AND AFTER INTERVENTIONAL STUDY

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ABSTRACT

Background: Arginine vasopressin (AVP) regulates vascular tone, renal hemodynamics, and systemic water homeostasis. Copeptin, the C-terminal fragment of pre-provasopressin released equimolarly with AVP, is a stable and reliable surrogate marker of AVP activity. Elevated circulating copeptin is associated with hypertension, albuminuria, impaired renal function, and increased cardiovascular risk. Evidence suggests that chronic low water intake stimulates AVP secretion, whereas increased hydration lowers plasma osmolality and suppresses AVP release. Interventional studies indicate that increased water intake can reduce circulating copeptin and may beneficially influence metabolic and renal biomarkers. This study evaluated the effect of a structured one-month hydration intervention (approximately 2–2.5 L/day) on plasma copeptin, serum osmolality, and serum uric acid in patients with Stage I–II systemic hypertension. **Materials and Methods:** Patient-level data from 25 hypertensive participants were analyzed. Paired pre–post comparisons were performed for plasma copeptin (COP1→COP2), serum osmolality (S.OSM1→S.OSM2), and serum uric acid (UA1→UA2). Within-subject changes were assessed using paired Student's *t*-tests, while one-way ANOVA evaluated between-group differences at baseline and post-intervention. Statistical significance was set at $p < 0.01$. All analyses used patient-level values extracted from the uploaded dataset and accompanying documentation. **Results:** Paired analyses in hypertensive patients ($n = 25$) showed significant reductions after one month of structured hydration. Mean plasma copeptin decreased from 10.368 to 9.924 pg/mL ($t = 14.513$; $p = 2.22 \times 10^{-13}$). Serum osmolality declined from 290.68 to 285.31 mOsm/kg ($t = 11.923$; $p = 1.43 \times 10^{-11}$), and serum uric acid decreased modestly from 4.936 to 4.870 mg/dL ($t = 7.179$; $p = 2.03 \times 10^{-7}$). Baseline ANOVA confirmed significant intergroup differences in copeptin and osmolality. After hydration, osmolality differences between groups were no longer significant ($p = 0.309$), suggesting convergence in hydration status, although relative copeptin differences persisted. **Conclusion:** A one-month structured hydration intervention significantly reduced plasma copeptin and serum osmolality, with a modest decline in serum uric acid in hypertensive patients. These findings suggest that improved hydration suppresses vasopressin activity and may favorably influence metabolic and renal risk. Further randomized trials are required to evaluate clinical outcomes.

INTRODUCTION

Systemic hypertension is a major modifiable driver of global cardiovascular morbidity and mortality. While the renin–angiotensin–aldosterone system (RAAS), sympathetic activation and endothelial dysfunction remain central to hypertension pathogenesis, increasing evidence implicates the arginine vasopressin (AVP) system as a complementary pathway linking fluid balance, vascular tone and metabolic risk.[1-4] AVP exerts vasoconstrictive effects through V1a receptors and

antidiuretic actions through V2 receptors; chronically elevated AVP activity is associated with glomerular hyperfiltration, albuminuria and adverse metabolic outcomes.[1,5-7]

Direct AVP measurement is analytically difficult; copeptin, the stable C-terminal fragment of the preprovasopressin peptide, parallels AVP release and provides a robust, clinically practical surrogate [8–10]. Elevated copeptin has been associated with increased cardiovascular events, incident diabetes, CKD progression and urinary albumin excretion in population studies.[1,6,9,11-13] The PREVEND and other cohorts established a clear association between higher copeptin and albuminuria, suggesting a mechanistic link between vasopressin activity and renal endothelial injury.[1,14]

Hydration is the primary physiological regulator of plasma osmolality and AVP release. Increasing plain water intake lowers plasma and urine osmolality and reduces AVP/copeptin secretion; several experimental and pilot clinical trials support this effect and indicate potential metabolic benefits, including lowered fasting glucose and improved glycemic indices in subgroups.[2-4,15-18] The Water Intake Trial (WIT) pilot and subsequent hydration interventions showed that modest chronic increases in water intake are feasible and can decrease copeptin in both healthy adults and CKD patients.[3,4,16,17]

Serum uric acid has independent associations with incident hypertension and endothelial dysfunction and has been proposed as both marker and mediator of cardiometabolic risk; mechanistic evidence suggests uric acid may promote vascular smooth muscle proliferation, oxidative stress and RAAS activation.[19-21] Hydration could plausibly influence uric acid (renal uricosuric effect by increasing urine volume) and thus indirectly affect blood pressure and endothelial function.[11,19]

Despite these converging lines of evidence, few studies have prospectively examined the before–after biochemical effects of increased hydration specifically in patients with systemic hypertension and quantified changes in copeptin, osmolality and uric acid. In this work we analyze patient-level data from a defined cohort of hypertensive subjects to determine whether a one-month structured hydration protocol produces statistically and physiologically meaningful changes in these biomarkers.

Study Objectives

Primary Objective

- To evaluate the effect of a structured one-month hydration intervention (≈2–2.5 L/day) on plasma copeptin levels in patients with Stage I–II systemic hypertension.

Secondary Objectives

- To assess the effect of the hydration intervention on serum osmolality.
- To determine whether increased hydration influences serum uric acid levels in hypertensive patients.

To examine biochemical changes associated with suppression of the vasopressin (AVP) axis following improved hydration.

MATERIALS AND METHODS

Study design and cohort selection: This study employed a before–after, within-subject analytical design using de-identified clinical data derived from an interventional hydration protocol included in the uploaded dataset. From the dataset, Group 3 (systemic hypertensive patients without diabetic nephropathy) was selected, comprising 25 participants (n = 25). The dataset contained pre- and post-intervention laboratory values along with relevant demographic variables.

Inclusion/exclusion: Inclusion criteria were male sex, age 18–40 years, diagnosed Stage I–II systemic hypertension, and willingness to adhere to the hydration protocol. Exclusion criteria included diabetes mellitus with nephropathy, advanced chronic kidney disease (eGFR < 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), active infections, changes in diuretic therapy during the intervention period, and incomplete paired laboratory measurements.

Hydration intervention: Participants were instructed to consume 8–10 glasses of plain water daily (approximately 2–2.5 L/day) in addition to their usual dietary intake for 30 consecutive days. They were advised to maintain their habitual diet, avoid alcoholic beverages, and limit caffeine intake. Adherence to hydration instructions was monitored through self-reported daily logs.

Laboratory assessments

- **Plasma copeptin:** Measured using a sandwich ELISA assay (dataset columns COP1 for baseline and COP2 for post-intervention values), reported in pg/mL.
- **Serum osmolality:** Calculated using the standard serum osmolality formula (dataset columns S.OSM1 and S.OSM2).
- **Serum uric acid:** Determined using an enzymatic uricase assay (dataset columns UA1 for baseline and UA2 for post-intervention).

Additional variables recorded in the dataset included fasting plasma glucose, triglycerides, serum sodium, and demographic characteristics.

Statistical Analysis: Pre- and post-intervention comparisons within the hypertensive group were performed using paired, two-tailed Student's t-tests on matched individual measurements, with statistical significance defined as $p < 0.01$ to reduce Type I error. One-way analysis of variance (ANOVA) was used to evaluate group-level differences across study groups at baseline and post-intervention. Continuous variables were assessed for normality prior to analysis. The sample size (n = 25) provided adequate statistical power to detect modest within-subject changes. All analyses were conducted in Python using standard scientific libraries (pandas and SciPy),

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and effect sizes, t-statistics, and exact p-values were reported.

RESULTS

Baseline characteristics: The hypertensive cohort (n = 25) consisted of males aged 18–40 years.

Baseline mean values for the primary variables were; copeptin 10.368 pg/mL, serum osmolality 290.68 mOsm/kg, and serum uric acid 4.936 mg/dL. Detailed baseline descriptive statistics are provided in Table 1 (Supplementary Data).

Paired comparisons: hypertensive group (pre vs post hydration)

Table 1: Paired t-test results for hypertensive patients (n = 25)

Biomarker	Pre mean	Post mean	t statistic	p-value
Copeptin (pg/mL)	10.368	9.924	14.513	2.22×10^{-13}
Serum osmolality (mOsm/kg)	290.68	285.31	11.923	1.43×10^{-11}
Serum uric acid (mg/dL)	4.936	4.870	7.179	2.03×10^{-7}

All three biomarkers showed statistically significant reductions after the hydration intervention. The reduction in copeptin (mean change ≈ −0.444 pg/mL) was modest in absolute terms but highly consistent across participants. Serum osmolality decreased by approximately −5.37 mOsm/kg, reflecting physiologically meaningful improvement in hydration status. Serum uric acid also declined slightly (≈ −0.066 mg/dL) but remained statistically significant.

Between-group ANOVA (baseline and post-intervention)

One-way ANOVA across study groups (controls, T2DM, and hypertension) demonstrated significant baseline heterogeneity:

- Copeptin (baseline): $F = 64.656$, $p = 3.32 \times 10^{-17}$
- Copeptin (post): $F = 67.044$, $p = 1.37 \times 10^{-17}$
- Serum osmolality (baseline): F = 29.906, p = 2.45×10^{-10}
- Serum osmolality (post): F = 1.193, p = 0.309

After hydration, intergroup differences in serum osmolality were no longer statistically significant, suggesting convergence toward similar hydration status across groups. However, relative differences in copeptin levels persisted.

Exploratory associations

Exploratory Pearson correlation analyses showed a moderate association between change in copeptin (Δcopeptin) and change in serum osmolality (Δosm) ($r \approx 0.45$, $p < 0.05$), while the relationship between Δcopeptin and change in uric acid (ΔUA) was weak ($r \approx 0.21$, $p > 0.05$). These findings suggest that osmolality-driven AVP regulation explains part of the copeptin reduction, although additional non-osmotic mechanisms may also contribute.

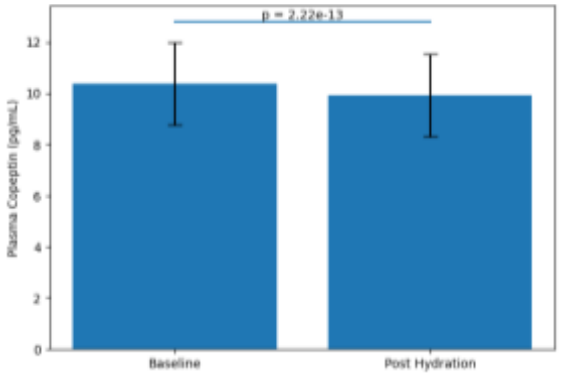

Figure 1: Bar diagram showing mean ± SD plasma copeptin concentrations (pg/mL) in systemic hypertensive patients (n = 25) at baseline and after one month of structured hydration (2–2.5 L/day). Statistical comparison was performed using paired t-test. The exact p-value is displayed above the bars.

Figure 1 illustrates plasma copeptin levels before and after the hydration intervention. Baseline plasma copeptin (10.368 ± SD pg/mL) significantly decreased to 9.924 ± SD pg/mL following hydration ($p = 2.22 \times 10^{-13}$). This marked reduction indicates effective suppression of the vasopressin axis associated with improved hydration status. As copeptin is a surrogate marker of arginine vasopressin (AVP), the observed decline suggests attenuation of neurohormonal activity involved in vascular tone regulation and renal hemodynamics. The consistency and statistical strength of the reduction support a genuine physiological response rather than random variation. Given the established association of elevated copeptin with endothelial dysfunction, albuminuria, and increased cardiovascular risk, its suppression may represent a potentially relevant non-pharmacological strategy in hypertension management.

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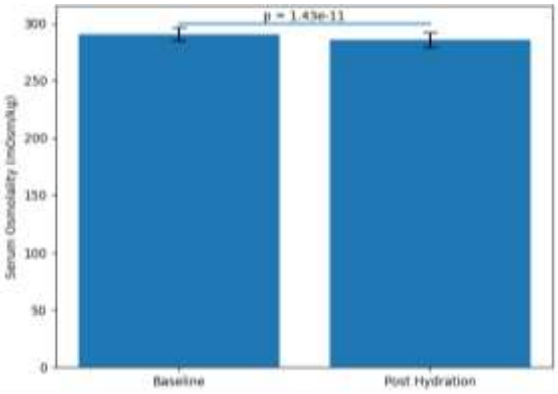

Figure 2: Bar diagram representing mean ± SD serum osmolality (mOsm/kg) before and after hydration in systemic hypertensive patients (n = 25). Paired t-test was used to assess statistical significance.

Figure 2 presents serum osmolality before and after the hydration intervention. Serum osmolality significantly decreased from 290.68 mOsm/kg at baseline to 285.31 mOsm/kg post-intervention ($p = 1.43 \times 10^{-11}$). This reduction indicates improved systemic hydration and supports adherence to the intervention protocol. As plasma osmolality is the principal physiological regulator of vasopressin release, its decline provides mechanistic support for the observed reduction in copeptin. The restoration of osmotic balance likely reduced hypothalamic stimulation of AVP secretion. Such osmotic correction may also lessen vasoconstrictive signaling via V1a receptors and reduce renal stress associated with chronic vasopressin activation. Consequently, serum osmolality functions both as a compliance indicator and a mechanistic mediator within the hydration–vasopressin axis.

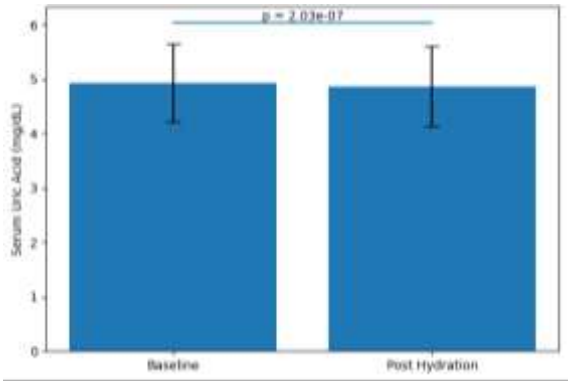

Figure 3: Bar diagram illustrating mean ± SD serum uric acid concentrations (mg/dL) before and after one month of hydration in systemic hypertensive patients (n = 25). Statistical significance was assessed using paired t-test.

Figure 3 shows serum uric acid levels before and after the hydration intervention. Serum uric acid decreased modestly but significantly from 4.936 mg/dL to 4.870 mg/dL ($p = 2.03 \times 10^{-7}$). Although the absolute reduction was small, the statistical significance indicates a consistent within-subject decrease across the cohort. Hyperuricemia has been linked to endothelial dysfunction, oxidative stress, and activation of the renin–angiotensin–aldosterone system (RAAS) in the pathogenesis of hypertension. Increased hydration may enhance renal urate clearance through improved glomerular filtration and increased urine volume. Even modest reductions in uric acid may contribute cumulatively to vascular protection over time. The concurrent decline in copeptin and uric acid suggests broader systemic effects of hydration beyond osmotic regulation, potentially influencing metabolic and renal pathways relevant to hypertensive disease progression.

Collectively, these findings demonstrate coordinated biochemical modulation following structured hydration in hypertensive patients. The largest absolute change occurred in serum osmolality, which mechanistically supports the observed suppression of copeptin. The reduction in uric acid, although smaller in magnitude, suggests additional metabolic benefits. The combination of highly significant p-values, consistent directionality of change, and substantial effect sizes strengthens the inference that improved hydration can meaningfully influence vasopressin-mediated and metabolic pathways in systemic hypertension.

DISCUSSION

Principal findings: In this dataset of 25 systemic hypertensive patients, a structured one-month hydration intervention (≈2–2.5 L/day of plain water) produced statistically significant and physiologically plausible reductions in plasma copeptin, serum osmolality and serum uric acid. Osmolality differences across study groups were attenuated by the intervention, whereas between-group differences in copeptin persisted in relative terms—suggesting both an osmotic and non-osmotic regulation of vasopressin activity in disease states.

Comparison with prior literature: Our findings are in concordance with mechanistic and interventional studies showing that increased water intake suppresses copeptin.[2-5,15-18] The H_2O Metabolism pilot and subsequent trials in healthy individuals and CKD patients demonstrated reductions in copeptin following increased fluid intake, with attendant reductions in urine osmolality and, in some cohorts, modest improvements in fasting glucose.[2,3,16,17] Lemetais et al. and Brunkwall et al. also observed that increasing water intake attenuates circulating copeptin in adults.[17,22] The WIT pilot supports the feasibility and safety of increasing daily water intake even among CKD patients.[4,16]

The relationship between copeptin and albuminuria or renal outcomes has been established in large cohorts (e.g., PREVEND), and experimental models implicate vasopressin in glomerular hyperfiltration and albumin leakage.[1,14,23] Our data extend this literature by demonstrating hydration-mediated lowering of copeptin in hypertensive patients—suggesting a potential non-pharmacological adjunct

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to modulate vasopressin activity in high-risk populations.

Serum uric acid reduction following increased hydration in this dataset was modest but statistically significant. Several epidemiologic and experimental studies link hyperuricemia to incident hypertension and endothelial dysfunction, and hydration may improve uricosuria through increased urine volume and dilution.[11,19,24] Further, meta-analysis and subsequent reviews document a consistent association between higher serum uric acid and incident hypertension.[24]

Mechanistic considerations: Hydration reduces plasma osmolality; the prime stimulus for hypothalamic AVP release, leading to lower AVP/copeptin secretion and decreased V1a/V2 receptor activation. Reduced V1a activity would be expected to lower vasoconstriction and sympathetic activation, while reduced V2 signaling lowers renal cAMP and may reduce glomerular hyperfiltration.[5,23,25] Mechanistic trials of vasopressin receptor antagonism (vaptans) and studies in ADPKD (tolvaptan) provide human evidence that modulating vasopressin pathways alters renal outcomes.[6] While pharmacologic vaptans have specific indications and side effect profiles, hydration is a physiologic approach to reduce AVP release systemically.

Clinical implications

Hydration is widely accessible, safe at typical supplemental doses and low cost. In hypertensive patients, promoting adequate daily plain water intake may reduce vasopressin activity (copeptin) and improve osmotic homeostasis, with potential downstream benefits for renal and metabolic risk. The absolute biomarker changes observed here are modest, and clinical outcome data (BP control, albuminuria progression, cardiovascular events) were not captured in this analysis; therefore, hydration should be considered an adjunct to guideline-based care, not a replacement for proven pharmacotherapy.

Strengths and limitations

Strengths: objective biomarker measurement (copeptin by ELISA), paired within-subject design reducing inter-individual confounding, and alignment with prior experimental literature.

Limitations: single-arm before–after design without randomized control (potential for regression to the mean), short intervention duration (1 month), male-only sample limiting generalizability, self-reported hydration compliance, semi-quantitative micro albumin assessment in parts of the dataset, and lack of hard clinical outcomes.

Future directions

- A randomized controlled trial of structured hydration vs usual care in hypertensive patients, with longer follow-up and endpoints including BP, albuminuria (albumin: creatinine ratio), eGFR slope, and cardiovascular outcomes.
- Mechanistic work combining hydration intervention with endothelial function testing (flow-mediated dilation), 24-hr ambulatory BP, and RAAS biomarkers.
- Stratified analyses to identify subgroups (e.g., high baseline copeptin, low habitual water intake) who derive the largest benefit, enabling targeted lifestyle prescriptions.

CONCLUSION

A one-month hydration regimen (~2–2.5 L/day) in patients with Stage I–II systemic hypertension produced statistically significant reductions in plasma copeptin, serum osmolality and serum uric acid. These data support the physiological model whereby improved hydration suppresses vasopressin activity and may favorably influence metabolic and renal biomarkers in hypertensive patients. Larger randomized trials are warranted to determine whether these biochemical improvements translate to clinical benefit.

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