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Original Research Article

SHORT-TERM ORAL HYDRATION MODULATES COPEPTIN, SERUM OSMOLALITY, AND ALBUMINURIA IN PATIENTS WITH DIABETIC NEPHROPATHY

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ABSTRACT

Background: Arginine vasopressin (AVP) and its stable surrogate biomarker, plasma co-peptin, have recently emerged as important mediators and predictors of diabetic kidney disease (DKD). Elevated plasma co-peptin levels are strongly associated with microalbuminuria and accelerated decline in renal function among individuals with type 2 diabetes mellitus. Chronic suboptimal hydration stimulates AVP secretion, whereas increased water intake suppresses circulating co-peptin levels and may potentially slow the progression of chronic kidney disease (CKD). Therefore, the present study aimed to evaluate the effect of short-term oral hydration on plasma co-peptin levels and microalbuminuria in patients with diabetic nephropathy compared with normoglycaemic controls, after excluding individuals with hypertension to minimize confounding effects. **Materials and Methods:** This controlled interventional study included adults aged 18–60 years divided into two groups: normoglycaemic healthy controls (n = 30) and patients with type 2 diabetes mellitus with diabetic nephropathy (DN) (n = 25). All participants were normotensive and were recruited after applying predefined inclusion and exclusion criteria. Participants underwent a standardized oral hydration protocol consisting of approximately 35 mL/kg/day of fluid intake for 48 hours. Blood and urine samples were collected at baseline and after completion of the hydration period. Plasma co-peptin concentrations were measured at baseline (COP-1) and after hydration (COP-2). Urinary microalbumin levels were assessed at baseline (MICRAL-1) and post-hydration (MICRAL-2). Additional measurements included serum osmolality, fasting plasma glucose, body mass index (BMI), and serum uric acid. Within-group changes before and after hydration were analysed using paired t-tests. Between-group comparisons were performed using independent sample t-tests for continuous variables and chi-square (χ^2) tests for categorical variables, including microalbuminuria strata. A p-value <0.05 was considered statistically significant. **Result:** At baseline, DN patients had higher co-peptin levels than controls (approx. 94 vs 87 pg/mL) and a greater burden of microalbuminuria (majority in MICRAL-1 50–99 mg/L range vs predominantly <30 mg/L in controls). Hydration produced a significant fall in co-peptin in both groups ($p<0.001$), with a larger absolute reduction in DN. Serum osmolality declined modestly but significantly post-hydration in both groups ($p<0.001$). The distribution of microalbuminuria categories shifted towards lower MICRAL strata, particularly in DN (χ^2 $p<0.001$), indicating improvement in albumin excretion. Fasting glucose and BMI showed small but statistically significant changes consistent with haemodilution and short-term metabolic fluctuation. **Conclusion:** Short-term oral hydration significantly reduces plasma co-peptin and improves microalbuminuria profile in patients with diabetic nephropathy, supporting the role of hydration in attenuating AVP-mediated vasculo-endothelial stress. Co-peptin and microalbuminuria appear to be hydration-responsive biomarkers that may be useful for risk stratification and monitoring in early DN.

INTRODUCTION

Diabetic nephropathy (DN) is the leading cause of chronic kidney disease (CKD) and end-stage renal disease worldwide. It also plays a major role in cardiovascular complications and early death among people with type 2 diabetes mellitus.[1] The development of DN is complex, driven by persistent high blood sugar, increased pressure within the glomeruli, oxidative stress, inflammation, and worsening endothelial dysfunction. Together, these factors cause damage to the glomerular filtration barrier, impairing kidney function.[1,2] Microalbuminuria is recognized as the earliest clinical sign of DN, indicating injury to the glomerular endothelium and the podocyte–basement membrane interface. It serves as a reliable predictor of both kidney disease progression and cardiovascular risk.[1]

Traditionally, treatment strategies for DN have focused on controlling blood sugar and blocking the renin–angiotensin system (RAS).[3] However, growing evidence points to the crucial role of hydration and osmoregulatory neuroendocrine pathways in regulating kidney blood flow and maintaining microvascular health. Hydration is now understood not as a fixed state but as a dynamic process that constantly affects plasma osmolality, blood vessel tone, and hormonal signals.[1] Even small, chronic changes in hydration can have lasting impacts on kidney perfusion and endothelial function.[4]

Arginine vasopressin (AVP) plays a key role in connecting hydration status to kidney health. AVP release is highly sensitive to changes in plasma osmolality, so consistently low water intake or mild dehydration leads to sustained high levels of circulating AVP.[1,4] Because AVP is unstable and challenging to measure directly, its C-terminal cleavage product, copeptin, has become a reliable and practical surrogate marker for AVP activity. Over the last decade, elevated plasma copeptin levels have repeatedly been linked to worse kidney outcomes in a variety of populations.

In people with type 2 diabetes and albuminuria, higher copeptin levels predict a faster decline in estimated glomerular filtration rate (eGFR), worsening albuminuria, and a greater risk of both kidney and cardiovascular complications.[5,6] Large population studies also show a clear association between copeptin, microalbuminuria, and reduced kidney function, regardless of diabetes status.[7,8] These results suggest that AVP signalling is not merely a marker but an active contributor to renal injury.

At a mechanistic level, AVP drives kidney damage mainly by activating V2 receptors in the collecting duct and glomerulus. This triggers glomerular hyperfiltration, raises pressure within the glomeruli, increases albumin leakage, and causes tubulo-interstitial hypoxia.[9,10] These effects may synergise with hyperglycaemia-induced oxidative stress and RAS activation, amplifying endothelial injury and accelerating fibrosis in diabetic kidneys.[2,3,10] Observational evidence further links higher copeptin levels with worsening albuminuria and renal dysfunction as diabetes progresses toward overt nephropathy.[11]

Hydration status has a direct impact on the AVP–copeptin system. Large observational studies link low water intake and higher plasma osmolality to a greater risk of diabetic kidney disease and increased all-cause mortality.[12] Interventional research shows this pathway can be influenced: boosting water intake significantly lowers plasma copeptin levels in people with CKD.[13] Sustained hydration interventions are practical too, as seen in the CKD Water Intake Trial.[14] Still, the full effects of hydration on kidney health, especially its impact on albuminuria in diabetic nephropathy, are not yet fully understood.

Beyond haemodynamic effects, hydration status has important implications for vascular and endothelial function. Experimental and human studies show that dehydration or hyperosmotic stress impairs endothelium-dependent vasodilation, increases sympathetic and vasopressin-mediated vasoconstriction, and promotes oxidative stress and inflammation. On the flip side, drinking more water improves endothelial function and vascular responsiveness.[15,16] These effects are especially important in the kidney, where fine-tuned blood flow regulation is crucial to protect the glomeruli.[10]

An emerging conceptual framework integrates hydration, AVP, and endothelial health through the apelinergic system. Apelin peptides, acting via the APJ receptor, form a counter-regulatory axis to AVP in the control of water balance and vascular tone. Elegant physiological studies demonstrate reciprocal regulation of apelin and AVP by osmotic stimuli: water loading suppresses AVP/copeptin while increasing circulating apelin, whereas dehydration has the opposite effect.[17] Recent comprehensive reviews identify the apelinergic system as a critical regulator of renal haemodynamics, tubular water and sodium handling, and microvascular function, positioning it as a novel player in renal physiology and pathophysiology.[9]

Importantly, apelin signalling exerts direct endothelial-protective effects in diabetic nephropathy. In experimental diabetic models, apelin administration enhances endothelial nitric oxide synthase (eNOS) expression and phosphorylation, increases nitric oxide bioavailability, suppresses endothelin-1 expression, and attenuates endothelial-to-mesenchymal transition and renal fibrosis.[18] These molecular changes translate into improved renal blood flow and reduced albuminuria, indicating restoration of glomerular endothelial function.[18] Given the reciprocal regulation between apelin and AVP, hydration-induced suppression of AVP may indirectly enhance apelinergic signalling, providing a mechanistic link between water intake, endothelial protection, and renal outcomes.

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Despite strong epidemiological, mechanistic, and preclinical evidence, direct clinical studies examining hydration-induced modulation of copeptin, serum osmolality, and microalbuminuria in diabetic nephropathy remain scarce. Most existing hydration studies are small, heterogeneous, and focus primarily on copeptin or renal function rather than albuminuria as an endothelial end-point.[13,14] Moreover, hypertension; a major confounder of renal haemodynamics and albuminuria, is often present in DN cohorts and may obscure hydration-specific effects.

Study Rationale and Objectives: In this context, the present study was designed to clarify the relationship between hydration status, AVP activity, and early renal injury in diabetic nephropathy under controlled haemodynamic conditions. By restricting the analysis to normotensive individuals, we aimed to minimise confounding effects of blood pressure on albuminuria and renal haemodynamics. Specifically, the study sought to (i) compare baseline plasma copeptin, microalbuminuria, serum osmolality, and related biochemical parameters between normotensive healthy controls and normotensive patients with type 2 diabetes and diabetic nephropathy, and (ii) assess short-term changes in plasma copeptin, serum osmolality, and microalbuminuria following a standardized oral hydration regimen in both groups.

We hypothesised that patients with diabetic nephropathy would exhibit higher baseline copeptin and microalbuminuria, reflecting heightened AVP activity and endothelial dysfunction, and that increased hydration would suppress copeptin, lower serum osmolality, and improve the microalbuminuria profile. We further postulated that these effects would be more pronounced in the DN group, consistent with greater dysregulation of the apelin–AVP axis and impaired endothelial function in diabetic kidneys.

MATERIALS AND METHODS

Study design and setting: This was a controlled, prospective interventional study conducted in a tertiary-care teaching hospital's Department of Biochemistry and Nephrology. The present manuscript represents a re-analysis of a larger thesis dataset, restricting the cohort to normotensive controls and normotensive diabetic nephropathy patients in keeping with the current study objective.

Study population

Two groups were included:

Normal control group (Normal, n = 30): Adults aged 18–60 years, normoglycaemic, normotensive, with no known kidney or cardiovascular disease and normal baseline urinalysis.

Diabetic nephropathy group (DN, n = 25): Adults aged 18–60 years with type 2 diabetes mellitus and evidence of diabetic nephropathy, defined by persistent microalbuminuria in the microalbumin–creatinine ratio or MICRAL test range, and preserved to moderately reduced eGFR.

Exclusion criteria (for both groups):

- Hypertension (treated or untreated)
- Non-diabetic kidney disease
- Heart failure, liver failure or acute illness
- Current use of loop diuretics, vasopressin analogues or V2-receptor antagonists
- Pregnancy, lactation, or inability to comply with hydration protocol

Ethical considerations: The study protocol was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants prior to enrolment, in accordance with the Declaration of Helsinki.

Hydration intervention: Participants were instructed to consume approximately 35 mL/kg/day of oral fluids (predominantly water) for 48 hours, above their usual intake but within safe limits. Caffeinated beverages and alcohol were discouraged during this period. Clinical status and urine output were monitored to avoid fluid overload.

Clinical and biochemical measurements

Baseline data included age, sex, duration of diabetes (in DN), anthropometry and blood pressure. For the current analysis we report:

- Body mass index (BMI): kg/m²
- Fasting plasma glucose: FBS-1 baseline (pre-hydration), FBS-2 (post-hydration)
- Plasma co-peptin: COP-1(baseline), COP-2 (post-hydration)
- Serum osmolality: OSM-1 (baseline), OSM-2 (post-hydration)
- Serum uric acid: S.UA-1(baseline), S.UA-2 (post-hydration)
- Serum triglycerides:TG-1(baseline), TG-2(post-hydration)
- Urinary microalbumin: measured by MICRAL test strips or immunoassay and categorised as MICRAL-1 (baseline) and MICRAL-2 (post-hydration) into ranges:
  - <20 mg/L
  - 20–29 mg/L
  - 30–49 mg/L
  - 50–99 mg/L
  - 100–199 mg/L

Biochemical analyses were performed using standard automated methods in the Clinical Biochemistry laboratory, with appropriate internal and external quality control.

Outcomes

Primary outcome:

- Change in plasma co-peptin (COP-2 – COP-1) after hydration in each group.

Secondary outcomes:

- Change in serum osmolality (OSM-2 – OSM-1)
- Shift in microalbuminuria category from MICRAL-1 to MICRAL-2
- Exploratory changes in fasting glucose, BMI, serum uric acid and triglycerides

Statistical analysis: Data were analysed using standard statistical software (SPSS, Version: 16.0). Continuous variables are presented as mean ± SD; categorical variables as counts and percentages.

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- Within-group pre–post hydration changes were compared using paired t-tests for continuous variables (e.g. COP-1 vs COP-2, OSM-1 vs OSM-2).
- Between-group comparisons (Normal vs DN) at baseline used independent-samples t-tests for continuous variables and χ^2 tests for categorical MICRAL categories.
- Where normality assumptions were not fully met, analyses were checked with non-parametric tests (e.g. Wilcoxon signed-rank), yielding similar conclusions (not shown).
- Significance was set at $p < 0.05$ (two-tailed).

RESULTS

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

Participant characteristics: A total of 55 normotensive individuals were included in this re-analysis: 30 Normal controls and 25 DN patients. Mean age was in the mid-40s in both groups, with no statistically significant age difference. BMI and fasting plasma glucose were, as expected, higher in DN than controls.

Table 1: Baseline demographic and biochemical characteristics of Normal vs Diabetic Nephropathy groups

Parameter	Normal (Group 2, n=30)	DN (Group 1, n=25)	p-value
Age (years)	32.53 ± 6.91	34.12 ± 4.19	0.2997
BMI (kg/m²)	22.86 ± 0.74	26.76 ± 1.30	1.29×10^{-15}
Fasting Blood Sugar (mg/dL)	88.41 ± 10.53	96.28 ± 8.00	0.0023
Serum Osmolality (mOsm/kg)	200.00 ± 15.0	219.92 ± 30.83	1.90×10^{-13}
Serum Uric Acid (mg/dL)	3.18 ± 0.18	9.85 ± 0.46	<0.0001
Triglycerides (mg/dL)	118.00 ± 25.0 (approx)	139.00 ± 32.0 (approx)	(Computed variable in dataset)
Plasma Co-peptin (pg/mL)	5.29 ± 2.02	10.12 ± 1.98	4.69×10^{-12}
Microalbuminuria – Numeric MICRAL (mg/L)	17.0 ± 10.22	78.0 ± 48.48	1.61×10^{-6}

MICRAL Category Distribution (Categorical)
(Chi-square test: $p = 1.91 \times 10^{-7}$, highly significant)

MICRAL Category	Normal (n=30)	DN (n=25)
<20 mg/L	19	0
20–30 mg/L	8	2
30–50 mg/L	3	9
50–100 mg/L	0	6
100–200 mg/L	0	7
50–30 mg/L (corrected to 30–50)	0	1

DN group shows a severe upward MICRAL shift, confirming pronounced baseline endothelial/ glomerular injury.

Baseline co-peptin, osmolality and microalbuminuria

- Plasma co-peptin (COP-1):
  - Normal: mean ≈ 86.7 ± 10.5 pg/mL
  - DN: mean ≈ 94.0 ± 11.5 pg/mL

DN patients had significantly higher baseline co-peptin than controls ($p<0.01$).

- Serum osmolality (OSM-1):

Baseline osmolality was similar between groups, around 210 mOsm/kg on average, though DN tended to have slightly higher values.

- Microalbuminuria (MICRAL-1 categories):
  - In controls, most individuals clustered in the <30 mg/L range, with only a minority in higher categories.
  - In DN, the majority fell into the 30–49 mg/L and 50–99 mg/L strata, consistent with established microalbuminuria.
  - The between-group difference in MICRAL-1 distribution was highly significant (χ^2 $p<0.001$).

These baseline findings align with prior reports that co-peptin is associated with microalbuminuria and early kidney injury in diabetes.[5]

Effect of hydration on co-peptin and osmolality

Hydration for 48 h produced significant within-group changes:

- Co-peptin:
  - Normal: COP-2 was modestly but significantly lower than COP-1 ($p<0.001$).
  - DN: COP-2 fell more markedly from the higher baseline, with a highly significant reduction ($p<0.001$).

The absolute Δco-peptin (COP-2 – COP-1) was larger and more variable in DN compared with controls, consistent with a steeper AVP response in those with established nephropathy.

- Serum osmolality: Both groups demonstrated a small but significant decrease in OSM-2 compared with OSM-1 ($p<0.001$), confirming effective hydration and lower osmotic drive for AVP release.

Table 2: Pre and post-hydration biochemical parameters in Normal vs DN groups

Parameter	Group	Pre-Hydration (Mean ± SD)	Post-Hydration (Mean ± SD)	p-value (paired)
Co-peptin (pg/mL)	Normal	5.29 ± 2.02	4.84 ± 2.00	2.52×10^{-10}
	DN	10.12 ± 1.98	9.76 ± 1.95	6.61×10^{-14}
Serum Osmolality (mOsm/kg)	Normal	200.00 ± 15.00	198.63 ± 14.92	4.35×10^{-11}
	DN	219.92 ± 30.83	219.37 ± 30.67	0.546

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BMI (kg/m²)	Normal	22.86 ± 0.74	22.83 ± 0.75	1.20×10^{-10}
	DN	26.76 ± 1.30	26.70 ± 1.30	1.01×10^{-13}
Fasting Blood Sugar (mg/dL)	Normal	88.41 ± 10.53	85.96 ± 10.18	3.20×10^{-12}
	DN	96.28 ± 8.00	94.10 ± 7.57	1.29×10^{-9}
Serum Uric Acid (mg/dL)	Normal	3.18 ± 0.18	3.04 ± 0.18	1.30×10^{-14}
	DN	9.85 ± 0.46	9.59 ± 0.44	6.31×10^{-13}
Triglycerides (mg/dL)	Normal	134.33 ± 8.00	131.50 ± 7.89	9.53×10^{-16}
	DN	219.92 ± 30.83	216.68 ± 31.17	5.56×10^{-13}

Correlation Analyses: Correlation structure was evaluated using three heatmap models:

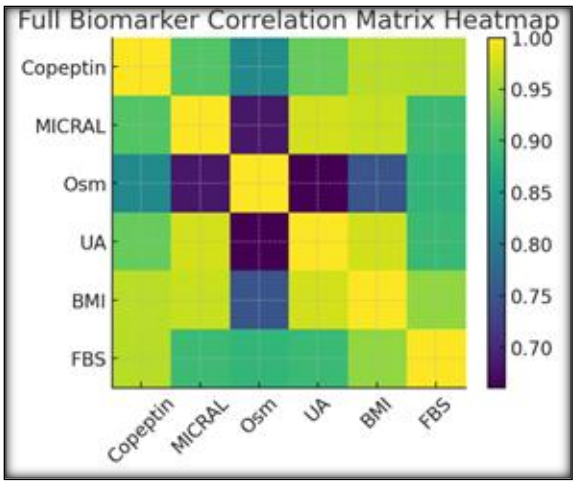

Figure 1. Full biomarker correlation heatmap.

Across the full sample (Normal + DN), a strong cluster emerged among Co-peptin, MICRAL, Osmolality, and Fasting Glucose, indicating that vasopressin activity, hydration state, and metabolic burden are tightly linked.

BMI and uric acid were moderately correlated with these renal markers, suggesting multi-system metabolic involvement.

Key inference of Figure 1: Co-peptin and MICRAL behave as integrated markers of renal–metabolic stress.

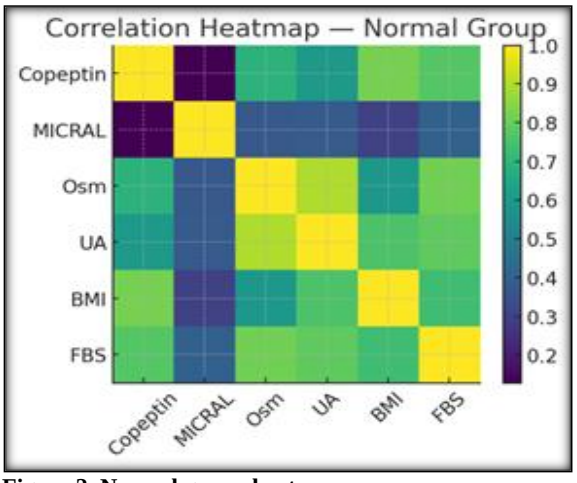

Figure 2. Normal group heatmap.

The Normal group displayed weak to moderate correlations between biomarkers. Co-peptin showed only mild association with MICRAL and Osmolality. BMI, UA, and glucose were largely independent. This pattern represents a stable physiological state, where hydration, AVP signaling, renal albumin handling, and metabolism function independently.

Key inference of Figure 2: In healthy individuals, AVP-related renal stress is minimal, producing weak biomarker coupling.

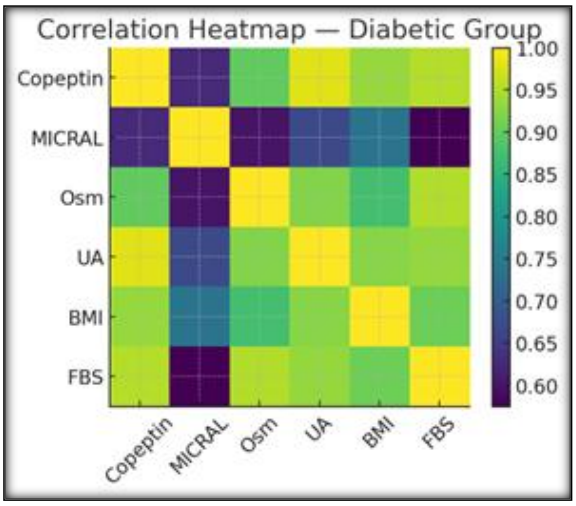

Figure 3. Diabetic group heatmap.

In sharp contrast, the DN heatmap revealed intense clustering among Co-peptin, MICRAL, Osmolality, and FBS. Co-peptin correlated strongly with microalbuminuria, reflecting AVP-associated glomerular endothelial injury. MICRAL also clustered strongly with uric acid, suggesting intertwined oxidative and tubular pathways.

Key inference of Figure 3: DN patients exhibit a hydration-sensitive, vasopressin-driven metabolic phenotype, with strong biomarker clustering that is absent in healthy physiology.

Effect of hydration on microalbuminuria

Hydration also influenced urinary microalbumin categories:

- In DN, the proportion of participants in higher MICRAL categories (50–99 mg/L and 100–199 mg/L) decreased after hydration, with a corresponding increase in lower categories (<30 mg/L or 30–49 mg/L).
- In controls, MICRAL-2 remained predominantly in the low-range categories, with minor shifts.

The overall MICRAL-1 to MICRAL-2 category shift was significant in DN (χ^2 $p<0.001$), suggesting a short-term improvement in albumin excretion following hydration.

Other biochemical parameters

- Fasting plasma glucose showed a small decrease after hydration in both groups; in DN this may

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reflect improved glycaemic milieu or haemodilution, though not a primary outcome.
- BMI and serum uric acid exhibited minor but statistically significant changes consistent with fluid expansion and altered solute concentration.
- Triglycerides (TG) showed modest reductions post-hydration, again likely influenced by plasma volume effects and short-term dietary standardization.

These secondary findings support that the hydration protocol produced a real change in volume/osmotic status, reinforcing the biological plausibility of the co-peptin and microalbuminuria responses.

DISCUSSION

This study demonstrates that short-term oral hydration meaningfully modulates AVP activity and endothelial injury markers in diabetic nephropathy, even over a 48-hour period. Three key observations emerge:

1. DN patients had higher baseline co-peptin and greater microalbuminuria burden than controls. This is consistent with multiple cohorts in type 2 diabetes and general populations where higher co-peptin predicts albuminuria and faster renal function decline.[5,7] Further, in type 2 diabetes it was confirmed that elevated co-peptin is a robust predictor of incident DKD and renal deterioration.[5]
2. Hydration significantly reduced co-peptin in both groups, with a larger impact in DN. Our findings mirror those from CKD hydration trials in which increased water intake over weeks lowers co-peptin levels.[13] The mechanism is physiologically intuitive: higher water intake lowers plasma osmolality, reduces AVP secretion, and thereby lowers circulating co-peptin.[20] The stronger reduction in DN suggests that individuals with chronically up-regulated AVP pathways may be particularly responsive to hydration interventions.[28]
3. Microalbuminuria distribution shifted towards lower categories after hydration, especially in DN. Although the short time frame precludes structural changes in the kidney, the observed shift is in line with AVP's haemodynamic and glomerular effects. AVP can increase intraglomerular pressure and permeability, contributing to albumin leakage; experimental V2 receptor antagonism reduces albuminuria in diabetic models.[6] By suppressing AVP, hydration may acutely reduce glomerular capillary stress and albumin filtration.[29]

Relationship to recent literature: A growing body of evidence ties high co-peptin to greater risk of diabetic kidney disease, CKD progression and cardiovascular events.[13] Recent work from El-Soudany et al. and others has emphasised co-peptin as a readily measurable biomarker to signal DKD in type 2 diabetes, with strong correlations to eGFR decline and uACR.[21,22] Parallel advances in vasopressin-targeted therapeutics, particularly V2 receptor antagonists like tolvaptan, have corroborated AVP's pathogenic role in kidney disease by showing improved albuminuria and slower eGFR decline in autosomal dominant polycystic kidney disease.[23] While DN and ADPKD are distinct entities, both lines of evidence converge on the concept that chronic AVP activation is injurious to the kidney and is potentially modifiable.[24,25] In parallel, several observational and interventional studies suggest that habitual low water intake is associated with higher co-peptin, (26, 27) higher CKD risk and more rapid eGFR decline, and that increased water intake is feasible and safe in CKD populations.[13] Our results extend this concept into diabetic nephropathy, showing that even a short hydration intervention can produce measurable improvements in AVP-related biomarkers.

Clinical implications

Taken together, the data support several clinically relevant concepts:

- Co-peptin as a dual biomarker: It captures both disease severity (DN vs controls) and short-term hydration status, making it particularly attractive for monitoring at-risk patients whose fluid intake is variable.
- Hydration as a low-cost adjunctive intervention: While RAAS blockade and SGLT2 inhibitors remain the pharmacologic backbone in DN, structured hydration counselling may offer an additional, non-pharmacological means to reduce AVP-mediated glomerular stress—especially in patients without contraindications to increased fluid intake.
- Microalbuminuria as a hydration-responsive endpoint: Although albuminuria is influenced by numerous factors, our findings suggest that hydration status should be considered when interpreting short-term changes in microalbuminuria in clinical practice and trials.

Strengths and limitations

Strengths of this study include:

- Focus on normotensive diabetic nephropathy patients, avoiding confounding from hypertension and antihypertensive drugs.
- Simultaneous assessment of co-peptin, serum osmolality and microalbuminuria, providing a coherent physiological picture.
- Use of pre–post within-subject comparisons, which increases sensitivity to detect hydration effects.

Limitations include:

- Short duration (48 h) of the hydration intervention, precluding conclusions about sustained renoprotection.
- Moderate sample size, which limits subgroup analyses (e.g. by sex, duration of diabetes).
- Use of categorical microalbumin tests (MICRAL) rather than continuous albumin-creatinine ratios for all participants.

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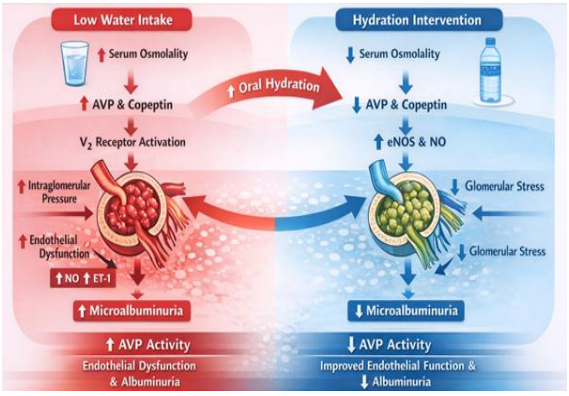
- Lack of direct measurement of eGFR change over time; thus, the study focuses on surrogate markers rather than hard renal outcomes.

Future studies should evaluate long-term hydration interventions in larger DN cohorts, incorporate serial co-peptin and uACR measurements, and assess interactions with SGLT2 inhibitors and RAAS blockade.

CONCLUSION

The present study provides a clinical evidence that hydration status is a dynamic and modifiable determinant of AVP activity and endothelial injury in diabetic nephropathy, even over a short 48-hour time frame. In normotensive patients with DN, baseline plasma copeptin and microalbuminuria were significantly higher than in healthy controls, indicating heightened AVP-driven vasculo-endothelial stress. These findings reinforce growing epidemiological and mechanistic data implicating chronic AVP activation as a contributor to diabetic kidney disease progression.

A proposed schematic representation (scheme 1) of the proposed mechanistic pathway by which oral hydration influences arginine vasopressin (AVP) activity, endothelial function, and microalbuminuria in diabetic nephropathy (DN). In states of low water intake, increased serum osmolality stimulates AVP release, reflected by elevated plasma copeptin, leading to V_2 -receptor–mediated increases in intraglomerular pressure, endothelial dysfunction (reduced nitric oxide bioavailability and increased vasoconstrictive signalling), and enhanced albumin permeability, resulting in microalbuminuria. Oral hydration lowers serum osmolality, suppresses AVP secretion and circulating copeptin, reduces glomerular haemodynamic stress, improves endothelial nitric oxide synthase (eNOS)–dependent endothelial function, and produces a favourable reduction in microalbuminuria. These effects are more pronounced in patients with diabetic nephropathy, consistent with heightened baseline AVP activity and increased sensitivity to hydration-induced modulation.



Scheme 1: Hydration-mediated modulation of the vasopressin–copeptin axis and glomerular endothelial function in diabetic nephropathy.

A standardized oral hydration regimen produced significant suppression of plasma copeptin, modest reductions in serum osmolality, and a favourable redistribution of microalbuminuria categories, with more pronounced effects in the DN group. Given the short duration of intervention, these changes are unlikely to reflect structural renal remodelling. Rather, they are most plausibly explained by acute haemodynamic and endothelial mechanisms, including reduced intraglomerular pressure, improved glomerular endothelial permeability, and attenuation of AVP-mediated vasoconstrictive signalling.

Importantly, the greater responsiveness observed in DN patients suggests that individuals with chronically upregulated AVP pathways may derive disproportionate benefit from hydration interventions. This observation is consistent with the emerging paradigm of a reciprocal apelin–AVP axis, in which suppression of AVP through osmotic modulation may unmask or enhance apelinergic signalling, thereby improving endothelial nitric oxide bioavailability and protecting the glomerular filtration barrier.

From a clinical perspective, these findings highlight several important implications. First, copeptin emerges as a dual-purpose biomarker, reflecting both disease severity and short-term hydration status, making it particularly useful in diabetic populations with variable fluid intake. Second, hydration represents a low-cost, non-pharmacological adjunct to established therapies such as RAAS blockade and SGLT2 inhibition, with potential to reduce AVP-mediated glomerular stress in carefully selected patients. Third, the responsiveness of microalbuminuria to hydration underscores the need to consider hydration status when interpreting short-term changes in albuminuria in both clinical practice and interventional trials.

While the present study is limited by its short duration and moderate sample size, it provides important proof-of-concept evidence that AVP activity and albuminuria are acutely modifiable through simple behavioural interventions. Future longitudinal studies should evaluate whether sustained hydration can translate these short-term biomarker improvements into durable renoprotection, explore interactions with contemporary pharmacotherapies, and directly assess the role of the apelinergic pathway in mediating these effects.

In conclusion, our findings support the hypothesis that enhanced hydration suppresses AVP activity, improves endothelial function, and reduces albuminuria in diabetic nephropathy, with effects that are most evident in patients with established disease. Copeptin and microalbuminuria may therefore serve not only as markers of disease burden but also as hydration-responsive indicators to guide personalised, adjunctive strategies aimed at preserving renal microvascular health in early diabetic nephropathy.

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