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Low Osmolar Diet and Adjusted Water Intake for Vasopressin Reduction in Autosomal Dominant Polycystic Kidney Disease: A Pilot Randomized Controlled Trial

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Abstract

Background—Autosomal dominant polycystic kidney disease (ADPKD) affects millions of people worldwide. Vasopressin promotes disease progression.

Study Design—A randomized controlled trial with equal (1:1) allocation.

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The other authors declare that they have no other relevant financial interests.

Contributions

Research idea and study design: OWA, RDP; data acquisition: OWA, RDP; data analysis/interpretation: OWA, FN, JKP, RDP; statistical analysis: OWA, FN, RDP; supervision or mentorship: FN, RDP. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. RDP takes full responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Peer Review

Evaluated by 2 external peer reviewers, a Statistical Editor, and the Acting Editor-in-Chief.

Supplementary Material

Figure S1: Study timeline.

Figure S2: Sample size estimation.

Figure S3: Urinary solute and volume outcomes.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

Supplementary Material Descriptive Text for Online Delivery

Supplementary Figure S1 (PDF). Study timeline.

Supplementary Figure S2 (PDF). Sample size estimation.

Supplementary Figure S3 (PDF). Urinary solute and volume outcomes.

Setting & Participants—This trial examined the effect of combining a low osmolar (low-sodium [1500 mg/d], low-protein [0.8 g per kilogram of body weight]) diet and adjusted water intake on vasopressin in 34 ADPKD patients.

Intervention—Participants were randomized to receive a low osmolar diet followed by adjusted water intake to achieve a urine osmolality of 280 mOsm/kg H₂O versus no intervention for two weeks.

Outcome—The primary outcome of the study was the change (delta) in copeptin and urine osmolality between intervention and control groups from baseline to two weeks

Measurements—Fasting plasma copeptin, 24 hour urine osmolality, and total solute intake

Results—Baseline characteristics of the two groups were similar. Mean plasma copeptin and urine osmolality declined from 6.2 ± 3.05 (SD) to 5.3 ± 2.5 pmol/L ($P=0.02$) and from 426 ± 193 to 258 ± 117 mOsm/Kg H₂O ($P=0.01$), respectively, in the intervention group compared to a non-significant change in the control group (4.7 ± 3.6 to 5.07 ± 4 pmol/L [$P=0.2$] and from 329 ± 159 to 349 ± 139 mOsm/kg H₂O [$P=0.3$], respectively). The change in copeptin (primary outcome) and urine osmolality was statistically significant between intervention and control groups (delta copeptin, -0.86 ± 1.3 versus $+0.39 \pm 1.2$ pmol/L [$P=0.009$]; delta urine osmolality, -167 ± 264 versus $+20 \pm 80$ mOsm/Kg H₂O [$P=0.007$], respectively). Total urinary solute decreased only in the intervention group and significantly differed between groups at week one ($P=0.03$) reducing mean water prescription from 3.2 to 2.6 L/day.

Limitations—Small sample size and short follow up duration.

Conclusions—We developed a step-wise dietary intervention that led to significant reduction in vasopressin in ADPKD patients. Furthermore, this intervention led to reduction in water required for vasopressin reduction.

Keywords

ADPKD; Vasopressin; Copeptin; Osmolality; Nutrition; Salt; Protein; Urea; Water; Clinical Trial

Autosomal dominant polycystic kidney disease (ADPKD) affects millions of people worldwide(1), and accounts for 8%-10% of end-stage renal disease (ESRD) patients in the United States and Europe(2). In spite of promising therapies, treatments that prevent development of ESRD in ADPKD do not currently exist(3).

Patients with ADPKD have impaired urine-concentrating ability(4) and higher levels of arginine vasopressin (AVP) (as reflected by plasma copeptin levels) as compared to healthy controls(5). This concentrating defect occurs in spite of overexpression of the vasopressin V2 receptor (6, 7). A powerful activator of adenylyl cyclase in collecting duct cells, AVP has an important role in ADPKD progression (7, 8). A host of experimental evidence obtained in animals with various renal cystic disorders indicates that physiologically normal levels of AVP have a major role in causing cysts to form and progressively enlarge. The inhibition of AVP V2 receptor controls disease progression in both animal models and humans, as does genetic elimination of vasopressin in the polycystic kidney (PCK) rat—thereby providing further support for a detrimental role of vasopressin(8-10) and indicating a promising target

for therapeutic intervention. Tolvaptan is the only AVP-V2 receptor blocker that has been shown to be effective in humans with ADPKD. In a large randomized trial for patients with ADPKD, tolvaptan reduced the rates of total kidney volume increase and the decline in kidney function over 3 years(10).

High fluid intake also lowers AVP and slows cyst progression in the PCK rat(11). However, adherence to high fluid intake is difficult to maintain in clinical practice(12, 13). Part of the difficulty in sustaining a low AVP level with daily water ingestion is the consumption of a high osmolar diet (diet high in protein and salt), which stimulates AVP secretion to maintain water homeostasis(14). To address the adherence challenges associated with a fluid-based treatment, we have combined a low osmolar diet with adjusted water intake, with the goal of lowering the amount of water intake needed to reduce AVP secretion.

We investigated the effect of a low osmolar diet and adjusted water intake on AVP secretion, as measured by change in copeptin levels and decreased urine osmolality, in subjects with ADPKD. Copeptin is a reliable marker of AVP secretion (15, 16), furthermore, plasma vasopressin and copeptin solidly correlate across a span of osmolalities and circulating copeptin levels, reflecting the antidiuretic effect of vasopressin at the level of the target organ(17). The long-term goal of this pilot study is to develop a safe, easily tolerated and affordable intervention that can be adopted early in the ADPKD process to slow cyst progression.

METHODS

Study Design

A randomized controlled trial in which patients with ADPKD were randomized with equal (1:1) allocation to receive either a low osmolar (low-sodium [1500 mg/d], low-protein (0.8 g/kg body weight)) diet and adjusted water prescription versus no intervention. Permuted block randomization was performed within strata of age (18-39 and 40-60 years) and sex (18, 19).

Study Population

Eligible patients were adults 18-60 years of age, who had ADPKD with an estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73m² determined using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation(20). Exclusion criteria included long-term use of medications known to affect AVP secretion (selective serotonin reuptake inhibitors, opioids, tricyclic antidepressants and tolvaptan), conditions influencing renal concentrating capacity other than ADPKD (diabetes insipidus, adrenal or thyroid insufficiency, present or prior use of lithium), hyponatremia (serum sodium below 135 mEq/L), presence of physical or cognitive impairments which prevent participation or consent, and pregnancy.

The study was approved by Tufts Medical Center institutional review board (IRB #11111). The study was conducted in adherence with the Declaration of Helsinki. All subjects signed an informed consent before participation.

Study Timeline and Procedures

Three visits, each one week apart, were conducted for study subjects (Figure S1, available as online supplementary material). At the 1st visit (baseline), subjects submitted a 24 hour urine collection and had blood collected. The intervention group received dietary counseling and was asked to adhere to a low osmolar diet. At the 2nd visit (week 1), all subjects repeated a 24 hour urine collection and had their second blood draw. Patients from the interventional group were given a water prescription to follow based on the results of their 2nd urine collection. At the 3rd visit (week 2), a final 24 urine collection and blood draw were performed. All subjects were asked to avoid caffeine intake for 24 hours prior to blood draws (21, 22).

Dietary Intervention and Control Group—The dietary intervention consisted of three elements: low sodium (1500 mg/d), low protein (daily protein dietary allowance, 0.8 g/kg body weight), and low urea (avoidance of preservatives, food additives, bulking agents, and chewing gum). Protein was factored by measured body weight to mirror the estimated average requirement of healthy adults, which is set on a grams per kilogram basis(23). Control subjects received no specific dietary intervention and were asked to follow their usual dietary intake of salt and water.

Water Prescriptions for Intervention Group—A specific water prescription was tailored for each patient in the intervention group based on the osmolar content of the 24 hour urine collection obtained after one week of the low osmolar diet; the water prescription was adjusted to produce a mean urine osmolality of 280 mOsm/Kg H₂O (24, 25). Subjects were asked to spread water consumption throughout the day.

$$\text{Water Prescription (in liters): } \frac{\text{Total solute (mOsm)}}{280 \text{ (mOsm/kg H}_2\text{O)}}$$

where Total solute = 24-hour urine volume (L) × urine osmolality (mOsm/Kg H₂O). One kilogram of fluid was assumed equal to 1,000 milliliters of fluid. An additional 500 ml water was added to account for insensible loss.

Outcome Measures

The primary outcome measure was the mean difference () of the plasma copeptin levels between baseline and the end of week 2, which reflects the combined effect of the low osmolar diet and adjusted water intake. Secondary outcome measures included total daily urinary solute reduction (total amount of osmoles detected in 24 hour urine collection, which is a surrogate for diet adherence), and 24 hour urine osmolality reduction.

Sample Size Justification

As there are no data available on the association between dietary habits and water intake and copeptin, we relied on a prior study of copeptin in ADPKD patients compared to healthy controls(5). Assuming a mean copeptin at baseline of 14.74 pmol/L (5) and that the lowest achievable copeptin after the intervention would be that previously observed among healthy controls (4.62 pmol/L), only 9 patients in each arm are required to achieve 80% power to

detect a mean difference (baseline copeptin – week 2 copeptin) of 10 pmol/L. Using a more conservative mean difference in copeptin value of 7 pmol/L in the intervention arm, 18 subjects (assuming 20% dropout rate) in each arm would be required to achieve 80% power (Figure S2).

Recruitment and Randomization

Subjects were recruited from the Tufts Polycystic Kidney Disease Research Registry. Using the R statistical software (26) package ‘blockrand’ a random assignment for the trial intervention was created. The software was then used to create a file of randomization cards based on the output from ‘blockrand.’ Printed cards in envelopes were used to assign subjects to treatment. Subjects in both groups were blinded to the outcome measures and were informed that the purpose of the trial was to learn if dietary habits can affect vasopressin secretion. It was not possible to blind subjects to the assignment group, as the intervention group received specific water prescriptions and counseling for sodium and protein reduction. The primary outcome (copeptin) was measured at the end of the study, and the technician was blinded to treatment assignments and the visit timeline.

Measurements and Definitions

Participants had been diagnosed with ADPKD (Ravine(27)) and followed up at the specialized ADPKD center at Tufts Medical Center. Complete medical records were available including imaging studies, and medication history. Patients also previously completed a questionnaire on disease factors, family and social history, and lifestyle including caffeine intake. At the study screening visit, the above information was verified with patients to ensure accuracy. Height and weight were recorded and body mass index (BMI) was calculated. Measurements of sodium, potassium, urea, creatinine, and osmolality were performed in three 24-hour urine samples. Extensive verbal and written instructions were provided on the collection procedure. Sodium, potassium and protein intake were estimated from the measurements of urine sodium, potassium and urea nitrogen respectively in the 24 hour urine collections (28, 29). Protein intake was factored by body weight.

Laboratory Tests—Standard biochemical evaluation was performed using fresh urine and plasma samples, using ARCHITECT ci8200 Integrated System (Abbot Diagnostics). The GFR was estimated with the CKD-EPI creatinine equation. Plasma and urine osmolality were measured directly via determination of freezing point depression (Advanced Instruments Osmometer 2020, Advanced Instruments, Inc).

Copeptin Measurement—Morning blood samples were collected during standardized hydration status (10 hours fasting) for all patients. Samples were collected into lavender Vacutainer tubes (#VT-6450) which contain EDTA. Those tubes were gently rocked several times immediately after collection for anti-coagulation. The blood was then transferred to centrifuge tubes and gently rocked several times to inhibit proteinase activity. The blood then was centrifuged at 1,600g for 15 minutes at 4°C and the plasma was collected and immediately frozen at –70°C for the duration of the study. Copeptin was measured using a sandwich immunoassay (B·R·A·H·M·S AG/ThermoFisher) (30).

To minimize inter-assay variability, all samples were thawed at the same time by one laboratory technician. The 3 samples for each subject were tested using the same kit.

Statistical Analysis

The analysis of the primary and secondary outcome was based on an intention-to-treat principle. Copeptin was measured in each subject at baseline and week 2 and the change from baseline to end point (“delta”) was calculated for all subjects. The delta copeptin between subjects in the intervention and control arms was compared with a two sample t test for independent groups. One sample t-tests of the delta (equivalent to a paired t-test) copeptin, urine osmolality and total solutes values (compared to a null value of 0) were used to examine whether there was any change over time for each group separately. A significance level of $\alpha = 0.05$ was used. All analyses were performed using the R statistical software package(26). The correlation of 24 hour urine osmolality and copeptin was evaluated using Pearson’s correlation coefficients.

Concerning missing data, there was only one patient who did not complete the protocol, which is likely related to the short study duration. One patient from the intervention group did not present for visits 2 and 3, citing a job conflict. We used a conservative approach by assuming no change in urine osmolality or copeptin for that patient, as this would bias our results towards the null.

RESULTS

Study Participants

From May 2014 through April 2015, the Tufts PKD registry was reviewed for eligible subjects and those who met inclusion criteria and provided informed consent were randomized to the study groups. Of 356 patients screened, 272 did not meet inclusion criteria due to age (n=61), low eGFR (n=176), selective serotonin reuptake inhibitor or opioid use (n=20), or other reasons (n=15). There were 84 patients who were approached, of whom 40 declined to participate (mainly due to residential location outside Boston or Massachusetts), and 10 could not be reached. Thus, 34 patients (28 women) were randomized to a low osmolar diet followed by adjusted water intake (n=17) or to no dietary intervention (n=17) (Figure 1). All patients completed the study protocol except one patient from the intervention group who withdrew citing a job conflict.

Baseline Characteristics

Baseline characteristics of the two groups were similar (Table 1) except for mean 24 hour urine volume, which was statistically significantly higher in the control group (2726 ± 995 [standard deviation] ml) compared to the intervention group (1903 ± 723 ml).

Diet and Water Intake Adherence

Estimation of dietary sodium and protein intake as measured in 24 hour urine collections indicated good adherence to sodium and protein targets. Compared with baseline, the mean daily sodium and protein intakes declined at week 1 from 2909 ± 1300 to 1937 ± 1044 mg and from 1.0 ± 0.24 to 0.9 ± 0.24 g/kg body weight, respectively. Sodium and protein intakes

remained stable over the study duration of 2 weeks in the control group (3591 ± 2645 to 3546 ± 2453 mg and from 1.1 ± 0.34 to 1.19 ± 0.45 g/kg body weight, respectively).

Effect of Low Osmolar Diet on Fasting Copeptin and Other Outcomes

Changes in outcome measures are summarized in Table 2. Fasting plasma copeptin and urine osmolality levels over the course of the trial are shown in Figure 2. At baseline, plasma copeptin was not significantly different between the intervention and the control groups (6.2 ± 3.05 and 4.7 ± 3.6 pmol/L respectively; $P = 0.2$). At visit 3 (week 2), copeptin significantly decreased from 6.2 ± 3.05 pmol/L at baseline to 5.3 ± 2.5 pmol/L ($P=0.02$) in the intervention group compared to a non-significant change in the control group (from 4.7 ± 3.6 to 5.07 ± 4 pmol/L; $P=0.2$). The change in mean plasma copeptin level between baseline and visit 3 (week 2) was statistically significantly different between intervention and control groups (-0.86 ± 1.3 versus $+0.39 \pm 1.2$ pmol/L, respectively; $P=0.009$).

A similar effect was observed with urine osmolality. Baseline urine osmolality was not significantly different between the intervention and control groups (426 ± 193 and 329 ± 151 mOsm/Kg H₂O, respectively; $P = 0.1$). At visit 3 (week 2), there was a significant decline from baseline in urine osmolality from 426 ± 193 to 258 ± 117 mOsm/kg water ($P=0.01$) in the intervention group compared to a non-significant change in the control group from 329 ± 159 to 349 ± 139 mOsm/Kg H₂O ($P=0.3$). The change in mean urine osmolality level between baseline and visit 3 was statistically significant between groups (-167 ± 264 mOsm/Kg H₂O in intervention group compared to $+20 \pm 80$ mOsm/Kg H₂O in control group; $P=0.007$).

Urinary solute (measured in a 24 hour urine collection) decreased only in the low osmolar diet group (from 722 ± 254 to 602 ± 202 mOsm/d [$P=0.02$] in intervention group compared to 856 ± 410 to 884 ± 467 mOsm/d [$P=0.7$] in control group) (Figure 3 and Figure S3). Mean urine volume increased from 1903 ± 732 to 2703 ± 974 mL/d ($P=0.008$) compared to a non-significant change in the control group (from 2726 ± 995 to 2506 ± 975 mL/d; $P=0.3$; Figure S3). Urine volume at week 2 for the intervention group was consistent with water prescription (2.6 L/d). The decline in total urinary solute led to a significant decrease in water requirement in order to achieve the target urine osmolality for the intervention group. The mean water prescription for the intervention group at visit 2 was 2.6 L/d (compared to 3.2 L/d required at baseline). Water requirements ranged between 2.5-5.02 liters at baseline compared to a range of 1.5-3.7 liters after adopting a low osmolar diet. In the control group, urinary solute was not statistically significantly different between the three visits. There was no hyponatremia (defined as Na < 135 mEq/L; mean Na, 141.4 ± 1.8 mEq/L) or other adverse events identified during the study period. Mean serum osmolality was 293.4 ± 5.2 mOsm/kg; potassium, 4.2 ± 0.28 mEq/L; and serum urea nitrogen, 15.3 ± 4.7 mg/dl.

Plasma Copeptin and Urine Osmolality Correlation

Plasma copeptin levels were directly correlated with 24 hour urine osmolality at baseline and throughout the study (Pearson's $r = 0.4$; $P < 0.001$; Figure 4).

DISCUSSION

In this randomized controlled trial, we identified a novel dietary approach that achieved a significant reduction in vasopressin, as measured by reduced plasma copeptin and urine osmolality after two weeks in ADPKD patients within CKD stage 1 and 2 categories of eGFR. The stepwise approach of reducing salt and protein intake followed by adjusting water intake led to significant reduction of water requirements (2.6 L) needed to achieve target urine osmolality (≥ 280 mOsm/Kg H_2O). This amount of water is reasonable in clinical practice and is likely to be well tolerated by a large number of patients.

A prior pilot study suggested feasibility and effectiveness of a dietary approach in reducing sodium and protein intake and increasing water intake in ADPKD(31). Our pilot study further supports the feasibility of dietary approaches in ADPKD treatment. The novel finding of the present study is targeting sodium and protein intake as a means to lower the water intake required to reduce vasopressin, as well as verifying a reduction in plasma copeptin and 24 hour urine osmolality.

Our approach showed a robust decrease in urine osmolality, which is used to assess the efficacy of vasopressin reduction or blockage. In fact, the reduction in mean urine osmolality achieved in this trial was equivalent to the one achieved with Tolvaptan in the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) trial (426 to 258 compared to 472 to 264 mOsm/Kg H_2O)(10, 32). It is important to point out that low urine osmolality can be a sign of advanced ADPKD with significant urinary concentrating defect, and, therefore, the change in osmolality rather than the absolute level is critical to assess the efficacy of therapeutic interventions targeting vasopressin, especially over a short time period. Participants from this trial had preserved eGFR, thus a defective urinary concentrating ability is unlikely.

The advantage of a stepwise approach of reducing osmolar intake followed by water adjustment to achieve target urine osmolality is underscored by describing the typical Western diet. Typically, 1200 mOsm of solute are ingested or generated by the metabolism of nutrients each day in the American diet. Nearly 40% of these solutes are intrinsic to food, another 35% is a food additive (i.e. salt as a preservative or flavoring), and the rest is mostly urea derived from protein metabolism (14). A person consuming 1200 mOsm/d will need to consume 4.8 L/d of water (assuming 0.5-L insensible loss) in order to achieve target urine osmolality of 280 mOsm/Kg water.

In this pilot trial, control-arm participants ingested over 3 L of water per day, which exceeds the average daily fluid ingestion of the average American (1.2 L/d) (33). This difference may be related to dietary counseling and behavioral health practices specific to individuals with ADPKD or impaired urinary concentrating ability due to ADPKD.

High copeptin levels are associated with disease progression in ADPKD as shown in a large observational study(34). This finding is consistent with the pathophysiological role of vasopressin in ADPKD. Our trial identified a dietary approach that can reduce copeptin and presumably vasopressin levels over a relatively short duration. Therefore, copeptin may prove to be a valuable biomarker to predict the risk of disease progression and monitor the

effectiveness of therapies and lifestyle modifications targeting vasopressin. In this pilot trial we aimed to standardize hydration status before copeptin measurement. Patients were asked not to drink for 10 hours prior to blood sampling. It is possible that the measured copeptin levels underestimate the degree of vasopressin suppression throughout the day, as suggested by a more profound reduction in 24 hour urine osmolality.

The major limitations of this pilot study are its small sample size and short duration of follow up. The small sample size may have given rise to baseline imbalances that are difficult to account for, and it is possible that these imbalances may drive some of the results. The unequal respective mean copeptin, fluid and osmolar intakes and urine volumes in the control and intervention groups limits the comparison of the two groups. In order to mitigate this inherent limitation of small pilot trials, each patient's response was compared to their own control at baseline value; however, it is important to interpret the findings with caution, and the effect of baseline imbalance in copeptin might be particularly relevant. The baseline imbalance, along with the effect of fasting, might explain why the decreased plasma copeptin from baseline to week 2 in the intervention group did not reach the levels of the control group during the study. In regards to the short trial duration, given that water homeostasis is expected to be achieved in 48 hours, we anticipate that the study duration was sufficient to reflect a true change in vasopressin secretion. Future studies are needed to explore the long-term adoption and maintenance of diet and water prescriptions in clinical practice. The trial has a disproportionate number of women, but blocked randomization by sex ensured balance between groups (17% males in each). Prior studies (18, 19) suggest that copeptin levels are higher in males; therefore, it is possible that the effect of low osmolar diet and adjusted water intake will be more prominent in male patients. Larger studies are needed to examine the generalizability of this pilot trial. Major study strengths include the controlled randomized design with rigorous study participant monitoring and objective measurements of outcomes, and the innovative step-wise approach with water prescription designed to compensate for incomplete adherence to a low-protein, low-salt diet.

In conclusion, we developed a dietary intervention that led to significant reduction in vasopressin secretion as measured by reduction in plasma copeptin and 24 hour urine osmolality in patients with early ADPKD. Furthermore, this dietary intervention significantly reduced the water required for vasopressin reduction. Long-term studies are needed to evaluate diet and adjusted water intake adherence, and determine if lowering vasopressin slows ADPKD progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Consolidated Standards of Reporting Trials (CONSORT) diagram. Of the 34 patients who were randomized, 33 (97%) completed the study and were included for analysis. One patient withdrew participation, citing a conflict with a job.

Figure 2.

Panel A: Plasma copeptin compared to baseline in the two study groups, over study visits. In the low osmolar diet group, plasma copeptin declined by 15% by visit 3 (week 2) ($P=0.02$), compared to non-significant change in the control group.

Panel B: The primary outcome of the study was the change (delta) in copeptin between intervention and control groups from baseline to two weeks. This change was statistically significant ($P=0.009$). Plasma copeptin (pmol/L) in each individual patient in control (left) and intervention (right) groups before (visit 1) and after 2 weeks of assignment (visit 3). The bold solid line represents the mean. V, visit

Panel C: In the intervention group, the 24 hour mean urine osmolality decreased by 40% on visit 3(week 2) ($P=0.01$) compared to no significant change in the control group during the study period.

Panel D: The change (delta) in urine osmolality (mOsm/Kg H₂O) between intervention and control groups at 2 weeks was statistically different ($P=0.007$). 24 hour urine osmolality in each individual patient in control (left) and intervention (right) groups before (visit 1) and after 2 weeks of treatment (visit 3). The bold solid line represents the mean. V, visit.

Figure 3.

Change in total solute^a and corresponding water requirement^b at visit 2 needed to reach a target urine osmolality of 280 mOsm/Kg H₂O. Total solute was similar between groups at baseline ($p=0.3$). Following intervention, total solute decreased only in the low osmolar diet group ($P=0.02$) reducing the mean water prescription for the intervention group from 3.2 L/daily at baseline to 2.6 L/daily at visit 2.

^a Total solute = urine volume (L) in 24 hours $\times$ urine osmolality (mOsm/Kg H₂O).

^b Including 0.5 liter for each individual to account for insensible loss.

Figure 4. Correlation between 24 hour urine osmolality (urine_osm) and fasting plasma copeptin. Plasma copeptin levels were directly correlated with 24 hour urine osmolality at baseline and throughout the study (Pearson's $r = 0.4$, $p < 0.001$).

Table 1

Baseline clinical and laboratory characteristics of study participants

Variable	Intervention (n = 17)	Control (n = 17)	P
Socio-demographic characteristics			
Age, y	43.1 ±13	44.4±9.8	0.7
Male sex	3(17)	3(17)	0.9
Race/Ethnicity ^a			
White	12(70)	14(80)	
Hispanic	4(23)	2(13)	
Asian/Pacific Islander	1(5)	1(5)	
Weight (kg)	68.5±15	68.9±14.6	0.9
BMI (kg/m ²)	24.4±5.6	24.1±4.0	0.9
Comorbidities			
Hypertension	7(41)	6(35)	0.7
Diuretic use	1(5)	1(5)	0.9
Laboratory Data			
Serum creatinine (mg/dl)	0.86±0.14	0.81±0.12	0.5
eGFR (ml/min/1.73m ²) ^b	89.3±19	91.8 ± 16	0.9
Serum sodium (mEq/L)	141.9±2	141.8±1.6	0.9
Plasma osmolality (mOsm/Kg water)	295±2.7	293.5 ±3.5	0.1
Urine volume (ml)	1903 ±723	2726 ± 995	0.01
Total solute intake (mOsm/d) ^c	722 ±254	856±410	0.3
Urine osmolality, mOsm/kg water	426 ±193	329 ±151	0.1
Sodium intake (mg/d) ^a	2909 ±1300	3591±2645	0.4
Protein intake (g/kg/d) ^d	1.00 ±0.24	1.12 ±0.34	0.2
Fasting copeptin (pmol/L)	6.2 ±3.05	4.7±3.6	0.2

Note: Values for categorical variables are given as number (percentage); for continuous variables, as mean ± standard deviation. Conversion factor for serum creatinine in mg/dL to umol/L, ×88.4.

BMI, body mass index; eGFR, estimated glomerular filtration rate

Race and ethnicity are self-reported

^b Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation

^c Total solute = urine volume (L) in 24 hours x urine osmolality (mOsm/Kg water)

^d Sodium and protein intakes were estimated from measurements of urine sodium and urea nitrogen, respectively, in 24 hour urine collection

Table 2

Change of baseline plasma copeptin, 24 hour urine osmolality, total solute intake, and urine volume from baseline to week 2

Outcome Measure	Intervention (n = 17)	Control (n = 17)
Copeptin ^a		
Baseline, pmol/L; <i>P</i> =0.2	6.2 ±3.05	4.7±3.6
copeptin, pmol/L	-0.86 ±1.3; <i>P</i> =0.02	+0.39±1.2; <i>P</i> =0.2
copeptin vs control, pmol/L	-1.26 (-0.33 to -2.18); <i>P</i> =0.009	----
Urine Osmolality ^b		
Baseline, mOsm/kg water; <i>P</i> =0.1	426 ±193	329 ±151
urine osmolality, mOsm/kg water	-167±264; <i>P</i> =0.01	20± 80; <i>P</i> =0.3
urine osmolality vs control, mOsm/kg water	-187 (-55.8 to -319.9); <i>P</i> =0.007	----
Total Solute Intake ^c		
Baseline, mOsm/d; <i>P</i> = 0.3	722 ±254	856±410
solute intake, mOsm/d	-120±212; <i>P</i> =0.02	+27±79; <i>P</i> =0.7
urine solute vs control, mOsm/d	-147 (+45.9 to -341); <i>P</i> =0.1	----
Urine Volume		
Baseline, mL/d; <i>P</i> = 0.01	1903±732	2726± 995
urine volume, mL/d	+804±1105; <i>P</i> =0.008	-220±885; <i>P</i> =0.3
urine volume vs control, mL/d	+1025 (+323.9 to +1726); <i>P</i> =0.005	----

Note: Values are given as mean ± standard deviation or mean (95% confidence interval).

^a10 hour fasting copeptin

^b24 hour urine osmolality

^cTotal solute = urine volume (L) in 24 hours × urine osmolality (mOsm/Kg water), total solute at visit 2 was used to calculate the water prescriptions that were given to subjects in the low osmolar diet group