HYDRATION STATUS & CKD: "WHAT IS THE EVIDENCE?"
CONFLICT OF INTEREST

• SPEAKING HONORARIUM, FLIGHT, ACCOMODATION EXPENSES AND GRANT SUPPORT FUNDED BY CIHR, KFOC, DANONE RESEARCH

• SPEAKING HONORARIUMS ASN, CSN, ALEXION, OCTAPHARMA, AKI-CRRT
THERAPEUTIC USE OF WATER IN CKD

• FOCUS: CKD although strong evidence for a role in ADPKD, renal calculi & heat stress nephropathy

• ANIMAL EXPERIMENTAL STUDIES

• HUMAN STUDIES

• 1) OBSERVATIONAL STUDIES

• 2) PILOT RCT & WIT RCT
1a) AVP inhibition in adult PCKD Slows Progression RCT >1100: Vincent Torres et al NEJM 2012 However not cost effective barring 95% reduction in cost Erickson et al Ann Intern Med 2013

1b) Increased Water intake slows progression in rat model of PCKD: Nagao et al JASN 2006 (EFFECT Cystogenesis) Await Australian RCT Gopala Rangan
MESO-AMERICAN NEPHROPATHY

An Epidemic of Kidney Disease in Central America

- SEVERE DEHYDRATION WITH ITS HIGH AVP LEVELS MAY BE CAUSE OF MESO-AMERICAN NEPHROPATHY AND PROGRESSIVE RENAL INJURY (DR L G SANCHEZ-LOZADA AND R JOHNSON)
Model of Heat-Induced Dehydration

Heating time at 39.5 °C
30 min every hour \times 10

No heating

TOTAL DURATION
5 weeks
WATER & RENAL CALCULI

• 4 LARGE POPULATION PROSPECTIVE OBSERVATIONAL STUDIES (3 BY CURHAN) >260,000 PARTICIPANTS
  SIGNIFICANT INVERSE RELATIONSHIP BETWEEN URINE OUTPUT (WATER INTAKE) AND STONE FORMATION

• 2 SMALLER RCTS N=256 & 70 SHOW INCREASED FLUID INTAKE ASSOCIATED WITH SIGNIFICANT REDUCTION IN STONE FORMATION IN HYDRATION GROUP
BIOLOGIC RATIONALE FOR WATER IN CKD

SUPPRESSION OF PATHOPHYSIOLOGIC EFFECTS OF AVP
AVP infusion increases proteinuria, renal plasma flow, and hyperfiltration, while administration of AVP antagonists reduces proteinuria and lowers blood pressure.
Beneficial effect of increased water intake in rats with chronic kidney disease

A 3-fold increase in water intake ameliorates proteinuria, blood pressure and glomerulosclerosis in rats with 5/6th nephrectomy (a classical model of progressive renal disease)

Bouby & Bankir, Am.J.Physiol., 1990
Sugiura et al 1999
CKD PROGRESSION IN MAN: OBSERVATIONAL STUDIES
HEBERT ET AL. AJKD 2003

• RETROSPECTIVE ANALYSIS OF MDRD STUDY N=581

• FASTER GFR DECLINE GREATER THE URINE VOLUME

• CKD ADJUSTED FOR DIURETICS, ACE INHIBITORS, B BLOCKERS AND CALCIUM CHANNEL ANTAGONISTS ASSOCIATION LOST!

• BP MEDS CAN DECREASE KIDNEY FUNCTION (HAEMODYNAMIC EFFECT) AND DIURETICS INCREASE URINE VOLUME INDEPENDENT OF HYDRATION
OBSERVATIONAL STUDIES IN MAN

- 2 CROSS SECTIONAL STUDIES

- 2 PROSPECTIVE LONGITUDINAL STUDIES
• 2 CROSS SECTIONAL STUDIES: FOOD FREQUENCY QUESTIONNAIRE PEOPLE > 50 IN DOOR TO DOOR CENSUS

• PARTICIPANTS WITH HIGHEST QUINTILE OF FLUID INTAKE (3.2 L) HAD A 50% REDUCTION IN CKD IN BOTH STUDY PERIODS. (CKD EGFR <50ML/MIN/1.73M2)
• SAME GROUP REPORTED IN A MORE RECENT STUDY NO SIGNIFICANT CORRELATION BETWEEN TOTAL FLUID INTAKE AND LONGITUDINAL LOSS OF KIDNEY FUNCTION

• THE N OF FIRST STUDY THAT NOTES SIGNIFICANT ASSOCIATION BETWEEN INCREASED FLUID INTAKE 5 FOLD GREATER THAN LONGITUDINAL STUDY (POWER ISSUE?)
Results:

Conclusions: adjusted for 10 baseline variables, study suggests a protective effect of higher water intake, particularly plain water on kidney function.
Results:

Decline of kidney functions is significantly slower with higher (≥3 L/d) versus lower (<1 L/d) urine volume.

Conclusion:

ASSOCIATION BETWEEN URINE OSMOLALITY AND PROGRESSION OF CKD (PLISCHKE ETAL JASN 2012)

• INCREASED RISK OF DIALYSIS INITIATION ASSOCIATED WITH HIGH BASELINE URINE OSMOLALITY IN 273 PATIENT WITH STAGE 1-4 CKD COHORT STUDY
INCREASED SERUM SODIUM AND SERUM OSMOLARITY ARE INDEPENDENT RISK FACTORS FOR DEVELOPING CHRONIC KIDNEY DISEASE; 5 YEAR COHORT STUDY

MASANARI KUWABARA ET R JOHNSON PLOS ONE 2017

**Cumulative incidence rates for CKD over 5 years in each serum sodium level**

![Graph showing cumulative incidence rates for CKD over 5 years in each serum sodium level.](image-url)
SUMMARY

• PROSPECTIVE COHORT STUDY OF 2000 HIGHER URINE VOLUME PREDICTS SLOWER RENAL DECLINE 7 YEAR FOLLOW-UP

• TWO CROSS-SECTIONAL COHORTS INVERSE ASSOCIATION BETWEEN SELF-REPORTED WATER INTAKE AND CKD N=8000

• CKD COHORT STUDY OF 273 ASSOCIATION BETWEEN DIALYSIS INITIATION AND URINE OSMOLALITY

• 5 YEAR COHORT STUDY: INCIDENCE CKD CORRELATES BASELINE OSMOLALITY N=12,000

• BUT THESE ARE OBSERVATIONAL STUDIES THAT MAY BE BIASED BY UNKNOWN SELECTION OR MISCLASSIFICATION
The Greatest Discovery of All

- The RCT – Randomized Controlled Trial
1) the hydration group 24-hour urine volume increased by 0.7 L/d (2.3 L/d to 3.0 L/d), and the control group’s decreased by 0.3 L/d (2.0 L/d to 1.7 L/d) (difference: 0.9 L/d; p=0.002).

2) no significant changes serum osmolality or sodium concentrations with no serious adverse events

3) and no changes in QoL reported
# Biologic Possibility

## Table 2  Effect of increased water intake on the plasma concentration of copeptin

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 weeks</th>
<th>Change*</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean urine volume, L/day (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=11)</td>
<td>2.0 (0.7)</td>
<td>1.7 (0.6)</td>
<td>-0.2 (p=0.07)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hydration (n=17)</td>
<td>2.3 (0.6)</td>
<td>3.0 (1.2)</td>
<td>0.7 (p=0.01)</td>
<td></td>
</tr>
<tr>
<td><strong>Median copeptin, pmol/L (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=11)</td>
<td>19.3 (12–36)</td>
<td>19.4 (14–33)</td>
<td>-1.1 (p=0.76)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hydration (n=17)</td>
<td>15.0 (8–29)</td>
<td>10.8 (6–26)</td>
<td>-3.6 (p=0.005)</td>
<td></td>
</tr>
</tbody>
</table>

*Follow-up—baseline; p value for within-group change calculated using the paired-samples t test (urine volume) and the related-samples Wilcoxon signed-rank test (copeptin).

†The between-group difference in change from baseline to week 6 was compared using the independent t test (urine volume) and the Mann-Whitney U test (copeptin).
The CKD Water Intake Trial (WIT) RESEARCH PROPOSAL(funded by DANONE)

Principal Investigator: Dr. William F. Clark, Nephrologist, MD FRCPC, FACP FASN

Co-Investigators:
Amit X. Garg MD, Nephrologist, FRCPC, PhD
Susan Huang MD, Nephrologist, FRCPC, PhD candidate
Andrew House, Nephrologist, MD, FRCPC, MSc
Louise Moist, Nephrologist, MD, FRCPC, MSc
Matthew Weir, Nephrologist, MD, FRCPC, MSc

Research Team:
Epidemiologist/biostatistician: Jessica M. Sontrop, PhD
Study Coordinator: Kerri Gallo, RN
Database Programmer/Manager: Dariusz Gozdik, BSc.

PLUS UPDATE JUNE 2015
Intervention

Randomization: Participants are randomized in block sizes of 4 by computer-generated randomization to the hydration or control group (1:1), stratified by gender and centre. The initial randomization algorithm produced imbalanced groups (1.3:1) and was adjusted for approximately 6 months to re-balance the groups.

Hydration intervention: Participants randomized to the hydration-intervention group were asked to consume 1.0 to 1.5 L water per day, depending on sex and weight, in addition to usual consumed beverages, for 12 months
Informed hydration coaching based on osmolality measured in spot urine samples taken at three weeks after randomization, and again at 3, 6, and 9 months after randomization.

<table>
<thead>
<tr>
<th>Trial Group</th>
<th>Urine osmolality</th>
<th>Hydration coaching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydration</td>
<td>&lt; 300 mosmol/kg</td>
<td>Maintain current fluid intake</td>
</tr>
<tr>
<td></td>
<td>300-500 mosmol/kg</td>
<td>Increase fluid intake by 1-2 cups/day</td>
</tr>
<tr>
<td></td>
<td>&gt;500 mosmol/kg</td>
<td>Increase fluid intake by 2 cups/day</td>
</tr>
<tr>
<td>Control</td>
<td>&lt; 300 mosmol/kg</td>
<td>Reduce fluid intake by 1-2 cups/day</td>
</tr>
<tr>
<td></td>
<td>300-500 mosmol/kg</td>
<td>Reduce fluid intake by 1 cup/day</td>
</tr>
<tr>
<td></td>
<td>&gt;500 mosmol/kg</td>
<td>Maintain current fluid intake</td>
</tr>
</tbody>
</table>
• Adherence almost always has major consequences.
Approached to be in Study (n=2387)

Excluded (n=1569)
- Ineligible or refusal
- Vacation or moving
- Language
- Fluid restriction

Consented (n=822)

Study withdrawal (n=93)
- Participant decision (n=86)
- Doctor decision (n=2)
- Death (n=1)

Ineligible (n=81)
- 24-hr urine volume >3L (n=46)
- Ineligible for other reasons (n=35)

Randomized (n=629)

Allocated to Hydration Group (n=315)

Withdrawal (n=42)
- Participant decision (n=30)
- Doctor decision (n=7)
- Death (n=5)

Allocated to Control Group (n=314)

Withdrawal (n=29)
- Participant decision (n=19)
- Doctor decision (n=0)
- Death (n=10)

Included in Interim Analysis (n=273)

Included in Interim Analysis (n=285)
water intake in CKD. Separation between groups means there will be scientifically reliable data on the association between fluid intake and kidney function.