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# Abstract

Dysgeusia (abnormal taste) is common in those with chronic kidney disease and contributes to poor nutritional intake. Previous sensory work has shown that taste improves after dialysis sessions. The goal of this pilot study was to characterize altered taste perceptions in patients on dialysis compared to healthy adults, and to evaluate relationships between serum parameters with taste perceptions. We hypothesized that patients undergoing dialysis would experience blunted taste intensities compared to controls, and that serum levels of potential tastants would be inversely related to taste perception of compounds. Using a cross-sectional design, we carried out supra-threshold sensory assessments (flavor intensity and liking) of tastants/flavors potentially influenced by kidney disease and/or the dialysis procedure. These included sodium chloride, potassium chloride, calcium chloride, sodium phosphate, phosphoric acid, urea, ferrous sulfate and monosodium glutamate. Individuals on maintenance hemodialysis (*n*= 17, 10 males, range 23-87 years) were compared to controls with normal gustatory function (*n*=29, 13 males, range 21-61 years). Unadjusted values for intensity and liking for the solutions showed minimal differences. However, when values were adjusted for participants' perceptions of water (as a control for taste abnormalities), intensity of monosodium glutamate, sodium chloride, and sodium phosphate solutions were more intense for patients on dialysis compared to controls. Some significant correlations were also observed between serum parameters, particularly potassium, for dialysis patients and sensory ratings. These results suggest altered taste perception in patients during dialysis warrants further study.

**Keywords:** Chronic kidney disease, dysgeusia, hemodialysis, taste

## Introduction

Chronic kidney disease (CKD) affects approximately 11-13% of the worldwide population (Hill, Fatoba et al. 2016). Progression of the disease can often warrant the commencement of dialysis, with hemodialysis being the most common modality of renal replacement therapy. Patients receiving dialysis are subject to prescriptive diets (Kalantar-Zadeh, Tortorici et al. 2015), which can help increase dialysis effectiveness by improving parameters such as serum electrolytes, acid-base balance, and blood pressure (Mc Causland, Waikar et al. 2012, Beerendrakumar and Haridasan 2018). Despite the multitude of benefits attributed to these prescribed diets, poor dietary adherence is still a major issue, as recent systematic review (Oquendo, Asencio et al. 2017) noted that 25% to 86% of hemodialysis patients do not adhere to these diets. This can predispose patients to a higher risk of malnutrition and hence, poorer survival outcomes and quality of life (Boltong and Campbell 2013, Lynch, Lynch et al. 2013).

One explanation for this poor adherence is dysgeusia, abnormal taste sensation, which affects approximately 35% of end-stage renal disease patients (Lynch, Lynch et al. 2013). Some commonly noted taste disturbances include reduced taste acuity, impaired detection of salty taste and reporting that certain foods taste ‘metallic-like’ (Boltong and Campbell 2013, McMahon, Campbell et al. 2014). Abnormalities in taste sensation may adversely affect the palatability of food and thus decrease adherence to renal diets.

Fluid imbalances, uremic toxin accumulation, metabolic derangements and zinc deficiency are some hypothesized mechanisms linked with the onset of dysgeusia (Carrero 2011, Boltong and Campbell 2013, Lynch, Lynch et al. 2013, Neto, Bacci et al. 2016). Specific to CKD patients, imbalances in ions, uremic toxins, or other small compounds in blood could be contributing to altered vascular and salivary concentrations of solutes (Manley, Haryono et al. 2012). This may alter the baseline at which oral chemoreceptor cells are responding to stimuli in foods. Vascular taste is when taste cells respond to tastants in the blood from the basolateral side of the receptor cell; as CKD patients have altered dynamics and levels of various taste active stimuli in blood (e.g., sodium, potassium, urea, etc.), vascular taste could be altered in these individuals. Further, oral chemosensation could also be altered through salivary changes, as prior

research has shown that CKD patients have altered salivary composition of several compounds that are active chemosensory stimuli in foods, including calcium, potassium and urea (Manley, Haryono et al. 2012, Seethalakshmi, Koteeswaran et al. 2014, Rodrigues and Franco 2015). This may be escalated by specific taste genetics that are sensitive to the increased salivary urea often found in this particular patient group (Manley 2015). Additionally, previous studies have implied that salivary and serum concentrations of these compounds are correlated and that taste sensations improve following dialysis sessions (Burge, Park et al. 1979, Shepherd, Farleigh et al. 1986, Farleigh, Shepherd et al. 1987, Seethalakshmi, Koteeswaran et al. 2014, Rodrigues and Franco 2015). Hence, alterations in saliva or vascular taste due to serum abnormalities may play a mechanistic role in these altered taste perceptions.

Previous studies have examined this hypothesis for five primary tastes: sweet, salty, bitter, sour, and umami (Burge, Park et al. 1979, Shepherd, Farleigh et al. 1986, Farleigh, Shepherd et al. 1987, Manley, Haryono et al. 2012, McMahon, Campbell et al. 2014). However, other salts and small molecules are also chemosensory stimuli, and the differences among these less prototypical "tastants" has not been evaluated. Thus, this pilot study aimed to test how hemodialysis patients perceive a wider range of chemosensory stimuli, specifically focusing on ions and other small molecules that are likely to be altered in serum for CKD patients compared to healthy controls.

# Materials and Methods

## Study Design

This pilot study used a cross-sectional design to compare perception of taste-active compounds in dialysis patients ($n$=17) versus a control group ($n$=29). A sensory assessment was conducted in which participants provided feedback on flavor intensity and liking/disliking for a variety of stimuli that may be present at abnormal concentrations in the blood and/or saliva of patients undergoing dialysis.

## Participants

The target population for this study was adult patients with end-stage renal disease attending a local dialysis clinic in Lafayette, IN for thrice weekly maintenance hemodialysis

(*n*=17). All participants were invited to take part in the study during their normal scheduled dialysis treatment session. Control subjects (*n*=29) were recruited through the Purdue University Sensory Perception Ingestion and Tongues (SPIT) Laboratory participant pool. Inclusion criteria for the control subjects included: self-reported normal gustatory function, no issues with salivation or dry mouth; 18 years of age or older; and no tongue, lip, or cheek piercings. All participants gave written informed consent prior to participating in this study. The protocol was approved by the Human Subjects Institutional Review Board of Purdue University and registered at www.clinicaltrials.gov (NCT03495271).

## Tasting Solutions

Solutions are listed in **Table 1**. All chemicals were food grade, and all were purchased from Sigma-Aldrich with the exception of calcium chloride (Modernist Pantry, USA); and monosodium glutamate (Ajinomoto, Japan). The solutions were presented to subjects in 15 mL aliquots at room temperature. All solutions were prepared on the day before each testing.

## Tasting Protocol

Each solution was presented at room temperature to participants in a blinded fashion and in counterbalanced order. We aimed to carry out the dialysis taste assessments at the beginning of the patient's dialysis session, but this was not always consistent due to the clinic set-up.

As these stimuli are generally unpleasant, all participants tasted a urea and potassium chloride sample first to control for bias as a result of the initial exposure to the unpleasant sensation (termed "first sample effect" in the sensory field, or "initial elevation bias" in psychology (Shrout, Stadler et al. 2018). Participants tasted 15 ml aliquots of each sample and expectorated after 10 seconds. After tasting each solution, participants reported perceived flavor intensity and liking/disliking of the solution. Participants rinsed their mouths with spring water (Ice Mountain brand bottled water) between each sample.

## Sensory Questionnaire

Sensory questions were asked verbally by experimenters and data were recorded using RedJade sensory software. For each sample, the experimenter asked the participant to rate the

overall flavor intensity of the solution on a scale from 0 – 100, with 0 being no sensation and 100 being the strongest sensation ever experienced. Participants were familiarized with this intensity scale using a warm-up questionnaire, which asked about the brightness of this room, the brightness of the sun, the loudness of a shout, the loudness of a whisper, the bitterness of black coffee, and the sweetness of pure sugar (adapted from (Hayes, Allen et al. 2013)). For the samples, participants also reported their liking for the sensation, with 0 being the "worst thing ever" and 100 being the "best thing ever".

## Blood Sample Collections

Non-fasting serum blood samples (8mL) were drawn from dialysis access following taste assessments and analyzed by Mid America Clinical Laboratories. Samples were targeted to be collected within 30 minutes of the taste assessment, but this varied considerably from subject to subject due to the active clinic environment.

## Statistical Analysis

Data were analyzed using SAS for Windows, version 9.4 (Cary, North Carolina, USA). Significant differences between the variables were assessed using mixed models controlling for year of birth, sex, order effects, and subjects (as a repeated measure); the Kenward Roger method was applied for calculation of degrees of freedom. The dependent variables were flavor intensity or liking/disliking rating, and the variables of interest were the sample type, group (control or dialysis), and the interaction of group and sample type. Statistical code is available in supplemental files. Sensory ratings were analyzed both as unadjusted as well as adjusted for each participant's perception of water (Water adjusted rating = Original rating – water rating). This approach controlled for between-subject variability in how they used the scale, but also controlled for baseline abnormalities in perception of water. Water is not a neutral stimulus, and different sources of water can lead to changes in perception of flavor intensity and/or sensitivity to tastes (Dalton, Nagata et al. 2000, Hoehl, Schoenberger et al. 2010). Deionized water, which was the solvent in this study, is often described as bitter or metallic, perhaps because the pH is actually below neutral (Whelton, Dietrich et al. 2007). Subtracting the rating of the water from the rating of the tastant solutions thus gives a better idea of how individual participants perceived

the solutes in contrast to a standard (deionized water) with minimal solutes. Thus, the water-adjusted ratings were calculated for each individuals' intensity and liking ratings for every test solution. Alpha was set at 0.05 across all tests. Spearman correlations were used to identify possible relationships between serum parameters and taste perceptions in the dialysis patients.

# Results

## Baseline Characteristics of the Study Population

Participant characteristics are reported in **Table 2.** The control group was significantly younger than the dialysis group (P<0.001). Baseline taste abnormalities were reported by 43.8% of the dialysis cohort. Abnormal sensations reported included that "everything tastes bitter/sour", "some fruits don't taste as sweet", "higher salt threshold", and "metallic tastes."

## Flavor Intensity

Unadjusted flavor intensity values are presented in **Figure 1** and showed no differences ($p$=0.73) between groups overall, only trends in effects for interactions within sample types. After adjustment for deionized water taste, significant differences emerged (**Figure 2**, $p$=0.044 between groups). Specifically, water-corrected ratings for monosodium glutamate ($p$=0.0016), sodium chloride ($p$=0.0018), and sodium phosphate ($p$=0.017) were higher for dialysis patients compared to control participants.

## Hedonic ratings

Liking/disliking values are presented in **Figure 3 & 4**. Unadjusted liking scores (**Figure 3**) highlights general, and similar ($p$=0.37 between groups, no significant interactions) disliking for the solutions across both groups, which is signified by a mean score of <50 (i.e. values were closer to 'worst ever' side of the scale). Adjusted liking data is shown in **Figure 4**, and are more negative due to more dislike for the flavors versus water. The dialysis group's adjusted liking ratings were less negative than the control group's, indicating the patients on dialysis rated the samples closer to water for liking than controls ($p$=0.023), which could indicate the dialysis group actually found the solutions closer to hedonically neutral than the control group. Specific samples driving this difference between the groups were ferrous sulfate ($p$= 0.0092), potassium chloride ($p$=0.014), sodium chloride ($p$=0.045), and sodium phosphate ($p$=0.042);

### Serum parameters and taste

Serum results for the patients on dialysis are reported in **Table 3,** and significant correlations are shown in **Table 4**. One sample was excluded due to hemolysis. Spearman correlations were conducted between the sensory ratings and serum levels of compounds of interest. In unadjusted ratings, a negative correlation was observed between serum glucose and urea flavor intensity ($p = 0.035$); negative correlations for unadjusted liking ratings were also observed between flavor intensity of monosodium glutamate and creatinine ($p = 0.033$). In water adjusted ratings, a positive correlation was observed between serum potassium and taste intensity of monosodium glutamate ($p = 0.019$); in adjusted liking ratings, positive correlations were observed between serum potassium and phosphoric acid ($p = 0.0008$), potassium chloride (($p = 0.027$), urea ($p = 0.028$), and calcium chloride ($p = 0.028$). Negative correlations were observed between adjusted liking ratings for urea and serum carbon dioxide ($p = 0.038$) and between ferrous sulfate and serum sodium ($p = 0.045$).

## Discussion

In the present pilot study, we found water-adjusted flavor and liking intensity scores were different between control and dialysis patients. Specifically, dialysis patients reported a more intense sensation for two sodium containing salts (monosodium glutamate, sodium chloride) and a less intense sensation for one compound, another sodium containing salt (sodium phosphate). Differences in adjusted liking ratings appear to be primarily due to ferrous sulfate, potassium chloride, sodium chloride, and sodium phosphate being rated closer to water ratings (near neutral on the hedonic scale) for the dialysis group compared to control. The differences found in the water-adjusted data, but not unadjusted data, suggest that baseline taste perception may be an important factor for dysgeusia in dialysis patients and should be better characterized in future studies.

Prior studies have generally shown that patients with CKD often experience lower taste intensity and/or sensitivity for sodium containing compounds, along with other tastants. One study (Manley, Haryono et al. 2012) conducted suggested that CKD patients have an impaired ability to identify sour, bitter and glutamate tastes. Another study (McMahon, Campbell et al. 2014) also reported significantly lower intensity scores for monosodium glutamate and sodium

chloride. In that particular study, higher salivary and serum sodium levels correlated with lower sensitivity to tasting sodium (McMahon, Campbell et al. 2014). A possible explanation for differences between these reports and our current work is that our taste assessments were not performed in the dialysis patients until they had undergone some of their dialysis treatment. Although we aimed to complete the assessment at the beginning of treatment, this was not feasible due to the busy clinical setting, and on occasion was not conducted until >30minutes after dialysis commencement. It is possible that excess salivary and serum sodium was filtered through the dialysate, reducing their sodium taste-threshold and improving sensitivity. Indeed, previous research has shown that dialysis treatment removes excess salivary metabolites in a mirror-like fashion to serum filtration (Seethalakshmi, Koteeswaran et al. 2014, Khanum, Mysore-Shivalingu et al. 2017). In addition, this has been linked to improved taste function post-dialysis (Burge, Park et al. 1979). Older studies have indicated increased sensitivity and decreased preference for sodium chloride post dialysis which may further explain the higher ratings noted in our dialysis group by comparison to healthy controls (Farleigh, Shepherd, et al. 1987, Shepherd, Farleigh et al. 1987, Leshem & Rudoy 1997) . Furthermore, given the difference in our findings between water-adjusted and unadjusted assessments, and the lack of major correlations with serum levels for sodium, it is possible that baseline abnormalities in taste are more important than acute changes during dialysis.

In our study, unadjusted liking scores were generally rated <50 on the scales in both patients and controls which indicated overall negative hedonic reaction to the solutions. These lower ratings were expected given that the solutions were characteristically unpalatable, with some leaving lingering tastes (e.g. ferrous sulfate and monosodium glutamate, in particular). However, food ingredients lead to very different affective responses when presented in foods versus in solution. Monosodium glutamate, for example, can make a variety of foods more palatable, but is generally unpleasant when tasted in isolation. Patients undergoing dialysis indicated that sodium phosphate, sodium chloride, potassium chloride, and ferrous sulfate solutions tasted closer to a “neutral” water their control counterparts. However, distractions from the dialysis procedure itself may have influenced these ratings. In general, we would expect the busy clinical environment of a dialysis unit to confound liking ratings. However, we would have expected the negative feelings of the environment (due to having to go through the process of dialysis) could leech into negative affect for the stimuli presented. This was not the case. Future

studies should be conducted in a better controlled environment, or with controls in a similar clinical environment to the patients attending dialysis.

We detected few associations between serum parameters and hemodialysis patient's flavor ratings in the present study. We did however observe that serum potassium, in particular, correlated with water-adjusted hedonic ratings for a number of compounds. This may imply a role for potassium in the hedonic perception of other flavors. As several potassium channels are proposed to influence different types of taste (particularly sour and fatty tastes (Gilbertson, Fontenot et al. 1997, Challis and Ma 2016)), imbalances in potassium may alter taste cell signaling, resulting in abnormalities in the quality of sensations and changes in effect. This should be pursued in further work, both in patients on dialysis as well as healthy controls.

Prior research indicates that taste thresholds of renal patients increase with age and this finding is also in agreement with results of studies on healthy subjects (Ogawa, Annear et al. 2017, Ng, Woo et al. 2004, Vreman, Venter et al. 1980, Ciechanover, Peresecenschi et al. 1980). Therefore, it is important to consider the fact that our dialysis and control groups were not demographically well matched, especially in terms of age. Age was included as a covariate in our statistical model and indeed indicated that younger subjects had higher ratings, even when adjusted for water. This is consistent with other work. However, our patients on dialysis actually gave higher ratings than the younger controls, which is directly the opposite of what we would expect for an age effect, and indeed is also opposite from what we saw in our own model's age effect Certainly, matching the groups for age could improve our understanding of these potential differences between groups, but a multitude of other confounding variables may also impact on our ability to conduct taste tests in renal patients. Medications, diet and other chronic diseases can play an influential role on taste perception, each of which are difficult to control for, especially in older subjects who have many health issues (Boltong and Campbell 2013).

There are several other limitations to this study which must also be considered. As a pilot study, the sample size was small and thus results should be considered preliminary. Secondly, the control group did not have serum parameters measured for comparison. Furthermore, our ability to assess the serum-taste perception relationship was restrained considering our serum samples were drawn late into the dialysis session. Future larger studies

should be pursued using controlled, or at least comparable, environments and protocols to minimize confounding factors in our clinical setting.

Finally, our findings of greater differences when controlling for water perception should be further investigated. Deionized water itself stimulates sensation in the mouth, often of greater intensity than tap or spring waters (Hoehl, Schoenberger et al. 2010). We did not find a difference in taste intensity of deionized water between our groups in the current study, but this concept should be further investigated to determine if individual differences in serum and salivary solutes contribute to differences in perception of water, or some sort of partitioning of solutes within the deionized water, which could then alter perception of other dissolved solids. Our findings indicate that it may be important to correct for this baseline sensation of the solvent in future work to investigate dysgeusia in patients undergoing hemodialysis.

## Conclusion

The findings of this study add to the body of evidence suggesting that taste changes occur with CKD. Our work emphasizes the need to investigate taste and flavor active compounds beyond the prototypical taste stimuli for sweet, sour, salty, bitter and umami tastes. As many known tastants are found in human serum and saliva, and are dysregulated with CKD, these non-typical stimuli are prime candidates for contributing to dysgeusia accompanying CKD. We identified CKD patients experienced altered taste intensity for compounds that include a sodium ion (greater intensity for monosodium glutamate and sodium chloride, and lesser intensity for sodium phosphate) and lesser dislike for ferrous sulfate, potassium chloride, sodium chloride, and sodium phosphate compared to healthy controls, when correcting for the subjects' perceptions of deionized water. More research is required to fully evaluate how dysgeusia is experienced by CKD patients.

**Conflicts of interests:** The authors have no conflicts of interest to declare.

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318 **Table 1: Concentration of Solutions used in the Taste Assessment**

| Compounds | Molarity (M) | %(w/w) | Sensory quality |
|---|---|---|---|
| Sodium Chloride | 0.2 | 1.16 | Salty |
| Potassium Chloride | 0.01 | 0.74 | Salty, bitter |
| Calcium Chloride | 0.15 | 1.62 | Calcium taste†, metallic |
| Sodium Phosphate | 0.0063 | 0.09 | Salty, phosphorous taste† |
| Phosphoric Acid | 0.007 | 0.37 | Sour |
| Urea | 0.5 | 2.91 | Bitter |
| Ferrous Sulfate | 0.025 | 0.69 | Metallic |
| Monosodium Glutamate | 0.01 | 0.17 | Umami |
| Deionised Water | - | - | Control (solvent) |

†*These "tastes" are under debate as potential gustatory sensations; we will refer to them as tastes for simplicity in this report, but readers should consult other articles to understand the state of the science regarding these compounds as taste stimuli (Tordoff, Alarcón et al. 2012, Tordoff 2017).*

319 **Table 2: Participant Characteristics**

| | Control | Dialysis |
|---|---|---|
| **N** | 29 | 17 |
| **Gender Male, N (%)** | 13 (48.1) | 10 (62.5) |
| **Female, N (%)** | 16 (51.9) | 7 (37.5) |
| **Age (years)** | 32 (range 21-61) | 61 (range 23-87)* |
| **Taste Abnormalities, N (%)** | - | 7 (43.8) |

*$p < 0.05$, Dialysis vs. Control

320 **Table 3: Serum Parameters for Dialysis Patients**

| **Blood Parameters** | **Ref. Range*** | **Mean** |
|---|---|---|
| Magnesium (mg/dL) | **1.6-2.6** | 2.04 ± 0.17 |
| Sodium (mmol/L) | **136-145** | 137.60 ± 2.06 |
| Potassium (mmol/L) | **3.5-5.1** | 4.31 ± 0.56 |
| Calcium (mg/dL) | **8.4-10.5** | 8.91 ± 0.63 |
| Phosphorous (mg/dL) | **2.5-4.7** | 3.37 ± 1.69 |
| Chloride (mmol/L) | **98-110** | 98.93 ± 2.25 |
| Carbon dioxide (mmol/L) | **20-29** | 24.27 ± 3.90 |
| Glucose (mg/dL) | **65-99** | 128.07 ± 58.39 |
| Urea Nitrogen (mg/dL) | **10-20** | 33.40 ± 17.14 |
| Creatinine (mg/dL) | **0.70-1.20** | 5.24± 3.14 |
| Albumin (mg/dL) | **3.5-5.0** | 3.57 ± .35 |

** reference range provided by Mid America Clinical Laboratories.*

**Table 4: Spearman correlations between sensory ratings and serum parameters**

| **Rating type** | **Sensory stimulus** | **Serum parameter** | **Spearman Rho** | ***p*-value** |
|---|---|---|---|---|
| Unadjusted flavor | Urea | Glucose | -0.55 | 0.035 |
| Water adjusted flavor | Monosodium glutamate | Potassium | 0.60 | 0.019 |
| Unadjusted liking | Monosodium glutamate | Creatinine | -0.55 | 0.033 |
| Water adjusted liking | Phosphoric acid | Potassium | 0.77 | 0.0008 |
| | Potassium chloride | Potassium | 0.57 | 0.027 |
| | Urea | Potassium | 0.57 | 0.028 |
| | Calcium chloride | Potassium | 0.56 | 0.028 |
| | Urea | Carbon dioxide | -0.54 | 0.038 |
| | Ferrous sulfate | Sodium | -0.52 | 0.045 |

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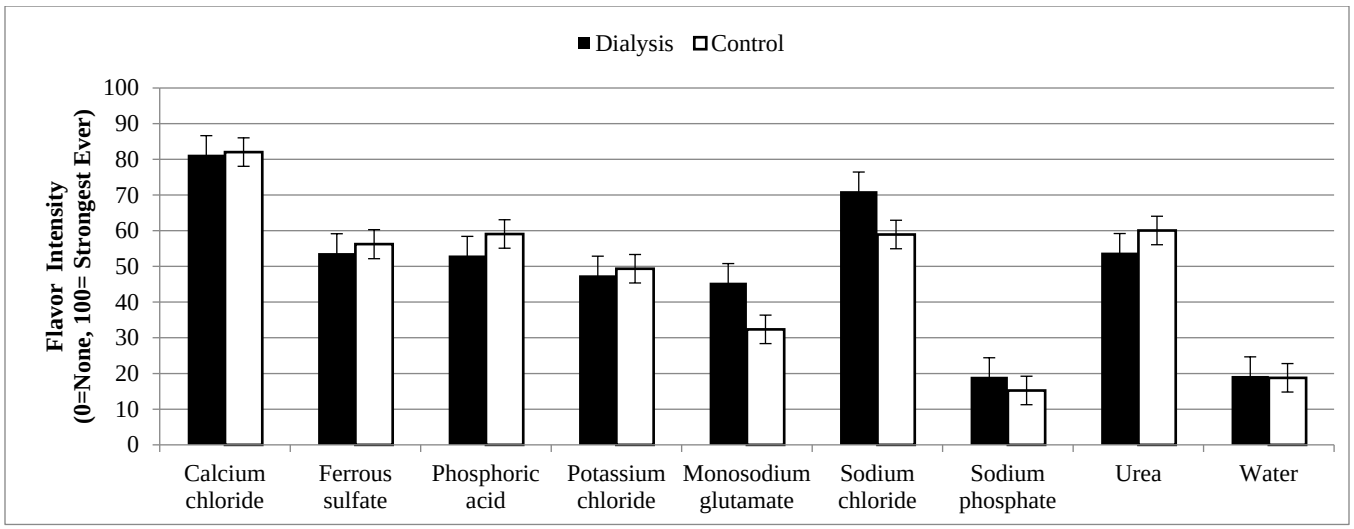


**Figure 1:** Mean and standard error for flavor intensity, unadjusted

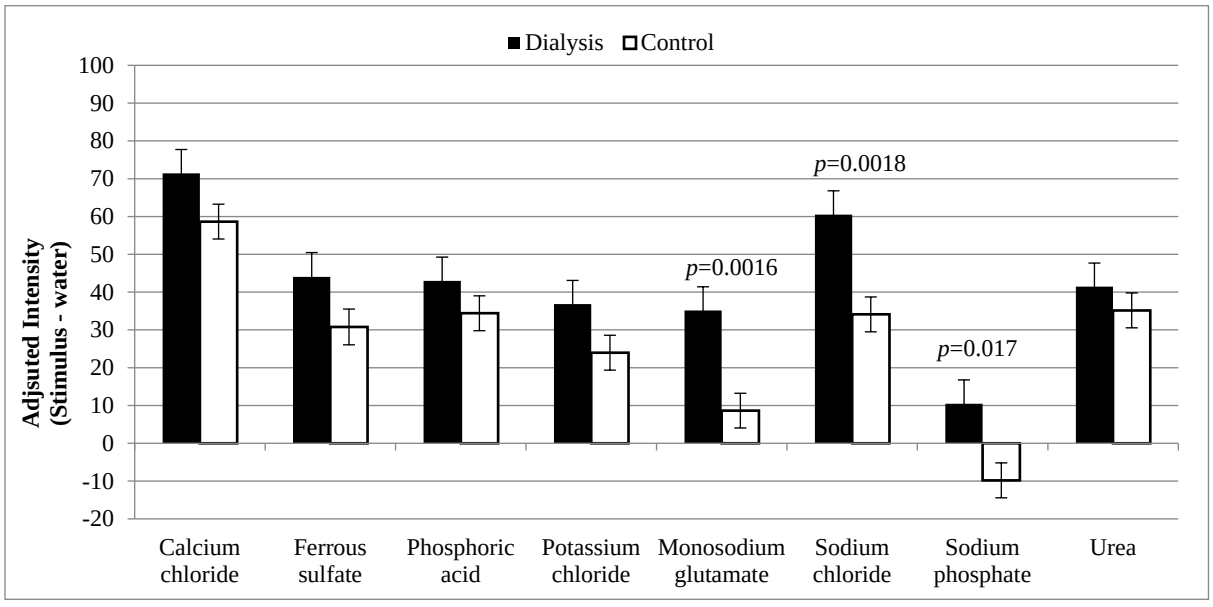


**Figure 2:** Mean and standard error for flavor intensity after adjustment for the perception of water (Original rating – water rating; positive values indicate the sample was rated as more intense than water)

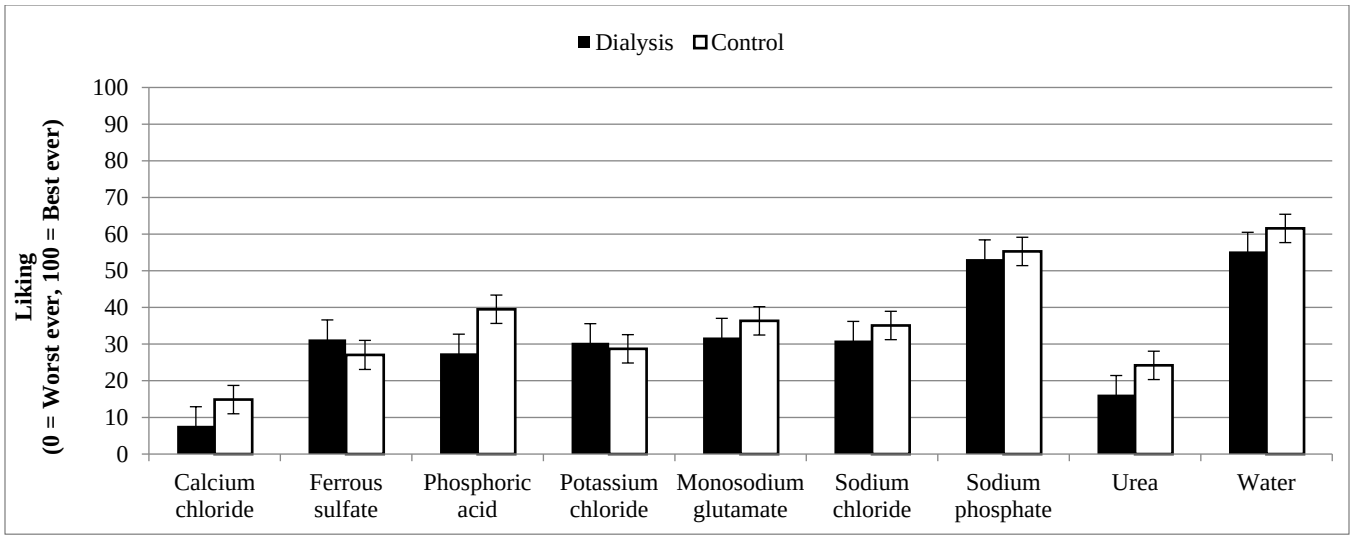


**Figure 3:** Mean and standard error for liking of compounds, unadjusted

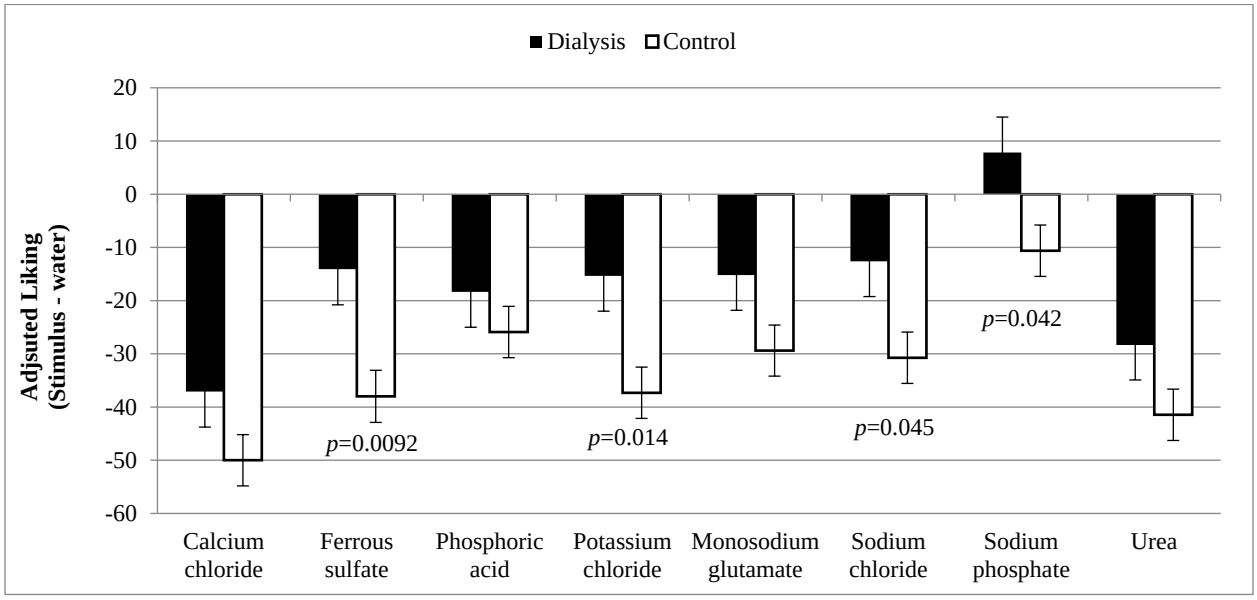


Figure 4: Mean and standard error for liking of compounds after adjustment for the perception of water (Original rating – water rating; negative numbers indicate water was liked more than the sample, and numbers to closer to zero mean the sample was rated more similarly to water).

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## Supplemental files

```
proc sort data=CKD;
by sample group cond id Order;
run;
ods graphics on;
ods output tests3=mixedtestsFlavorV;
ods output diffs=FVdiff;
Title 'Flavor tests';
proc mixed data=ckd;
class id Sample sex group order;
model flavor =  sample group sex YOB sample*group/ residual outp=FTVresid
ddfm=KR;
repeated order/ subject=id type= ar(1);
lsmeans group / pdiff  ADJDFE=ROW;
lsmeans sample*group/ pdiff ADJDFE=ROW;
run;
quit;
ods graphics off;


proc sort data=CKD;
by sample group cond id Order;
run;
ods graphics on;
ods output tests3=mixedtestsLikingV;
ods output diffs=LVdiff;
Title 'Liking tests';
proc mixed data=ckd;
class id Sample sex group order;
model liking=  sample group sex YOB sample*group/ residual outp=LTVresid
ddfm=KR;
repeated order / subject=id type= ar(1);
lsmeans group / pdiff ADJDFE=ROW;
lsmeans sample*group/ pdiff  ADJDFE=ROW;
run;
quit;
ods graphics off;


proc sort data=CKD;
by sample group cond id Order;
run;
ods graphics on;
ods output tests3=mixedtestsFlavorVW;
ods output diffs=FWVdiff;
Title 'Flavor tests corrected for water';
proc mixed data=ckd;
where sample ne 'Water';
class id Sample sex group order;
model FlSam_H2O =  sample group sex YOB sample*group/ residual outp=FTVWresid
ddfm=KR;
repeated order/ subject=id type= ar(1);
lsmeans group / pdiff ADJDFE=ROW;
```

```
475   lsmeans sample*group/ pdiff ADJDFE=ROW;
476   run;
477   quit;
478   ods graphics off;
479
480
481   proc sort data=CKD;
482   by sample group cond id Order;
483   run;
484   ods graphics on;
485   ods output tests3=mixedtestsLikingVW;
486   ods output diffs=LWVdiff;
487   Title 'Liking tests Corrected for water';
488   proc mixed data=ckd;
489   where sample ne 'Water';
490   class id Sample sex group order;
491   model lSam_H2O=  sample group sex YOB sample*group/ residual outp=LTVWresid
492   ddfm=KR;
493   repeated order / subject=id type= ar(1);
494   lsmeans group / pdiff ADJDFE=ROW;
495   lsmeans sample*group/ pdiff ADJDFE=ROW;
496   run;
497   quit;
498   ods graphics off;
499
```

**Flavor: Unadjusted ratings**

**Least Squares Means**

| Effect | Sample | Group | Estimate | Standard Error | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|---|---|---|
| **Group** | | **Control** | 50.5126 | 2.0603 | 100 | 24.52 | <.0001 |
| **Group** | | **Dialysis** | 49.0696 | 2.9437 | 101 | 16.67 | <.0001 |
| **Sample*Group** | **CaCl** | **Control** | 81.9541 | 4.0147 | 432 | 20.41 | <.0001 |
| **Sample*Group** | **CaCl** | **Dialysis** | 81.2260 | 5.3834 | 420 | 15.09 | <.0001 |
| **Sample*Group** | **FeSO4** | **Control** | 56.0913 | 4.0975 | 417 | 13.69 | <.0001 |
| **Sample*Group** | **FeSO4** | **Dialysis** | 53.4420 | 5.4846 | 402 | 9.74 | <.0001 |
| **Sample*Group** | **First** | **Control** | 74.2222 | 4.0975 | 417 | 18.11 | <.0001 |
| **Sample*Group** | **First** | **Dialysis** | 47.2262 | 5.4847 | 402 | 8.61 | <.0001 |
| **Sample*Group** | **H3PO4** | **Control** | 58.9556 | 4.0146 | 432 | 14.69 | <.0001 |
| **Sample*Group** | **H3PO4** | **Dialysis** | 53.0668 | 5.3831 | 420 | 9.86 | <.0001 |
| **Sample*Group** | **KCl** | **Control** | 49.1579 | 4.0147 | 432 | 12.24 | <.0001 |
| **Sample*Group** | **KCl** | **Dialysis** | 47.6526 | 5.3796 | 421 | 8.86 | <.0001 |
| **Sample*Group** | **MSG** | **Control** | 32.2199 | 4.0125 | 433 | 8.03 | <.0001 |
| **Sample*Group** | **MSG** | **Dialysis** | 45.4563 | 5.3819 | 421 | 8.45 | <.0001 |
| **Sample*Group** | **NaCl** | **Control** | 58.7771 | 4.0147 | 432 | 14.64 | <.0001 |
| **Sample*Group** | **NaCl** | **Dialysis** | 70.9695 | 5.3767 | 422 | 13.20 | <.0001 |
| **Sample*Group** | **NaPO4** | **Control** | 15.1123 | 4.0147 | 432 | 3.76 | 0.0002 |
| **Sample*Group** | **NaPO4** | **Dialysis** | 18.8517 | 5.3820 | 421 | 3.50 | 0.0005 |
| **Sample*Group** | **Urea** | **Control** | 59.9295 | 4.0151 | 432 | 14.93 | <.0001 |
| **Sample*Group** | **Urea** | **Dialysis** | 53.8460 | 5.3721 | 423 | 10.02 | <.0001 |
| **Sample*Group** | **Water** | **Control** | 18.7061 | 4.0128 | 433 | 4.66 | <.0001 |
| **Sample*Group** | **Water** | **Dialysis** | 18.9590 | 5.3865 | 419 | 3.52 | 0.0005 |

**Type 3 Tests of Fixed Effects**

| Effect | Num DF | Den DF | F Value | Pr > F | Effect |
|---|---|---|---|---|---|
| **Sample** | 9 | 351 | 46.99 | <.0001 | |
| **Group** | 1 | 101 | 0.12 | 0.7267 | |
| **Sex** | 1 | 104 | 6.40 | 0.0129 | Female>male |
| **YOB** | 1 | 104 | 0.40 | 0.5298 | |
| **Sample*Group** | 9 | 351 | 3.22 | 0.0009 | See below |

**Differences of Least Squares Means**

| Effect | Sample | Group | _Sample | _Group | Estimate | Standard Error | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|---|---|---|---|---|
| Group | | Control | | Dialysis | 1.4430 | 4.1167 | 101 | 0.35 | 0.7267 |
| Sample*Group | CaCl | Control | CaCl | Dialysis | 0.7281 | 7.0097 | 400 | 0.10 | 0.9173 |
| Sample*Group | FeSO4 | Control | FeSO4 | Dialysis | 2.6493 | 7.1349 | 379 | 0.37 | 0.7106 |
| Sample*Group | First | Control | First | Dialysis | 26.9960 | 7.1350 | 379 | 3.78 | 0.0002 |
| Sample*Group | H3PO4 | Control | H3PO4 | Dialysis | 5.8888 | 7.0093 | 400 | 0.84 | 0.4013 |
| Sample*Group | KCl | Control | KCl | Dialysis | 1.5053 | 7.0068 | 401 | 0.21 | 0.8300 |
| Sample*Group | MSG | Control | MSG | Dialysis | -13.2365 | 7.0072 | 401 | -1.89 | 0.0596 |
| Sample*Group | NaCl | Control | NaCl | Dialysis | -12.1924 | 7.0046 | 401 | -1.74 | 0.0825 |
| Sample*Group | NaPO4 | Control | NaPO4 | Dialysis | -3.7394 | 7.0087 | 400 | -0.53 | 0.5940 |
| Sample*Group | Urea | Control | Urea | Dialysis | 6.0835 | 7.0013 | 402 | 0.87 | 0.3854 |
| Sample*Group | Water | Control | Water | Dialysis | -0.2528 | 7.0110 | 400 | -0.04 | 0.9713 |

**Liking Unadjusted ratings**

**Least Squares Means**

| Effect | Sample | Group | Estimate | Standard Error | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|---|---|---|
| **Group** | | **Control** | 34.3014 | 2.2049 | 93.9 | 15.56 | <.0001 |
| **Group** | | **Dialysis** | 30.4141 | 3.1490 | 94.4 | 9.66 | <.0001 |
| **Sample*Group** | **CaCl** | **Control** | 14.7844 | 3.8895 | 409 | 3.80 | 0.0002 |
| **Sample*Group** | **CaCl** | **Dialysis** | 7.3999 | 5.2444 | 386 | 1.41 | 0.1590 |
| **Sample*Group** | **FeSO4** | **Control** | 26.9180 | 3.9907 | 396 | 6.75 | <.0001 |
| **Sample*Group** | **FeSO4** | **Dialysis** | 30.9796 | 5.3675 | 374 | 5.77 | <.0001 |
| **Sample*Group** | **First** | **Control** | 21.2500 | 3.9907 | 396 | 5.32 | <.0001 |
| **Sample*Group** | **First** | **Dialysis** | 20.9210 | 5.3676 | 374 | 3.90 | 0.0001 |
| **Sample*Group** | **H3PO4** | **Control** | 39.4327 | 3.8894 | 409 | 10.14 | <.0001 |
| **Sample*Group** | **H3PO4** | **Dialysis** | 27.4197 | 5.2442 | 386 | 5.23 | <.0001 |
| **Sample*Group** | **KCl** | **Control** | 28.6136 | 3.8895 | 409 | 7.36 | <.0001 |
| **Sample*Group** | **KCl** | **Dialysis** | 30.3835 | 5.2398 | 387 | 5.80 | <.0001 |
| **Sample*Group** | **MSG** | **Control** | 36.2537 | 3.8862 | 410 | 9.33 | <.0001 |
| **Sample*Group** | **MSG** | **Dialysis** | 31.7734 | 5.2426 | 386 | 6.06 | <.0001 |
| **Sample*Group** | **NaCl** | **Control** | 34.9941 | 3.8895 | 409 | 9.00 | <.0001 |
| **Sample*Group** | **NaCl** | **Dialysis** | 30.8173 | 5.2351 | 388 | 5.89 | <.0001 |
| **Sample*Group** | **NaPO4** | **Control** | 55.1876 | 3.8895 | 409 | 14.19 | <.0001 |
| **Sample*Group** | **NaPO4** | **Dialysis** | 52.8365 | 5.2427 | 386 | 10.08 | <.0001 |
| **Sample*Group** | **Urea** | **Control** | 24.1239 | 3.8900 | 409 | 6.20 | <.0001 |
| **Sample*Group** | **Urea** | **Dialysis** | 16.2154 | 5.2280 | 390 | 3.10 | 0.0021 |
| **Sample*Group** | **Water** | **Control** | 61.4560 | 3.8865 | 410 | 15.81 | <.0001 |
| **Sample*Group** | **Water** | **Dialysis** | 55.3946 | 5.2498 | 384 | 10.55 | <.0001 |

**Type 3 Tests of Fixed Effects**

| Effect | Num DF | Den DF | F Value | Pr > F |
|---|---|---|---|---|
| **Sample** | 9 | 343 | 28.12 | <.0001 |
| **Group** | 1 | 95 | 0.78 | 0.3794 |
| **Sex** | 1 | 97.5 | 0.01 | 0.9423 |
| **YOB** | 1 | 97.5 | 0.00 | 0.9626 |
| **Sample*Group** | 9 | 343 | 0.72 | 0.6940 |

**Differences of Least Squares Means**

| Effect | Sample | Group | _Sample | _Group | Estimate | Standard Error | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | | **Control** | | **Dialysis** | 3.8873 | 4.4018 | 95 | 0.88 | 0.3794 |
| **Sample*Group** | **CaCl** | **Control** | **CaCl** | **Dialysis** | 7.3844 | 6.8725 | 355 | 1.07 | 0.2833 |
| **Sample*Group** | **FeSO4** | **Control** | **FeSO4** | **Dialysis** | -4.0616 | 7.0238 | 344 | -0.58 | 0.5635 |
| **Sample*Group** | **First** | **Control** | **First** | **Dialysis** | 0.3290 | 7.0239 | 344 | 0.05 | 0.9627 |
| **Sample*Group** | **H3PO4** | **Control** | **H3PO4** | **Dialysis** | 12.0130 | 6.8721 | 355 | 1.75 | 0.0813 |
| **Sample*Group** | **KCl** | **Control** | **KCl** | **Dialysis** | -1.7699 | 6.8689 | 356 | -0.26 | 0.7968 |
| **Sample*Group** | **MSG** | **Control** | **MSG** | **Dialysis** | 4.4803 | 6.8691 | 356 | 0.65 | 0.5147 |
| **Sample*Group** | **NaCl** | **Control** | **NaCl** | **Dialysis** | 4.1768 | 6.8654 | 357 | 0.61 | 0.5433 |
| **Sample*Group** | **NaPO4** | **Control** | **NaPO4** | **Dialysis** | 2.3511 | 6.8712 | 355 | 0.34 | 0.7324 |
| **Sample*Group** | **Urea** | **Control** | **Urea** | **Dialysis** | 7.9085 | 6.8602 | 358 | 1.15 | 0.2498 |
| **Sample*Group** | **Water** | **Control** | **Water** | **Dialysis** | 6.0613 | 6.8748 | 355 | 0.88 | 0.3786 |

**Flavor adjusted for water rating**

**Least Squares Means**

| Effect | Sample | Group | Estimate | Standard Error | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|---|---|---|
| Group | | Control | 29.8934 | 3.0605 | 76 | 9.77 | <.0001 |
| Group | | Dialysis | 42.3710 | 4.3675 | 76.4 | 9.70 | <.0001 |
| Sample*Group | CaCl | Control | 58.7834 | 4.5965 | 282 | 12.79 | <.0001 |
| Sample*Group | CaCl | Dialysis | 71.7251 | 6.3080 | 258 | 11.37 | <.0001 |
| Sample*Group | FeSO4 | Control | 30.9222 | 4.7210 | 298 | 6.55 | <.0001 |
| Sample*Group | FeSO4 | Dialysis | 43.8567 | 6.3994 | 270 | 6.85 | <.0001 |
| Sample*Group | First | Control | 52.0630 | 4.7206 | 298 | 11.03 | <.0001 |
| Sample*Group | First | Dialysis | 37.5424 | 6.3816 | 271 | 5.88 | <.0001 |
| Sample*Group | H3PO4 | Control | 34.5357 | 4.6018 | 284 | 7.50 | <.0001 |
| Sample*Group | H3PO4 | Dialysis | 43.1431 | 6.2871 | 257 | 6.86 | <.0001 |
| Sample*Group | KCl | Control | 24.1049 | 4.6039 | 285 | 5.24 | <.0001 |
| Sample*Group | KCl | Dialysis | 37.0968 | 6.2610 | 255 | 5.93 | <.0001 |
| Sample*Group | MSG | Control | 8.7732 | 4.5852 | 287 | 1.91 | 0.0567 |
| Sample*Group | MSG | Dialysis | 35.3913 | 6.2643 | 259 | 5.65 | <.0001 |
| Sample*Group | NaCl | Control | 34.2395 | 4.6024 | 282 | 7.44 | <.0001 |
| Sample*Group | NaCl | Dialysis | 60.5436 | 6.2646 | 257 | 9.66 | <.0001 |
| Sample*Group | NaPO4 | Control | -9.6758 | 4.6100 | 284 | -2.10 | 0.0367 |
| Sample*Group | NaPO4 | Dialysis | 10.4004 | 6.2775 | 256 | 1.66 | 0.0988 |
| Sample*Group | Urea | Control | 35.2947 | 4.6043 | 284 | 7.67 | <.0001 |
| Sample*Group | Urea | Dialysis | 41.6400 | 6.2119 | 259 | 6.70 | <.0001 |

**Type 3 Tests of Fixed Effects**

| Effect | Num DF | Den DF | F Value | Pr > F | |
|---|---|---|---|---|---|
| Sample | 8 | 296 | 38.40 | <.0001 | |
| Group | 1 | 76.8 | 4.18 | 0.0443 | See below |
| Sex | 1 | 78.7 | 1.98 | 0.1636 | |
| YOB | 1 | 78.7 | 15.02 | 0.0002 | 0.5685 +/- 0.1467 |
| Sample*Group | 8 | 296 | 3.75 | 0.0003 | See below |

| Differences of Least Squares Means | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Effect** | **Sample** | **Group** | **_Sample** | **_Group** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > \|t\|** |
| **Group** | | **Control** | | **Dialysis** | -12.4776 | 6.1024 | 76.8 | -2.04 | 0.0443 |
| **Sample*Group** | **CaCl** | **Control** | **CaCl** | **Dialysis** | -12.9416 | 8.3506 | 227 | -1.55 | 0.1226 |
| **Sample*Group** | **FeSO4** | **Control** | **FeSO4** | **Dialysis** | -12.9345 | 8.4852 | 238 | -1.52 | 0.1287 |
| **Sample*Group** | **First** | **Control** | **First** | **Dialysis** | 14.5206 | 8.4729 | 239 | 1.71 | 0.0879 |
| **Sample*Group** | **H3PO4** | **Control** | **H3PO4** | **Dialysis** | -8.6074 | 8.3379 | 227 | -1.03 | 0.3030 |
| **Sample*Group** | **KCl** | **Control** | **KCl** | **Dialysis** | -12.9919 | 8.3199 | 226 | -1.56 | 0.1198 |
| **Sample*Group** | **MSG** | **Control** | **MSG** | **Dialysis** | -26.6181 | 8.3112 | 228 | -3.20 | 0.0016 |
| **Sample*Group** | **NaCl** | **Control** | **NaCl** | **Dialysis** | -26.3041 | 8.3136 | 226 | -3.16 | 0.0018 |
| **Sample*Group** | **NaPO4** | **Control** | **NaPO4** | **Dialysis** | -20.0762 | 8.3413 | 227 | -2.41 | 0.0169 |
| **Sample*Group** | **Urea** | **Control** | **Urea** | **Dialysis** | -6.3453 | 8.2794 | 227 | -0.77 | 0.4442 |

**Liking ratings adjusted for water**

**Least Squares Means**

| Effect | Sample | Group | Estimate | Standard Error | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|---|---|---|
| **Group** | | **Control** | -34.3982 | 3.6389 | 64.5 | -9.45 | <.0001 |
| **Group** | | **Dialysis** | -17.5703 | 5.1894 | 64.8 | -3.39 | 0.0012 |
| **Sample*Group** | **CaCl** | **Control** | -50.0028 | 4.8227 | 178 | -10.37 | <.0001 |
| **Sample*Group** | **CaCl** | **Dialysis** | -37.1318 | 6.6786 | 163 | -5.56 | <.0001 |
| **Sample*Group** | **FeSO4** | **Control** | -37.9895 | 4.9022 | 206 | -7.75 | <.0001 |
| **Sample*Group** | **FeSO4** | **Dialysis** | -14.1806 | 6.7215 | 181 | -2.11 | 0.0363 |
| **Sample*Group** | **First** | **Control** | -46.1758 | 4.9018 | 206 | -9.42 | <.0001 |
| **Sample*Group** | **First** | **Dialysis** | -24.8966 | 6.7026 | 181 | -3.71 | 0.0003 |
| **Sample*Group** | **H3PO4** | **Control** | -25.8989 | 4.8243 | 180 | -5.37 | <.0001 |
| **Sample*Group** | **H3PO4** | **Dialysis** | -18.3216 | 6.6612 | 161 | -2.75 | 0.0066 |
| **Sample*Group** | **KCl** | **Control** | -37.3160 | 4.8245 | 180 | -7.73 | <.0001 |
| **Sample*Group** | **KCl** | **Dialysis** | -15.2039 | 6.6388 | 160 | -2.29 | 0.0233 |
| **Sample*Group** | **MSG** | **Control** | -29.3898 | 4.8039 | 180 | -6.12 | <.0001 |
| **Sample*Group** | **MSG** | **Dialysis** | -15.0603 | 6.6339 | 161 | -2.27 | 0.0245 |
| **Sample*Group** | **NaCl** | **Control** | -30.7353 | 4.8284 | 178 | -6.37 | <.0001 |
| **Sample*Group** | **NaCl** | **Dialysis** | -12.7240 | 6.6366 | 161 | -1.92 | 0.0570 |
| **Sample*Group** | **NaPO4** | **Control** | -10.6184 | 4.8332 | 180 | -2.20 | 0.0293 |
| **Sample*Group** | **NaPO4** | **Dialysis** | 7.7008 | 6.6521 | 161 | 1.16 | 0.2487 |
| **Sample*Group** | **Urea** | **Control** | -41.4573 | 4.8277 | 179 | -8.59 | <.0001 |
| **Sample*Group** | **Urea** | **Dialysis** | -28.3149 | 6.5822 | 160 | -4.30 | <.0001 |

**Type 3 Tests of Fixed Effects**

| Effect | Num DF | Den DF | F Value | Pr > F | |
|---|---|---|---|---|---|
| **Sample** | 8 | 296 | 20.34 | <.0001 | |
| **Group** | 1 | 65 | 5.39 | 0.0234 | See below |
| **Sex** | 1 | 66.1 | 0.10 | 0.7543 | |
| **YOB** | 1 | 66.1 | 5.02 | 0.0284 | 0.3893 +/- 0.1738 |
| **Sample*Group** | 8 | 296 | 0.88 | 0.5326 | Ignore this, and see below (we don't care about all the possible comparisons, which this value is using) |

**Differences of Least Squares Means**

| Effect | Sample | Group | _Sample | _Group | Estimate | Standard Error | DF | t Value | Pr > \|t\| |
|---|---|---|---|---|---|---|---|---|---|
| Group | | Control | | Dialysis | -16.8279 | 7.2466 | 65 | -2.32 | 0.0234 |
| Sample*Group | CaCl | Control | CaCl | Dialysis | -12.8710 | 8.9565 | 143 | -1.44 | 0.1529 |
| Sample*Group | FeSO4 | Control | FeSO4 | Dialysis | -23.8088 | 9.0286 | 158 | -2.64 | 0.0092 |
| Sample*Group | First | Control | First | Dialysis | -21.2793 | 9.0156 | 158 | -2.36 | 0.0195 |
| Sample*Group | H3PO4 | Control | H3PO4 | Dialysis | -7.5773 | 8.9445 | 143 | -0.85 | 0.3983 |
| Sample*Group | KCl | Control | KCl | Dialysis | -22.1121 | 8.9283 | 142 | -2.48 | 0.0144 |
| Sample*Group | MSG | Control | MSG | Dialysis | -14.3295 | 8.9128 | 143 | -1.61 | 0.1101 |
| Sample*Group | NaCl | Control | NaCl | Dialysis | -18.0113 | 8.9226 | 142 | -2.02 | 0.0454 |
| Sample*Group | NaPO4 | Control | NaPO4 | Dialysis | -18.3192 | 8.9469 | 143 | -2.05 | 0.0424 |
| Sample*Group | Urea | Control | Urea | Dialysis | -13.1423 | 8.8851 | 141 | -1.48 | 0.1413 |