Published in final edited form as:

J Urol. 2014 March ; 191(3): 703–709. doi:10.1016/j.juro.2013.10.051.

Inflammatory and Tissue Remodeling Urinary Biomarkers Before and After Midurethral Sling Surgery for Stress Urinary Incontinence

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Abstract

Objective—Urinary biomarkers were measured from women at baseline and 1 post-surgery for stress urinary incontinence (SUI) and associations with clinicodemographic covariates and outcomes were analyzed.

Methods—Pre- and post-surgery urine specimens from 150 women were assayed for inflammatory biomarkers (TNF- α , IFN- γ , IL-1 β , IL6, IL10, IL12p70, IL17, NGF) and tissue remodeling biomarkers (collagenase activity, MMPs-1, 2, 9, 13, N-telopeptide cross-linked collagen (NTx), EGF, HB-EGF). Paired t-tests compared changes in biomarker over 1 year (significance $p < 0.05$). Linear regression models correlated baseline and changes in biomarker levels with covariates (significance $p = 0.001$). Logistic regression models, controlling for age, analyzed associations of baseline and changes in biomarker levels with surgical failure (significance $p < 0.05$).

Results—Over one year, IL12p70 decreased (0.53 ± 1.4 to 0.28 ± 0.62 pg/mg Cr, $p = 0.04$) and NGF increased (0.034 ± 0.046 to 0.044 ± 0.060 pg/ml/mOsm, $p = 0.03$). Baseline NTx level/mg Cr was positively associated with age and post-menopausal status ($p = 0.001$), and negatively associated with current estrogen use ($p = 0.0001$). Baseline collagenase activity/mg Cr was positively associated with age ($p = 0.001$). EGF/mOsm, NTx/mOsm and IFN- γ /mOsm were negatively correlated with age, current estrogen use, and UDI-irritative score, respectively ($p = 0.001$). Subjects with lower baseline NTx/mg Cr were less likely to experience surgical failure (OR 0.49, 95% CI 0.26, 0.93, $p = 0.03$). Changes in biomarker levels were neither associated with any covariates nor surgical failure.

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Conclusions—Women with lower baseline NTx levels were significantly less likely to fail SUI surgery. Studies are needed to validate NTx as a possible independent biomarker for SUI surgery outcomes.

Introduction

Stress urinary incontinence (SUI) is a highly prevalent and bothersome condition. While there has been increasing interest in the identification and use of biomarkers for lower urinary tract dysfunction, there have been few studies of biomarkers in women with SUI.^{1–3} The identification of clinically useful biomarkers in women with SUI may aid in diagnosis, elucidate its pathophysiology, and improve counseling regarding the prognosis of this condition including treatment.

Urinary nerve growth factor (NGF) has been considered a marker for lower urinary tract symptoms (LUTS) secondary to bladder outlet obstruction⁴, overactive bladder (OAB)⁵ and interstitial cystitis/painful bladder syndrome (IC/PBS).^{6–7} Heparin-binding epidermal growth factor-like growth factor (HB-EGF), epidermal growth factor (EGF) and anti-proliferative factor (APF) have been proposed as biomarkers for IC/PBS.⁸ Ultimately, urinary biomarkers may help to understand the pathophysiology of LUTS, provide an objective measure of symptom severity, and to predict likelihood of a successful treatment outcome. Although SUI is not generally regarded as a “functional” bladder problem, sling surgery often increases bladder outlet resistance⁹ which could result in changes in urinary biomarkers of tissue remodeling and inflammation.

This current report analyzed urinary inflammatory and tissue remodeling biomarkers measured before and one year after continence surgery in a sub-sample of women participating in the Value of Urodynamics Evaluation (ValUE) trial.¹⁰ The primary hypothesis was that increased urethral resistance after midurethral sling may result in measureable changes in the amount of certain urinary biomarkers after 1 year. Secondary goals included determining whether preoperative and changes in biomarker levels were associated with baseline clinico-demographic variables, surgical outcomes (success/failure), and baseline lower urinary tract symptoms measured with validated patient reported instruments.

Materials and Methods

This UMACS (Urinary Markers after Continence Surgery) trial was an ancillary study to the ValUE trial and received IRB approval at each participating institution. UMACS was initiated approximately 8 months after ValUE enrollment began. The details and outcomes of ValUE have been published.¹⁰ Ninety-five percent of UMACS subjects received a midurethral sling. Successful outcomes at 12 months were defined as a 70% reduction on the Urogenital Distress Inventory (UDI)¹¹, a response of “much better” or “very much better” on the Patient Global Impression of Improvement (PGI-I)¹², and a negative provocative stress test. Clean catch urine specimens were obtained just prior to urodynamics randomization (preoperatively) and at 1-year postoperative.

Standardized urine specimen processing was performed. All specimens were immediately chilled in ice, centrifuged at 4°C, and the supernatant stored at -80°C until assayed. All assays were performed in triplicate as described below and normalized to urinary creatinine (Cr, mg/dl) and osmolality (mOsm). Matched specimens (pre- and post-operative specimens) were always assayed on the same experimental assay plates to minimize effects from inter-test variability. Standard curves were obtained to ensure quality for every biomarker measurement experiment. Tissue remodeling markers included: total collagenase activity, MMP (matrix metalloproteinase)-1, MMP-2, MMP-9, MMP-13, NTx (N-telopeptide cross-linked collagen), EGF and HB-EGF. Inflammatory markers included: TNF (tumor necrosis factor)- α , IFN (interferon)- γ , IL (interleukin)-1 β , IL-6, IL-10, IL-12p70, IL-17 and NGF. Personnel performing assays were masked to clinical information of the subjects.

Urinary Biomarker Measurements

For HB-EGF measurement, a non-commercial ELISA using anti-HB-EGF antibody (R&D Systems, Minneapolis, MN) and a goat anti-mouse IgG secondary were used. EGF and MMP-2 were measured by ELISA using kits from R&D Systems. MMP-1 was measured using an ELISA kit from Calbiochem (Billerica, MA). ELISA multiplex assay kits (Millipore, Billerica, MA) were utilized to measure inflammatory markers (NGF, IL-6, IL-1 β , TNF- α , IL-10, IL-17, IL-12p70). The amounts of active MMP-9 and -13 were quantified using a Fluorokine E enzyme assay (human active MMP-9 or -13, R&D System). The concentration of urinary NTx was measured using an ELISA kit (OsteomarkNTx Urine, Wampole Laboratories, Princeton, NJ). Total collagenases activity was measured using a collagenase activity assay (Chondrex Inc. Redmond, WA) as previously described.¹³

Urinary Cr and mOsm

We *a priori* decided to normalize to both Cr and mOsm based on lack of clear evidence that one method was superior. Cr was measured by ELISA using a kit from Arbor Assays (Ann Arbor, MI). Urinary mOsm was measured using an osmometer per standardized protocol.

Self-Report Questionnaires and Clinico-demographic Characteristics

Frequency of stress and urge incontinence symptoms were obtained from the Medical, Epidemiological and Social Aspects of Aging (MESA) questionnaire¹⁴ and the Urogenital Distress Inventory questionnaire.¹¹ Post-operatively, self-reported impression of improvement was obtained with the Patient Global Impression of Improvement (PGI-I).¹² Clinico-demographic factors included age, BMI, menopausal status, current estrogen use, history of any non-surgical treatment for UI, history of pelvic surgeries, Q-max on non-instrumented uroflow and maximum cystometric capacity (MCC).

Statistical Analyses

We compared clinico-demographic variables from women who had both pre- and postoperative urine specimens analyzed to those who did not using the Chi-square test of homogeneity for categorical characteristics and the t-tests were for continuous measures. The distributions of the biomarker levels were evaluated and all biomarkers were log-

transformed to reduce skewness. To compare biomarker changes from baseline to one year after surgery, we used the paired t-test on the log-transformed values, with $p < 0.05$ considered as statistically significant. Linear regression models were used to test for associations between covariates and biomarkers (baseline biomarker levels and changes in biomarker levels). For this analysis, to adjust for the large number of variables tested, we used a p value < 0.001 to denote statistical significance. Logistic regression analysis was utilized to examine the associations of baseline and changes in biomarker levels with surgical success/failure after adjusting for age, with $p < 0.05$ considered as significant. All analyses were performed with SAS statistical software (9.2, SAS Institute, Cary, NC).

This study had 80% power to detect small to moderate changes in urinary markers at the 5% significance level. The effect size is the mean change divided by the standard deviation of the change and in general an effect size of 0.2 is considered small while an effect size of 0.5 is considered moderate. Our sample of 150 women provided 80% power to detect effects of 0.23 or larger and 90% power to detect effects of 0.27 or larger at the 5% significance level.

Results

Among the 630 women enrolled in the ValUE trial, 169 provided both baseline and 1-year post-surgery samples of which 150 had complete data for this study. Baseline clinico-demographic factors and rates of surgical success for participants and non-participants in UMACS are shown in Table 1. Women participating in UMACS had a lower post-void residual at baseline and were less likely to have a positive provocative stress test at 12 months compared to women who did not participate in UMACS.

Mean normalized (to both Cr and mOsm) urinary biomarker levels at baseline and 1 year post-operatively are shown in Tables 2a and 2b. Only 2 biomarkers showed a statistically significant change from baseline by the paired t-test (Table 2b in **bold** and Figure 1). IL12p70, normalized for both urine Cr and mOsm, decreased significantly (difference of -0.24 ± 1.4 and -0.0003 ± 0.0018 , $p = 0.04$ for both). NGF, normalized for urine mOsm, increased significantly (difference of $+0.011 \pm 0.06$, $p = 0.03$).

Significant associations between baseline clinico-demographics and baseline biomarker levels are shown in Table 3. Baseline NTx (normalized to Cr) was positively associated with age and post-menopausal status (women who were older or post-menopausal had higher NTx levels). Baseline NTx (normalized to both Cr and mOsm) were negatively associated with current estrogen use. Baseline collagenase activity (normalized to Cr) was positively associated with age. Baseline EGF (normalized to mOsm) was negatively associated with age. Baseline IFN- γ (normalized to mOsm) was negatively associated with UDI-irritative symptoms scores.

In multivariable logistic regression analyses, only baseline NTx level (normalized to Cr) was a statistically significant predictor of surgical failure (Table 4). Subjects with lower baseline NTx levels were less likely to be surgical failures (OR 0.49, 95% CI 0.26, 0.93, $p = 0.03$). While NTx levels normalized to mOsm, was not predictive of outcomes, it showed the same trend as NTx normalized to Cr with OR of surgical failure to be 0.59 (95% CI 0.29 – 1.19).

(Table 4). When age and BMI were controlled for, NTx normalized to Cr still was a significant predictor for surgical failure (OR = 0.45, 95% CI 0.23, 0.89, $p=0.02$). NTx normalized to Osm remained almost statistically significant (OR = 0.61, 95% CI 0.30–1.26, $p=0.18$).

Changes in biomarker levels (normalized to either Cr or mOsm), were not significantly associated with baseline clinico-demographic covariates, urinary incontinence symptoms as measured by changes in MESA urge score, changes in UDI-irritative scores, occurrence of postoperative urinary tract infections (UTI), or surgical outcomes (data not shown).

Discussion

We measured baseline and post-midurethral sling levels of urinary biomarkers to examine their associations with clinicodemographic variables and an *a priori* definition of surgical success/failure. Among 16 biomarkers measured, two biomarker levels changed significantly 12 months after surgery: IL12p70 (normalized to Cr or mOsm) significantly decreased and NGF levels (normalized to mOsm) significantly increased. A potentially important finding was that women with lower NTx levels at baseline were about one-half as likely to experience a surgical failure as compared to women with higher levels of NTx.

IL12p70, a cytokine produced by macrophages, neutrophilic granulocytes and dendritic cells appears to be involved in the regulation of natural killer (NK) and T cells stimulating the production of interferon- γ .¹⁵ A previous report¹⁶ failed to find a statistically significant difference in IL12p70 levels between asymptomatic, UTI and OAB subjects. However, there was a trend toward an increase in IL12p70 level in women with UTI's consistent with the induction of IL12 secretion in response to microbial stimuli.¹⁷

The increase in NGF that we observed may be related to an increase in bladder outlet resistance resulting from sling placement.⁹ Bladder NGF has been shown to increase in a bladder outlet obstruction model in female rats⁴ suggesting that bladder and neuronal remodeling may occur after a midurethral sling procedure.

Urinary NGF levels in our study can be compared to those previously described in patients with OAB.⁵ We found a mean non-normalized NGF level of 10.95 pg/ml at baseline and 12.68 pg/ml one year after surgery. Kuo et al⁵ observed a mean non-normalized NGF level of 1.52 pg/ml, 6.92 pg/ml and 49.34 pg/ml for control, OAB dry and OAB wet patients, respectively. Unfortunately, we cannot compare normalized NGF values because the urinary Cr unit value was not stated in Kuo's study (our Cr value was mg/dl).

Women with lower levels of baseline NTx were approximately one-half as likely to achieve our definition of surgical failure compared to those with higher baseline NTx levels. Since higher levels of NTx would be found in patients with overall increased collagen-based connective tissue turn-over such as in women with osteoporosis or increased connective tissue turnover associated with menopause, it is interesting to note that there have been studies that associated women with osteoporosis having an increased prevalence and severity of weekly urinary incontinence^{18,19} and SUI.²⁰

Urodynamic studies, which are more invasive tests than urinary biomarkers, have been found to be variable in their ability to predict surgical outcomes. Low leak point pressure (VLPP), low maximum urethral closure pressure (MUCP) and presence of urodynamic SUI are urodynamic parameters associated with objective failures for midurethral slings.²¹ The ability of NTx levels to predict post-operative outcomes at one year, based on odds ratios, was similar to VLPP and MUCP, though it should be noted that the definition of outcomes was slightly different in these trials. For Burch colposuspension and autologous slings, urodynamic variables were neither associated with outcomes²² nor post-op voiding dysfunction.²³

The significant observed associations between several urinary biomarkers and baseline clinico-demographic variables are biologically plausible. The positive association of NTx levels with age (as age increases, NTx increases) and post-menopausal status (post-menopausal patients have higher NTx) and negative association with estrogen use (patients who use estrogen have lower NTx) is consistent with what has been published in previous studies.^{24,25} Therefore, older women not on estrogen may tend to have a higher collagen turnover which may translate to a less favorable environment for connective tissue in-growth into the sling. Previously, we have shown that the factor “menopausal status not on hormone replacement therapy” was a predictor of both 24-month²⁶ and longer-term (up to 7 years)²⁷ surgical treatment failure. We also showed that increasing age was predictive of objective surgical failure one year after surgery.²⁸

The negative association between urinary EGF and age corroborates observations by Chou et al, 1997.²⁹ It was theorized that the aging kidney produced less urinary EGF levels (the assumption that the kidney is the main source of urinary EGF). The finding that collagenase activity in urine is positively associated with age suggests that increased tissue remodeling occurs in older women who have undergone a continence procedure.

The finding that urinary IFN- γ was negatively associated with UDI-irritative symptom scores conflicts with the notion of an IFN- γ mediated inflammatory process in the pathogenesis of irritative symptoms (OAB). The fact that there was no association between IL12p70 and UDI-irritative scores is in conflict with published findings of 5-fold increased IL12p70 in OAB subjects compared to controls.³⁰ However, the sample we studied was very different from the OAB study population described in that paper. Further, a measure of this change at 1 year post operatively may not be sensitive to acute changes at an earlier time-point.

Our study had several strengths. First, biomarkers were selected in a hypothesis-driven manner as related to potential post-surgical bladder responses. Second, the size of our study population was relatively large and the women were well characterized. Third, careful attention was paid to sample collection and processing and all sites followed standardized protocol. Assays were performed both at baseline and 1 year post surgery to permit assessment of changes as a result of surgery. We also considered a robust set of patient-centered outcomes. Lastly, we utilized activity assays including total urinary collagenase enzymatic activity and NTx in addition to the traditional measures of biomarker concentrations.

Several shortcomings should be considered. Urine specimens were not collected at a standardized time of the day, but were normalized to urinary Cr and mOsm. We analyzed samples from only one-fourth of the women enrolled in ValUE. A large number of assays were performed which led to multiple statistical comparisons. However, there are several caveats. The use of paired t-test for assessing biomarker changes meant that each UMACS subject served as her own control. Therefore, variabilities in biomarker levels between subjects were lessened. For associations between the biomarkers and clinico-demographic variables, because of multiple comparisons, we used a more stringent p-value for statistical significance to avoid a type I error. We used multivariable logistic regression, controlling for age (Table 4), which is a standard statistical methodology to calculate predictive or risk factors in trials with multiple variables.

Conclusions

Significant changes in IL12p70 and NGF levels were observed from baseline to 1 year continence surgery. NTx levels, were positively associated with age and being pre-menopausal, and negatively associated with estrogen use. NTx level was also predictive of surgical outcome from midurethral sling surgery.

Acknowledgments

Source of Funding: National Institute of Health; National Institute of Diabetes and Digestive and Kidney Disease 3U01DK060397-08S2

We acknowledge the efforts of Dr Elena Lobashevsky and Ms Alice Howell at the University of Alabama at Birmingham and Dr. Chen-Ou Zhang at the University of Maryland, Baltimore.

Key to Abbreviations

NTx	N-telopeptide cross-linked collagen
SUI	stress urinary incontinence
Cr	creatinine
mOsm	milliosmoles
UMACS	Urinary Markers after Continence Surgery

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Figure 1.

Figure 1 – Significant changes in biomarker levels between baseline and 1 year post-operatively

Figure 1A – Significant decrease in mean IL-12p70 levels, normalized to Cr, $p=0.04$

Figure 1B – Significant decrease in mean IL-12p70 levels, normalized to mOsm, $p=0.04$

Figure 1C – Significant increase in mean NGF levels, normalized to mOsm, $p=0.03$

Table 1
Comparison of Baseline Clinicodemographics of Women in UMACS Versus Not in UMACS

Variable	UMACS Participant (n=150)		non-UMACS Participant (n=480)		P-value
	Mean or %	Std Dev	Mean or %	Std Dev	
Age – yr	51.40	10.09	51.36	10.44	0.97
BMI -kg/m ²	28.79	5.17	29.38	6.31	0.31
Non-Hispanic white	80.0%		72.5%		0.07
Parous (1+ pregnancies)	96.7%		95.2%		0.45
Duration of incontinence – mo	109.44	102.52	94.20	84.20	0.07
Post-menopausal	47.3%		43.9%		0.47
Current estrogen-replacement therapy	31.9%		31.0%		0.87
Current smoker	7.3%		12.9%		0.06
History of any non-surgical treatment for UI	58.7%		62.1%		0.46
History of pelvic surgery	77.3%		67.7%		0.03
Urethral mobility	93.3%		90.2%		0.24
PVR – ml	19.15	23.50	26.51	29.66	0.006
UDI: irritative symptoms	34.96	22.78	35.81	24.09	0.70
ISI Scale	7.77	2.66	7.72	2.77	0.83
MESA: Stress Index	74.04	17.71	72.36	17.90	0.32
MESA: Urge Index	31.87	22.71	32.36	21.66	0.81
IIQ	39.97	21.97	43.75	23.35	0.08
SF-12	96.16	13.81	97.07	14.17	0.49
PGI-S	3.09	0.78	3.18	0.76	0.18
Score of 0 on the Charlson comorbidity index	76.0%		70.2%		0.17
Assigned to UDS	47.3%		50.8%		0.46
MUS surgery	95.3%		94.7%		0.77
RMUS surgery	66.0%		64.1%		0.68
70% decrease in UDI from baseline to 12 mos and score of 1 or 2 on PGI-I at 12 mos and negative stress test (success)*	76.0%		68.6%		0.10
Positive provocative stress test at 12 mo**	7.3%		17.2%		0.005

* Primary Outcome available for 388 non-UMACS participants

** Stress test available for 297 non-UMACS participants

Table 2a

Tissue Remodeling Urinary Biomarkers Baseline and 1 Year Postoperatively

Tissue remodeling markers	Normalized to Cr			Normalized to mOsm		
	Baseline Mean (SD) *	1 Year Post-Op Mean (SD) *	Paired t-test	Baseline Mean (SD) **	1 Year Post-Op Mean (SD) **	Paired t-test
Collagenase Activity (Cleavage of 1mg collagen per minute)	3.57 (6.98)	3.08 (5.69)	0.36	0.0056 (0.0086)	0.0057 (0.010)	0.87
MMP-1	0.64 (0.93)	0.55 (0.67)	0.17	0.0010 (0.0013)	0.0010 (0.0008)	0.62
MMP-2	2.74 (3.97)	2.71 (3.53)	0.92	0.0051 (0.0051)	0.0055 (0.0050)	0.30
MMP-9	0.51 (1.43)	0.88 (4.00)	0.27	0.0010 (0.0025)	0.0014 (0.0041)	0.24
MMP-13	0.32 (0.87)	0.22 (0.45)	0.15	0.0007 (0.0017)	0.0005 (0.0008)	0.08
NTx	37.71 (26.15)	37.86 (24.73)	0.93	0.54 (0.32)	0.59 (0.36)	0.12
HB-EGF	7.28 (11.48)	8.69 (12.86)	0.18	0.013 (0.020)	0.017 (0.022)	0.06
EGF	25.96 (17.52)	25.71 (15.71)	0.81	0.053 (0.035)	0.058 (0.039)	0.10

* All values in this column are ng/mg Cr **except** for Collagenase Activity unit which is (Cleavage of 1 mg collagen per minute)/mg Cr and NTx unit which is nmol/mmol Cr

** All values in this column are ng/ml/mOsm, except for Collagenase Activity which is (Cleavage of 1 mg collagen per minute)/mOsm and NTx which is nM BCE/mOsm

Table 2b

Inflammatory Urinary Biomarkers Baseline and 1 Year Postoperatively

Inflammatory markers	Normalized to Cr			Normalized to mOsm		
	Pre-Op Mean (SD) *	1 Year Post-Op Mean (SD) *	Paired t-test	Pre-Op Mean (SD) **	1 Year Post-Op Mean (SD) **	Paired t-test
TNF-α	0.367 (1.13)	0.29 (0.92)	0.51	0.0006 (0.0012)	0.0004 (0.0010)	0.31
INF-γ	0.32 (0.45)	0.27 (0.85)	0.50	0.0006 (0.0007)	0.0005 (0.0013)	0.47
IL-1β	3.79 (6.90)	3.62 (5.91)	0.75	0.0051 (0.0093)	0.0062 (0.0095)	0.20
IL-6	4.87 (19.49)	3.15 (3.69)	0.29	0.0084 (0.0315)	0.0061 (0.0071)	0.39
IL-10	0.77 (1.83)	0.77 (2.80)	0.98	0.0014 (0.0025)	0.0013 (0.0038)	0.88
IL-12p70	0.53 (1.44)	0.29 (0.62)	0.04	0.0009 (0.0017)	0.0006 (0.0011)	0.04
IL-17	0.380 (1.05)	0.39 (2.21)	0.95	0.0006 (0.0014)	0.0006 (0.0031)	0.99
NGF	24.23 (39.69)	26.10 (40.82)	0.58	0.034 (0.046)	0.044 (0.060)	0.03

* All units in this column are pg/mg Cr
** All units in this column are pg/ml/mOsm

Table 3

Associations Between Baseline Biomarkers and Clinicodemographic Characteristics (Baseline Covariates) **

Normalization Factor	Baseline biomarker	Baseline covariate	Coefficient (SE)	p-value
Cr	NTx (nmol/mmol Cr)	Age (y)	0.02 (0.006)	0.001
	NTx (nmol/mmol Cr)	Post-menopausal (yes vs. no)	0.44 (0.13)	0.001
	NTx (nmol/mmol Cr)	Current Estrogen (yes vs. no)	-0.63 (0.15)	0.0001
mOsm	Collagenase activity (unit */mg Cr)	Age (y)	0.04 (0.01)	0.001
	NTx (nM BCE [†] /mOsm)	Current Estrogen (yes vs. no)	-0.47 (0.14)	0.001
	EGF (ng/ml/mOsm)	Age (y)	-0.02 (0.006)	0.0004
	IFN- γ (pg/ml/mOsm)	UDI-Irritative symptoms	-0.01 (0.003)	0.001

* unit = Cleavage of 1 mg collagen per minute

[†] BCE = bovine collagen equivalent

** Only significant results are presented, p 0.001.

** None of covariates were significantly associated with changes in biomarkers.

Table 4

Multivariable Analysis of Association Between Baseline Biomarkers with Surgical Failure - Only NTx Statistically Significant

Logistic Regression Between Baseline Biomarker and Outcome Failure	Biomarker	Odds Ratio (95% CI)	p-value
Markers Normalized to Cr	NTx	0.49 (0.26 – 0.93)	0.03
Markers Normalized to mOsm	NTx	0.59 (0.29 – 1.19)	0.14