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Time-dependent changes in kidney injury biomarkers in patients receiving multiple cycles of cisplatin chemotherapy

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ABSTRACT

Proteins secreted into urine following tubular injury are being increasingly used as biomarkers of clinical and subclinical nephrotoxicity. In the present study, we sought to characterize the time-dependent urinary excretion of three promising biomarkers, kidney injury molecule-1 (KIM-1), calbindin, and trefoil factor 3 (TFF3), during two different chemotherapy cycles in 27 patients with solid tumors prescribed the anticancer drug cisplatin (≥ 25 mg/m^2). Urinary biomarkers were evaluated at Days 3 and 10 during an initial and a subsequent cycle of cisplatin chemotherapy. Longitudinal analyses compared the mean difference estimations for biomarker concentrations during and across the initial and subsequent cycles of cisplatin treatment. Traditional biomarkers including serum creatinine, estimated glomerular filtration rate, and blood urea nitrogen were unchanged during and across both cycles of cisplatin therapy. In response to the initial cycle, urinary KIM-1 concentrations increased from baseline and remained elevated through a subsequent cycle of cisplatin chemotherapy. By comparison, urinary levels of calbindin were elevated 10 days after the initial cisplatin treatment, but largely unchanged by cisplatin exposure in a subsequent cycle. Early elevations in urinary TFF3 at 3 days after cisplatin administration were observed consistently in both the initial and subsequent cycle of cisplatin treatment. In conclusion, the longitudinal assessment of biomarker performance in the same cohort of oncology patients reveals different patterns of urinary excretion between initial and subsequent cycles of cisplatin-containing chemotherapy. These data add novel cycle-dependent insight to the growing literature addressing the ability of urinary biomarkers to detect subclinical renal injury in patients receiving cisplatin.

1. Introduction

Cisplatin is a commonly used chemotherapeutic drug effective in treating solid cancers. Success of cisplatin therapy is limited, in part, by acute kidney injury resulting from toxicity to proximal tubules. Up to a third of patients develop nephrotoxicity after a single dose of cisplatin, despite preventive strategies such as hydration that limit renal platinum exposure [1] This is problematic for patients as renal toxicity can delay further treatment and reduce the total number of chemotherapy cycles received, thereby decreasing the overall efficacy of cisplatin-containing chemotherapy regimens. While preclinical evaluation of novel interventions is underway [2–5], there is a need to develop effective measures that assess tubular injury in human patients.

Recognizing the limitations of traditional clinical measures of acute kidney injury (AKI) including serum creatinine (SCr) and estimated glomerular function rate (eGFR), novel urinary protein biomarkers are increasingly being investigated for their ability to identify damage earlier and with more sensitive detection. Several promising urinary proteins, including kidney injury molecule-1 (KIM-1), exhibit a high sensitivity to identify renal damage in preclinical models as well as in patients with mixed etiologies of AKI [6–9]. In 2016, the Food and Drug Administration issued a letter of support for several novel urinary biomarkers (KIM-1, neutrophil gelatinase-associated lipocalin, osteopontin, albumin, and total urinary protein) for use in detecting drug-

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induced renal tubular injury in early clinical trials [10]. Our laboratory previously demonstrated significant time-dependent changes in the urinary excretion of biomarkers (KIM-1, calbindin, and trefoil factor 3 (TFF3)) in predominantly treatment-naïve patients receiving cisplatin [11]. Emerging data have characterized the intrarenal localization of each protein as well as their biological responses to injury. KIM-1 is a transmembrane protein found on the apical surface of proximal tubules. Following injury, the ectodomain of KIM-1 is shed into the tubular lumen [12,13]. Calbindin is a cytosolic calcium-binding protein localized primarily to distal tubules and collecting ducts. Calbindin concentrations are elevated in urine following cisplatin treatment in rodents, cynomolgus monkeys, as well as in patients [11,14–16]. TFF3 is a small peptide hormone secreted by mucus-producing epithelial cells and has been demonstrated to inhibit apoptosis as well as promote cell survival and migration [17]. While urinary TFF3 concentrations were shown to decrease with cisplatin-induced kidney injury in rodents [18], we have demonstrated that concentrations of TFF3 are increased in the urine of patients treated with cisplatin [11].

Previous studies have documented elevations in SCr after the first dose of cisplatin [19,20]. Additionally, chronic elevations in SCr after completion of chemotherapy have been recently described [21]. In order to understand whether elevations in newer urinary biomarkers follow this similar pattern of expression, we sought to extend our prior observations [11] and compare time-dependent changes in the patterns of urinary excretion of three biomarker proteins (KIM-1, calbindin, and TFF3) in the same patients during an initial and subsequent cycle of cisplatin chemotherapy. Notably, this particular set of patients was previously demonstrated to have little to no change in traditional AKI markers (i.e., SCr, eGFR, or blood urea nitrogen, BUN) following cisplatin administration [11]. As a result, the current investigation enabled assessment of time-dependent changes in each urinary protein biomarker as an indication of tubular damage in the subclinical nephrotoxicity domain.

2. Materials and methods

2.1. Selection of participants

A prospective study of patients receiving outpatient chemotherapy for various solid tumors at the University of Colorado Cancer Center, Aurora, CO, a National Cancer Institute-Designated Consortium Comprehensive Cancer Center was conducted. Twenty-seven patients prescribed cisplatin-containing ($\geq$ 25 mg/m^2) chemotherapy participated in the study and were monitored at two different chemotherapy cycles, designated as *initial* and *subsequent* cycles, with follow-up assessments at Days 3 and 10 post dosing. Clinical data and urine specimens were collected at each cycle. The cycles for which each patient participated in the study varied across chemotherapy cycles 1–4.

Study inclusion criteria included: [1] age $\geq$ 18 years [2]; hemoglobin $\geq$ 10 g/dL [3]; no consumption of grapefruit juice or alcohol within 7 days [4]; no history of alcohol consumption of > 14 drinks/week; [5]; no history of organ transplantation or kidney dialysis [6]; willingness to comply with study [7]; not pregnant or lactating [8]; no changes in medications within previous 4 weeks [9]; normal liver function (alanine aminotransferase and aspartate aminotransferase < 2-3 upper limit of normal); and [10] baseline eGFR > 60 mL/min/m^2 (using the four-variable Modification of Diet in Renal Disease equation) [22,23]. Exclusion criteria included [1]: diagnosis of kidney cancer [2]; previous exposure to platinum-based chemotherapy (other than the currently prescribed regimen) [3]; herbal supplement use [4]; exposure to other known nephrotoxins (including contrast agents) within the previous 30 days; and [5] concurrent use of inhibitors of transport proteins involved in cisplatin secretion into urine. Twenty-six patients received cisplatin intravenously whereas one patient was administered cisplatin intra-peritoneally. Patients were hydrated pre- and post-treatment with saline (1–2 L). The Institutional Review Boards at the University of Colorado (Protocol 12-1510) and Rutgers University (Protocol E13-716) approved the protocols for recruitment, consent, and sample collection.

Table 1
Demographic Information for Patients Receiving Cisplatin[a].

Age (mean ± SE)	59.0 ± 1.8 years
Sex	Male = 13, Female = 14
BMI (mean ± SE)	26.2 ± 1.1 kg/m^2
Initial Cisplatin Dose (mean ± SE)	61.0 ± 4.5 mg/m^2
Ethnicity	White = 26, Hispanic = 1

[a] Abbreviations: BMI: body mass index; SE: standard error.

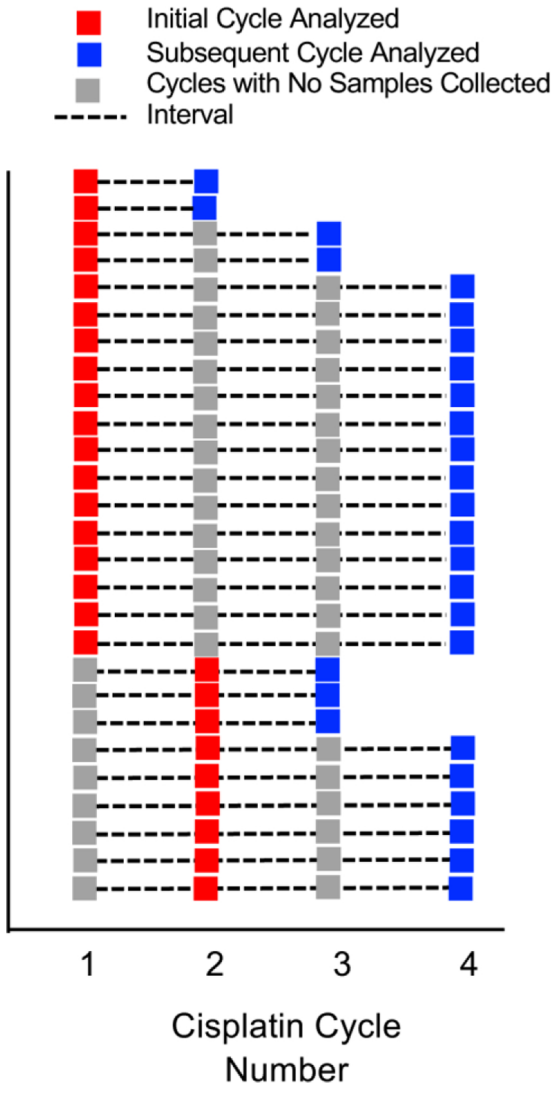

Fig. 1. Timing of Cisplatin Chemotherapy Cycles Collected and Analyzed in this Study. Each row on the y-axis represents a different patient (N = 27). Each patient is depicted according to the cycles of chemotherapy analyzed as the initial *(red)* and subsequent *(blue)* cycles. *Gray* symbols represent cycles where no samples were collected or analyzed. The average interval of time between the initial and subsequent cycles of cisplatin was 36 days (range, 14–70 days). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

2.2. Urine samples

Urine was collected from spontaneous voids at baseline (pre-cisplatin infusion), between 2 and 5 days (designated as Day 3) and 9 and

Table 2
Clinical Laboratory Values Pre- and Post-Cisplatin Infusion at Initial and Subsequent Cycles.

	Initial Cycle			Subsequent Cycle		
	Pre Mean ± SE *Range Median N = 27*	Post[a] Mean ± SE *Range Median N = 27*	P	Pre Mean ± SE *Range Median N = 27*	Post[a] Mean ± SE *Range Median N = 23*	P
SCr (mg/dL)	0.85 ± 0.04 *(0.40 – 1.53)* *0.81*	0.84 ± 0.04 *(0.58 – 1.63)* *0.81*	0.774	0.83 ± 0.04 *(0.53 – 1.52)* *0.79*	0.84 ± 0.03 *(0.53 – 1.25)* *0.86*	0.863
BUN (mg/dL)	15 ± 1 *(6 – 28)* *13*	15 ± 1 *(8 – 28)* *14*	0.614	13 ± 0.8 *(7 – 20)* *13*	14 ± 0.9 *(8 – 22)* *14*	0.191
eGFR (mL/min)	90.6 ± 4.8 *(50.3 – 176.1)* *86.9*	94.2 ± 5.2 *(50.3 – 186.5)* *80.4*	0.445	93.3 ± 4.1 *(58.8 – 139.7)* *88.7*	89.8 ± 3.9 *(60.2 – 127.3)* *91.7*	0.547

[1]Abbreviations: BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; SCr: serum creatinine; SE: standard error.
[a] The time frame for assessment of clinical parameters was 12 ± 9 days post cisplatin infusion.

11 days (designated as Day 10) post-cisplatin infusion. Urine was centrifuged at 3,000x*g* and supernatant was aliquoted into 2 mL collection tubes and frozen within 30–60 min of collection at −80 °C. At the time of analysis, samples were thawed and placed on ice and centrifuged at 200 x *g* for 5 min. A 12.5 µl aliquot of supernatant was used for biomarker analysis.

2.3. Quantification of urinary protein biomarkers

KIM-1, calbindin, and TFF3 were measured using the Milliplex MAP Human Kidney Injury Magnetic Bead Panel 1 (MilliporeSigma, Burlington, MA). Washing steps were conducted using the Bio-Plex Pro II wash station (Bio-Rad Life Science, Hercules, CA). Samples were analyzed using a Bio-Plex, MagPix Multiplex Reader (Bio-Rad), which reports the mean fluorescence intensity proportional to the concentration of analyte bound to each bead. Concentrations were extrapolated from a known standard curve using a five-parameter logistic curve. Recommended dilutions of urine samples in dilution buffer provided in the assay kit were followed (1:2). Values that were above the detection limit were extrapolated from the standard curve. Concentrations below the limit of detection were substituted with the lower limit of quantification divided by 2. Data are presented as concentrations normalized to urinary creatinine concentrations quantified using the DCA Vantage Analyzer (Siemens, Princeton, NJ).

2.4. Data and statistical analysis

Descriptive statistics were performed using the mean and standard error for demographic information and clinical laboratory values for patients receiving cisplatin. Longitudinal data analyses were used for the urinary concentration estimations of protein biomarkers at time point (days). Cisplatin urinary biomarker (KIM-1, calbindin and TFF3) concentrations were normalized before performing longitudinal modeling. Mixed models were utilized to account for concentration measurements at different time points (e.g. Days 0, 3, and 10 after cisplatin dosing) as a categorical covariate variable. The initial measure (Day 0) was assigned as the baseline measure and occurred prior to a patient receiving their first dose of cisplatin. The average interval between the initial and subsequent dosing cycle was 36 days. Subsequent measures were used to describe urinary biomarker measures at a later cisplatin treatment cycles, for example, dosing at Day 36, with urinary biomarkers at Day 39 and Day 46. The data were analyzed in a longitudinal fashion to build the mixed-effect model for the over time measures. The random effects included intercept using standard variance components (VC) and restricted maximum likelihood (REML) estimation. VC structure models a different variance component for the random effect. Day was used as a categorical variable such that the means (Least squares means) could be compared between the baseline and a time point (3, 10, 36, 39 and 46 days). The concentration estimations and comparisons of the biomarkers using least square (LS) means at different time points with 95 % confidence intervals were calculated. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using SAS 9.4 software (SAS Institute Inc., Cary, North Carolina).

3. Results

Twenty-seven patients were included in the study and patient characteristics are shown in Table 1. All but one patient identified as white (96 %), with an even distribution of male and female patients. The mean and range of patient age was 59 years (range, 35–72 years) and body mass index (BMI) was 26.2 kg/m^2 (range, 19.1–43.1 kg/m^2).

Urine was collected from individual patients following their evaluated cycles of cisplatin therapy and termed *initial* and *subsequent* cycles. The two cycles that were collected varied across individual patients as shown in Fig. 1. Urine was collected from patients during either cycle 1 (n = 18) or cycle 2 of cisplatin therapy (n = 9) for the *initial* cycle. For samples designated as the *subsequent cycle*, urine was collected from two patients during cycle 2, five patients during cycle 3, and twenty patients during cycle 4. The average length of time between the initial and subsequent cycles of cisplatin was 36 days (range, 14–70 days). The average prescribed cisplatin dose across initial and subsequent cycle was 59.3 mg/m^2 (range, 25–100 mg/m^2) and was not significantly different.

Using the Kidney Disease Improving Global Outcomes (KDIGO) criteria [24,25], AKI is defined as an increase in SCr > 0.3 mg/dL over 48 h or 1.5 times baseline after one dose of cisplatin. None of the twenty-seven patients who were evaluated at cisplatin cycle 1 or cycle 2 developed AKI based on these criteria. Mean SCr, BUN, eGFR, and urinary albumin-to-creatinine ratio were not significantly changed 12 ± 9 days post-cisplatin infusion compared to pre-cisplatin levels (Table 2 and data not shown). No differences were detected in these parameters across cycles.

Despite a lack of clinical AKI according to the KDIGO definition, all three urinary protein biomarkers exhibited temporal increases following cisplatin treatment. Notably, there were significant time-dependent changes in urinary KIM-1 concentrations in response to cisplatin treatment (Fig. 2, Table 3). There was a significant difference between the mean KIM-1 concentration at Day 3 after cisplatin versus the initial baseline, with an estimated regression coefficient ± SE of 1.08 ± 0.54 ($p = 0.0489$). By comparison, no significant differences were observed between Day 10 and Day 0 of that cycle (1.02 ± 0.54, $p = 0.0579$). There were also significant differences observed between the KIM-1 mean concentrations at Day 0 (36 days) and Day 3 (39 days) in evaluations at the subsequent cycle vs. initial baseline (Day 0). Interestingly, urinary KIM-1 concentrations remained elevated after the initial baseline (Day 0) at the time of subsequent cycles of cisplatin, perhaps reaching a threshold with no further changes in KIM-1 excretion into urine.

Significant time-dependent changes in urinary calbindin

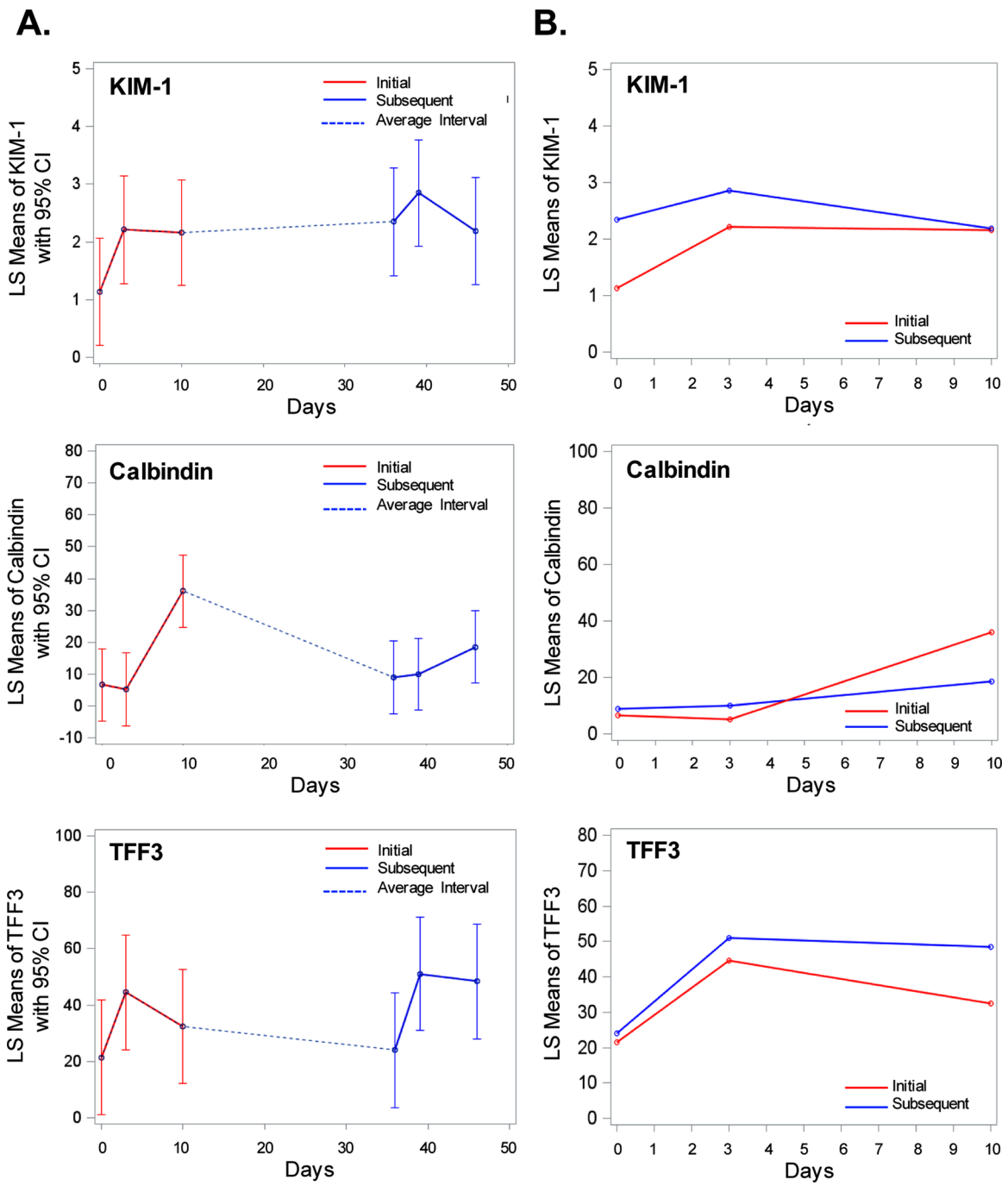

Fig. 2. Estimated Least Squares Means of Normalized Urinary Concentrations of Protein Biomarkers following Initial and Subsequent Cycles of Cisplatin Infusion by a Mixed Model. Urinary protein concentrations for kidney injury molecule-1 (KIM-1), calbindin, and trefoil factor 3 (TFF3) were quantified using a multiplex assay at baseline (n = 27), 3 days (range, 2–5 days; n = 27), and 10 days (range, 9–11 days; n = 27) post cisplatin treatment during the first or second or subsequent (2 or 5) cycles of chemotherapy, with an average of 36 intervening days between cycles. Concentrations were measured in urine supernatants and normalized to urinary creatinine levels. (A) The LS means of the biomarkers at time points (days post dosing) with 95 % confidence intervals (CI). (B) LS Means were overlaid to compare patterns of biomarker changes during initial and subsequent cycles.

concentrations occurred during the initial cycles, but were not observed with subsequent cisplatin infusions (Fig. 2, Table 3). During the initial cycle that was monitored, a significant difference was noted between the mean calbindin concentrations (29.4 ± 7.51, p = 0.0001) in the urine on Day 10 versus baseline. By comparison, there was only a non-significant increase on Day 10 of the subsequent cycle versus baseline (11.93 ± 7.51, p = 0.1146) (Fig. 2, Table 3). Notably, the Day 0 concentrations of calbindin did not significantly differ between the initial and subsequent cycles suggesting calbindin levels return to baseline between the cycles of cisplatin chemotherapy.

Significant changes in urinary concentrations of TFF3 were observed in both the initial and subsequent cycles (Fig. 2, Table 3). During the initial cycle, TFF3 levels had a mean difference of 23.07 ± 9.79 (p = 0.02) between initial baseline and Day 3, whereas a difference of 11.0 ± 9.68 (p = 0.26) was detected between the initial baseline and Day 10. During the subsequent cycle, a similar mean difference in urinary TFF3 concentrations was observed at Day 3 (29.66 ± 9.68, p = 0.0027) vs. baseline and remained elevated at Day 10 (27 ± 9.79, p =

Table 3
Estimated Regression Coefficient and SEs of Biomarker Concentrations based on a Mixed-Effects Model with Time Points (days) Defined at Initial Cycle (Days 0, 3 and 10), and Subsequent Cycle (Days 0, 3 and 10)[a].

Biomarkers[b]	Group	Days	Time point vs. Baseline (Days)	Estimated Regression Coefficients[c]	SE	P value
KIM-1	Initial	0	Intercept	1.14	0.47	0.0232
		3	3 vs. baseline	1.08	0.54	0.0489
		10	10 vs. baseline	1.02	0.54	0.0579
	Subsequent	0	36 vs. baseline	1.21	0.54	0.0261
		3	39 vs. baseline	1.72	0.54	0.0017
		10	46 vs. baseline	1.05	0.54	0.0543
Calbindin	Initial	0	Intercept	6.64	5.77	0.2608
		3	3 vs. baseline	−1.38	7.51	0.8540
		10	10 vs. baseline	29.40	7.51	0.0001
	Subsequent	0	36 vs. baseline	2.32	7.50	0.7578
		3	39 vs. baseline	3.45	7.43	0.6433
		10	46 vs. baseline	11.93	7.51	0.1146
TFF3	Initial	0	Intercept	21.42	10.26	0.0467
		3	3 vs. baseline	23.07	9.79	0.0200
		10	10 vs. baseline	11.00	9.68	0.2581
	Subsequent	0	36 vs. baseline	2.58	9.76	0.7915
		3	39 vs. baseline	29.66	9.68	0.0027
		10	46 vs. baseline	27.00	9.79	0.0067

[a] Abbreviations: KIM-1: kidney injury molecule 1, TFF3: trefoil factor 3.
[b] Biomarker concentrations were normalized to urinary creatinine levels.
[c] Estimated regression coefficients and standard errors (SE) were obtained using a Mixed-Effects Model with time as a categorical covariate variable and intercept as a random effect. Initial Day 0 is referenced as baseline.

0.0067). Similar to calbindin, the Day 0 concentrations of TFF3 were not significantly different between initial and subsequent cycles, suggesting this biomarker returns to baseline between cycles of cisplatin chemotherapy.

4. Discussion

It was recently shown that cisplatin treatment results in permanent declines in eGFR [21]. However, small changes in kidney function, as measured by eGFR, between cisplatin cycles are often only marginally observed or are not detectable. The assessment of novel and sensitive urinary biomarker changes between cisplatin treatment cycles fills the gap of knowledge pertaining to subclinical kidney injury with repeated cisplatin dosing cycles. This is the first study to compare time-dependent changes in the urinary biomarkers KIM-1, calbindin, and TFF3 in the same set of patients across cycles of cisplatin. A consistent finding in the current study was that the urinary concentrations of all three biomarkers, KIM-1, calbindin, and TFF3, increased during the initial cycle of cisplatin treatment. However, the patterns of biomarker secretion into urine differed during subsequent cycles of cisplatin chemotherapy. Importantly, for KIM-1, there were elevated levels at Day 0 of successive cycles, suggesting sustained subclinical injury with subsequent cisplatin dosing. As a result, the magnitude of KIM-1 elevations was somewhat blunted in the subsequent cisplatin cycle compared to the initial cycle. Although this variation may be dependent on the dose of cisplatin or the time between treatments, similar relationships (i.e., dampened response) have been previously reported for the urinary biomarkers beta-2-microglobulin and N-acetyl-Beta-D-glycosaminidase with additional courses of cisplatin [26].

Ideally, predictors of AKI should be able to reflect the progression of injury over at least the course of treatment. From the current study, it is evident that when utilizing novel urinary protein biomarkers for monitoring the progression of drug-induced kidney injury, it is worthwhile to compare back to a treatment-naïve baseline versus a subsequent cycle in order to detect the full range of changes predictive of a kidney injury response. Our results contribute to the existing literature [27–30] demonstrating that subclinical damage to the nephron can be assessed through quantification of urinary protein biomarkers in patients that do not otherwise exhibit changes in functional measures such as BUN and eGFR. However, the current study was unable to evaluate the urinary biomarker changes beyond the length of cisplatin therapy, limiting our understanding of long-term consequences.

As the field of biomarkers progresses, it will be critical to define reference ranges for normal urinary levels of KIM-1, calbindin, and TFF3 in cancer patients as baseline levels can exceed those observed in healthy volunteers [11]. In our prior study of 57 patients assessed for subclinical kidney injury following cisplatin-containing chemotherapy, we observed median fold-changes for each urinary protein biomarker of between 1.5-fold to 3.7-fold [11]. For KIM-1, we observed a median fold-change of 1.5-fold at Day 3 and 1.8-fold at Day 10. For calbindin, we observed a median fold-change of 1.7-fold at Day 3 and 3.7-fold at Day 10. For TFF3, we observed a median fold change of 2.4-fold at Day 3 and 1.9-fold at Day 10. These fold-changes are of similar magnitude that elicits concern in the clinical environment for liver injury biomarkers (e.g. ALT, bilirubin). However, there are currently no established normal urinary concentration ranges for these proteins that account for patient race/ethnicity, age, cancer status, or age and in turn, enable actionable fold-change thresholds of clinical concern. With larger controlled studies, there is the opportunity to establish normal ranges of each biomarker as well as thresholds or fold-changes that would inform clinical decision making processes.

In summary, this study reported time-dependent changes in three urinary protein biomarkers, KIM-1, calbindin, and TFF3 during an initial and subsequent cycle of cisplatin-containing chemotherapy. KIM-1 concentrations failed to return to the initial baseline levels (pre-cisplatin exposure) after subsequent cycles, whereas calbindin and TFF3 concentrations did return to baseline. The observation of TFF3 returning to baseline between cisplatin cycles and reaching similar magnitudes of increase within each cycle points to the consistency of this biomarker in detecting subclinical kidney injury. Larger longitudinal studies of kidney injury biomarkers, in particular TFF3, in a more diverse population exhibiting cisplatin-induced subclinical and clinical AKI are needed to fully understand their long-term performance and utility in predicting responses to repeated nephrotoxin exposures as well as the development of chronic kidney injury and disease.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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