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RESEARCH ARTICLE

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Sexually transmitted doping: The impact of urine contamination of semen

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Abstract

The high sensitivity of antidoping detection tests creates the possibility of inadvertent doping due to an athlete's unknowing ingestion of contaminated environmental sources such as dietary supplements, food, or drinks. Recently, athletes denying use of a prohibited substance have claimed that the positive antidoping tests was due to exchange of bodily fluids with a nonathlete partner using a prohibited substance. Measurement of drugs in semen is largely limited to one or very few samples due to the inaccessibility of sufficiently frequent semen samples for detailed pharmacokinetics. An emerging issue in semen drug measurements is that semen samples may contain residual urine from ejaculation left in the urethra; however, the urine content in semen samples has not been studied. In the present study, we employed concurrent creatinine measurements in urine and seminal plasma to determine the urine content of semen samples.

KEYWORDS
doping, semen, seminal plasma, urine

1 | INTRODUCTION

Doping in elite sports is deterred by the sensitive detection tests for prohibited substances developed by World Anti-Doping Agency (WADA)-approved antidoping laboratories coupled with strong sanctions under the WADA Code for antidoping rule violations (ADRV). A key element of the WADA Code is its strict liability regimen whereby the presence of a prohibited substances in an athlete's body creates an ADRV regardless of intent, negligence, or other reasons leading to sanctions. Under the WADA Code, exculpatory evidence proving how inadvertent contamination occurred may mitigate sanctions for an ADRV. Progressive improvements in analytical steroid mass spectrometry increasing the sensitivity of detection tests create the possibility of positive findings arising from an athlete's unknowing exposure to traces amounts of prohibited substances from contaminated environmental sources such as dietary supplements, food, or drinks.

Recently female athletes with a positive urine test but denying ingestion of any prohibited substance have claimed inadvertent doping due to exchange of bodily fluids (e.g., saliva and semen) with a nonathlete partner using a prohibited substance. Given the increasing prevalence in the community of androgen abuse for bodybuilding image, rather than athletic performance, enhancement this mostly involves abuse of synthetic androgens.[1,2] Three illustrative cases known to anti-doping authorities are outlined below excluding potentially identifying details. In all three cases, the female athlete denied use of any prohibited substances and had sexual intercourse (vaginal, anal, oral) with a male boyfriend using a prohibited substance close to the time of the positive urine anti-doping test. In each case,

the inadvertent exposure to a prohibited substance was accepted as plausible given the minimal literature on the appearance of prohibited substances in semen and its sexual transmissibility to female partners.

> *Case* 1. 22-year-old female athlete produced a urine sample containing low concentrations of LGD-4033 (detectable but below minimum required performance limits [MRPL] of 2 ng/ml) and its dihydroxy metabolite (detectable but not qualifiable without reference standard) in A sample with confirmation of detectable metabolite in the B sample. Her boyfriend was taking Ligandrol (LGD-4033) 12 mg per dose sporadically but about twice weekly including taking multiple doses over the week prior to athlete's test with the last dose 3 days prior to sex with the athlete.

> *Case* 2. 21-year-old female athlete produced a urine test containing low but detectable concentrations of letrozole metabolite (bis(4-cyanophenyl) methanol) and GW1516 (GW1516 sulfoxide & GW1516 sulfone). All positives were detectable but below MRPL (20 ng/ml). Her boyfriend was taking oral solutions of Letrozole and GW1516 daily for between 2 to 3 weeks over the period of the athlete's positive urine test when they had frequent sex.

> *Case* 3. 20-year-old female athlete with multiple negative anti-doping tests over the previous 2 years produced a urine sample with low concentrations of mesterolone metabolite (1α-methyl-5α-androstan-3α-ol-17-one) in the A sample and confirmed in the B sample. Boyfriend was taking mesterolone (50 mg daily) with additional 25 mg doses prior to sex.

Drug pharmacokinetic studies required for marketing measure drug in the bloodstream and, less often in urine, which is the focus of antidoping tests but of limited interest in modern therapeutics. However, there is little systematic study of drug pharmacokinetics in other bodily fluids such as semen, sweat, breast milk, tears, respiratory tract fluid, bile, or cerebrospinal fluid. These attract medical attention when drug therapeutics or toxicology raises concerns such as drug contamination of breast milk,[3] genital tract bacterial,[4–8] or viral[9] infections, or potential teratogenic effects of semen.[4,5] Otherwise such drug delivery routes are of subordinate concern, considered *"… quantitatively unimportant …"* by a major pharmacology textbook.[10] The limited pharmacokinetic data available for such niche biological fluids is largely due to the inaccessibility of such biological fluids for sufficiently frequent measurement of drug concentrations required for sound pharmacokinetics. With limited exceptions,[11] the available drug measurements in these fluids mostly comprises single or few time-point concentrations, creating a dearth of sound drug pharmacokinetics in such niche fluids.

In evaluating semen drug pharmacokinetics, an issue arises whether residual urine contamination of ejaculated semen in passing through the urethra could contribute to measurable drug concentrations in seminal plasma. This study was therefore designed to quantify the volume of residual urine present in an ejaculate to evaluate whether it could transmit sufficient prohibited substances to cause a positive anti-doping test.

2 | MATERIALS AND METHOD

The study was a prospective, single-center study with participants recruited from men attending the Clinical Andrology laboratory for a semen analysis ordered by their doctor or fertility specialist. None were recruited from, or known to be, competitive athletes. The primary study cohort involved investigation of concurrent semen and urine samples to calculate the urine content of semen. An extended cohort was used to characterize seminal variables including semen creatinine but without concurrent urine samples. The only exclusion criterion was prior lower urinary tract surgery. The study was approved by the Sydney Local Health District Human Ethics Committee (Concord zone).

2.1 | Biological samples*

Semen samples were collected by masturbation in a room adjacent to the Clinical Andrology Laboratory, Concord Hospital. For some patients, a spot urine sample was collected immediately after the semen collection.

2.2 | Assays

Semen analysis was performed according to the WHO Semen Manual. Semen analysis is performed by the laboratory's routine WHO-based and National Association of Testing Agencies (NATA)-accredited methods.

Creatinine was measured using the enzymatic creatininase assay (Cobas CREP2 assay, Roche Diagnostics) considered the most accurate chemical method for human serum and urine.[12,13] This autoanalyzer method involves a series of three enzymatic reactions generating hydrogen peroxide which reacts to generate a chromogen (quinone imine) where the color intensity is proportional to the creatinine concentrations in the sample. Using a sample volume of 5 µl, the limits of detection are 5 µmol/L for serum and 100 µmol/L for urine with a coefficient of variation of <1.5% for normal and high creatine concentrations. The enzymatic method was preferred over the conventional alkaline picrate (Jaffe) reaction due to possible interference from seminal plasma autofluorescence in the Jaffe reaction. Validation of the enzymatic creatinine assay in seminal plasma was investigated by two means. In one, serial dilution of high values using phosphate-buffered saline diluent were re-measured. In the second, mixed

dilution experiments combined various fractions (3:1, 2:1, 1:1, 1:2, 1:3) of two pools, comprising pooled semen samples with high or low creatinine concentrations, respectively, and comparing measurements with the expected concentrations based on direct measurement of the high and low pools.

2.3 | Data analysis

Descriptive data are presented as mean and standard error of the mean with quartiles and range and Pearson linear correlations using NCSS 2022 software (NCSS, Kaysville, Utah, ncss.com).

The volume of urine in the semen sample was calculated by dividing creatinine content of seminal plasma by the creatinine concentration in the corresponding urine sample. The creatinine content of the seminal plasma is the seminal plasma creatinine concentration (SPc, μmol/L) multiplied by the semen volume (V. mL) and divided by the urine creatine concentration (Uc, μmol/L) with adjustment for volume units.

$$\text{Urine volume in seminal plasma} = \text{SPc}^{*}\text{V}/\text{Uc}.$$

3 | RESULTS

The primary study cohort of 27 men is described in Table 1. Age did not correlate significantly with any other semen or urine variable.

In the extended cohort of semen samples from 50 men, after adjustment for abstinence interval, semen creatinine concentration was significantly correlated positively with sperm concentration, sperm output, rapidly progressive motility and negatively with age and non-progressive motility (Table 2).

The creatininase enzymatic method showed strong linearity in serial dilutions of high values as well as high correlation ($r = 0.9996$) between measured and expected values in mixture dilutions (Figure 1).

Median seminal plasma creatinine was 1.3% of concurrent urine creatine concentration but there was no correlation between seminal and urine creatinine concentration ($r = -0.1$, $p > 0.5$). The calculated volume of urine in seminal plasma was a median of 52 μl (IQR 18, 82 μl) (Table 1).

In a wider sampling of seminal plasma with more complete semen analysis data (Table 2), seminal plasma creatine was correlated significantly with sperm concentration and output as well as progressive

TABLE 1 Calculation of urine volume from semen and urine creatinine

	n	Mean (SEM)	Median	Q1, Q3[a]	Min, max[b]
Age	27	36.6 (1.0)	36	32, 42	28, 46
Semen volume (ml)	27	3.4 (0.3)	3.1	2.4, 4.3	0.7, 7.0
Semen creatinine (μmol/L)	27	214 (24)	178	139, 288	69, 623
Urine creatinine (mmol/L)	27	14.8 (1.5)	13.8	8.9, 18.3	3.7, 41.2
Semen creatinine (μmol)	27	0.72 (0.09)	0.60	0.37, 0.90	0.05, 2.18
Urine volume (μl)	27	72 (21)	52	18, 82	4, 589

[a]Q1 and Q3 are the first and third quartiles of the distribution.
[b]Range of data expressed as Min (minimum) and Max (maximum).

TABLE 2 Semen creatinine and semen analysis variables

	n	Mean (SEM)	Median	Q1, Q3[a]	Min, Max[b]	*R*[c]
Age (years)	50	35.6 (0.8)	35	32, 39	20, 49	**−0.25**
Semen creatinine (μmol/L)	50	288 (52)	159	130, 271	93, 2,176	1.00
Abstinence (days)	50	4.2 (0.7)	3	2, 4	1, 34	--
Semen volume (mL)	50	3.9 (0.2)	3.8	3.1, 4.6	1.5, 7.1	−0.22
Sperm concentration (M/mL)	48	59 (7)	59	13, 86	0, 171	**0.44**
Sperm output (M)	48	222 (25)	216	67, 353	0, 702	**0.28**
Rapidly progressive motility (%)	50	16 (1.4)	18	10, 24	0, 34	**0.42**
Slowly progressive motility(%)	50	23 (1.4)	26	22, 28	0, 36	−0.19
Non-progressive motility (%)	50	12 (1)	13	9, 17	0, 23	**−0.29**
Vitality (%)	47	75 (4)	82	74, 87	0, 95	0.13
Normal morphology (%)	47	4.6 (0.4)	4	3, 6	0, 13	**0.32**
Motility index	50	107 (6.7)	123	104, 136	0, 165	**0.32**
Teratozoospermia index (TZI)	47	1.40 (0.06)	1.52	1.48, 1.55	0, 1.65	−0.19

Note: M is million.
[a]Q1 and Q3 are the first and third quartiles of the distribution.
[b]Range of data expressed as Min (minimum) and Max (maximum).
[c]Linear correlation adjusted for abstinence interval with seminal creatinine concentration with significant ($r \geq 0.24$, $p < 0.05$) values in bold.

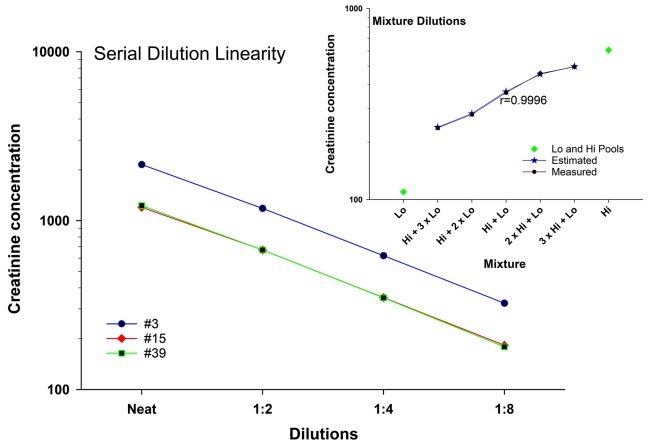

FIGURE 1 Validation of enzymatic creatininase assay for seminal plasma. Main panel—Three seminal plasma samples (#3, #15, #39) with the highest creatinine measurements in neat sample plus serial dilutions (1:2, 1:4, 1:8) in phosphate-buffered saline showing strong linearity of measurements. Note log scale on y axis. Inset panel—Mixed dilutions of seminal plasma composed of various mixtures of pools composed of low (lo) and high (hi) seminal plasma creatinine samples. Pool values are shown in separate green symbols. The mixtures examined were hi and lo in the volume: Volume ratios 1:3, 1:2, 1:1, 2:1, and 3:1 showing a high linear correlation ($r = 0.9996$) between measured and expected creatinine measurements. Note log scale on y axis [Colour figure can be viewed at wileyonlinelibrary.com]

motility and normal forms but no other semen analysis variables. Stepwise regression showed that, after addition of sperm concentration, no other semen analysis variables remained significant predictors of seminal plasma creatinine. Partial correlation adjusting for age did not change the significant correlations.

4 | DISCUSSION

The present study shows that, using a validated enzymatic measurement of creatinine in seminal plasma, there remains a small residual volume of urine (median 52 μl) present in the average seminal ejaculate immediately after ejaculation. How long this small volume of residual urine remains after ejaculation was not determined in this study. That would depend on the balance between the capillary action of fluid remaining in a flattened urethral muscular tube working against distal, gravity-driven drainage of residual urine exiting the urethral orifice, facilitated by the pseudostratified urethral epithelium that promotes smooth fluid flow. A complementary approach of measuring seminal plasma contamination of urine has been recently suggested by measuring semenogelin, an endogenous seminal protein originating exclusively within the reproductive tract, in urine samples.[14]

Creatinine is produced within muscle and excreted by the kidneys so is measurable in both serum and urine. In addition to its wide usage in evaluating renal function in kidney diseases, creatinine is also used to index and adjust calculations of renal excretion of other analytes (e.g., protein, albumin, and drugs). Accordingly, in this study, we used creatinine as a tracing metric for urine volume from concurrently measured concentration of creatinine in urine and seminal plasma. Few previous studies have reported measuring creatinine in semen samples[15–17] but none measured urine creatinine concurrently to quantify urine content of semen samples. One study of eight men after resection of the bladder base displayed pathological leakage of urine into the ejaculate[17] whereas the present study investigated men with normal bladder base sphincter function. Two studies used the alkaline picrate (Jaffe) method to measure creatinine[15,17] while the third did not specify analytical methodology.[16] Our present findings support the validity of the enzymatic method for seminal plasma, considered the most accurate chemical method for creatinine measurement.[12,13] By contrast the alkaline picrate method may be subject to interference from seminal plasma autofluorescence which is well known in forensic medicine for identifying semen when sperm cannot be identified due to its high content of endogenous chromogens.[18]

Assumptions underlying the present approach includes that creatinine in urine is a convenient, easily measured distinctive tracer for urine content of seminal plasma. Seminal fluid is derived from the seminal vesicles (60%), with a lesser fraction from the prostate (30%), and the remainder from the testis, epididymis, and minor sex accessory glands (10%). The present calculations assume that the testis, seminal vesicles, and prostate secrete no significant amounts of creatinine directly into seminal fluids so that creatinine in semen reflecting purely urine contamination. This assumption could be evaluated by examining seminal plasma creatinine before and after vasectomy; however, to our knowledge, there are no such studies. Nevertheless, it seems a reasonable assumption consistent with the use of creatinine as a tracer for urine in other biomedical and research applications.

A drug appearing in seminal fluid must be secreted from the seminal vesicles and/or prostate although modeling to quantifying this distinction is complex.[19,20] Semen drug concentrations may depend on the drug's lipid solubility and its acid/base status, with the latter causing "ion trapping" within seminal plasma. Seminal vesicle secretions are alkaline, favoring entry of lipid-soluble acidic drugs, whereas prostatic secretions are acidic, favoring entry of lipid-soluble basic drugs. Once in seminal fluid, these drugs become "trapped" by seminal fluid pH.[21] Nevertheless, prediction models based on these considerations overestimate drug concentrations in semen[5,6] and more comprehensive pharmacokinetic data is required to strengthen such predictive models.

From more than 20,000 drugs with FDA marketing approval (https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance), fewer than 60 are reported to have been measured in semen (Supplementary Information Table 1). With few exceptions,[19,20,22] this is usually with only single or very few timepoint concentrations measured in seminal plasma using measurement methods of uncertain validity for that biological matrix. Among drugs reportedly measured in seminal plasma, only two (cocaine, amphetamine) are on the WADA Prohibited List but many others used illicitly, especially synthetic androgens, have rarely if ever had seminal plasma measurements.

Endogenous steroids, including androgens, estrogens, and glucocorticoids together with their precursors and metabolites, are produced within the reproductive tract and are thereby measurable in seminal plasma but without entering seminal fluid from exogenous sources.[23,24] Exogenous synthetic steroids measured in seminal plasma are reported for a synthetic progestin dienogest[11] together with statements in marketing product information (without peer-reviewed publication) of some others (mesterolone, dutasteride).

Obtaining semen for clinical research from healthy volunteers not concerned about their fertility is notoriously difficult with a low acceptance rate[25,26] making it very difficult to gather sufficiently intensive multiple sampling for conventional pharmacokinetic modeling.[19,20,22] As a result, most studies reporting seminal plasma drug measurements involve a single or a few timepoints. A common simplification for the limited sample availability has been using ratios of drug concentration in semen versus blood or urine. However, delays in tissue transit and/or accumulation of drug and/or its metabolites in a noncirculating compartment, characteristic of differences between pharmacokinetics in blood and urine, may dictate that the time-course of drugs in seminal plasma would be delayed at least relative to blood leading to variability in the seminal plasma/serum ratios with time. Whereas drug concentrations in blood typically rise steeply to a peak and then slowly decline over time, the arbitrary chosen time of a single semen sample makes a large difference to the apparent ratio of semen to blood drug ratio. Conversely, where there is apparent synchronicity of drug appearance between semen and blood,[11] the present study suggests that this may be at least partially due to urine contamination of semen. Future studies of drug concentrations in semen should also consider the concurrent urine content of the seminal plasma.

Key issues remain to be clarified for inadvertent sexually transmitted doping include (a) the pharmacokinetics of prohibited substances and/or their metabolites in semen, adjusted for residual urine contamination, (b) estimating a time interval after partner's latest ingestion of a prohibited substance when detection in the athlete's urine could not be considered a plausible scenario (vs. athlete's ingestion), (c) the time-course and effectiveness of vaginal or anal (vs. oral) absorption of drugs in semen and (d) the possibility of homosexual transmission involving non-vaginal semen deposition.

The practical application of the present findings in anti-doping is likely to be mainly in evaluation of the plausibility of sexually transmitted doping according to the temporal sequence of prohibited drug ingestion relative to the pharmacokinetics of drug and/or its metabolites. Such calculation will usually be based mainly on urine pharmacokinetics if such data is available. Future analytical research on semen drug pharmacokinetics should consider the impact of residual urine contamination to define the seminal plasma content more accurately.

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CONFLICT OF INTEREST

No author has a relevant disclosure.

DATA AVAILABILITY STATEMENT

Data generated can be made available on reasonable request to the corresponding author

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ENDNOTE

* Reference to semen means the ejaculated fluid, investigated after coagulation and liquefaction. Seminal plasma is the liquefied post-coagulum fluid obtained after centrifugation to remove sperm and cellular debris.

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