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Evaluation and analytical validation of a handheld digital refractometer for urine specific gravity measurement

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ABSTRACT

Objectives: Refractometers are commonly used to determine urine specific gravity (SG) in the assessment of hydration status and urine specimen validity testing. Few comprehensive performance evaluations are available demonstrating refractometer capability from a clinical laboratory perspective. The objective of this study was therefore to conduct an analytical validation of a handheld digital refractometer used for human urine SG testing.

Design and methods: A MISCO Palm Abbe[™] refractometer was used for all experiments, including device familiarization, carryover, precision, accuracy, linearity, analytical sensitivity, evaluation of potential substances which contribute to SG (i.e. "interference"), and reference interval evaluation. A manual refractometer, urine osmometer, and a solute score (sum of urine chloride, creatinine, glucose, potassium, sodium, total protein, and urea nitrogen; all in mg/dL) were used as comparative methods for accuracy assessment. *Results:* Significant carryover was not observed. A wash step was still included as good laboratory practice. Low imprecision (%CV, < 0.01) was demonstrated using low and high QC material. Accuracy studies showed strong correlation to manual refractometry. Linear correlation was also demonstrated between SG, osmolality, and solute score. Linearity of Palm Abbe performance was verified with observed error of ≤ 0.1%. Increases in SG were observed with increasing concentrations of albumin, creatinine, glucose, hemoglobin, sodium chloride, and urea. Transference of a previously published urine SG reference interval of 1.0020–1.0300 was validated.

Conclusions: The Palm Abbe digital refractometer was a fast, simple, and accurate way to measure urine SG. Analytical validity was confirmed by the present experiments.

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Abbreviations: ; *ACSM*, American College of Sports Medicine; *ALB*, albumin; *AMR*, analytical measurement range; *ARUP*, Associated Regional & University Pathologists; *Cl*, chloride; *CLSI*, Clinical & Laboratory Standards Institute; *CR*, creatinine; *CV*, coefficient of variation; *ddH2O*, demineralized distilled water; *FDA*, Food and Drug Administration; *GLU*, glucose; *IRB*, Institutional Review Board; *K*⁺, potassium; *LIMS*, laboratory information management system; *LLMI*, lower limit of the measuring interval; *LOB*, limit of blank; *LOD*, limit of detection; *LOQ*, limit of quantitation; *Na*, sodium; *NATA*, National Athletic Trainers Association; *NCAA*, National Collegiate Athletic Association; *POC*, point of care; *QC*, quality control; *RI*, reference interval; *SAMHSA*, Substance Abuse and Mental Health Services Administration; *SD*, standard deviation; *SG*, specific gravity; *TAE*, total allowable error; *TE*, total error; *TP*, total protein; *UN*, urea nitrogen

1. Introduction

Specific gravity (SG) is the ratio of the density of a substance (e.g. a fluid) to the density of a standard (e.g. distilled water). SG of a solution is affected by the number and molecular weight of all solutes present [1–3]. While the generally accepted clinical standard for accurate measurement of urine concentration is osmolality [2–4], osmometers are expensive and are neither integrated into routine urinalysis instruments nor available as point of care (POC) devices. SG is therefore commonly used as a surrogate initial assessment of urine concentration.

In routine clinical laboratory settings, SG measurements are commonly performed using either refractometry or reagent strip methods. With reagent strip determination of SG, observed color change is due to the changes in the pKa and ionic strength [5–7]. Refractometers measure a solution's refractive index (i.e. the ratio of the refraction of light in air versus the urine specimen), which is affected by solute concentration [1,6]. Colorimetric SG assays are available on automated chemistry analyzers (and infer SG based on chloride concentration [8] or changes in ionic strength [9,10]), although they are generally only used for specimen validity screening purposes. Refractometers may either be integrated into urinalysis instruments, or alternatively as separate manual or digital devices. Superior performance of refractometers (versus reagent strips) for the assessment of urine SG has been demonstrated in many previous reports [11–17].

Along with clinical patient management, SG measurements by refractometry are also commonly used in: (a) specimen validity testing for the identification of adulterated and diluted specimens (e.g., U.S. Federal workplace drug testing) [18], and (b) the assessment of hydration status in athletes [19–23]. While most refractometers are exempt from FDA-premarket notification as Class 1 devices [24], the need for thorough verification of device analytical performance is still imperative, as SG results may clearly impact employment, eligibility for athletic competition, and accurate assessment of hydration status in health and disease. The purpose of the present investigation was therefore to conduct a thorough performance evaluation and clinical laboratory validation of a refractometer (Palm AbbeTM model PA202X; MISCO; Solon, OH). This particular device was chosen as it is small ($5.7 \times 2.95 \times 1.46$ in.) [25], handheld, and battery operated ($2 \times$ AAA batteries), thus it is potentially operable in most laboratory, field use, and/or point of care (POC) settings. Additionally, digital result display eliminates subjective interpretation observed with manual refractometry.

2. Materials and methods

A Palm Abbe[™] model PA202X (Fig. 1) was used as the digital refractometer for all experiments using a human urine SG scale (D20/20, #093) [26]. The Palm Abbe reports SG to 4 decimal places (e.g. 1.0000). While the device supports automatic



Fig. 1. Palm Abbe Model PA202X Digital Refractometer. The refractometer includes a blue lid (A) to minimize evaporation and exclude ambient light. Sapphire optics (B) used for SG measurement are located in the center of a stainless steel well. SG results (to four decimal places) are displayed on an LCD screen (C). Scale bar=1 in. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

temperature compensation [25], all studies were conducted with the instrument and materials at ambient temperature (room temperature monitored daily) to preclude the need for specimen temperature equilibration delays. All four authors participated in the validation studies as instrument operators.

2.1. Specimens

Using an Institutional Review Board (IRB)-approved protocol (University of Utah IRB Protocol #0007275), previously tested clinical urine specimens at ARUP Laboratories (Salt Lake City, UT) were obtained from frozen storage (-20 °C) and deidentified for use in validation experiments. Urine specimens obtained from apparently healthy donors (collected using IRB Protocol #0007740) were also used for reference interval (RI) verification studies.

2.2. Device familiarization

Instrument familiarization studies consisted of running low and high SG quality control (QC) material (qUAntify[®] Plus Control 962x; Bio-Rad Laboratories, Inc.; Hercules, CA) in 10 replicates each. Familiarization studies were used to determine acceptable QC ranges for the duration of the studies.

2.3. Minimum Volume

Minimum volume studies were conducted using low SG material (dilute urine pool) and high SG material (5% sodium chloride (NaCl) in demineralized distilled water (ddH₂O)). 11 sample volumes were tested (5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 μ L); each volume was tested with 4 replicates for both low and high SG material.

2.4. Carryover

Carryover was evaluated using: (a) low and high SG QC material (qUAntify[®] Plus Control 962x), and (b) patient urine pools with low and high SG. Carryover studies were conducted using the following test order: low, high, low (4 replicates of each set).

2.5. Precision

Precision experiments were conducted over 20 days, with 2 runs daily (run=duplicates of each QC concentration separated by at least 2 h) using commercially available qUAntify[®] Plus Control 962x QC material.

2.6. Accuracy

Accuracy experiments were conducted using residual patient urine specimens spanning the analytical measurement range (AMR) of four previously tested urine solutes: chloride (Cl^- ; n=20), glucose (GLU; n=20), creatinine (Cr; n=20), and total protein (TP; n=20), for a total of 80 specimens. Specimens were tested over 5 days (n=16 per day) on both the Palm Abbe and a manual refractometer (URC-NE: Atago; Tokyo, JP) performed in duplicate on both instruments, with reverse order between duplicate runs (i.e., first run 1,2,3,4; second run 4,3,2,1). Within the same freeze thaw cycle all specimens were also tested in singlicate for urine osmolality (Advanced[®] Model 3250, Advanced Instruments; Norwood, MA), as well as for Cl⁻, Cr, GLU, potassium (K⁺), sodium (Na⁺), TP, and urea nitrogen (UN) measured on a cobas 8000 system (Roche Diagnostics; Indianapolis, IN) using Roche reagents. The primary evaluation of accuracy was determined by comparison of Palm Abbe SG results to SG from the manual refractometer. Between-method outliers (n=2) identified by StatisProTM 2.51 (a partnership of the Clinical and Laboratory Standard Institute (CLSI), Wayne, PA & Analyze-it® Software, Leeds, UK) were repeated on both platforms prior to analysis. Data are plotted as the mean result of duplicate values. Two methods of alternative evaluation included: (1) comparison to urine osmolality, and (2) comparison to a solute score defined as the sum of urine Cl⁻, Cr, GLU, K⁺, Na⁺, TP, and UN (all converted to mg/dL). The following standard deviations (SD) were used in Deming regression: Palm Abbe, SD 0.00009 (from low concentration precision study, present report); solute score, SD 38.6 mg/dL (sum of all component SDs from individual precision studies in prior method validations, data not shown); osmolality, SD 1.7 mOsm (average SD across 3 levels daily QC over 2 months, data not shown); manual refractometry, SD 0.000492 (SD of 6 months daily QC, data not shown).

2.7. Linearity

Linearity was assessed using high patient urine pool diluted with either low patient urine pool or ddH₂O at 11 dilutions (0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%). All dilutions were tested in triplicate in alternating orders. Assigned SG was based on percent-split dilution from original high SG pool and low SG (or ddH₂O) pools.

2.8. Analytical sensitivity

Since there is no true "zero" concentration material available in regards to SG (ddH₂O has an SG of 1.0000 by definition), conventional limit of blank (LOB) and limit of detection (LOD) studies were not feasible. To assess the limit of quantitation (LOQ), 8 specimen pools spanning the entire AMR were prepared using human urine and diluting with ddH₂O or spiking with NaCl. ddH₂O was also used to evaluate the lowest measurable SG. For each pool (as well as ddH2O), the "reference" SG value was established for each specimen using a manual refractometer and taking the mean SG determined by 4 operators testing each specimen in duplicate. Each specimen was tested in triplicate for 3 consecutive days using the Palm Abbe. The "observed" mean and SD are derived from these Palm Abbe measurements. Data was analyzed using the Westgard model: Total Error (TE)=|Bias|+2 SD. The TE(%)=(TE ÷ reference mean) × 100. The threshold used for acceptable percent total allowable error (TAE%) for urine SG was \pm 0.6% [27]. Results provided from analytical sensitivity experiments were rounded to 4 decimal places, except TE(%) which was rounded to 2 decimal places.

2.9. Solute contribution to SG

Traditional CLSI-based interference testing was not applicable, as by definition all dissolved solutes contribute to SG depending on their concentration and molecular weight. Alternate experiments evaluating the extent of SG changes with increasing concentration of common urine solutes – albumin (bovine ALB; AMRESCO; Dallas, TX), Cr (Sigma Aldrich; St. Louis, MO), human hemoglobin (Hb; Sigma Aldrich), NaCl (BDH Chemicals, VWR; Radnor, PA), anhydrous p-glucose (VWR), and urea (Sigma Aldrich) – were therefore conducted. Bovine source ALB was chosen due to decreased cost and similar molecular weight (~ 66.5 kDa) to human albumin. Reconstituted human Hb was found to be in methemoglobin form [not detectable by Roche cobas 8000 H indices which use 600/570 nm wavelengths, but quantifiable by a COULTER Ac \cdot T diff2 analyzer (Beckman Coulter; Brea, CA) using a cyanmethemoglobin method]. As hemolysate contains all RBC constituents (in addition to Hb) it was not appropriate for the present studies, as any additional solutes would also contribute to SG. Experiments were performed with serial dilutions (n=5) with solutes dissolved in a dilute urine pool matrix (baseline SG 1.0007).

2.10. Reference intervals (RIs)

Transference of a previously published SG RI for random urine collections [28], SG 1.0020–1.0300, was evaluated according to CLSI EP28-A3c guidelines [29] using 20 urine samples from healthy adult donors (gender not specified). Data was analyzed using the Verification of Reference Interval module in EP Evaluator[®] 10 (Data Innovations; South Burlington, VT).

2.11. Data analysis

Data was analyzed using EP Evaluator, StatisProTM 2.51, Microsoft Excel 2010 (Redmond, WA), and SigmaPlot 11 (Systat). Data is presented as mean \pm standard deviation (SD) unless otherwise indicated. Graphs were prepared using SigmaPlot.

3. Results

Familiarization studies demonstrated ease of instrument operation. As the device manufacturer provides general advice for specimen volumes ("a few drops" in the instruction manual; 0.3 mL minimum volume in accompanying specifications table) [25], volume studies were conducted to establish and validate a recommended minimum specimen volume. Increased

Table 1

Minimum volume studies.

	LOW SG POOL	LOW SG POOL			HICH SG POOL		
Volume (µL)	Average	SD	%CV	Average	SD	%CV	
5	1.0027	0.0007	0.0737	1.0233	0.0002	0.0187	
10	1.0028	0.0003	0.0262	1.0236	0.0000	0.0000	
20	1.0030	0.0000	0.0050	1.0233	0.0000	0.0049	
30	1.0029	0.0001	0.0150	1.0234	0.0000	0.0049	
40	1.0030	0.0000	0.0050	1.0234	0.0000	0.0000	
50	1.0030	0.0000	0.0000	1.0234	0.0000	0.0049	
60	1.0030	0.0001	0.0050	1.0234	0.0000	0.0049	
70	1.0030	0.0000	0.0050	1.0234	0.0000	0.0000	
80	1.0030	0.0000	0.0000	1.0234	0.0000	0.0000	
90	1.0030	0.0000	0.0050	1.0234	0.0000	0.0000	
100	1.0030	0.0001	0.0050	1.0234	0.0001	0.0056	

Table 2
Imprecision.

Material	Mean SG of material	Total imprecision (SD)	Total imprecision (%CV)	Within run (SD)	Between run (SD)	Between day (SD)
Low QC	1.0093	0.00009	< 0.01	0.00008	0.00000	0.00004
High QC	1.0180	0.00008	< 0.01	0.00007	0.00001	0.00005

imprecision was observed using low specimen volumes (Table 1), particularly with the low SG pool. Consistent SG measurements could be obtained at approximately 60 μ L. It should be noted that erroneous results were sometimes observed when bubbles were present (not shown), therefore our minimum recommended volume was set at 60 μ L (with no bubbles).

Carryover was not observed in low-high-low QC studies which did not include a ddH2O wash step. Introduction of a wash step between measurements did not have any adverse effect. Carryover was also not observed using low-high-low studies of patient urine pools (including a wash step). As good laboratory practice, a ddH2O wash step was included in our procedure and all subsequent experiments.

Results from precision studies are shown in Table 2. Very low total imprecision was demonstrated using both low QC (% CV, <0.01) and high QC (%CV, <0.01) material. Overall precision estimates (SD, in SG "units") were better than manufacturer claims (SG \pm 0.0005) [26]. These precision estimates (within run, between run, between day) shown in Table 2 are also all below the minimum resolution of the device (SG 0.0001).

Accuracy studies (Fig. 2A) demonstrated strong correlation to manual refractometry with a slight negative absolute bias (Fig. 2B) and percent bias (Fig. 2C) versus the more subjective manual method (Deming regression, y=0.979x+0.02, r=0.998; absolute bias, -0.00116; percent bias, -0.1%; n=80 specimens, Palm Abbe SG range 1.0039-1.0293). The two outliers identified by StatisPro (see *Methods*) that were repeated prior to statistical analysis were due to discordant manual refractometry results (Specimen A - initial 1.015, repeat 1.025; Specimen B - initial 1.016, repeat 1.026), while the digital refractometer results were consistent between initial and repeat measurements. Outliers were attributed to either in-adequate specimen mixing, operator interpretation error, or result transcription error.

Linear correlation was also observed between Palm Abbe results and the solute score (Fig. 2D; Deming regression, y=0.000095x+1.0003, r=0.875), providing independent evidence that increasing Palm Abbe SG results indeed reflect increasing concentrations of dissolved solutes. As further confirmation, similar linear correlation was also observed between Palm Abbe results and urine osmolality (Fig. 2E; Deming regression, y=0.0000239x+1.0029, r=0.868). Manual refractometry results also correlated to urine osmolality (Fig. 2F; Deming regression, y=0.0000221x+1.0052, r=0.828).

Linearity of Palm Abbe performance was verified using high patient urine pools diluted with either low patient urine pools (Fig. 3A; slope=0.991, r=0.999; measuring range SG 1.0060–1.0418) or ddH₂O (Fig. 3B; slope=0.996, r=0.999; measuring range SG 1.0001–1.0418). Observed error was $\leq 0.1\%$.

Analytical sensitivity experiments demonstrated acceptable TE(%) (defined as < 0.6% TAE(%)) [27] at all SG levels tested (Table 3). The Lower Limit of the Measuring Interval (LLMI) was therefore set at 1.0000.

To evaluate the extent of SG changes due to increasing solute concentration, serial dilution studies were conducted using solutes commonly observed at widely varying concentrations in the urine (Fig. 4). These include ALB, Cr, GLU, Hb, NaCl, and urea. As expected, increasing concentrations of solute increased SG in a linear fashion (Fig. 4 and Table 4).

RIs were evaluated using 20 random urine specimens from healthy donors. Transference of a previously published RI [28] for random urine (SG 1.0020–1.0300) was validated using these specimens. The average SG of random urine specimens from these donors was 1.0140 ± 0.0073 (range: SG 1.0043–1.0332).

4. Discussion

Experiments demonstrated acceptable clinical laboratory performance of the Palm Abbe handheld digital refractometer for urine SG, including carryover, precision, accuracy, linearity, analytical sensitivity, and reference interval verification. A characterization of solute contribution to SG was completed and can be used to predict SG changes due to increases in individual solutes.

The instrument worked reliably with small volumes of specimens (60 μ L), which is important in settings where specimen volume may be limited (e.g., laboratories dependent on low-volume aliquots). We did not encounter ambient lighting-related difficulties (which others have reported with digital refractometers) [30], presumably because the Palm Abbe has a sample cover which is closed prior to measurement. No scratches to the sapphire optics were observed over the course of our experiments. We did not achieve the refractometer battery life reported in MISCO specifications (\sim 3500+ readings) [25], although heavy use in these validation studies may not represent typical operation. Furthermore, this was easily rectified with replacement AAA batteries.

Our analytical sensitivity experiments demonstrated acceptable TE(%) for low SG measurements (Table 3). Given the ability of the Palm Abbe to calibrate to water and the very low TE(%) observed at extremely low SG levels, we have set our lower limit of the measuring interval (LLMI) to SG 1.0000. While physiologically there is little reason to ever expect SG results that low in unadulterated human urine, we choose this LLMI to minimize the risk of manual decimal place



Fig. 2. Accuracy. A. Comparison of Palm Abbe (y-axis) versus manual refractometry (x-axis) results. Solid line is unity; dotted line is Deming regression. B. Absolute bias (in SG "units") of Palm Abbe versus manual refractometry. Solid line is zero bias reference; dotted line is absolute bias. C. Percent bias of Palm Abbe versus manual refractometry. Solid line is zero bias reference; dotted line is percent bias. D. Correlation between Palm Abbe SG results and the solute score (in mg/dL). Dotted line is Deming regression. E. Correlation between Palm Abbe SG results and urine osmolality (mOsm). Dotted line is Deming regression. F. Correlation between manual refractometry SG results and urine osmolality (mOsm). Dotted line is Deming regression.



Fig. 3. Linearity. Linearity results plotted for (A) high SG patient urine pools diluted with low SG patient urine pools or (B) high patient urine pools diluted with ddH₂0. Solid lines are linear regression (extended to axes in A). Error bars (\pm SD) are hidden behind data points; too small to visualize.

Table 3.Analytical sensitivity.

Specimen	Reference mean SG	Observed mean SG	Observed SD	Bias	TE	TE (%)
1 ^a	1.0000	1.0000	0.0000	0.0000	0.0000	0.00
2 ^b	1.0003	1.0002	0.0001	-0.0001	0.0004	0.04
3 ^b	1.0014	1.0012	0.0002	-0.0002	0.0005	0.05
$4^{\rm b}$	1.0026	1.0022	0.0002	-0.0004	0.0008	0.08
5 ^b	1.0060	1.0052	0.0001	-0.0008	0.0010	0.10
6 ^b	1.0110	1.0101	0.0002	-0.0009	0.0012	0.12
7 ^b	1.0210	1.0202	0.0002	-0.0008	0.0012	0.12
8 ^b	1.0311	1.0302	0.0002	-0.0009	0.0013	0.12
9 ^b	1.0408	1.0403	0.0002	-0.0005	0.0009	0.09

^a ddH₂O.

^b Human urine specimen pool; see Section 2.8.

transcription errors (i.e., the reported results would match exactly what is displayed on the digital screen).

Handheld digital refractometers have been described and are widely used in veterinary practice, particularly for assessment of urine concentration in cats and dogs [31–34]. There have been fewer reports describing their use with human urine specimens [23,30], although there are a number of commercially available options including Palm Abbe (MISCO); PEN, UG- α , PAL-10S (Atago); Clinic-Chek, USG-Check, TS METER D (Reichert; Depew, NY).

Similar to our findings in human urine for accuracy compared to manual refractometry (Fig. 2A–C), several veterinary studies have also demonstrated slightly lower results using digital (versus manual) refractometers [32–34]. A similar observation was observed using human urine as SG increases [30]. We have no definitive evidence as to which method is indeed more accurate. Minor differences in results, however, may slightly impact athlete classification into the National Collegiate Athletic Association (NCAA) criteria of *euhydration* (SG \leq 1.020) [19,20,35] and the American College of Sports Medicine (ACSM) & National Athletic Trainers Association (NATA) criteria of *euhydration* (SG 1.000–1.020), *hypohydration* (SG 1.021–1.029), and *significant hypohydration* (SG \geq 1.030) [19,36–38].

Rules for Federal workplace drug testing under the Substance Abuse and Mental Health Services Administration (SAMHSA) require, among other things, specimen validity testing consisting of (at minimum) creatinine and pH on each specimen [18]. Additionally, when creatinine is < 20 mg/dL, SG testing (by refractometry) is required [18]. It should be emphasized that the refractometer used in the present report is not appropriate for SAMSHA Federal workplace testing, as it does not interface with "a laboratory information management system (LIMS), computer, and/or generate a paper copy of the digital electronic display to document the numerical values of the specific gravity test results" [Section 11.18 (b)(2)] [18].

In conclusion, the Palm Abbe handheld digital refractometer was demonstrated to be a fast, simple, and accurate way to measure urine SG. The results from this report may prove valuable for those interested in evaluating handheld digital refractometers for use in a variety of settings.



Fig. 4. Serial Dilution of Common Urine Solutes. Relationship between solute concentration and change (Δ) in SG over baseline urine pool SG for common urine solutes (A, NaCl; B, Cr; C, Urea; D, GLU; E, ALB; F, Hb). Dotted line is linear regression. Error bars (± SD) are hidden behind data points; too small to visualize.

Table 4.					
Serial dilution	studies	of	common	urine	solutes.

Solute	Units	Intercept	Slope	r	Predicted Δ SG
NaCl	mM	0.0012730	0.0000239	0.998	+0.0239 per 1000 mM NaCl
Cr	mg/dL	0.0002460	0.0000051	0.999	+0.0051 per 1000 mg/dL Cr
Urea	mg/dL	0.0007299	0.0000033	0.999	+0.0033 per 1000 mg/dL Urea
GLU	mg/dL	0.0008066	0.0000033	0.999	+0.0033 per
ALB	mg/dL	0.0007968	0.0000043	0.999	+0.0043 per
Hb	mg/dL	0.0000412	0.0000042	0.999	+0.0042 per 1000 mg/dL Hb

Conflict of interest

None.

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