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Point-of-Care Glucose and Lipid Profile Measures Using a Human Point-of-Care Device in Mouse Models of Type 2 Diabetes Mellitus, Aging, and Alzheimer Disease

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A point-of-care (POC) device to measure mouse glucose and lipid profiles is an important unmet need for cost-effective, immediate decision making in research. We compared metabolic analyte profiles obtained using a human clinical POC device with those from a veterinary laboratory chemical analyzer (LCA). Unfasted terminal blood samples were obtained by cardiac puncture from C57Bl/6J mice used in a diet-induced obesity model of type 2 diabetes mellitus; age-matched C57Bl/6J controls; a transgenic mouse model of Alzheimer's disease on a C57BL/6J background (16 wk old); and aged C57BL/6J mice (24 to 60 wk old). Aliquots of the blood were immediately assayed onsite using the POC device. Corresponding serum aliquots were sent analyzed by LCA. Measures from the POC and LCA devices were compared by using the Bland–Altman and Passing–Bablok methods. Of a total of 40 aliquots, LCA results were within reported reference ranges for each model. POC results that fell beyond the device range were excluded from the analyses. The coefficient of determination and Passing–Bablok analysis demonstrated that POC glucose and HDL had the best agreement with LCA. The Bland–Altman analysis found no value-dependent bias in glucose and no significant bias in HDL. The remaining lipid analytes (cholesterol and triglyceride) showed significant bias. Until an improved, validated mouse POC device with lipid profile capability is available, the POC device that we tested appears adequate for screening glucose and HDL in mouse blood. Disadvantages of this clinical POC device are the narrow human ranges relative to ranges found in mice and its limited precision as compared with the LCA. This study demonstrates that when the samples are within the device range limits, this human POC device can accurately track metabolic syndrome and be used to compare patterns in glucose and HDL.

Abbreviations: AD, Alzheimer disease; DIO, diet-induced obesity; LCA, laboratory clinical analyzer; POC, point-of-care; T2DM, type 2 diabetes mellitus

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During the last few decades, clinical point-of-care (POC) testing technology has been a fast-growing field with a variety of medical applications. The benefits of POC devices include streamlining the treatment process, reducing lab costs, and operating in low resource environments.[13] In the domains of diagnostic testing and disorders requiring continuous monitoring, POC devices fill a gap in healthcare that provides better patient experiences and quality of care.

Currently a limited number of POC devices have been designed for veterinary use,[9,16,23] and only a few of the available human clinical POC devices have been tested for accuracy when used in preclinical animal models.[10,16,22,23] The ability to conduct a POC analysis for type 2 diabetes mellitus (T2DM) and aging mice would provide several benefits to animal research, including diagnostic test convenience and immediate results. POC testing requires only a small blood volume of 5 to 40 µL, thus simplifying the blood collection process and allowing repeated and frequent sampling from each subject. Finally, use of POC devices provides a less costly alternative to the cost of a laboratory clinical analyzer (LCA) or a contract with a commercial veterinary laboratory. Within the past few years, several POC devices for human use have been modified and further developed to become self-testing devices for blood oxygen, continuous glucose monitoring, lipid profile or analytes such as lactate, creatinine, cholesterol, uric acid, hemoglobin, and illicit drugs.[4,21] However, none of these extended POC devices have been assessed for use in mice.

Our laboratory studies mouse metabolic models of T2DM, aging, and Alzheimer disease (AD). To track diabetes severity and determine on the onset of a metabolic syndrome, the mice undergo frequent longitudinal glucose and lipid profile screening, which requires methodologies that require a very small blood sample for each draw.[7] The present pilot study evaluates a recently developed human POC device that can measure glucose and a full lipid profile for its utility in mice. Groups of mice with normal and abnormal glucose and lipid profiles were used to test the full range of potential results. Our analysis compares values obtained with the POC device and with a veterinary LCA (as a 'gold standard').

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Materials and Methods

Research compliance. All experiments were approved by the Committee on the Use and Care of Animals at Washington University (St Louis, MO). All procedures were performed in AAALAC-accredited facilities and in accordance with the *Guide for the Care and Use of Laboratory Animals*.[7]

Mice. Four groups of male mice were used for this study: 1) 15 diet-induced obesity (DIO) C57BL/6J mice (a model of T2DM), tested at 10 to 21 wk old; 2) 16 C57 controls age-matched to the DIO mice, tested at 12 to 21 wk old; 3) 5 5XFAD mice (complete nomenclature is B6SJL-Tg [APPSwFlLon,PSEN1*M 146L*L286V]6799Vas/Mmjax) on a C57 background (model of AD) tested at 16 wk old; and 4) 4 aged C57 mice tested at 28 to 60 wk old. Mice for groups 1 through 3 were obtained from The Jackson Laboratory (Bar Harbor, ME); group 4 mice were obtained from our inhouse colony. The latter 4 mice were the total number available for this study, based on the criteria of normal/abnormal glucose and lipid profiles due to age and comorbid conditions.

The C57 control mice and the AD mice were fed a normal mouse diet (LabDiet 5053, Richmond, IN). The DIO mice were placed on a high-fat chow (diet no. D12492, 60 kcal% fat; Research Diets, New Brunswick, NJ) at 6 wk of age to induce T2DM. Both the DIO mice and their age-matched C57 controls were housed on aspen bedding (Aspen Chip, Northeastern Products, Warrensburg, NY), due to the propensity of the DIO mice to eat corncob bedding.[9] The AD mice and their controls (the aged C57 mice) were housed on corncob bedding (Bed-o'Cobs, The Andersons, Quakertown, PA).

All 4 groups of mice were housed in solid-bottom, polycarbonate, shoebox-style caging (4/cage) in a HEPA-filtered room with controlled temperature (72 ± 2 °F [22.2 ± 0.5 °C]) and humidity (30% to 70%) on a 12:12-h light:dark cycle. The mice had ad libitum access to irradiated food and autoclaved water. Daily health checks were conducted on all mice.

All mice were free of pneumonia virus of mice, reovirus 3, Sendai virus, *Mycoplasma pulmonis*, minute virus of mice, Theiler murine encephalomyelitis virus, lymphocytic choriomeningitis virus, polyoma virus, mouse rotavirus, ectromelia virus, mouse adenovirus, K virus, mouse parvovirus, Cytomegalovirus, mouse hepatitis virus, *Clostridium piliforme*, *Streptococcus pneumonia, Bordetella bronchiseptica*, *Streptobacillus moniliformis*, *Corynebacterium kutcheri*, *Salmonella* spp., *Citrobacter rodentium*, and murine pinworms and fur mites.

Blood collection and processing. Samples of nonfasted blood were drawn at 12 to 24 wk of age from the DIO mice and their controls, at 20 wk of age from the AD mice, and at 28 to 60 wk of age from the AD control group. Mice were transported to the lab in late morning. Each mouse was anesthetized (tribromoethanol, 250 mg/kg IP), and sufficient blood for analysis (200 to 300 µL) was obtained from the left ventricle via terminal cardiac puncture (22-gauge needle, 1-mL syringe). Blood chemistry analysis was performed on both the onsite POC device (CardioChekPlus, PTS Diagnostics, Indianapolis, IN) and the LCA (model AU480, Beckman Coulter, Brea, CA), performed by Advanced Veterinary Laboratory (St Louis, MO). The POC device was calibrated immediately before use, based on the manufacturer's calibration solutions and protocol.

Blood (5 µL) from the cardiac puncture was immediately applied by capillary action to the POC device's glucose test strip and reported in glucose plasma equivalents. For the lipid profile, blood (50 µL) was injected into the blood application window of each lipid test strip. Plasma was extracted by the test strip's filtration, and analytes were reported in terms of plasma levels.

For the LCA, the remaining blood from the cardiac puncture was placed in a 1.5-mL centrifuge tube without anticoagulants and was centrifuged (704 × *g* for 10 min at 4 °C). The serum was recovered, aliquoted (50 µL) into cryovials, and stored at –70 °C until assay. Storage of serum for up to 90 d at –80 °C was previously shown not to affect the analytes measured in this study.[6,20] Serum samples (50 µL) were diluted to a volume of 150 µL for Beckman analysis with the following reagents: Glucose SL Assay (235-60), Cholesterol-SL Assay (234-99), N-geneous LDL Cholesterol Assay (R1: 80-4598-00, R2: 80-4601-00), and Triglyceride-SL Assay (236-60) (all from Sekisui Diagnostics, Burlington, MA).

Statistical analysis. Analyte measurements from LCA were considered to be the reliable values. The statistical analysis for POC samples included only those values that fell within the quantitation limits of device. After exclusion of those samples, descriptive statistics were calculated and scatter plots were created (JMP, version 14, SAS Institute, Cary, NC). Simple linear regression (POC [*y* axis] compared with LCA [*x* axis]) showed that the relationship of the analyte measurements from the 2 devices could be approximated by a line. The linear relationship allowed further comparisons of discrepancies between the 2 forms of measurement.[3] The similarity of POC and LCA analyte results was determined by calculating the coefficient of determination (r^2). To assess direct exchangeability of measurement values between devices, we further applied the nonparametric Passing–Bablok regression algorithm[18] (MedCalc Statistical Software version 17.8.6, Med-Calc Software, Ostend, Belgium) and the Bland–Altman plotting algorithm[2,3,14] (JMP, version 14, SAS Institute). The level of significance was set to a *P* value of 0.05 or less.

Results

Initial assessment of the POC compared with the LCA in mice. A total of 40 aliquots from normal healthy (n = 20) and metabolically diseased (n = 20) mice was used to compare the POC and LCA devices for glucose and lipid profile analytes (Table 1). Results outside of the POC device range were excluded. The useable number of samples and percentage of usable values for each analyte (n; %) were glucose (34; 85%), cholesterol (20; 50%), HDL (30; 75%) and triglycerides (19; 48%). In general, except for the triglyceride results, the LCA glucose, total cholesterol, and HDL results were higher than results from the POC device (that is, the LCA – POC difference was a positive result, Table 1), as previously reported[12,24] for other POC devices The LCA – POC analyte result differences (in mg/dL; mean ± 1 SD) were: glucose, 37 ± 143; cholesterol, 3 ± 33; HDL, 14 ± 16; and triglycerides, –4 ± 26 (Table 1). The descriptive statistics for the full analyte dataset (included and excluded) are shown in Table 2.

Table 3 lists the normal ranges we measured compared with reported reference ranges.[2,5,7] Our LCA results found that the control C57 mice that we measured were within normal reference ranges[1,8,17] for nonfasting glucose and lipid profile analytes[7,17] consistent with their age (young or aged), weight and health status. In contrast, data from many of the DIO and C57-AD mice showed the expected metabolic derangements indicative of metabolic syndrome (C57-DIO) and hypercholesterolemia (C57-AD).[2,5,7,17]

Comparison of device results. Table 4 shows the statistical analysis of the coefficient of determination (r^2) of POC compared with LCA predictability and our POC feasibility assessment. The r^2 indicates the proportion of variation in the dependent variable that is predicted from the independent variable. The r^2 values calculated for each analyte are as follows: glucose:(0.34, total

Table 1. Data of 40 mouse blood and serum analytes measured via POC and LCA and their differences (in mg/dL)

	Age	Weight	Glucose				Total cholesterol				HDL				Triglycerides			
Group	(wk)	(g)	POC	LCA	Avg	Diff	POC	LCA	Avg	Diff	POC	LCA	Avg	Diff	POC	LCA	Avg	Diff
DIO	16	34.9	572	376	474	196	113	96	105	17	71	46.6	59	24	165	144	155	21
DIO	18	36.8	538	567	553	−29	155	186	171	−31	cens	97.9			56	57	57	−1
DIO	20	38.5	500	598	549	−98	125	147	136	−22	98	76.6	87	21	60	82	71	−22
DIO	20	41.4	343	505	424	−162	164	213	189	−49	cens	83.6			cens	44		
DIO	20	40.1	cens	705			160	191	176	−31	cens	89.9			74	64	69	10
DIO	20	38.6	cens	659			122	189	156	−67	88	80	84	8	cens	79		
DIO	20	50.1	cens	458			152	128	140	24	cens	52.4			67	32	50	35
DIO	20	42.8	552	330	441	222	154	144	149	10	cens	57.4			cens	24		
DIO	21	41.4	343	469	406	−126	164	180	172	−16	cens	66.9			cens	51		
DIO	21	40.1	cens	554			160	193	177	−33	cens	88.4			74	44	59	30
DIO	21	38.6	cens	412			122	147	135	−25	80	60.8	70	19	cens	37		
DIO	21	50.1	cens	202			152	188	170	−36	cens	65.4			67	90	79	−23
DIO	21	43.4	578	451	515	127	151	154	153	−3	cens	58.8			cens	51		
DIO	21	42.8	552	374	463	178	154	198	176	−44	cens	72.9			cens	44		
DIO	21	38.5	500	270	385	230	125	90	108	35	98	39.6	69	58	60	46	53	14
DIO	10	28.8	273	240	257	33	cens	110			50	46.6	48	3	cens	72		
C57	12	23.7	123	153	138	−30	cens	69			46	33.6	40	12	cens	54		
C57	12	24.8	234	144	189	90	cens	87			46	43.2	45	3	55	93	74	−38
C57	18	27.6	152	146	149	6	cens	58			42	33.8	38	8	66	50	58	16
C57	18	22.8	223	146	185	77	cens	58			42	32.8	37	9	58	48	53	10
C57	18	24.7	167	164	166	3	cens	50			36	26.2	31	10	cens	42		
C57	20	27.2	143	204	174	−61	cens	84			37	45.6	41	−9	cens	74		
C57	20	26.7	194	160	177	34	cens	64			39	36	38	3	cens	46		
C57	20	25	237	156	197	81	cens	52			40	28.2	34	12	cens	60		
C57	20	21.7	204	343	274	−139	cens	135			56	76.7	66	−21	63	75	69	−12
C57	21	24.5	202	162	182	40	cens	64			48	44.1	46	4	cens	34		
C57	21	25	237	104	171	133	cens	65			40	40.7	40	−1	cens	27		
C57	21	24.8	71	184	128	−113	cens	82			41	50.3	46	−9	cens	79		
C57	21	26.7	194	640	417	−446	cens	79			39	33.2	36	6	cens	123		
C57	21	27.2	146	191	169	−45	cens	86			55	53.2	54	2	cens	37		
C57	21	27.2	143	172	158	−29	cens	58			37	36.8	37	0	cens	18		
CC57-AD	**16**	**18.2**	305	289	297	16	cens	125			71	65.6	68	5	183	230	207	−47
CC57-AD	**16**	**18.7**	293	310	302	−17	106	130	118	−24	70	68.2	69	2	130	155	143	−25
CC57-AD	**16**	**23.7**	440	378	409	62	107	145	126	−38	84	74.6	79	9	144	163	154	−19
CC57-AD	**16**	**23.7**	548	475	512	73	113	97	105	16	86	52.5	69	34	139	128	134	11
C57-aged	**28**	**25**	238	120	179	118	116	118	117	−2	76	70.6	73	5	cens	76		
C57-aged	**28**	**26.3**	288	122	205	166	102	116	109	−14	76	60.6	68	15	53	92	73	−39
C57-aged	**52**	**22.4**	222	252	237	−30	cens	78			54	37.5	46	17	cens	99		
C57-aged	**56**	**36**	446	322	384	124	cens	82			48	42.2	45	6	110	82	96	28
C57-aged	**60**	**21**	267	105	186	162	cens	33			39	17.5	28	22	59	20	40	39
n						34				20				30				19
Mean						25				−17				9				−1
1 SD						134				27				14				27

ADC, control group for AD mice; cens, POC excluded (censored) data because values were outside ranges.
Bolded text indicates mice housed on corncob bedding; all other mice were on aspen bedding.
Statistical analysis was restricted to uncensored results with usable observation pairs.

cholesterol (0.45), HDL (0.51) and triglycerides (0.51). The POC glucose and HDL analytes show the best predictability (lowest r^2 value) as compared with LCA measurements. A lower r^2 for a given analyte indicates less reliance of the dependent upon the independent variable.[19] An important caveat of the POC device is the low precision of glucose and HDL specifically for extended range values. The cholesterol and triglycerides POC values showed less correlation and predictability and may be only useful for measuring elevated levels (see Table 3 for potential analyte cutoff ranges). All calculated statistical estimates may be biased by the exclusion of out-of-range values.

The Passing–Bablok regression test[18] demonstrated good exchangeability between the POC and LCA methods for the glucose and HDL analytes because 0 was within the confidence

Table 2. Descriptive statistics for analytes measured by POC and LCA and their differences

Analyte	Device	Mean	SE	Median	1 SD	Kurtosis	Skew	Minimum	Maximum	Usable values[a]
Glucose										
	POC	352	28	291	177	−1.55	0.25	71	601	34
	LCA	315	28	280	174	−0.69	0.66	104	705	40
	LCA – POC	−37	0	−11	−3	0.86	0.41	33	104	6
Total cholesterol										
	POC	117	4	101	24	−0.84	0.94	99	164	20
	LCA	114	8	104	50	−1.03	0.4	33	213	40
	LCA – POC	−3	4	3	26	−0.19	−0.54	−66	49	20
	POC	69	4	71	26	−1.71	0.12	36	101	30
HDL										
	LCA	55	3	52	20	−0.71	0.31	17.5	97.9	40
	LCA – POC	−14	−1	−19	−6	1	0.19	−18.5	−3.1	10
Triglycerides										
	POC	68	6	49	35	3.7	2.16	49	183	19
	LCA	72	7	59	44	3.28	1.63	18	230	40
	LCA – POC	4	1	10	9	−0.42	−0.53	−31	47	21

[a]Total number of values is 40 per analyte

Table 3. Analyte range for the mice groups and corresponding reference ranges

	Analyte (mg/dL)							
	Glucose		Total cholesterol		HDL		Triglycerides	
Strain	POC	LCA	POC	LCA	POC	LCA	POC	LCA
C57 normal mice (n = 15)	71–237	104–640	N/A	50–87	36–55	26.2–53.2	55–63	18–123
C57 DIO mice (n = 16)	273–578	270–705	113–164	90–213	50–98	39.6–97.9	56–165	24–144
C57 aged mice (n = 5)	204–446	105–343	102 – 116	33–135	39–76	17.5–76.7	53–110	20–99
C57 AD mice (n = 4)	305–548	289–475	106–113	97–145	70–86	52.5–72.6	130–183	128–230
JAX normal range[a]	177–227		138–184		108–134		76–136	
JAX diabetic range[a]	205–293		193–229		140–160		105–205	
POC censoring limits	right-censored >600		left-censored <100		left-censored <15 right–censored >100		left-censored <50	

This table shows uncensored data only.
[a]Data adapted from reference.[5]

Table 4. Summary of statistical analysis and assessment of the coefficient of determination

Analyte	POC (y axis) limits	LCA (x axis) limits	r^2	n	Assessment
Glucose	Censored (601 = ">600")	none	0.34	34	Feasible, but very low precision
Total cholesterol	Censored (99 = "<100")	none	0.45	20	Feasible for elevated cholesterol
HDL	Censored (14 = "<15", 101 = ">100")	none	0.51	30	Feasible for low HDL but not for very low HDL or for elevated HDL > 100
Triglycerides	Censored (49 = "<50")	none	0.51	19	Feasible for high values, but not for normal range

interval of the intercept, and the value 1 was in the confidence interval of the slope (Table 5). This implies that the POC glucose and HDL were directly comparable with LCA results within certain analyte ranges (Table 3). In contrast, for POC cholesterol and triglyceride, analytes were not directly comparable because the confidence interval for A did not include 0 and for B did not include 1, indicating systematic and proportional differences.[18]

The Bland–Altman plotting method displays the level of device agreement, providing a clear graphical representation of the deviation of the POC and LCA values (Figure 1).[1] The difference between analyte measures from the 2 devices is plotted as a function of the mean analyte difference (values

Table 5. Passing–Bablok test of exchangeability

Parameter	Glucose	Total cholesterol	HDL	Triglycerides
Intercept (A)	−24.7	59.5	1.11	29.7
95% CI for intercept	**−146 to 64.5**	11.8 to 105	**−14.7 to 14.2**	13.1 to 55.1
Slope (B)	1.22	0.503	1.11	0.667
95% CI for slope	**0.838 to 1.75**	0.243 to 0.773	**0.849 to 1.49**	0.219 to 0.936

Bolded text indicates confidence intervals that meet the conditions for good exchangeability.

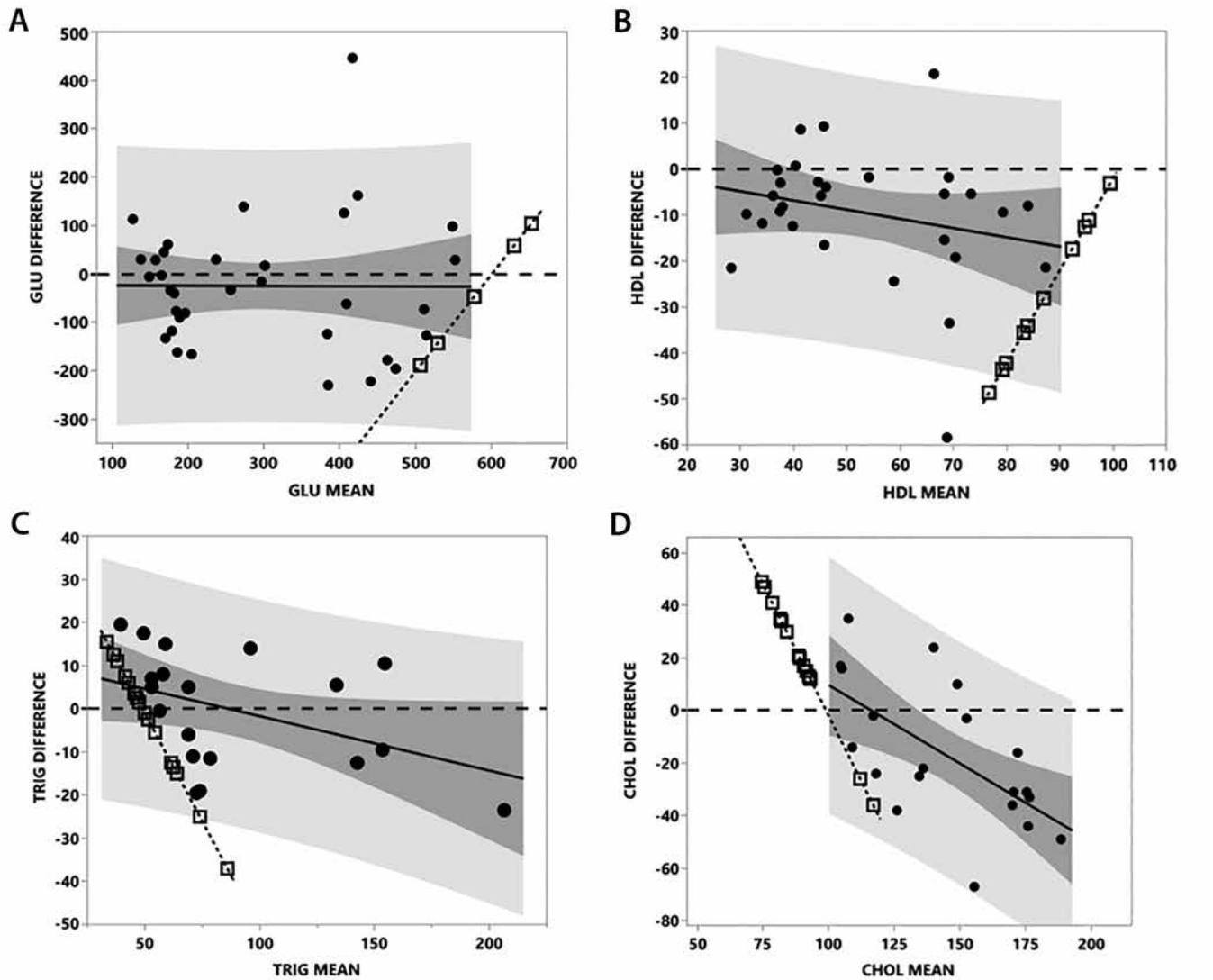

Figure 1. Bland–Altman plots of the differences between mean analyte concentrations (mg/dL) measured by POC and LCA devices. Solid circles indicate included values; open squares indicate excluded values.

listed in Table 1). The ability of the POC to provide reliable and exchangeable data with the LCA is represented by the solid line, with the shaded region depicting the CI. The dashed horizontal line indicates exchangeability between the 2 devices. The glucose results (Figure 1 A) are widely dispersed with a solid horizontal but displaced line that is below the dashed line indicating perfect exchangeability. The wide glucose data dispersion outside the CI indicates poor POC precision. The displacement line has no slope, indicating good agreement between the devices, but a fixed yet nonsignificant value-dependent bias (P = 0.500). In contrast, the HDL measures (Figure 1 B) show good precision with a proportional bias that did not reach the level of statistical significance (P = 0.096). Both cholesterol (Figure 1 C) and triglycerides (Figure 1 D) show no agreement (that is, nonzero slope) and significant bias (P = 0.002 and 0.031, respectively).

Discussion

The availability of mouse POC methods would simplify and provide rapid and repeated metabolic analyte measurements that are frequently required to study mouse models of T2DM and aging. The goal of this study was to directly compare the mouse glucose and lipid profile obtained using a human POC device with those obtained using LCA. The aim was to determine whether a human POC device would be valid for quick and repeated metabolic screening and monitoring in mice with metabolic disorders, thus replacing lengthy, expensive and non-repeatable measurement that commonly require using a standard diagnostic veterinary laboratory.

The mouse models selected for this study exhibited a variety of metabolic disorders that were appropriate for our objectives. The T2DM DIO mice showed increases in glucose and all components of the lipid profile. In contrast, the AD mice had normal glucose but aberrant lipid profiles. Finally, the 2 control groups, C57 mice age-matched to the T2DM DIO mice and aged C57 mice, show changes only in their glucose values. The variation in the mouse models with respect to their glucose and lipid profile allowed a nuanced comparison of the POC and LCA assays.

An important aspect of this study was to evaluate feasibility (when and in what capacity) a POC device, specifically the POC device we tested, is an effective research and clinical tool. Our measures of device performance were based on precision and accuracy. The data analysis steps and statistical methods chosen for this study have been substantially reviewed elsewhere.[3] The methods of data analysis show agreement numerically

and visually between the POC and LCA data. As shown in the Bland–Altman plot (Figure 1), the POC device glucose measurements agree best with the LCA measurements (see solid line, Figure 1 A). With the exception of HDL (Figure 1 B), the other analytes measured by the POC device were not accurate as compared with the LCA.

For all analytes, data points are widely dispersed indicating less precision in the POC device as compared with the LCA (see CI, Table 4 and Figure 1). Future studies that incorporate a larger sample size would improve the estimate of the relationship between the POC and LCA assays. The results of the current study demonstrate that this POC device can identify patterns of glucose and lipid levels over time or between different mice.

A critical barrier to the use of a human POC device for mice is the narrow range of values it measures for each analyte, requiring the exclusion of data that is beyond the device's limits. The excluded values also complicate data analysis because different statistical analytic techniques must be used with both quantitative and qualitative data. Some values that are in the normal range for mice are beyond the human POC device measurement limit. In our data, the excluded (out-of-range) values affected the analysis of exchangeability between the POC and LCA devices. However, even when including the out-of-range data, the coefficient of determination, Passing–Bablok and Bland–Altman results indicate that the POC device can be used to identify patterns of glucose and lipid levels over time or between different mice. An important feature for future POC devices will be to expand the measurement limits. This change would allow a wider range of samples to be measured and provide more precise and unbiased exchangeability between the POC and LCA devices.

An additional challenge in adapting human POC devices for use in mice is the critical differences between mouse and human blood. The concentration of HDL is higher in mice and the levels of lipids and glucose between healthy and diabetic mice are more disparate than in humans.[12,15] The differences in blood composition is another complicating factor in translating from human to mouse applications. Mouse blood typically has a higher hematocrit (40% to 50% compared with 36% to 50% for humans) due to smaller RBC and a shorter half-life of RBC in the mice.[12] The shorter half-life of RBC is relevant for longitudinal measurements because the mice have accelerated replacement of lost blood volume.[12] These differences in blood composition and serum density impair the development of a universal POC device that can easily be used for humans and mice.

Recent developments in POC devices have produced instruments specifically for various animal species, including mice.[9,11,12,16] These devices are programmed to include appropriate ranges of values based on the species being assessed. Limitations of these devices include their lack of lipid analysis and inaccuracies that they have shown when compared with LCA analysis. A customized device could include a selection screen to identify the animal species being tested and provide specific test strips with ranges based on each species' unique blood chemistry.[9,16] A further enhancement would be the ability to accurately measure a complete lipid panel including glucose, cholesterol, triglycerides, and HDL immediately and repeatedly from a mouse, which would be invaluable to metabolic disease and cancer research. In fact, the impetus of the current study was that the lack of a POC device compatible with mouse models impeded our ability to establish a relationship between metabolic disease or T2DM, hearing loss, and neuropathy.

The results described in this paper demonstrate that the CardioChek POC device investigated herein can be used to identify patterns of glucose and lipid levels between healthy and diabetic, aged, or AD mice. With further development to widen the range and thus improve the estimate of the POC to LCA relationship, it could become widely accepted as a new standard. The current value of this device is that its agreement with LCA measurements is adequate for identification of patterns and correlations for glucose and HDL in mice, but not for cholesterol and triglycerides.

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References

1. **Bland JM, Altman DG.** 1986. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet **1:**307–310. https://doi.org/10.1016/S0140-6736(86)90837-8.
2. **Castro Cabezas M, Botham KM, Mamo JC, Proctor SD.** 2012. Novel aspects of nonfasting lipemia in relation to vascular biology. Int J Vasc Med **2012:**1–2. https://doi.org/10.1155/2012/419015.
3. **Giavarina D.** 2015. Understanding Bland Altman analysis. Biochem Med (Zagreb) **25:**141–151. https://doi.org/10.11613/BM.2015.015.
4. **Giriraja KV, Govindaraj S, Chandrakumar HP, Ramesh B, Prasad L, Priyanka BR, Shaikh S, Rana V, Trivedi V, Ramanathan S, Laxminarayan R, Rangarajan R.** 2020. Clinical validation of integrated point-of-care devices for the management of noncommunicable diseases. Diagnostics (Basel) **10:**1–8. https://doi.org/10.3390/diagnostics10050320.
5. **Hendrix RD, Ou Y, Davis JE, Odle AK, Groves TR, Allen AR, Childs GV, Barger SW.** 2021. Alzheimer amyloid-β peptide disrupts membrane localization of glucose transporter 1 in astrocytes: implications for glucose levels in brain and blood. Neurobiol Aging **97:**73–88. https://doi.org/10.1016/j.neurobiolaging.2020.10.001.
6. **Ikeda K, Ichihara K, Hashiguchi T, Hidaka Y, Kang D, Maekawa M, Matsumoto H, Matsushita K, Okubo S, Tsuchiya T, Furuta K, Committee for Standardization, The Japanese Society of Laboratory Medicine (JSLM).** 2015. Evaluation of the short-term stability of specimens for clinical laboratory testing. Biopreserv Biobank **13:**135–143. https://doi.org/10.1089/bio.2014.0072.
7. **Institute for Laboratory Animal Research.** 2011. Guide for the care and use of laboratory animals, 8th ed. Washington (DC): National Academies Press.
8. **Jackson Laboratory.** [Internet]. 2020. Physiological data summary—diet-induced obese (DIO) C57BL/6J (380050) 27 January 2021. Available at: http://jackson.jax.org/rs/444-BUH-304/images/physiological_data_380050.pdf
9. **The Jackson Laboratory and Garcia-Arocena D.** 2014. Seven tips every DIO mice user should know. The Jackson Laboratory. Retrieved 15 April 2020 from https://www.jax.org/news-and-insights/jax-blog/2014/may/seven-tips-every-dio-mice-user-should-know
10. **Kang MH, Kim DH, Jeong IS, Choi GC, Park HM.** 2016. Evaluation of 4 portable blood glucose meters in diabetic and nondiabetic dogs and cats. Vet Q **36:**2–9. https://doi.org/10.1080/01652176.2015.1092617.
11. **Kiechle FL, Main RI.** 2000. Blood glucose: measurement in the point-of-care setting. Lab Med **31:**276–282. https://doi.org/10.1309/4BF1-ET6T-WFE3-M7XA.

12. **Kong DY, Park JH, Lee KW, Park H, Ho JA.** 2016. Comparative analysis of 3 experimental mouse model for blood hematology and chemistry. Biomedical Science Letters **22:**75–82. https://doi.org/10.15616/BSL.2016.22.3.75.
13. **Kosack CS, Page A-L, Klaster PR.** 2017. A guide to aid the selection of diagnostic tests. Bull World Health Organ **95:**639–645. https://doi.org/10.2471/BLT.16.187468.
14. **Lehman A, O'Rourke N, Hatcher L, Stepanski EJ.** 2005. JMP for basic univariate and multivariate statistics: a step-by-step guide. p 123. Cary (NC): SAS Press. ISBN 978-1-59047-576-8.
15. **Mazzaccara C, Labruna G, Cito G, Scarfò M, De Felice M, Pastore L, Sacchetti L.** 2008. Age-related reference intervals of the main biochemical and hematological analytes in C57BL/6J, 129SV/EV and C3H/HeJ mouse strains. PLoS One **3:**1–7. https://doi.org/10.1371/journal.pone.0003772.
16. **Morley LA, Gomez TH, Goldman JL, Flores R, Robinson MA.** 2018. Accuracy of 5 point-of-care glucometers in C57BL/6J mice. J Am Assoc Lab Anim Sci **57:**44–50.
17. **Otto GP, Rathkolb B, Oestereicher MA, Lengger CJ, Moerth C, Micklich K, Fuchs H, Gailus-Durner V, Wolf E, Hrabě de Angelis M.** 2016. Clinical chemistry reference intervals for C57BL/6J, C57BL/6N, and C3HeB/FeJ mice (*Mus musculus*). J Am Assoc Lab Anim Sci **55:**375–386.
18. **Passing H, Bablok W.** 1983. A new biometrical procedure for testing the equality of measurements from 2 different analytical methods. J Clin Chem Clin Biochem **21:**709–720.
19. **Rahman MM, Govidarajulu Z.** 1997. A modification of the test of Shapiro and Wilk for normality. J Appl Stat **24:**219–236. https://doi.org/10.1080/02664769723828.
20. **Shimizu Y, Ichihara K.** 2019. Elucidation of stability profiles of common chemistry analytes in serum stored at 6 graded temperatures. Clin Chem Lab Med **57:**1388–1396. https://doi.org/10.1515/cclm-2018-1109.
21. **Spindel S, Sapsford KE.** 2014. Evaluation of optical detection platforms for multiplexed detection of proteins and the need for point-of-care biosensors for clinical use. Sensors (Basel) **14:**22313–22341. https://doi.org/10.3390/s141222313.
22. **Tinkey P, Lembo T, Craig S, West C, Van Pelt C.** 2006. Use of the iSTAT portable clinical analyzer in mice. Lab Anim (NY) **35:**45–50. https://doi.org/10.1038/laban0206-45.
23. **Togashi Y, Shirakawa J, Okuyama T, Yamazaki S, Kyohara M, Miyazawa A, Suzuki T, Hamada M, Terauchi Y.** 2016. Evaluation of the appropriateness of using glucometers for measuring the blood glucose levels in mice. Sci Rep **6:**1–9. https://doi.org/10.1038/srep25465.
24. **Xavier HT, Ruiz RM, Kencis L, Melone G, Costa W, Fraga RF, Wajman L, Krakauer M, Scartezini M.** 2016. Clinical correlation between the point-of-care testing method and the traditional clinical laboratory diagnosis in the measure of the lipid profile in patients seen in medical offices. J Bras Patol Med Lab **52:**387–390. https://doi.org/10.5935/1676-2444.20160057.