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Evaluation of L-index interference limits on Roche cobas c502 and c702 immunoturbidimetric assays using endogenously lipemic specimens and intralipid spiking

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ABSTRACT

Objectives: Specimen lipemia is a primary concern with turbidimetric and nephelometric assays due the potential interference caused by light scattering or absorption. The purpose of this study was to evaluate lipemic interference thresholds across seven FDA-cleared assays using patient specimens with varying degrees of endogenous lipemia pre- and post-ultracentrifugation (UC) and with Intralipid spiking.

Methods: Using an IRB-approved protocol, residual human serum specimens (n = 42; L-indices, 1-1769; H-index ≤ 85; I-index ≤ 2) were obtained. Baseline and post-UC testing was conducted across assays on cobas c502 and c702 instruments (Roche Diagnostics; Indianapolis, IN). Serum indices and triglyceride (TRIG) concentrations were also measured pre- and post-UC. Intralipid spiking studies with human AB serum were also conducted. Lipoprotein subfraction analysis (Lipoprint; Quantimetrix; Redondo Beach, CA) was performed on three additional patient specimens with elevated TRIG post-UC to determine which TRIG-containing lipoprotein fraction(s) remain.

Results: Several assays showed L-index thresholds derived from endogenously lipemic specimens that were below previously defined limits from the package inserts (PIs) [new (prior)]: AAT 400 (500); CERU 100 (200); HAPTO 450 (600); TRSF 250 (500). L-index limits derived from Intralipid spiking were generally higher than those listed in PIs. UC did not adversely impact results in non-lipemic or lipemic specimens. UC was effective at clearing lipemic interference, although persistence of residual VLDL was often observed.

Conclusions: This study provides an analysis of L-index thresholds for seven immunoturbidimetric assays. Due to the variety of human lipoproteins, limits defined using endogenously lipemic patient specimens may be different from those derived from spiking studies using Intralipid.

1. Introduction

Interference due to specimen lipemia is a potential source of laboratory error [1–4]. Lipemia is the presence of increased lipoproteins in the blood. Lipoproteins vary in size, with the largest particles (e.g. chylomicrons) being the greatest contributor to sample turbidity [5]. The most common cause of lipemia is non-fasting status prior to specimen collection [6]. Other frequent causes include administration of intravenous infusions of lipid-containing formulations, diabetes mellitus, and dyslipidemias [1,5,7,8]. For turbidimetric and nephelometric assays, lipemic interference can result in inaccurate measurement of analyte concentrations [5]. Additional non-lipid causes of specimen turbidity include other particulate matter (e.g. cellular debris), fibrin clots, excess protein, or other exogenous substances [9–12].

Lipemia is typically quantified through measurement of lipemic index (L-index). Many analytical platforms automatically determine L-index through light absorbance methods [6,9,13]. Triglyceride (TRIG) concentrations may be used to assess lipemia, although generally poor correlation exists between absolute results of L-Index and TRIG measurements [13]. In settings without analytical methods for lipemia

Abbreviations: AAT, α1-antitrypsin; *C3*, complement C3c; *C4*, compliment C4; *CERU*, ceruloplasmin; *CHOL*, cholesterol; *FDA*, Food and Drug Administration; GLU, glucose; *HAPTO*, haptoglobin; *H-index*, hemolysis index; *HDL*, high-density lipoprotein; *I-index*, icterus index; *LDL*, low-density lipoprotein; *L-index*, lipemic index; *PI*, package insert; *PREA*, prealbumin; *TRIG*, triglyceride; *TRSF*, transferrin; *UC*, ultracentrifugation; *VLDL*, very low-density lipoprotein

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measurement, visual assessment is commonly used [6]. Assay manufacturers may provide L-index or TRIG thresholds for which interference may affect analytical measurements. These thresholds are often derived through interference studies using soy-based lipid emulsions (e.g. Intralipid) [14,15]. There are, however, limitations to using such compounds to emulate endogenous lipemia due to the complexity of human lipoproteins [1,5,6].

The purpose of this study was to compare lipemic interference thresholds across seven FDA-cleared assays using patient specimens with varying degrees of endogenous lipemia pre- and post-ultracentrifugation (UC) as well as through Intralipid spiking studies of human serum. In addition, L-index and TRIG concentrations pre- and post- UC were further evaluated to characterize the effectiveness of UC in clearing various lipoprotein subclasses.

2. Materials and methods

2.1. General

Patient specimens were de-identified following an Institutional Review Board (IRB)-approved protocol (University of Utah IRB Protocol #0007275).

2.2. Evaluation of L-index interference limits – UC of endogenously lipemic specimens

Serum specimens (n = 42) were selected based on prior measurements of L-index and/or TRIG in addition to exhibiting minimal hemolysis (H-index, ≤85) and icterus (I-index, ≤2). Samples were tested both with and without UC. UC was performed using an Airfuge (Beckman Coulter; Brea, CA) for 10 min at approximately 178,000 × *g*. Baseline and post-UC testing was conducted on two clinical chemistry analyzers (Roche Diagnostics; Indianapolis, IN) - *cobas c502*: α1-antitrypsin (AAT), complement C3c (C3), haptoglobin (HAPTO); and *cobas c702*: complement C4 (C4), ceruloplasmin (CERU), prealbumin (PREA), and transferrin (TRSF). TRIG concentrations and serum indices - hemolysis (H), icterus (I), and lipemia (L) - were also measured pre- and post-UC. Results that fell outside the analytical measurement range for any assay were excluded due to the confounding effect of manual or auto-dilution on baseline lipemia. Specimens with pre-UC analyte results of zero were also excluded, as percent (%) interference calculations could not be performed. % interference of assay results pre- and post-UC was calculated as:

$$\%\text{Interference}_a = \left(\frac{\text{Pre-UC Result} - \text{Post-UC Result}}{\text{Post-UC Result}}\right) \times 100$$

2.3. Evaluation of L-index interference limits – intralipid spiking

Dilutions of human AB sera (Mediatech; Manassa, VA) were made using admixtures of Intralipid and saline added to serum to create spiked serum pools with increasing concentrations of Intralipid (900 uL serum; constant spiked admixture volume of 100 ; e.g. 100 μL Intralipid + 0 μL saline, 90 μL Intralipid + 10 μL saline, etc; n = 4 series of dilutions; L-Index ranging 14-2184). Aliquots were then tested for all analytes. Serum spiked with saline only (no Intralipid) was used as a baseline control. % interference across increasing concentrations of Intralipid was calculated for these experiments as:

$$\%\text{Interference}_b = \left(\frac{\text{Intralipid Spiked Result} - \text{Saline Spiked Control Result}}{\text{Saline Spiked Control Result}}\right) \times 100$$

2.4. Intralipid spike-and-removal experiments

Human AB sera was separated into aliquots (n = 4 per treatment). Four aliquots were left untreated (baseline control). Four aliquots were spiked with 30 μL Intralipid in 970 μL serum, vortexed, and subject to UC. An additional four aliquots were spiked with 30 μL Intralipid in 970 μL serum but not subject to UC, in order to measure TRIG and L-index results in spiked pools. All aliquots were then tested for each analyte. A dilution correction factor (+2.47%) was applied to results from post-UC specimens to account for the residual aqueous volume introduced with spiked Intralipid that would not be removed by UC [e.g. Intralipid is a ~20% lipid emulsion in water, with the aqueous phase accounting for ~24 μL of the 30 μL spiked Intralipid]. % interference was calculated between results from the adjusted post-UC aliquots and baseline pools in these experiments as:

$$\%\text{Interference}_c = \left(\frac{\text{Post-UC Result} - \text{Baseline Control Result}}{\text{Baseline Control Result}}\right) \times 100$$

2.5. Lipoprotein subfraction analysis

Three additional serum samples with elevated TRIG levels (> 1,000 mg/dL) were obtained for investigation. Cholesterol (CHOL), high-density lipoproteins (HDL), low-density lipoproteins (LDL), glucose (GLU), TRIG, and serum indices were measured on the cobas 8000 system. All tests were conducted both pre- and post-UC. Lipoprotein subfraction analysis (Lipoprint; Quantimetrix; Redondo Beach, CA) was performed on the post-UC samples to identify which lipid subfractions comprise any remaining TRIG post-UC. Pre-UC testing of lipemic samples by lipoprotein subfraction analysis was not conducted due to chylomicron interference with subfraction cholesterol measurement in that assay [16].

2.6. Data analysis

Data was analyzed using Excel 2010 (Microsoft; Redmond, WA). Graphs were prepared using SigmaPlot 13 (Systat Software; San Jose, CA). Curve fits were performed dynamically using the Regression Wizard in SigmaPlot based on goodness of fit (UC experiments, exponential rise to maximum, single, 3 parameter equations; Intralipid spiking experiments, cubic equations). L-index interference thresholds (± 10%) were derived from these curve fits and were rounded down to the nearest interval of 50 L-index units. Data are presented as mean ± SD unless otherwise indicated. Statistical analysis was conducted using the Student's t-test (significance level of $p < 0.05$).

3. Results

Comparison of analytes pre- and post-UC (Fig. 1, left *i* panels) demonstrated that increased endogenous lipemia caused a negative % interference in AAT (Fig. 1*A-i*), HAPTO (Fig. 1*E-i*), PREA (Fig. 1*F-i*), and TRSF (Fig. 1*G-i*) assays, a positive % interference in CERU (Fig. 1*D-i*), and negligible effect on C3 (Fig. 1*B-i*) and C4 (Fig. 1*C-i*) assays across the L-index ranges evaluated. Based on UC lipid removal experiments, several assays showed L-index thresholds that were below previously defined limits from the package inserts [see Table 1; new (from insert)]: AAT 400 (500); CERU 100 (200); HAPTO 450 (600); TRSF 250 (500).

Intralipid spiking experiments into human serum (Fig. 1, right *ii* panels), however, revealed positive % interference for AAT (Fig. 1*A-ii*) and HAPTO (Fig. 1*E-ii*), biphasic (negative then positive) % interference with increasing Intralipid concentrations for CERU (Fig. 1*D-ii*) and and PREA (Fig. 1*F-ii*), and negligible effect on C3 (Fig. 1*B-ii*), C4 (Fig. 1*C-ii*), and TRSF (Fig. 1*G-ii*) assays across the L-index ranges evaluated. Intralipid spiking in the present experiments demonstrated L-index thresholds that were generally above previously defined limits from the package inserts [see Table 1; new (from insert)]: AAT 1,150 (500); CERU 350(200); HAPTO 1,000 (600); and PREA 600 (100).

UC was effective at clearing endogenous lipemic interference (as determined by L-index; post-UC L-index: 16 ± 8; n = 42) across all specimens (Fig. 2*A*), although persistence of residual TRIG was

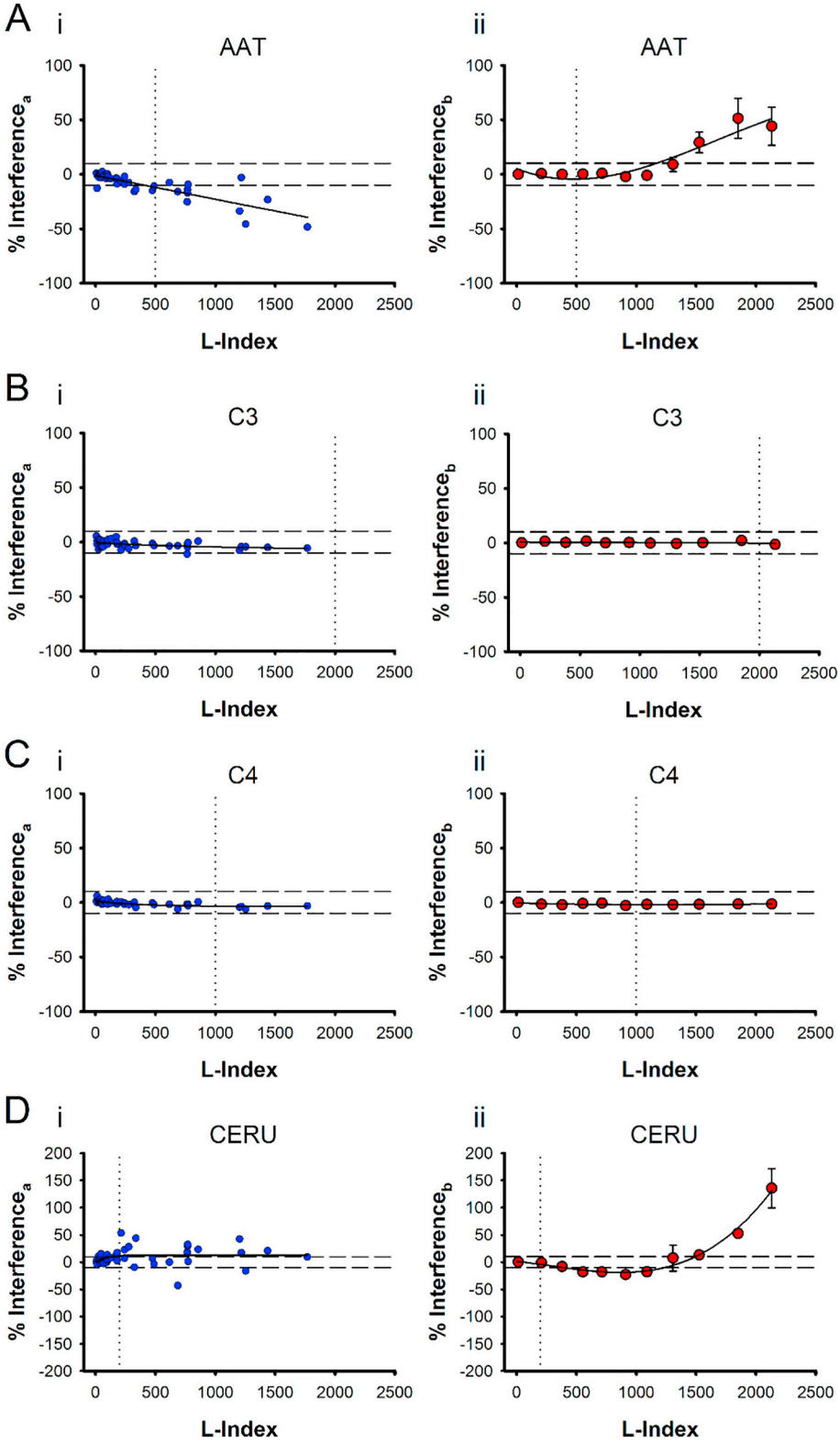

Fig. 1. Percent (%) Interference Derived from Ultracentrifugation and Intralipid Spiking Studies for Seven FDA-Cleared Assays. % interference derived from UC removal of endogenous lipids (*i*; blue circles) and Intralipid spiking (*ii*, red circles) for AAT (*A*), C3 (*B*), C4 (*C*), CERU (*D*), HAPTO (*E*), PREA (*F*), and TRSF (*G*). Dashed lines show ± 10% difference. Dotted lines show vendor PI-derived limits. Solid lines show non-linear regression (Methods Section 2.6). See Methods for % interference$_a$ (*i*, UC, Section 2.2) and % interference$_b$ (*ii*, Intralipid, Section 2.3) for calculations. Note, Y-axes are expanded for CERU (*D*) and PREA (*F*) to show all data. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

observed in 29 of 42 specimens (Post-UC TRIG ≥ 150 mg/dL without corresponding L-index elevation; see Fig. 2*B*). Lipoprotein subfraction analysis of three additional specimens post-UC (Fig. 2*C*) with pre-UC TRIG values > 1,000 mg/dL revealed the presence of residual VLDL post-UC, indicating that this UC method of clearing lipemia does not fully clear all VLDL from samples.

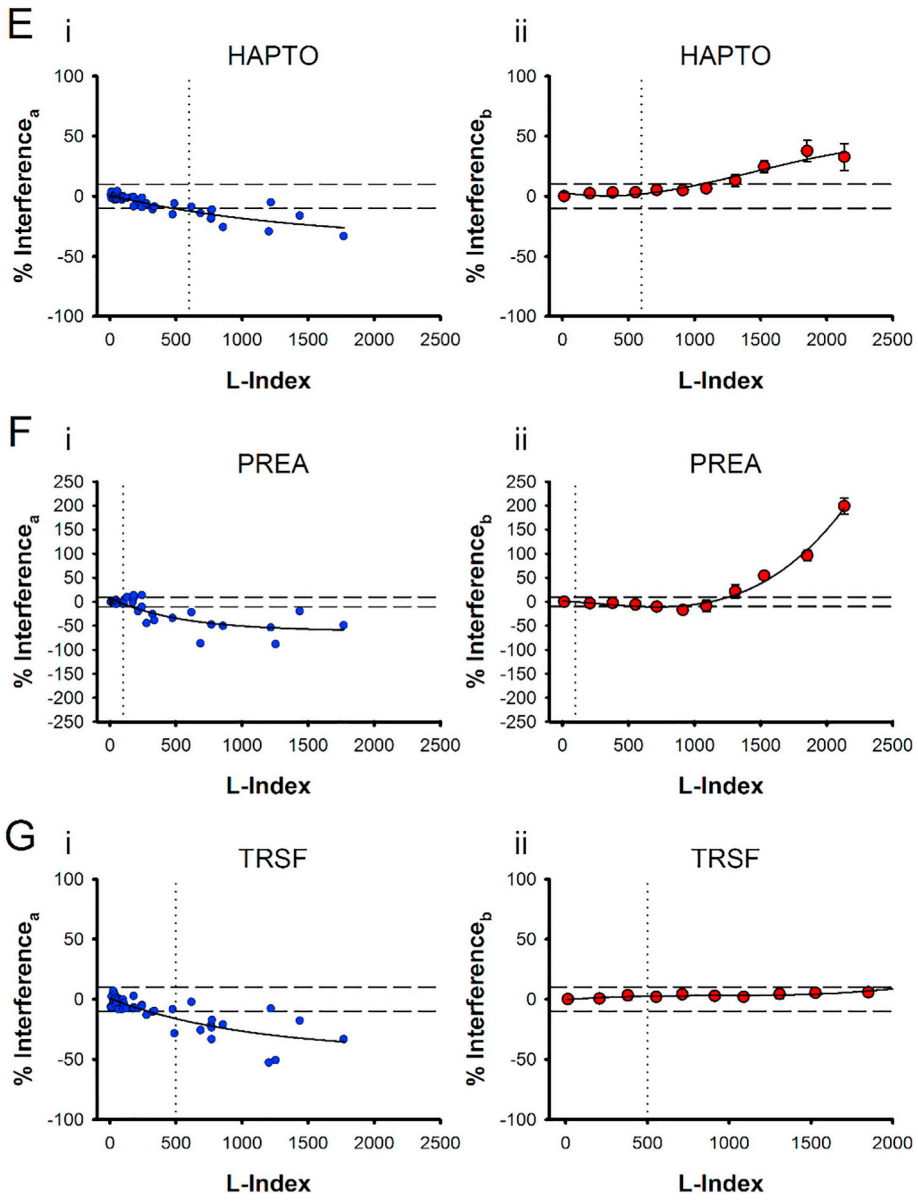

Fig. 1. (*continued*)

Table 1
L-index Interference Thresholds.

	Interference threshold		
Analyte	Vendor PI	UC removal of endogenous lipids	Intralipid spiking
AAT	500	400	1,150
C3	2,000	ND	ND
C4	1,000	ND	ND
CERU	200	100	350
HAPTO	600	450	1,000
PREA	100	150	600
TRSF	500	250	ND

ND – Interference not observed at the concentrations tested in the present experiments.

In order to evaluate whether the presence of increased concentrations of lipid could affect baseline analyte concentrations (e.g. partitioning) during UC, analyte concentrations were tested in baseline (untreated) pools of human serum and compared to those measured after spiking with Intralipid followed by UC. TRIG and L-index results in a) baseline, b) Intralipid-spiked, and c) post-Intralipid / UC specimens were as follows: a) baseline [TRIG 40.8 ± 0.5, L-index 15.3 ± 1.5]; b) Intralipid-spiked [TRIG 1268.5 ± 2.7, L-index 595.5 ± 16.6]; and c) post-Intralipid/UC [TRIG 764.0 ± 26.7, L-index 42.8 ± 14.5]. Analyte concentrations were similar between baseline controls and post-Intralipid/UC specimens (Table 2). Analyte measurements in Intralipid-spiked material (data not shown) was consistent with interference patterns observed in prior comprehensive Intralipid spiking experiments (Fig. 1, *ii* panels). % interference comparing baseline serum to post-Intralipid/UC aliquots was less than ± 2% for all analytes (Table 2), with only one analyte (CERU) demonstrating a minor difference in results (-1.8 ± 0.8%; p = 0.024) that is not considered clinically significant.

4. Discussion

The present report describes L-index interference limits across seven immunoturbidimetric assays on the Roche cobas 8000 system, established using endogenously lipemic specimens and Intralipid spiking methods. Results from the present report adds to growing literature on

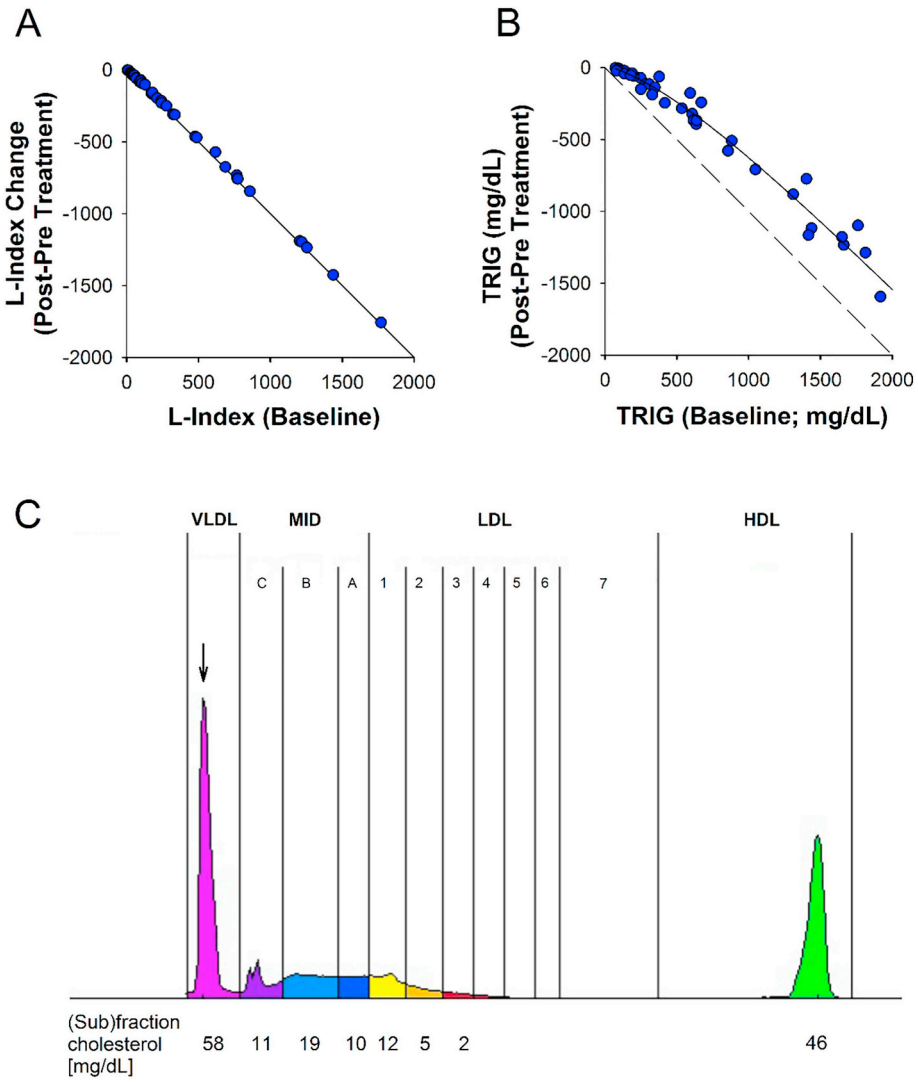

Fig. 2. Effect of UC on L-Index, TRIG, and Lipoprotein Subfractions. *A*, *B*. Change in L-index (*A*) and TRIG (*B*) measurements pre- and post-UC versus baseline measurements. *C*. Lipoprotein subclass analysis of an example post-UC specimen. VLDL fraction is shown at the left (magenta; labeled with down arrow).

Table 2
Intralipid Spike-and-Removal Studies.

Analyte	Baseline control result (mg/dL)	Post Intralipid/UC result (mg/dL)	% Interference*	p-value
AAT	119.3 ± 1.0	120.4 ± 0.8	0.9 ± 0.6	0.146
C3	144.0 ± 1.6	144.7 ± 1.3	0.5 ± 0.9	0.501
C4	25.0 ± 0.4	25.1 ± 0.7	0.5 ± 2.7	0.741
CERU	24.5 ± 0.2	24.0 ± 0.2	-1.8 ± 0.8	0.024*
HAPTO	111.5 ± 0.8	111.1 ± 0.6	-0.4 ± 0.6	0.441
PREA	25.1 ± 0.4	25.4 ± 0.3	1.1 ± 1.2	0.285
TRSF	257.3 ± 7.2	257.5 ± 7.2	0.3 ± 2.8	0.972

* See Methods (Section 2.4) for % interference$_c$ calculation.

lipemic interferences across a diverse array of analytes and instruments [2,8,17–24]. While Intralipid is commonly used with lipemic interference assessments [2,8,15,18,20,22,23], studies using endogenous lipemic specimens have also been reported [17–19,21,25,26]. Methods for removing lipemic interference include UC (or high-speed centrifugation) [8,17–21,25,26], lipid-removal reagents [2,20,25,26], and/or dilution [18,26]. It is important to note that both intravenous (IV) infusions of lipids (i.e. fat emulsions), as well as endogenous causes of hyperlipidemia (e.g. type 2 diabetes) have been shown to be common causes of lipemia [1]. While L-index limits based on endogenous lipids may be desirable to more accurately reflect human physiology, there is still a strong clinical relevance to Intralipid-based limits, given that IV lipid-infusion was the most common cause of severe lipemia identified in this previous report [1].

Lipemic interferences for several assays included in the present report have previously been investigated with a preceding generation of Roche chemistry instruments (AAT, HAPTO, TRSF, PREA, and CERU; Modular Analytics P 800) [18]. It is important to note that the methods of analyses differ between the current study and this previously published report – *current* v. *prior*: results analyzed as % interference v. ratios, x-axes as L-index v. TRIG, Intralipid obtained from Sigma Aldrich v. Baxter Healthcare (Deerfield, IL), an Airfuge time of 10 min v. 5 min, and testing on Roche cobas (c502 and c702) v. Modular P instruments. It is also possible that assay components and/or configurations may have been changed by the vendor between the respective assays across instrument generations. The above factors may contribute to differences in interference patterns observed between these studies. Lipemic interference with AAT, CERU, C3, C4, HAPTO, and PREA have also been investigated using Intralipid spiking studies with Roche cobas 6000 instruments in a separate previously published report [22]. General interference patterns evaluated using Intralipid for AAT, C3, C4, and HAPTO were similar between studies, whereas the present experiments show higher L-index interference limits for CERU and PREA.

It should be noted that a 10% threshold for interference was utilized in the present experiments, based on vendor use of this cutoff in package inserts (PIs) for these respective assays. While 10% thresholds have been commonly used in previously published reports [11,22,24,27], CLSI EP07 provides additional approaches for conducting interference studies and in considering how interference goals can be determined [28]. CLSI EP37 also provides useful tables for interference testing of exogenous and endogenous substances [29].

A recent report by Wiencek et al. (2017) describes the identification of lipemic interference in carbon dioxide (CO_2) enzymatic assays, as investigated with the use of mixing studies showing non-linearity [30]. In this previous report, an alternative non-enzymatic method for CO_2 (e.g. a blood gas analyzer) was available to provide a more accurate assessment of true analyte concentration. In the present report, a gold-standard method to determine true analyte concentrations in lipemic specimens was not available. We therefore conducted additional Intralipid spike-and-removal studies (see Table 2) to demonstrate that the removal of lipids during UC does not alter the baseline concentration of analytes investigated. Such interferences would be expected with non-polar analytes, which are more likely to partition in the lipid phase with centrifugation [4,6,9].

An unexpected observation of UC experiments was the presence of residual TRIG after UC in many specimens, even in the context of low L-index measurements (Fig. 2*A,B*). Previous NMR-based studies have categorized VLDL as large (60-200 nm), intermediate (35-60 nm), and small (27-35 nm) [31]. Given their size, the large and intermediate size VLDL (along with chylomicrons) are more likely to contribute to lipemic interference [6]. We hypothesize that the residual VLDL (post-UC) could be of smaller particle size, and therefore could explain the presence of residual TRIG in the context of low L-index measurements. In the absence of L-index elevations, however, residual VLDL would be unlikely to cause significant interference in turbidimetric assays.

In conclusion, due to the variety of human lipoproteins, limits and interference patterns derived using endogenously lipemic patient specimens may be different from those derived from spiking studies using Intralipid. The present results demonstrate the importance of assessing for specimen lipemia to avoid erroneous results. Laboratories should be cautious in drawing conclusions regarding assay interference patterns without supportive data for their respective instrumentation.

Conflict of interests

The authors have no relevant conflicts of interest to disclose.

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