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Evaluating Interference of Lipemia on Routine Clinical Biochemical Tests

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Abstract

Objective Lipemia is an important cause of preanalytical errors in laboratory results. They affect the specimen integrity and trustworthiness of laboratory results. The present study was to assess the impact of lipemia on routine clinical chemistry analytes.

Methods Anonymous leftover serum samples with normal levels of routine biochemical parameters were pooled. Twenty such pooled serum samples were used for the study. The samples were spiked with commercially available intralipid solution (20%) to produce lipemic concentrations of 0, 400 (mild, 20 µL), 1,000 (moderate, 50 µL), and 2,000 mg/dL (severe, 100 µL). Glucose, renal function test, electrolytes, and liver function test were estimated in all the samples. Baseline data without the effect of interference was considered as true value and percentage bias for the spiked samples was calculated. Interference was considered significant if the interference bias percentage exceeded 10%.

Result Parameters like glucose, urea, creatinine, direct bilirubin, sodium, potassium, and chloride showed negative interference at mild and moderate lipemic concentration and positive interference at severe lipemic concentration. Parameters like aspartate transaminase (AST) and alanine transaminase (ALT) showed negative interference at mild and positive interference at moderate and severe lipemic concentration. Whereas uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, gamma-glutamyl transferase, calcium, magnesium, and phosphorous showed positive interference at all concentrations. Significant interference ($>$ 10%) was shown for magnesium (mild lipemia), albumin, direct bilirubin, ALT, and AST at moderate lipemic concentration. All parameters showed significant interference at severe lipemic concentration.

Conclusion All the study parameters are affected by lipemic interference at varying levels. Laboratory-specific data regarding lipemic interference at various concentrations on the clinical biochemistry parameters is needed.

Keywords
- lipemia
- interference
- preanalytical errors

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Introduction

Interference in laboratory medicine is defined as the process that the presence of a substance in the sample leads to a change in the measured value of another parameter.[1] The presence of these substances in the sample leads to biased results that can seriously harm the patients.[2] The common interferences that affect laboratory results include hemolysis, lipemia, and icterus. More than two-thirds of the laboratory errors can be attributed to the preanalytical phase. Interferences are a significant source of these laboratory errors that can affect the specimen integrity and reliability of laboratory results and also could lead to adverse clinical outcomes. Lipemia plays a significant role in causing preanalytical errors by increasing the turbidity of the sample due to the presence of a high concentration of lipoprotein particles.[3]

The most common cause of lipemia is inadequate fasting and patient preparation before blood sampling. Postprandial lipemia can cause error even in the parameters that are not affected by food intake due to the increase in the turbidity of sample.[4] Hypertriglyceridemia due to any cause can lead to a lipemic sample. Primary causes of hypertriglyceridemia include type I, IV, and V hyperlipidemia according to Fredrickson classification. Secondary causes include intralipid administration via parenteral route among hospitalized patients, diabetes, alcoholism, nephritic syndrome, anatomical malformations with the lymphatics (e.g., fistula), and drugs.[5]

Identification of the lipemia sample can be done using visual detection, measurement of triglyceride concentration, or automatic detection by L-index. Visual detection is the most widely used approach in the clinical laboratory for lipemia detection.[6] Nowadays automatic detection by L-index is being incorporated into the autoanalyzers. Even though automatic detection has advantages such as low cost, high spaced, and increased reproducibility there are some disadvantages also such as lack of standardization among manufacturers and a high false-positive rate due to the presence of substances other than lipids like paraproteins.[7]

Interference testing is a necessary step to understanding how the substances present in the sample can affect the result of the other parameters. It is an obligation on the part of reagent manufacturers to test the interferences by common substances such as hemolysis, icteric, and lipemia.[8] The best method to test for interference is by measuring the analytes by test method and reference method and then comparing the results and calculating bias between them. Since interference-free reference methods are hard to come, interference in lipemic samples was calculated usually by spiking the sample with interferent substance at various concentrations and then bias can be calculated for each one.[8] Similar studies done by Agarwal et al and Biljali et al have also evaluated the effects of lipid interference on routine biochemical parameters.[9,10] Intralipid emulsion (20%) which is a mixture of phospholipids, soybean oil, and glycerin was used in the present study for spiking of the samples to mimic lipemic interference.[3] It has been used previously to assess lipid interference.[2]

The study was planned to establish the laboratory-specific data regarding lipid interference on various biochemical parameters and to assess the discrepancy if any, in the information provided by the reagent manufacturers about the interference caused by lipemia, which is not properly quantified or specific to the instruments used in a clinical laboratory. To identify the parameters that are affected/not affected by lipemia and to provide some guidelines regarding the decision limits for rejection of lipemic samples for each parameter to strike a balance between a lower rejection rate and to avoid the risk of adverse clinical outcomes. The objectives of the study are to evaluate the effect of lipemic interference on routine biochemical parameters used in a clinical laboratory and to estimate the percentage of bias at different levels of lipemia such as mild, moderate, and severe.

Materials and Methods

Samples

This study was conducted in the Department of Biochemistry of Mahatma Gandhi Medical College and Research Institute (Puducherry, India), from February to July 2019. This is a teaching and research institute with a tertiary hospital that processes 200 to 300 samples for routine biochemical analysis among which 1 to 3% samples are lipemic (0.6–1.0%). Ethical clearance was obtained from the institutional research committee and the Institute Ethics Committee. This was a laboratory-based analytical study. Anonymous leftover serum samples were collected from the biochemical laboratory after routine analysis. For the study purpose we pooled only the samples with normal value of all the study parameters. A total of 200 mL of pooled serum was collected. Then, 2 mL of 20 samples were aliquoted separately to measure baseline, mild, moderate, and severe lipemia (total 80 samples). All samples were run in duplicate and mean value is taken for analysis. To maintain the stability of the study parameters till analysis, samples were stored in deep freezer at –20°C. Four aliquots were made from each sample and each aliquot was spiked with commercially available Intralipid (20%) to prepare lipemic samples at varying concentrations of 0, 400 (mild lipemia), 1,000 (moderate lipemia), and 2,000 mg/dL (severe lipemia).[9,11] The volume of intralipid solution added to get mild, moderate, and severe lipemic concentration is 20, 50, and 100 µL, respectively. All samples were run in duplicate and mean value was taken for analysis. Intralipid emulsion (20%) which is a mixture of egg yolk phospholipids, soybean oil, and glycerin is used to mimic lipemic samples.

Method

The routine biochemical parameters determined in all of the four aliquots were the following: glucose, urea, creatinine, uric acid, total bilirubin, direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl

Table 1 List of routine biochemical tests and their method used in our study

Serial no.	Parameter	Reagent company	Method
1	Glucose (mg/dL)	Accurex	Glucose-oxidase method
2	Urea (mg/dL)	Diasys	Kinetic–urease
3	Creatinine (mg/dL)	Diasys	Kinetic Jaffe
4	Uric acid (mg/dL)	Human	Uricase
5	Total bilirubin (mg/dL)	Diasys	Dichlorophenyldiazonium tetrafluroborate (DPD)
6	Direct bilirubin (mg/dL)	Diasys	Jendrassik–Grof
7	Total protein (g/dL)	Erba	Biuret
8	Albumin (g/dL)	Erba	BCG
9	Alanine aminotransferase (U/L)	Diasys	IFCC (PLP)
10	Aspartate aminotransferase (U/L)	Diasys	IFCC (PLP)
11	Alkaline phosphorous (IU/L)	Diasys	Aminoantipyrine
12	Gamma-glutamyl transferase (IU/L)	Diasys	UV kinetic using carboxy substrate
13	Sodium (mEq/L)	Medica	ISE
14	Potassium (mEq/L)	Medica	ISE
15	Chloride (mEq/L)	Medica	ISE
16	Calcium (mg/dL)	Erba	O-cresolphthalein complexone
17	Phosphorous (mg/dL)	Diasys	Molybdate UV
18	Magnesium (mg/dL)	Diasys	Xylidyl

Abbreviations: BCG, bromocresol green; IFCC, International Federation of Clinical Chemistry; ISE, ion selective electrode; PLP, pyridoxal phosphate; UV, ultraviolet.

transferase (GGT), sodium, potassium, chloride, calcium, phosphorus, and magnesium. All routine biochemical parameters were estimated using Hitachi 902 automated clinical chemistry analyzer. The dilutional effect caused by the addition of Intralipid emulsion was normalized by multiplying by a factor of dilution volume divided by the net volume. The analytical methods used for the estimation of biochemical parameters in this study are listed in ►**Table 1**.

Statistical Analysis

The test for normality was done on all variables. Normally distributed data were presented using mean ± standard deviation. To compare the means of normally distributed data between groups one-way analysis of variance was used. Percentage bias was calculated for each analyte and compared for significant change. Baseline data from unspiked aliquot, without the effect of interference, was considered as the true value for calculation of bias for the spiked samples and the percentage bias was calculated using the formula, Interference bias% = (true value – measured value)/true value * 100. Interference was considered significant if the interference bias percentage exceeded 10%. All statistical analysis was performed using SPSS version 20 software.

Results

This study was planned to evaluate the impact of lipemia interference on the estimation of routine clinical chemistry analytes in a biochemistry laboratory. This was achieved by spiking 20 normal pooled serum with Intralipid emulsion to mimic lipemic samples at varying concentrations in the laboratory. The study parameters were estimated in all the samples including the unspiked sample. The values of the study parameters are shown in ►**Table 2**. All the study parameters showed significant interference at a concentration of 2,000 mg/dL. The bias percentage was calculated for all the parameters by taking the baseline value obtained from the unspiked sample as the true value.

Lipid Interference on the Glucose and Renal Function Test Parameters

Glucose, urea, and creatinine exhibited negative interference at mild and moderate lipemic concentrations but showed significant positive interference at severe lipemic concentrations. Uric acid showed positive interference at mild, moderate, and severe lipemic concentration. Bias percentage analysis showed significant interference at severe lipemic concentrations for all four parameters (►**Table 3**, ►**Fig. 1**).

Lipid Interference on Liver Function Test Parameters

Among the liver function test (LFT) parameters, total protein, albumin, total bilirubin, ALP, and GGT exhibited positive interference with an increasing trend due to lipemia in all three concentrations. AST and ALT showed negative interference at mild lipemia and positive interference from moderate and severe lipemic concentrations whereas direct bilirubin showed negative interference at both mild and moderate lipemic levels and positive interference at severe lipemic level.

Significant interference was seen at moderate lipemic concentrations for albumin (positive), ALT (positive), AST

Table 2 Effect of lipemia on various routine clinical chemistry analytes

Parameter	Base line	Mild lipemic	Moderate lipemic	Severe lipemic
Glucose (mg/dL)	97.57 ± 9.99	95.58 ± 9.12	97.13 ± 10.06	120.33 ± 18.03[a]
Urea (mg/dL)	35.9 ± 12.78	35.1 ± 12.1	35.5 ± 13.36	39.2 ± 13.43[a]
Creatinine (mg/dL)	1.16 ± 0.46	1.14 ± 0.47	1.15 ± 0.45	1.29 ± 0.52[a]
Uric acid (mg/dL)	4.33 ± 0.82	4.47 ± 0.85	4.66 ± 0.88	6.14 ± 1.88[a]
Total bilirubin (mg/dL)	0.73 ± 0.3	0.78 ± 0.33	0.76 ± 0.26	0.94 ± 0.3[a]
Direct bilirubin (mg/dL)	0.27 ± 0.21	0.26 ± 0.19	0.24 ± 0.21[a]	0.35 ± 0.22[a]
Total protein (g/dL)	6.86 ± 0.59	6.94 ± 0.5	7.07 ± 0.55	8.72 ± 1.42[a]
Albumin (g/dL)	2.74 ± 0.35	2.91 ± 0.36	3.09 ± 0.48[a]	3.78 ± 0.78[a]
ALT (U/L)	26.53 ± 15.59	25.2 ± 16.23	29.75 ± 18.64[a]	32.97 ± 26.1[a]
AST (U/L)	45.96 ± 21.82	44.52 ± 21.86	51.29 ± 24.19[a]	58.13 ± 26.59[a]
ALP (IU/L)	108.01 ± 20.39	110.01 ± 21.68	111.78 ± 21.42	129.43 ± 23.74[a]
GGT (IU/L)	45.07 ± 19.32	45.74 ± 19.84	45.85 ± 19.72	52.84 ± 24.18[a]
Sodium (mEq/L)	137.57 ± 3.9	132.71 ± 4.77	134.33 ± 4.74	151.74 ± 5.77[a]
Potassium (mEq/L)	3.33 ± 0.17	3.24 ± 0.15	3.31 ± 0.15	3.81 ± 0.2[a]
Chloride (mEq/L)	92.45 ± 2.98	89.3 ± 3.6	90.51 ± 3.22	102.49 ± 3.96[a]
Calcium (mg/dL)	7.92 ± 0.37	7.99 ± 0.27	8.34 ± 0.51	9.77 ± 1[a]
Phosphorous (mg/dL)	3.65 ± 0.22	3.67 ± 0.17	3.87 ± 0.3	5.41 ± 1.16[a]
Magnesium (mg/dL)	1.57 ± 0.14	2.14 ± 0.8[a]	2.34 ± 0.42[a]	3.44 ± 1.44[a]

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase.
Note: The volume of intralipid solution added to get mild, moderate, and severe lipemic concentration is 20, 50, and 100 µL. All the study parameters showed positive interference at a concentration of 2,000 mg/dL. Bias percentage was calculated for all the parameters by taking the baseline value as true value. This is shown in ►**Table 3**.
[a]$p < 0.05$, statistically significant.

Table 3 Effect of lipid interference on the glucose and RFT expressed as bias percentage

Parameter	Bias %		
	400 mg/dL	1,000 mg/dL	2,000 mg/dL
Glucose (mg/dL)	−2.05	−0.46	23.32[a]
Urea (mg/dL)	−2.23	−1.11	9.9[a]
Creatinine (mg/dL)	−1.97	−1.59	10.45[a]
Uric acid (mg/dL)	3.08	7.44	41.79[a]

Abbreviation: RFT, renal function test.
Note: Glucose, urea, and creatinine showed negative interference at 400 and 1,000 mg/dL but showed positive interference at 2,000 mg/dL. Uric acid showed positive inference even at mild lipemic concentration.
[a]$p < 0.05$ statistically significant.

(positive), and direct bilirubin (negative). All the LFT parameters showed significant positive interference with severe lipemic samples. These are shown in ►**Table 4** and ►**Fig. 2**.

Lipid Interference on Serum Electrolytes

Serum levels of sodium, potassium, and chloride showed negative interference in both mild and moderate lipemic samples and positive interference with severe lipemia. Calcium, phosphorous, and magnesium showed positive interference throughout all three increasing concentrations of lipemia. Serum electrolytes showed significant bias at severe lipemia and magnesium showed significant bias even at mild lipemia as shown in ►**Table 5** and ►**Fig. 3**.

Discussion

The majority of errors in the postautomation era in a clinical laboratory are attributed to the preanalytical phase which is complex and has a lot of human involvement. Therefore, the laboratories need to deal with interferences due to various substances to ensure accurate results. The three major interferences encountered in the clinical laboratory are hemolysis, icterus, and lipemia.[9]

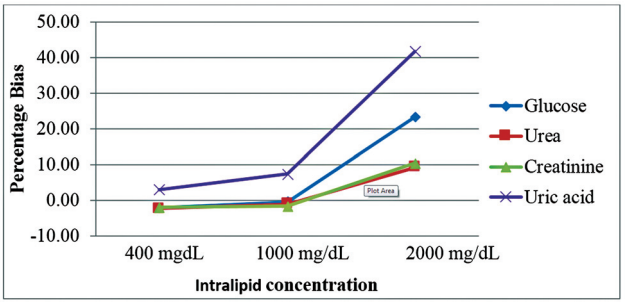

Fig. 1 Effect of lipemia on glucose, urea, creatinine, and uric acid levels expressed as percentage of bias.

Table 4 Lipid interference on liver function test parameters expressed as bias percentage

Parameter	Bias %		
	400 mg/dL	1,000 mg/dL	2,000 mg/dL
Total protein (g/dL)	1.23	3.09	27.16[a]
Albumin (g/dL)	6.50	13.01[a]	38.21[a]
Total bilirubin (mg/dL)	7.68	4.15	29.68[a]
Direct bilirubin (mg/dL)	−3.33	−9.91[a]	30.41[a]
Alanine aminotransferase (U/L)	−5.02	12.15[a]	24.27[a]
Aspartate aminotransferase (U/L)	−3.14	11.59[a]	26.48[a]
Alkaline phosphorous (IU/L)	1.85	3.49	19.84[a]
Gamma-glutamyl transferase (IU/L)	1.48	1.72	17.24[a]

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; LFT, liver function test.
Note: Among the liver function test parameters, total protein, albumin, total bilirubin, ALP, and GGT showed positive interference due to lipemia up to the concentration 2,000 mg/dL. Direct bilirubin, AST, and ALT showed negative interference at 400 mg/dL and positive interference from 1,000 mg/dL expect for direct bilirubin which showed negative interference at 1,000 mg/dL. Significant interference was seen at 1,000 mg/dL for albumin (positive), ALT (positive), AST (positive), and direct bilirubin (negative). All the LFT parameters showed significant positive interference at 2,000 mg/dL.
[a]$p < 0.05$ statistically significant.

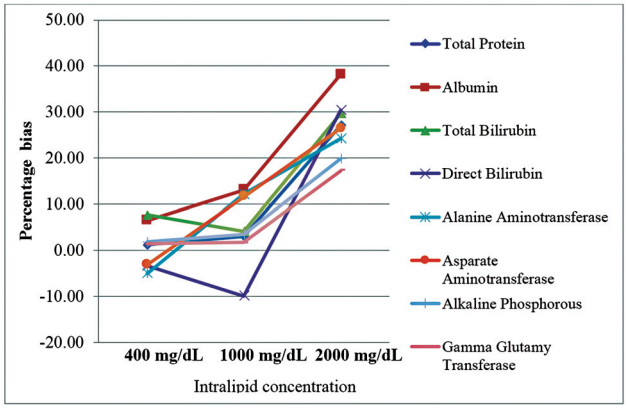

Fig. 2 Effect of lipemia on liver function test (LFT) parameters expressed as percentage of bias.

There is a lack of data regarding interference due to lipemia across different reagents and instrument manufacturers.[12] Verification of the manufacturer's claim by the laboratories specific to them was a necessary step recommended by accreditation bodies to reduce the adverse outcomes. Hence, the present study was intended to study the lipemia interference on various biochemical parameters.

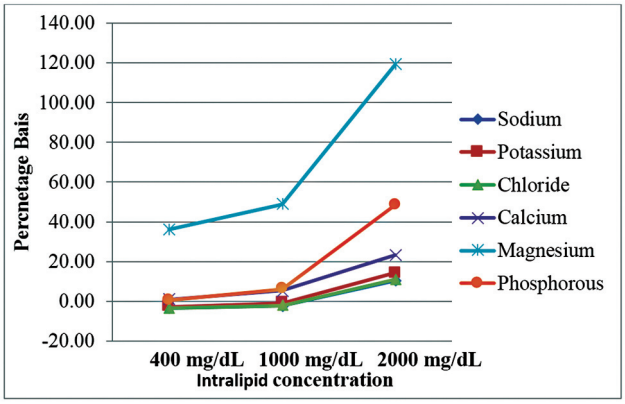

Fig. 3 Effect of lipemia on electrolyte levels expressed as percentage of bias.

Table 5 Lipid interference on serum electrolytes expressed as bias percentage

Parameter	Bias %		
	400 mg/dL	1,000 mg/dL	2,000 mg/dL
Sodium (mEq/L)	−3.53	−2.36	10.30[a]
Potassium (mEq/L)	−2.83	−0.87	14.27[a]
Chloride (mEq/L)	−3.40	−2.09	10.86[a]
Calcium (mg/dL)	0.95	5.37	23.38[a]
Phosphorous (mg/dL)	0.61	6.10	48.48[a]
Magnesium (mg/dL)	36.05[a]	48.73[a]	119.19[a]

Note: Serum levels of sodium, potassium, and chloride showed negative interference up to 1,000 mg/dL and positive interference at 2,000 mg/dL. Calcium, phosphorous, and magnesium showed positive interference throughout. Serum electrolytes showed significant bias at 2,000 mg/dL and magnesium showed significant bias even at 400 mg/dL.
[a]$p < 0.05$ statistically significant.

All the study parameters are affected by lipemic interference. Parameters like glucose, urea, creatinine, direct bilirubin, sodium, potassium, and chloride showed negative interference at mild and moderate lipemic concentration and positive interference at severe lipemic concentration. Parameters such as AST and ALT showed negative interference at mild lipemic concentration and positive interference at moderate and severe lipemic concentration. Whereas uric acid, total protein, albumin, total bilirubin, ALP, GGT,

calcium, magnesium, and phosphorous showed positive interference at all concentrations.

Significant interference (> 10%) was shown for magnesium (mild lipemia), albumin, direct bilirubin, ALT, and AST at moderate lipemic concentration. All parameters showed significant positive interference at severe lipemic concentration.

Similar findings were reported by various authors who studied the effect of the hemoglobin, icterus, and lipemia interference on biochemical parameters.[9,13,14] Interference in the lipemia sample can occur by several mechanisms. Physical and chemical interaction with measured analyte can interfere in several immunoassays nonspecifically by blocking the binding sites on antibodies.[15] The most common interference in the lipemia sample is caused by the absorption of light by the lipoprotein particle which interferes with the spectrophotometric assays.[1] Lower wavelengths are most affected by lipemia due to increased absorbance seen in that part of the spectra. Therefore, methods like ALT, AST, and glucose are more affected parameters.[1] Chylomicrons and very-low-density lipoprotein (VLDL) particles in lipemic sample will scatter light and make the sample turbid. Hence, the assays which use detection of transmittant light are affected more.[13]

Another important aspect that could cause lipemic interference is due to nonhomogeneity of the sample. After centrifugation of blood for separation of serum/plasma, lipid particles accumulate at the top of the tube due to lower density and hydrophobic constituents distribute in the top lipid layer. Hence, small molecules and electrolytes that are soluble in the aqueous phase are confined to the lower part of the tube. Most of the autoanalyzers will take the sample from the upper part leading to falsely decreased concentration of these analytes. The opposite is true for polar substances like valproic acid and steroid hormone which will be distributed in the upper lipid layer. Volume displacement effects can strongly interfere with electrolyte analysis as they are excluded from the upper lipid layer. Thus, flame photometry and indirect potentiometry that measures electrolyte concentration in total volume can result in falsely decreased concentration, whereas direct potentiometry that measures electrolyte concentration only in the aqueous layer is not affected by lipemia.[16]

In the present study, only normal serum was taken to assess the lipemic interference. But the concentration of the analyte in the baseline sample will affect the amount of interference. Percentage change will be different even for constant interference measured at low or high baseline concentration.

Early identification of erroneous reports and the cause for the inappropriateness of the samples for processing will reduce turnaround time and further workup investigations.[17] Lipemic samples can be treated to remove lipids by ultracentrifugation or extraction with polar solvents such as polyethylene glycol or cyclodextrin.[14,18] These methods are carefully chosen depending upon the analyte to be measured. For nonpolar substances that are distributed only in the lipid layer such as therapeutic drugs, removal methods are not acceptable. The best approach in such cases is sample dilution to minimize interference due to turbidity.

The strength of the study was that we have examined the effects of mild, moderate, and severe lipemia on routine biochemical parameters, which can help to generate laboratory-specific data for making an informed decision on the appropriateness of the lipemic sample for analysis of a particular parameter in a clinical biochemistry laboratory. Since the lipemic patient's samples were found to have varying concentrations and compositions of lipid particles compounded with the nonavailability of homogenous lipid preparations that would better represent physiological lipemia, researchers commonly use standardized lipid solutions of known concentrations.

Intralipid is the most commonly used preparation which is given as an intravenous infusion to those patients requiring parenteral nutrition. Even though intralipid is the best choice available for studying lipemic interferences, the problem lies with the size of lipid particles in it. The average particle size in intralipid ranges from 200 to 600 nm which are smaller than chylomicrons and larger than VLDL particles.[1,8,17] Other limitations of this study include not evaluating the effect of ultracentrifugation and LipoClear to remove the lipemia in the present study.

We conclude that lipemia interference accounts for a significant amount of laboratory errors. Increased awareness is needed regarding lipemic interference on various biochemical parameters. The manufacturer's claim should be verified using evidence-based acceptance criteria. Every laboratory should have a written protocol for identification of lipemic samples, decision limit for rejecting lipemic samples for each parameter to increase efficiency and decrease the turnaround time or adverse outcomes, methods to remove lipemia interference, and reporting of results from those samples.

Authors' Contributions

S.A. contributed to the design of the study and analysis of the samples. P.S.M. contributed to the design of the study and statistical analysis. R.R. contributed to the design of the study and expert guidelines.

Conflict of Interest

None declared.

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