Posted December 18, 2024. doi: https://doi.org/10.57187/preprint.14

A milky blood test

What is your diagnosis?

Olivier Milliet - Internal Medicine Department, Riviera-Chablais Hospital Rennaz (HRC)
Dr. Victoria Ando - Internal Medicine Department, Vaud University Hospital Center
Dr. Nora Schwotzer - Nephrology Department, Vaud University Hospital Center
Dr. Malik Benmachiche - Internal Medicine Department, Vaud University Hospital Center

A 51-year-old female patient, with a history of type 2 diabetes, is referred to the emergency department for hyperglycemia > 40 mmol/L. She describes polyuria, polydipsia, nausea and epigastric pain. She reports having undergone IVF in Egypt 3 weeks prior, for which she is taking oestrogen and corticosteroids.
Clinically, she has epigastric pain on palpation without guarding or rebound tenderness. The rest of the clinical examination is normal.
Arterial blood gas analysis shows a metabolic acidosis with an increased anion gap. Ketone bodies are at 3.1 mmol/L. Potassium levels are normal. A urine pregnancy test is negative. A diagnosis of diabetic ketoacidosis (DKA) is made, and IV insulin treatment is started. Blood is drawn but is described as unanalysable due to its consistency (see Figure 1).

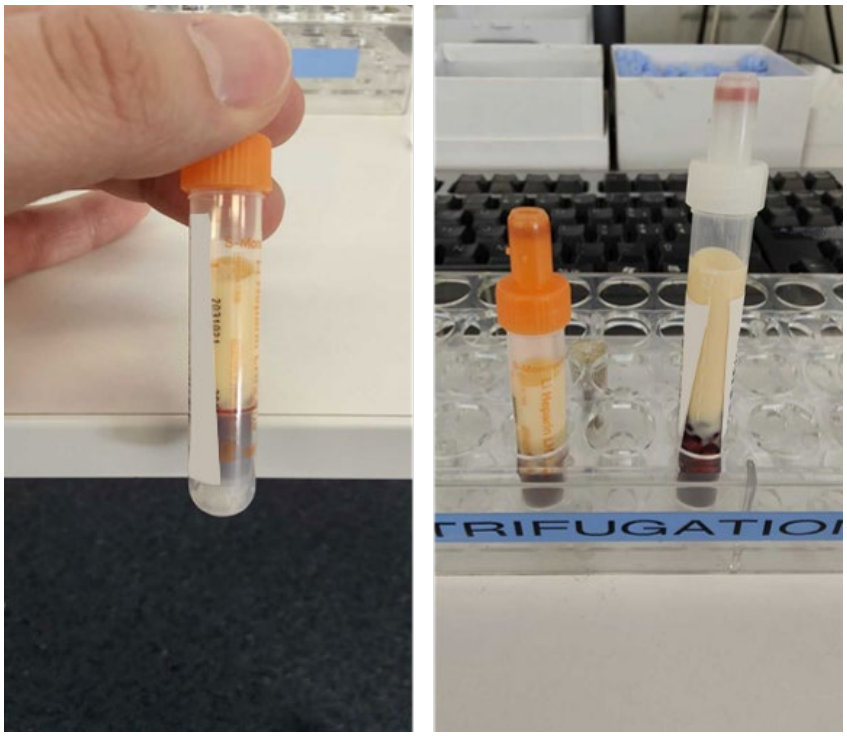


Figure 1: Blood tubes from the patient after centrifugation.
(Images from the clinical chemistry laboratory of CHUV)

Question 1: What is the most likely cause of this milky appearance?

a) Severe hyperglycaemia

b) Cryoglobulinemia

c) Raised lipase levels

d) Hypertriglyceridemia (HTG)

e) Severe leucocytosis

HTG is the most probable cause of milky blood due to an increase in triglyceride (TG) transporters, mainly very low-density lipoproteins (VLDL). The resulting high lipid content is the cause.
In the case of cryoglobulinemia, a sand-like appearance can be observed at the bottom of the tube due to protein cryoprecipitation in the serum.[1]
Severe leucocytosis can have a macroscopic impact on the blood after centrifugation, increasing the "buffy coat" (leucocyte-platelet layer) that lies between the plasma layer and the red blood cells.[2]
Increased lipases and severe hyperglycaemia do not change the macroscopic appearance of blood.
The lipid profile of our patient reveals extremely severe HTG at 164.7 mmol/L, which corresponds to a value 7 times higher than the threshold for severe HTG.

Question 2: Which of these statements is correct regarding the analysis of milky serum in the context of severe HTG?

a) May cause pseudohyponatremia

b) Decreases coagulation activity

c) May cause pseudohyponatremia

d) Results is falsely low haemoglobin levels

e) Results in falsely elevated serum amylase values

HTG can cause pseudohyponatremia as a result of the processing method for measuring serum sodium. With the usual method, known as indirect potentiometry, the proportion of plasma water is considered fixed and is not corrected in the presence of excess solute (proteins or triglycerides). The problem is circumvented with direct selective ion electrode methods used with blood gas analysers.

HTG can also result in falsely normal amylase values due to the presence of a circulating inhibitor of serum amylase that interferes with the assay.[3] Glucose and LDL cholesterol values can also be influenced, as well as other electrolytes. Additionally, coagulation is altered by an increase in coagulation factors leading to hypercoagulability.[4]

Repeated dilution and ultracentrifugation can help reduce these analytical errors.[5]

For our patient, despite several attempts at dilution techniques and ultracentrifugation, the HTG was so severe that laboratory analysis was impossible.

Question 3: Which of these treatments is the *least* appropriate for the acute management of severe HTG?

a) Continuous IV insulin

b) Plasmapheresis

c) Fibrates

d) IV heparin

e) Low-fat diet

Continuous IV insulin is recommended in the context of HTG associated with hyperglycaemia or diabetic ketoacidosis. Insulin acts at multiple levels in lipid metabolism to limit the circulation of lipids (cholesterol, TG).[6,7] The various roles of insulin are summarized in Figure 2.

Plasmapheresis is a recommended treatment in the context of acute pancreatitis and is suggested in severe HTG where there is a risk of pancreatitis with associated signs of severity.[8] However, several studies have not demonstrated a benefit on mortality or length of hospital stay.[7] There is also little evidence regarding benefits of plasmapheresis in cases of severe HTG without pancreatitis.
The introduction of fibrate treatment and a low-fat diet is recommended, but they will not quickly lower TG levels. Their impact will be to maintain low levels in the medium- to long-term.
IV heparin has shown beneficial effects on lowering TG levels. However, due to the risk of rebound HTG and haemorrhagic risk regarding the during the acute phase, this treatment is no longer recommended.[7]
In this case of extremely severe HTG, the difficulties primarily stemmed from not having access to many laboratory results. After initiating IV insulin, we started plasmapheresis to accelerate the decrease in TG levels to facilitate laboratory analyses that would allow us to guide overall management, namely of the DKA. The decision to perform plasmapheresis was also made to reduce the risk of complications, notably pancreatitis.

Question 4: Among these possibilities, which can cause HTG?

a) Corticosteroid therapy

b) Pregnancy (or hormone therapy)

c) DKA

d) Immunosuppressants

e) All of the above

Each of these factors may increase TG levels. Corticosteroid therapy stimulates lipolysis, elevates plasma fatty acid concentration, and decreases peripheral TG consumption by inhibiting lipoprotein lipase activity at the muscular level.[9]
Pregnancy causes an increase in plasma lipids to meet foetal needs. This occurs during the third trimester, but TG levels rarely exceed 3 mmol/L.[10]
DKA is the most frequent cause of HTG. Insulin plays a central role in lipid metabolism, which is impaired during DKA. Insulin resistance leads to increased activity of apolipoprotein C, which has an inhibitory effect on lipoprotein lipase activity, reducing the hydrolysis of plasma TG and increasing plasma TG concentration and accumulation of VLDL in circulation.
Several immunosuppressants affect bile acid biosynthesis by modifying the activity of certain lipoprotein receptors (LDL-R) or the expression of various apolipoproteins that serve as cofactors in the transport of cholesterol and TG by lipoproteins.[11,12]
In our patient's case, she presents several risk factors for developing HTG, including corticosteroid therapy, hormone therapy, and DKA.

Question 5: Among these possibilities, which is the *least* appropriate for long-term management of HTG?

a) Genetic analysis

b) Diet and weight loss

c) Fibrates

d) Strict monitoring and treatment of diabetes

e) Statins

Fibrates lowers TG levels in the long term. They activate receptors that regulate the transcription of genes involved in the metabolism of TG-rich lipoproteins (chylomicrons and VLDL) and HDL.[13] It should be noted that fibrates have not been proven to reduce cardiovascular events.
Strict monitoring and treatment of diabetes, along with an appropriate diet and weight loss, are essential in the long-term management of HTG.
Statin treatment does not have a direct effect on lowering TG levels. Statins inhibit HMG-CoA reductase activity and thus the synthesis of intracellular cholesterol, without impacting TG metabolism.[14] However, some high-intensity statins allow for a 20-40% reduction of TG levels, which is why this treatment is often added in high-risk patients.[15]
The investigation of a genetic component is not routine and is suggested only in cases of HTG without an identified metabolic or drug-related cause.
Several studies have investigated high-dose Omega-3 for the treatment of HTG. Despite conflicting results, it is currently recognized as a possible treatment and is used on a case-by-case basis in the long-term management of HTG.[16,17]
Regarding our patient, there was rapid improvement after plasmapheresis and IV insulin therapy. Fibrate treatment was introduced, and strict monitoring of her diabetes was implemented. Three months after her discharge from the hospital, the patient had a triglyceride level of 2.9 mmol/L.

Discussion:

Triglycerides are composed of fatty acids and glycerol. They are formed from our diet in the small intestine, as well as in the liver. They are primarily stored in adipose tissue and muscles and are an important source of energy. However, elevated TG levels, with or without increased LDL cholesterol, are a risk factor for complications such as pancreatitis or cardiovascular diseases.
Normal TG levels in the blood are below 1.7 mmol/L. The severity of HTG and its potential complications are assessed based on the circulating TG level.[18] HTG is considered severe at a level > 5.6 mmol/L and very severe at a level > 11.2 mmol/L. There are numerous causes of HTG that must be investigated to ensure optimal management.[19] Primary causes such as familial HTG or lipoprotein lipase deficiency are rare but should be considered in the absence of an identified secondary cause.
Secondary causes are numerous, such as uncontrolled diabetes, metabolic syndrome, hypothyroidism, or chronic kidney failure. Many medications, such as corticosteroids, oral oestrogens, or thiazide diuretics, can lead to increased triglyceride levels through various mechanisms. Each identified secondary cause should be treated to reduce TG levels and avoid complications.

The most feared acute complication of HTG is pancreatitis. Severe HTG is the third most common cause of pancreatitis after alcohol consumption and gallstones, accounting for about 10% of pancreatitis cases.[20,21] About 15-20% of patients with TG levels above 11.2 mmol/L will develop acute pancreatitis.

In this patient's case, HTG was quickly identified. Additionally, the medical history revealed several secondary causes. The main challenge encountered during the initial phase was the lack of access to the patient's laboratory results. This, along with the need to prevent a complication such as pancreatitis, justified performing plasmapheresis as quickly as possible.

Responses:

Question 1: **d** - Question 2: **c** - Question 3: **d** - Question 4: **e** - Question 5: **a**

Bibliography

[1] Motyckova G, Murali M. Laboratory testing for cryoglobulins. Am J Hematol 2011;86:500–2. https://doi.org/10.1002/ajh.22023.

[2] Mauro MJ. Hyperleukocytosis in Acute Myeloid Leukemia. N Engl J Med 2003;349:767–767. https://doi.org/10.1056/NEJMicm010149.

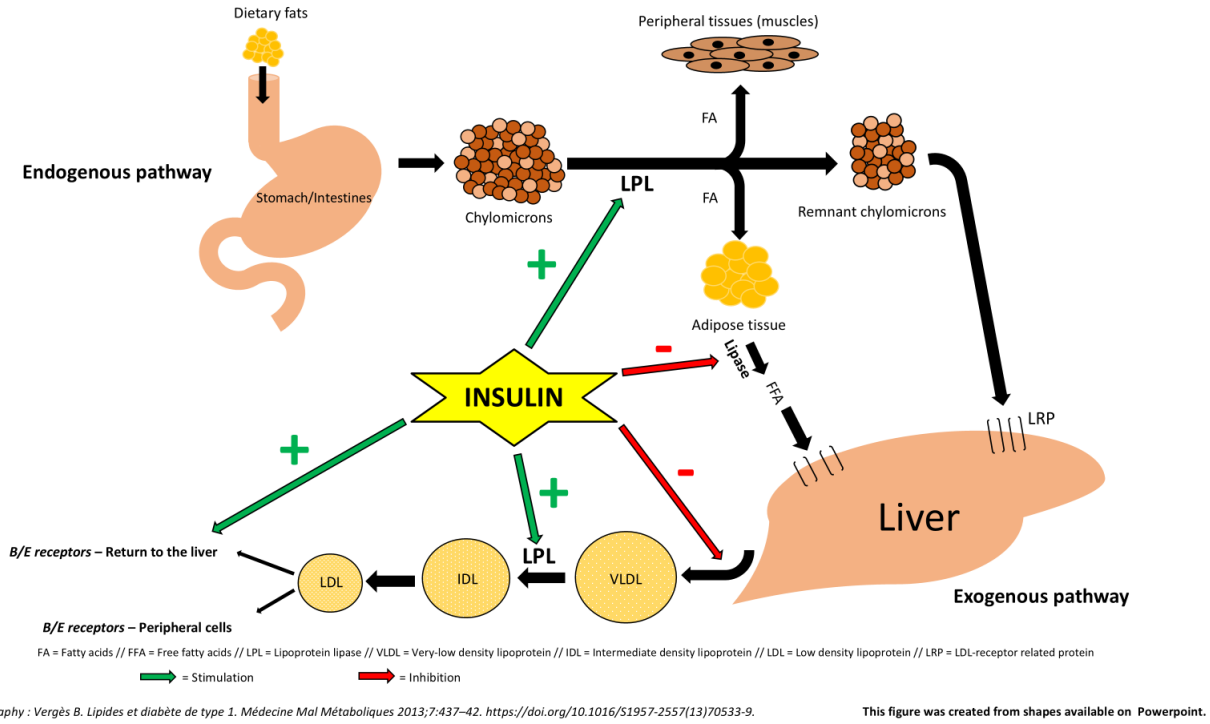
[3] Lankisch PG, Burchard-Reckert S, Lehnick D. Underestimation of acute pancreatitis: patients with only a small increase in amylase/lipase levels can also have or develop severe acute pancreatitis. Gut 1999;44:542–4. https://doi.org/10.1136/gut.44.4.542.

[4] Kim J-A, Kim J-E, Song SH, Kim HK. Influence of Blood Lipids on Global Coagulation Test Results. Ann Lab Med 2015;35:15–21. https://doi.org/10.3343/alm.2015.35.1.15.

[5] Cornes M, Simundic A-M, de la Salle B, Kristensen GBB, Guimaraes JT, Grankvist K, et al. European survey on preanalytical sample handling – Part 2: Practices of European laboratories on monitoring and processing haemolytic, icteric and lipemic samples. On behalf of the European Federation of Clinical Chemistry and Laboratory Medicine (EF. Biochem Medica 2019;29:334–45. https://doi.org/10.11613/BM.2019.020705.

[6] Vergès B. Physiopathologie de la dyslipidémie du syndrome métabolique et du diabète de type 2. Nutr Clin Métabolisme 2007;21:9–16. https://doi.org/10.1016/j.nupar.2007.01.011.

[7] Garg R, Rustagi T. Management of Hypertriglyceridemia Induced Acute Pancreatitis. BioMed Res Int 2018;2018:4721357. https://doi.org/10.1155/2018/4721357.
[8] Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue. J Clin Apheresis 2023;38:77–278. https://doi.org/10.1002/jca.22043.
[9] Devaud JC, Voirol P, Marques-Vidal P, Tappy L, Rodondi N, Berger MM, Chiolero R, Pannatier A. Facteurs de risque de l'hypertriglycéridémie dans une unité de soins intensifs (SI) : une étude exploratoire 2010.
[10] Huissoud C, Robert J-M, Bakrin N, Rudigoz R-C, Levrat A. Hypertriglycéridémies gestationnelles sévères : complications et principes de prise en charge. J Gynécologie Obstétrique Biol Reprod 2008;37:517–20. https://doi.org/10.1016/j.jgyn.2007.12.007.
[11] Gueguen Y, Ferrari L, Batt A-M. Mécanismes des hyperlipidémies dues aux immunosuppresseurs. Therapies 2004;59:463–9. https://doi.org/10.2515/therapie:2004078.
[12] Tziomalos K. Dyslipidemia Induced by Drugs Used for the Prevention and Treatment of Vascular Diseases. Open Cardiovasc Med J 2011;5:85–9. https://doi.org/10.2174/1874192401105010085.
[13] Fruchart J-C, Duriez P, Staels B. Mode d'action moléculaire des fibrates. J Société Biol 1999;193:67–75. https://doi.org/10.1051/jbio/1999193010067.
[14] Duriez P. Mécanismes d'action des statines et des fibrates. Therapies 2003;58:5–14. https://doi.org/10.2515/therapie:2003002.
[15] Hunninghake DB, Stein EA, Bays HE, Rader DJ, Chitra RR, Simonson SG, et al. Rosuvastatin improves the atherogenic and atheroprotective lipid profiles in patients with hypertriglyceridemia. Coron Artery Dis 2004;15:115–23. https://doi.org/10.1097/00019501-200403000-00008.
[16] Bhatt DL, Steg PhG, Brinton EA, Jacobson TA, Miller M, Tardif J, et al. Rationale and design of REDUCE-IT : Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. Clin Cardiol 2017;40:138–48. https://doi.org/10.1002/clc.22692.
[17] Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. JAMA 2020;324:2268. https://doi.org/10.1001/jama.2020.22258.
[18] Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, et al. Evaluation and Treatment of Hypertriglyceridemia: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2012;97:2969–89. https://doi.org/10.1210/jc.2011-3213.
[19] Rygiel K. Hypertriglyceridemia - Common Causes, Prevention and treatment Strategies. Curr Cardiol Rev 2018;14:67–76. https://doi.org/10.2174/1573403X14666180123165542.
[20] Andres Gelrud (MD, MMSc), David C Whitcomb (MD, PhD). Hypertriglyceridemia-induced acute pancreatitis n.d.
[21] Valdivielso P, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. Eur J Intern Med 2014;25:689–94. https://doi.org/10.1016/j.ejim.2014.08.008.
[22] Vergès B. Lipides et diabète de type 1. Médecine Mal Métaboliques 2013;7:437–42. https://doi.org/10.1016/S1957-2557(13)70533-9.



Legends for Figure 2:
FA = Fatty acids // FFA = Free fatty acids // LPL = Lipoprotein lipase // VLDL = Very-low density lipoprotein // IDL = Intermediate density lipoprotein // LDL = Low density lipoprotein // LRP = LDL-receptor related protein

This figure was created using shapes available in PowerPoint.
Reference for Figure 2: [22]

Author Contributions Statement

O.M. wrote the manuscript with the support of V.A.
M.B. and N.S. assisted in supervising the manuscript writing while providing revisions.
All authors discussed the results and contributed to the final version of the manuscript.
All authors approved the final version of the manuscript.