53F WITH HYPERTRIGLYCERIDEMIA & PANCREATITIS

Isabel Casimiro, MD PhD
October 13, 2016

HPI

- 53 year old female with PMHx most significant for hyperlipidemia (since infancy) & chronic pancreatitis 2/2 hypertriglyceridemia,
- Presents to the ER with persistent epigastric pain, nausea recurrent vomiting over the past few days,
- First started having pancreatitis ~ 2 years ago and is on a fibrate, statin, fish oil & pioglitazone.
- She reports that usually with her pancreatitis flares she puts herself on bowel rest for 2 to 3 days, then clear liquids, takes pain medications and sleeps a lot; This time the pain grew more intense & did not go away
- Underwent testing at the NIH as an infant.
- At that time in the 1960s there were only 5 people with her condition (she was the only female and only infant)
- She has followed a low fat diet her entire life to prevent “flares”
- Her flares consist of significant abdominal pain, and change in the color of her sclera (blueish) with floaters in her vision.

PMH

- Ectopic pregnancy
- GERD (gastroesophageal reflux disease)
- Hyperlipidemia
- Hypertriglyceridemia
- Legg-Calve-Perthes disease
- Ovarian cyst

FAMILY HISTORY

- Mother: Diabetes - Type 2, Hypertension, HCV cirrhosis
- Paternal Grandmother: T2Diabetes
- Son is in good health

SOCIAL HISTORY

- Used to work as a secretary and most recently in transportation of large materials via big rigs
- Ethnic background: German/Native American/Polish
- Smoker (tobacco & MJ), no alcohol

MEDICATIONS

atorvastatin (LIPITOR) 80 mg Oral tablet

BAYER ASPIRIN 81 mg by Oral route daily.

pioglitazone (ACTOS) 30 mg Oral tablet

fenofibrate (TRICOR) 145 mg Oral tablet

cyclobenzaprine (FLEXERIL) 10 mg Oral tablet

icosapent ethyl (VASCEPA) 2 g by Oral route twice daily.

lipase-protease-amylase (CREON) 36,000-114,000- 180,000 unit Oral cpDR

HYDROcodone-acetaminophen (ANEXSIA) 7.5-325 mg Oral tablet

LANSOPRAZOLE (PREVACID ORAL)

ondansetron-ODT (ZOFRAN-ODT) 4 mg Oral disintegrating tablet

ALBUTEROL

citalopram (CELEXA) 20 mg Oral tablet

sulindac (CLINORIL) 200 mg by Oral route twice daily.

PHYSICAL EXAM

Well developed female sitting upright in NAD, having received pain relief from IV Dilaudid given in ER.

HEENT unremarkable. PERRLA, EOMI, no conjunctivitis, no scleral icterus. Oropharynx clear.

Neck supple without adenopathy, no TM.

Chest with fair air movement bilaterally, somewhat decreased breath sounds throughout bilateral lung fields and clear, no wheezes, ronchi or rales.

Heart sounds with a normal S1 S2, RRR without murmur, gallop or rub.

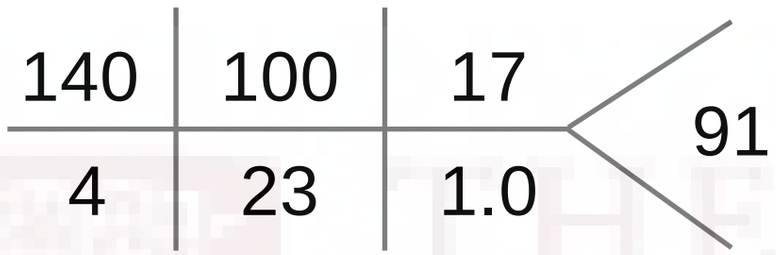
Abdomen soft, moderately distended with normoactive bowel sounds and focal tenderness to palpation of epigastrium and right upper quadrant. No rebound tenderness or guarding.

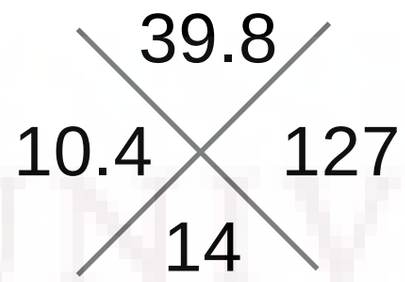
Extremities are asymmetrical, right greater and longer than left; both are thin and left shorter than right. No edema.

Skin warm and dry. No rash. No xanthomas.

Neurological: weakness on left leg, walks with a cane.

LABS ON ADMISSION





Protein 8.4

Albumin 4.7

tBili 1.4

Ca++ 8.4

Mg 1.4

Phos 4.7

Lipase 205

Cholesterol 221

HDL 16

LDL unable to calc

TGs 1607

cBili 1.3

ubili 0.1

Alk phos 133

AST 50

ALT 42

PATHOPHYSIOLOGY OF TG INDUCED PANCREATITIS

Excess TG is hydrolyzed by high levels of pancreatic lipase released in the vascular bed of the pancreas.

↓

Free fatty acids (FFAs) are formed in high concentrations, which overwhelm the binding capacity of albumin; they self-aggregate to micellar structures with detergent properties.

↓

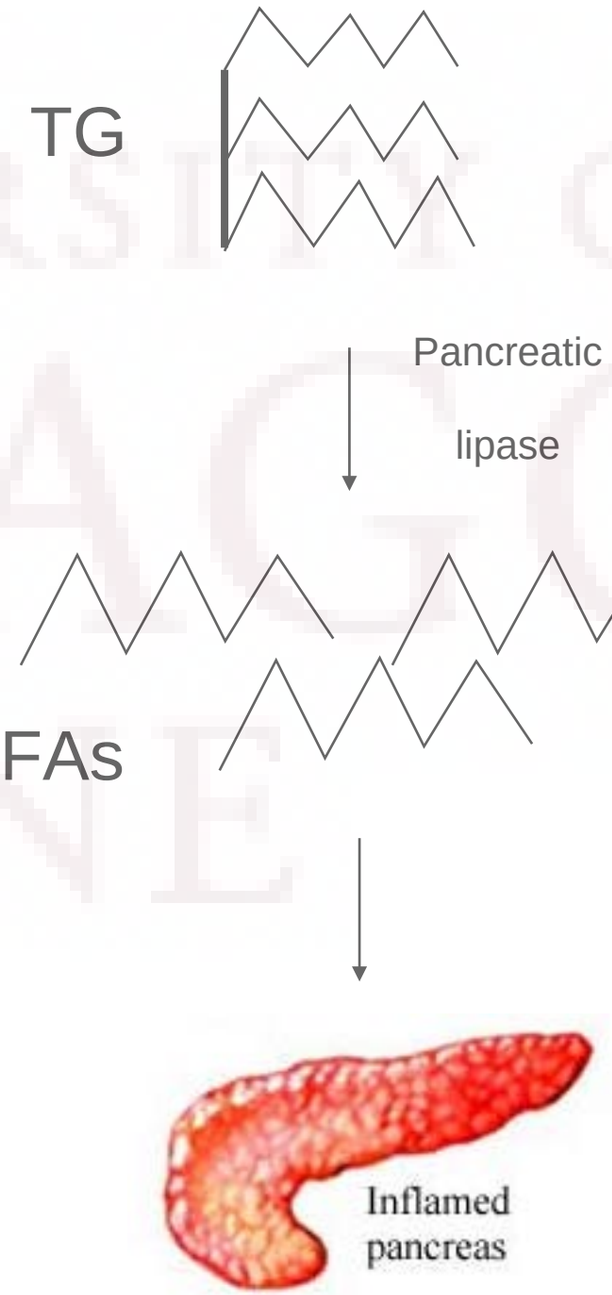
Acinar cell and pancreatic capillary injury is promoted.

↓

Resultant ischemia creates an acidic environment, which further triggers FFA toxicity

↓

Elevated levels of chylomicrons increase the viscosity of blood & therefore impair the blood flow in the pancreas causing ischemia and acidosis within the pancreas.



HYPERTRIGLYCERIDEMIA (HTG)

- HTG is third most common cause of acute pancreatitis

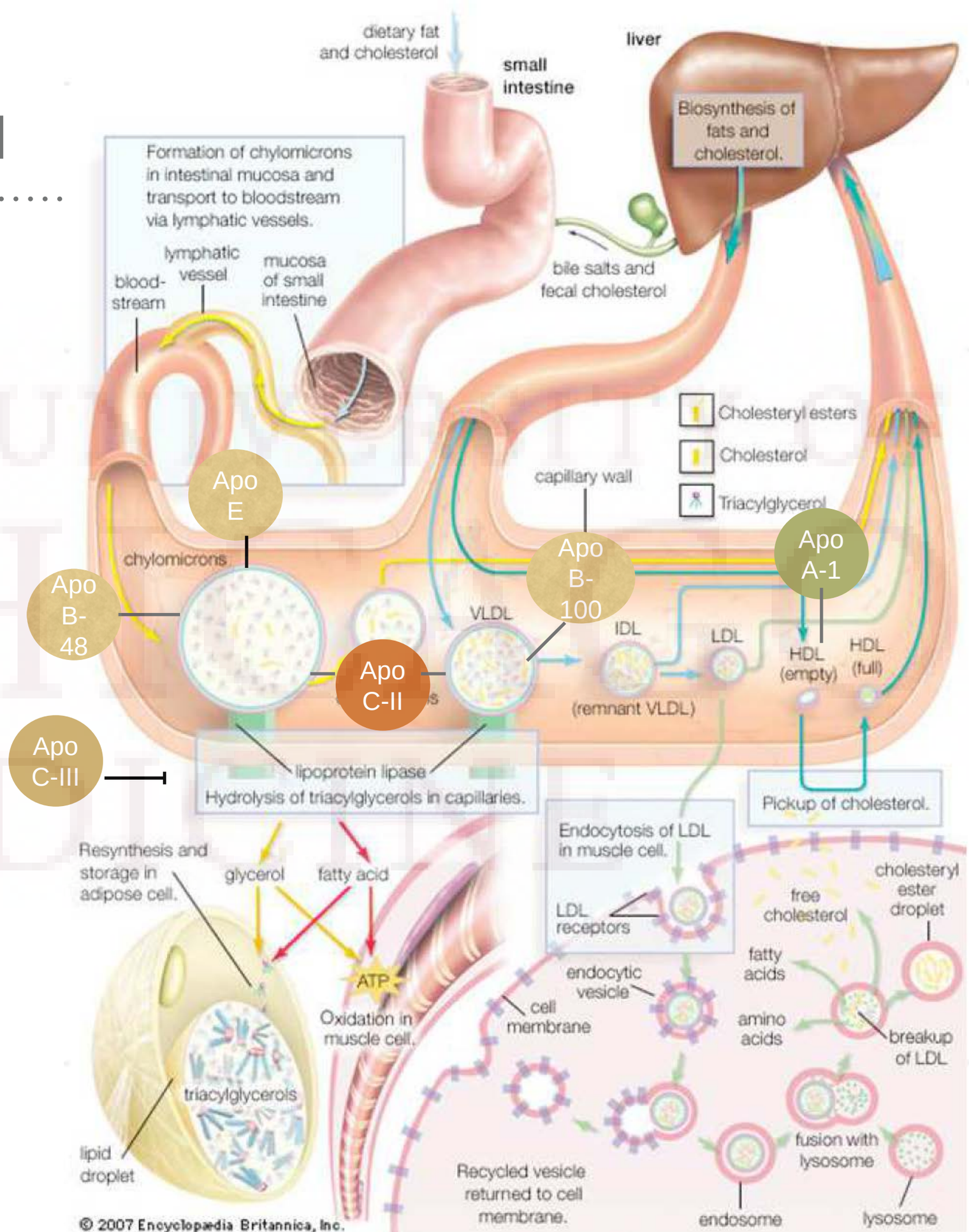
- Defined as fasting serum TG>150mg/dl (Endocrine Soc.)
  - Mild: 150-199mg/dl
  - Moderate: 200-999 mg/dl
  - Severe: 1000-1999 mg/dl

- TG > 1000mg/dl increased risk of acute pancreatitis

- Both primary (genetic) and secondary disorders of lipoprotein metabolism are associated with HTG-associated pancreatitis

LIPID METABOLISM

- TGs are predominantly carried in CMs & VLDL
- CMs & VLDL are transported to muscle & adipose & metabolized by LPL to meet energy demands or for storage
- They pass to venous circulation ultimately acquiring ApoC-II (critical LPL co-factor)
- ApoC-III inhibits LPL; Increased Apoc-III associated with impaired TG clearance



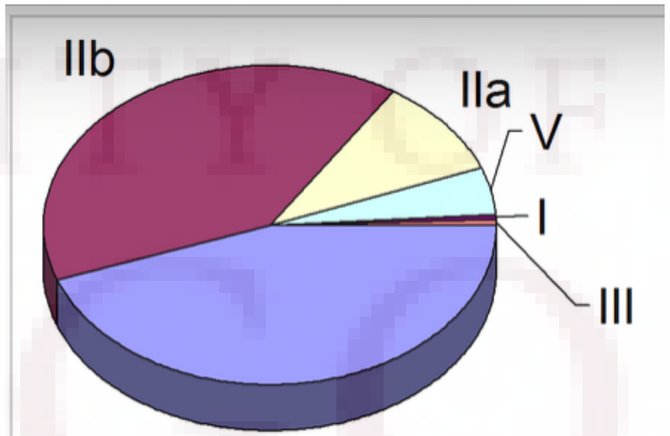
PRIMARY HTG (GENETICALLY BASED)

- Frederickson classification I (high chylomicrons)
  - Familial chylomicronemia or Type I hyperlipoproteinemia caused by LPL deficiency
  - Familial apoprotein CII deficiency (altered ApoC2)
  - often presents in infancy; lipemia retinalis, hepatosplenomegaly

- Frederickson type III (high IDL)
  - AKA Familial dysbetalipoproteinemia
  - Defect in ApoE2 synthesis

- Frederickson classification IV (high VLDL)
  - AKA Familial hypertriglyceridemia or familial combined hyperlipidemia
  - presents in adulthood

- Frederickson classification V (high CM & VLDL)
  - Probably plurigenetic



Relative prevalence of familial forms of hyperlipoproteinemia[6]

SECONDARY HTG

- DM with DKA
- Alcohol
- Hypothyroidism
- Hormone supplementation with estrogen or tamoxifen
- Some medications: clomiphene, protease inhibitors, propofol, olanzapine, mirtazapine, retinoids, thiazide diuretics, & beta blockers
- pregnancy

CONSULT QUESTION

- Does Pt need insulin drip for elevated TGs?

INSULIN

Use of insulin in treatment of severe hypertriglyceridemia in nondiabetic patients

Patient and reference	Triglyceride level at presentation	Method of insulin administration	Results
39-year-old woman "on contraception" for 5 years presenting with acute pancreatitis [3]	7699 mg/dL (87.5 mmol/L)	Insulin intravenous drip 3-9 units/h for 4 days, and maintain blood glucose 120-160 mg/dL (6.7-8.9 mmol/L)	Triglyceride levels decreased to ~4000 mg/dL (45.4 mmol/L) by day 1, and 246 mg/dL (2.8 mmol/L) by day 4
13-year-old adolescent [4]	1893 mg/dL (21.5 mmol/L)	Single dose of regular insulin (0.1 units/kg)	Triglyceride levels decreased to 1015 mg/dL (11.5 mmol/L) in 4 hours
Present case: 39-year-old woman on estrogen-containing contraceptive patch presenting with acute pancreatitis	10 560 mg/dL (120 mmol/L)	10% dextrose infusion at 200 mL/h and insulin lispro 4 units subcutaneously every 4 hours for every 50 mg/dL of blood-glucose increment above 150 mg/dL	Triglyceride levels decreased to 1479 mg/dL (16.8 mmol/L) by day 1, and 712 mg/dL (8.1 mmol/L) by day 2, 718 mg/dL (8.1 mmol/L) by day 3, and 656 mg/dL (7.4 mmol/L) by day 4

Mikhail, N et al. Treatment of severe hypertriglyceridemia in non diabetic patients with insulin.

Am J Emerg med 2005; 23:415-417

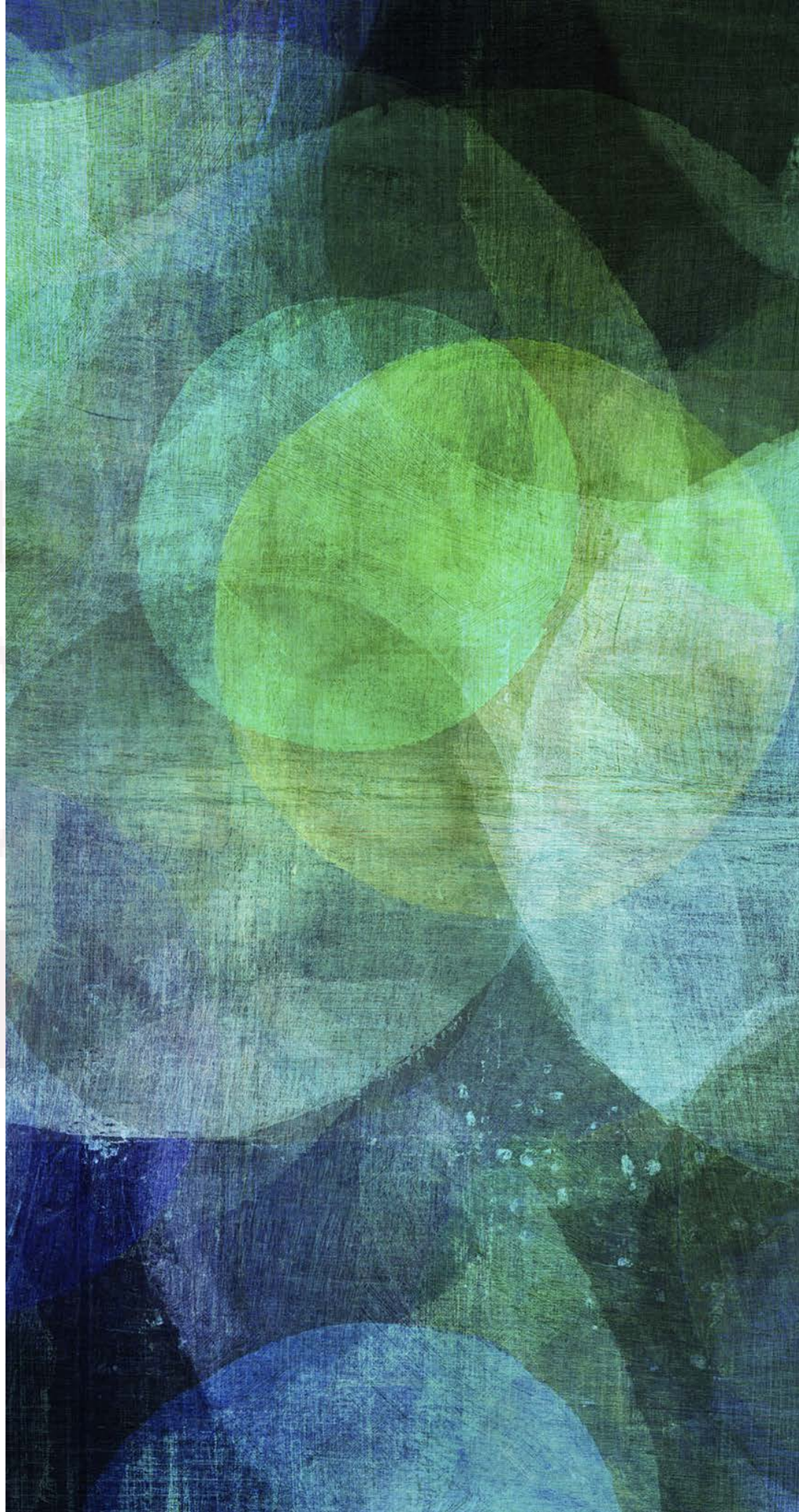
- Insulin activates LPL which accelerates CM & VLDL degradation
- Inhibits pancreatic lipase in adipocytes to reduce TG breakdown and release of FFA

INPATIENT TREATMENT OF HTG-AP

- Conventional: Hydration, analgesia, NPO

- Criteria for apheresis or insulin drip:
  - TG level >1000 mg/dl
  - & lipase >3x ULN
  - & signs of ischemia, lactic acidosis, or signs of organ dysfunction

- Insulin drip should be initiated at rate of 0.1-0.3U/kg/hr with D5 if BG<200 with Q1hr BG checks; TGs monitored Q12-24hrs; insulin drip stopped when TGs<500



APHERESIS

Table 5 Comparison of patients with severe hyperlipidemic pancreatitis receiving plasma exchange and not receiving plasma exchange.

Ranson >3	Group A: PE (+) (%, *n* = 10)	Group B: PE (-) (%, *n* = 19)	*P* value
Mortality	30(3)	15.8(3)	0.369
Systemic complications	70(7)	42.1(8)	0.153
Local complications	10(1)	21.1(4)	0.454

PE (+): With plasma exchange; PE (-): Without plasma exchange.

The mean serum concentration of TG and lipase fell significantly after plasma exchange. The serum TG level declined from 2 019 ± 780 mg/dL to 691 ± 331 mg/dL (65.8% reduction) and the serum lipase level declined from 4 007 ± 355 U/L to 447 ± 35 U/L (88.8% reduction).

Chen et al. Therapeutic plasma exchange in patients with hyperlipidemic pancreatitis. World J Gastroenterol 2004; 10:2272-2274

- Achieves rapid decrease in CM & TG levels by direct elimination
- There is no benefit in overall mortality & complications
- Expensive & not widely available; Controversy in technical details (plasma exchange vs double membrane filtration)

Table 1 Available treatment modalities for hypertriglyceridemic pancreatitis

Treatment modality	Mechanism of action	Comment	Limitations
Apheresis	Direct elimination of TG, removing of the causative agent	Potent treatment modality, must be used early in HTGP	Limited availability, invasive and expensive tool
Insulin	Activation of LPL leading to an acceleration of chylomicron degradation	Useful especially in the treatment of poorly controlled diabetic patients with HTG	Only of limited efficiency
Heparin	Stimulation of release of endothelial LPL	Not recommended as a monotherapy	Cave: increased LPL degradation and depletion of LPL plasma stores

Essential concomitant treatment: Conventional treatment of acute pancreatitis, including aggressive hydration, potent analgesia and evaluation of further underlying causes (e.g. gal necessity of ERCP). Treatment of underlying HTG (screening for secondary causes). ERCP, endoscopic retrograde cholangiopancreatography; FA, fatty acids; FFA, free fatty a 3-methylglutaryl; HTG, hypertriglyceridemia; HTGP, hypertriglyceridemic pancreatitis; LPL, lipoprotein lipase; MCT, medium-chain triglycerides; TG, triglycerides.

Severe hypertriglyceridemia and pancreatitis: presentation and management.
Ewald, Nils; Hardt, Philip; Kloer, Hans-Ulrich

Current Opinion in Lipidology. 20(6):497-504, December 2009.
DOI: 10.1097/MOL.0b013e3283319a1d

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Oral Pharmacological Agents			
Fibrates	Increase of LPL level, decrease in hepatic TG synthesis by induction of hepatic FFA oxidation and stimulation of reverse cholesterol transport	Considered drugs of first choice	Slow onset of TG lowering
Omega-3-FA	Reduced hepatic TG synthesis, enhanced peroxisomal β-oxidation, increased LPL activity and adipose tissue LPL expression	Potent drug with no side effects, immediate onset of action	No limitations
Nicotinic acid	Reducing VLDL secretion via receptor	Reliable long-term effect on TG level	Prominent side effects such as facial flushing, slow onset of TG lowering
HMG-CoA reductase inhibitors	Inhibition of cholesterol synthesis	Only of use in combination with other drugs such as fibrates in order to achieve synergistic effects	Higher risk of myositis or myopathy, no drug of first choice
MCT	No chylomicron formation, no chylomyicron synthesis, induction of mitochondrial β-oxidation of FA	Immediate onset of action on TG levels	No limitations

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Rich sources for commercial extraction of beneficial MCTs include palm kernel oil and coconut oil.

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EFFICACY OF ORAL AGENTS (SUMMARY FROM 3 META ANALYSIS)

	Statins[a]	Fibrates[b]	Niacin[b]	Omega-3 fatty acids (baseline TG < 2.0 mmol/L)[c]	Omega-3 fatty acids (baseline TG ≥ 2.0 mmol/L)[c]
Number of studies	91	53	30	16	20
Agents included in studies	Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin	Bezafibrate, Ciprofibrate, Clofibrate, Fenofibrate, Gemfibrozil	Acipimox, ER-niacin, IR-niacin, SR-niacin	Ropufa, MaxEPA, Promega, cod liver oil, Omacor, Efamed, ResQ, EPA ethyl ester	MaxEPA, Promega, Epagis, Fatty acid ethyl ester, Almarin
Number of participants					
Total	45,405	16,802	4749	281	254
Mean	510	304	144	18	13
Range	20–10,269	11–4081	11–2248	5–43	6–32
Duration of studies, weeks					
Total	4385	2643	916	155	133
Mean	50	47	28	10	7
Range	12–281	3–222	8–312	2–52	2–26
Dose, mg/day, Range	0.025–80	50–2000	100–4500	1.6–7	2.4–6
Mean baseline TC levels of studies, mmol/L					
Mean[a]	6.1 to 7.5	6.1	6.8	5.3	6.5
Range	NA	3.8–12.2	3.7–9.1	3.8–6.3	4.9–8.5
Mean baseline TG levels of studies, mmol/L					
Mean[a]	1.8 to 2.1	2.2	2.7	1.3	3.9
Range	NA	1.1–28.2	1.6–6.7	0.7–1.9	2.1–6.5
Mean baseline LDL-C levels of studies, mmol/L					
Mean[a]	4.0 to 5.3	3.8	4.3	3.5	4.0
Range	NA	2.4–6.6	1.9–6.2	2.0–4.5	2.6–5.8
Mean baseline HDL-C levels, mmol/L					
Mean[a]	1.0 to 1.3	1.1	1.1	1.2	0.9
Range	NA	0.6–1.6	0.7–1.3	1.0–1.5	0.7–1.4
Mean change in lipid parameters, %					
TC	−17 to −31	−10.8	−9.7	1.4	−1.0
TG	−10 to −18	−36.3	−20.0	−25.2	−33.8
LDL-C	−26 to −46	−7.8	−12.4	4.5	10.8
HDL-C	6 to 12	10.0	15.7	2.9	1.2

Ito, M. Long chain omega 3 fatty acids, vibrates and niacin as therapeutic options in the treatment of H
A review of the literature. Athero 242(2);Oct 2015; 647-656

BACK TO OUR PATIENT

Labs from Oct 2015

	Laboratory Test	Notes	High Risk	Intermediate Risk	Optimal	High Risk Range	Intermediate Risk Range	Optimal Range	Previous Results
Lipids	Total Cholesterol (mg/dL)			231		≥ 240	200 - 239	< 200	
	LDL-C Direct (mg/dL)				12	≥ 130 CHD & CHD risk eq. > 100	100 - 129 CHD & CHD risk eq. 70 - 100	< 100 CHD & CHD risk eq. < 70	
	HDL-C (mg/dL)		18			< 50		≥ 50	
	Triglycerides (mg/dL)		2519			> 199	150 - 199	< 150	
	Non-HDL-C (mg/dL) (calculated)		212			≥ 160	130 - 159	< 130	
Lipoprotein Particles and Apolipoproteins	Apo B (mg/dL)				28	≥ 80	60 - 79	< 60	
	sdLDL-C (mg/dL)[5]				11	> 30	21 - 30	< 21	
	Apo A-I (mg/dL)		103			< 130	130 - 150	> 150	
	HDL2-C (mg/dL)[5]		6			≤ 12	13 - 16	≥ 17	
	Apo B:Apo A-I Ratio (calculated)				0.27	≥ 0.81	0.61 - 0.80	≤ 0.60	
	Lp(a)-P (nmol/L)[5]				< 50	> 125	75 - 125	< 75	

	Laboratory Test	Notes	High Risk	Intermediate Risk	Optimal	High Risk Range	Intermediate Risk Range	Optimal Range	Previous Results
Index	HS-Omega-3 Index® (RBC EPA+DHA)[8]		2.2			< 4.0%	4.0% - 8.0%	> 8.0%	

Comments:

Your HS-Omega-3 Index is well below the target range of 8%.

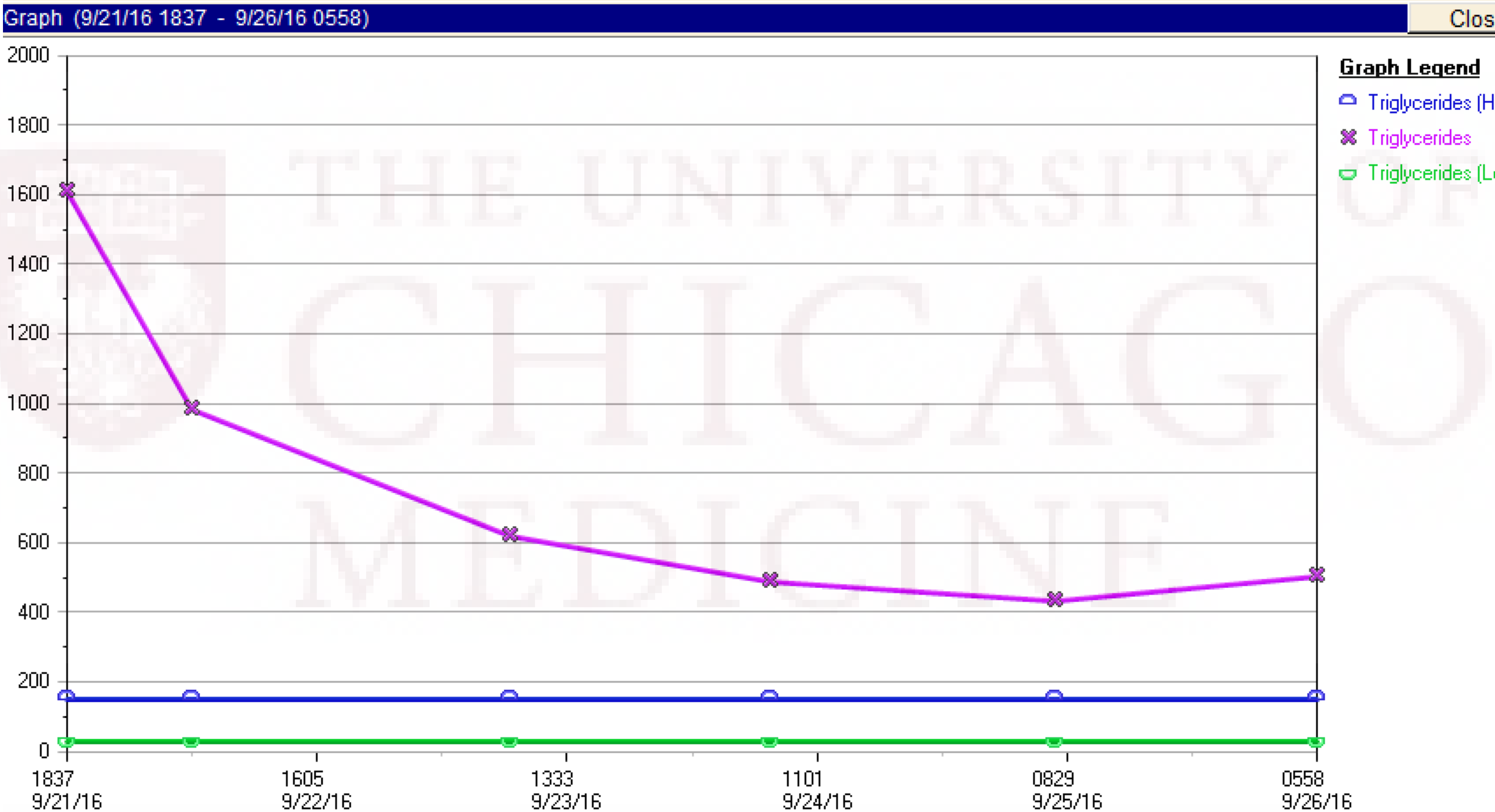
The HS-Omega-3 Index is the EPA+DHA content of RBC membranes. Increasing the intake of EPA+DHA by 1 to 2 grams (1,000 - 2,000 mg) per day, from

HOSPITAL COURSE

- Recs: Continue fibrate, statin, pioglitazone & consider adding fish oil/omega 3 FAs (on vascepa at home); Insulin drip not recommended at this time given TGs are downtrending & currently not meeting indications

- Why Pioglitazone?
  - A significant reduction in TGs has been observed with acarbose, pioglitazone, and DPP-4 inhibitors; Pioglitazone (PPAR-gamma agonist) has also been shown to increase HDL-C in 3 meta analysis (Effects of lipid profile of DPP-4 inhibitors, pioglitazone, acarbose & sulfonylureas: Meta analysis of placebo controlled trials; Monami et al Adv Therapy 2012; 29(9): 736-746)

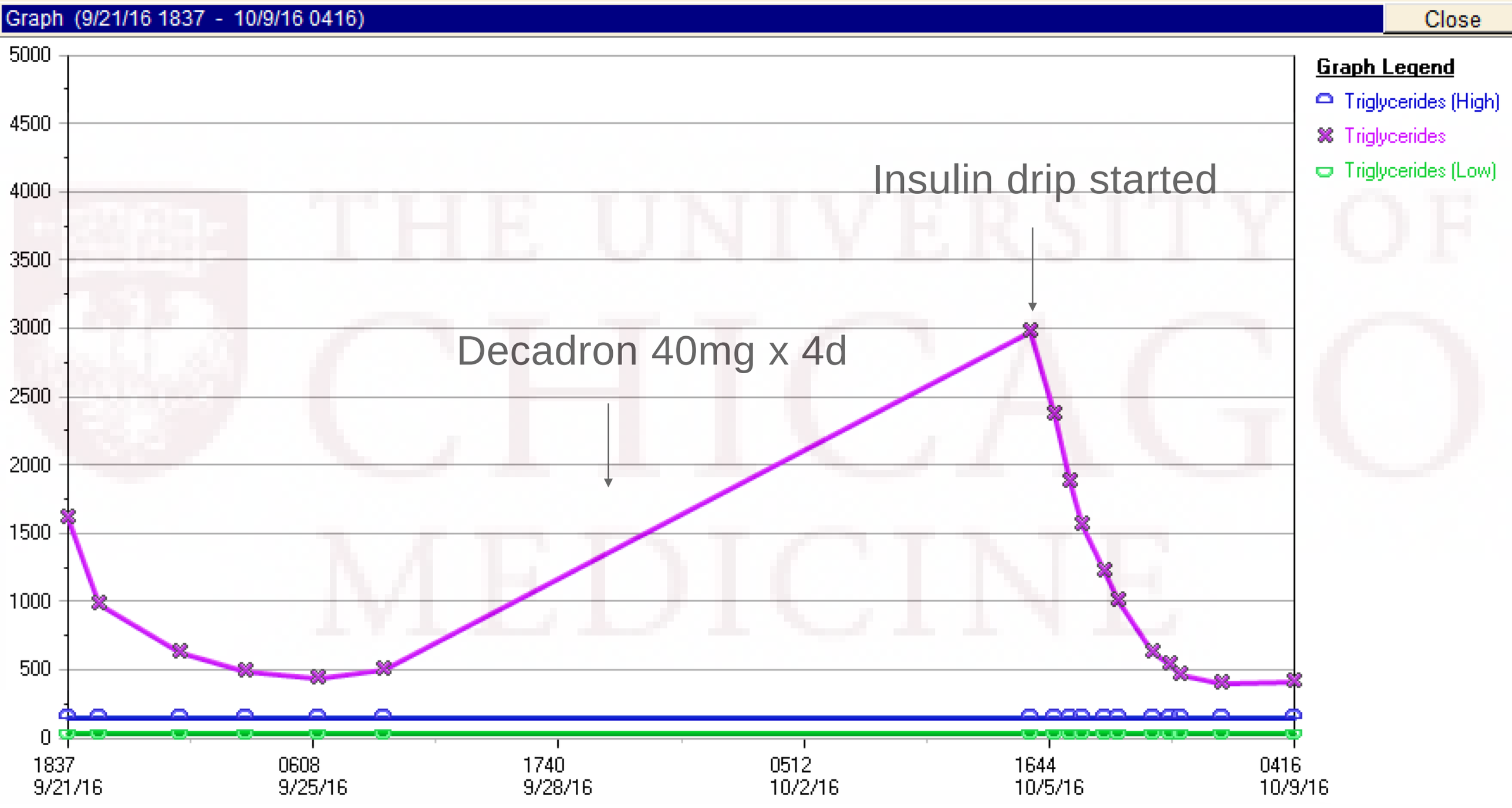
HOSPITAL COURSE



CONTINUED HOSPITAL COURSE

- Pt found to have splenic vein thrombosis & splenomegaly; MRCP showed peri-pancreatic fluid collections
  - Pancreatic duct stent placement with NJ feeding tube placement
- Pt developed pancytopenia; thought to be due to splenic sequestration; conservative management recommended
- PLTs continued to downtrend (127 ->50s -> 17); BM biopsy performed, concern for immunogenic process; ITP? steroids recommended

HOSPITAL COURSE



CONTINUED HOSPITAL COURSE

- Pt given IVIG for ITP

- She was started on TPN, now with rising BGs, currently controlled on pioglitazone & 2U lantus/Qd

DIETARY RECOMMENDATIONS FOR PTS WITH HTG

- Dietary Recommendations: Strict adherence to a low fat diet consisting of:
  - Approximately 15% of total calories and between 10 and 15 g of fat daily.
  - Both unsaturated and saturated fats should be limited.
  - Medium-chain triglycerides (MCT), which are also capable of decreasing TG levels effectively should be added in order to give sufficient calories

PHARMACOLOGIC RECOMMENDATIONS FOR PTS WITH HTG

Guideline	Category	Recommendation
Endocrine Society	TG 150-199 mg/dl	Lifestyle Intervention
	TG 200-1999 mg/dl	Fibrate, niacin or long chain omega-3-FA, alone or in combination with statin should be considered
	TG >1000 mg/dl	Fibrate as first line therapy; drug therapy & reduction of dietary fat
American Association of Clinical Endocrinologists (AACE)	All	Lifestyle Intervention
	TG 150-499 & HDL<40 men <50 women	Niacin or fibrates in combination with statins
	TG > 499mg/dl	Fibrates +/- 2-4g long chain omega-3-FAs if necessary
National Lipid Association	TG 200-499 mg/dl	Statins as first line therapy; TG lowering agent if max tolerated statin does not lower HDL-C below goal
	TG >500 mg/dl	Low fat diet (<15%); TG lowering agent (fibrate, LC omega-3-FAs or niacin) or statins as fist line therapy
	TG >1000 mg/dl	Fibrates, high dose LC omega-3 FAs (2-4g/d), or niacin as first line therapy
American Heart Association	All	Lifestyle Intervention
	TG 200-499 & HDL<40 men <50 women	Statin or fibrate monotherapy
Association	TG > 500mg/dl	Intensive therapeutic lifestyle intervention & pharmacological therapy with TG-lowering agent

APOLIPOPROTEIN C-III

- Apolipoprotein C-III (APOC3) is a key regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma triglyceride levels.

- Elevated levels of APOC3 in plasma have been associated with both impaired lipolysis and impaired clearance of triglyceride-rich lipoproteins from the circulation. This impairment results in the accumulation of atherogenic VLDL and chylomicron remnants.

- Phase 1 clinical trial currently underway: Placebo-Controlled, Dose-Escalation Study to Assess Safety, Tolerability, PK and PD of a GalNAc3 Conjugated Antisense Oligonucleotide Targeting ApoC-III, Administered Subcutaneously to Healthy Volunteers with elevated TGs

CONCLUSIONS

- Hydrolysis of TGs by pancreatic lipase & accumulation of FFAs that induce inflammatory changes are thought to account for the development of HTG-associated pancreatitis
- Several studies have shown that apheresis and insulin drips can lower TGs in the acute setting
- Pharmacologic therapy for HTG includes fibrates, statins, niacin, & fish oil (omega-3FAs); Addition of DDP4 inhibitors & piaoglitazone may further reduce TG levels & increase HDL
- A new clinical trial is currently accepting patients with HTG to evaluate the effect of inhibition of ApoC3 on TG levels

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LEARNING OBJECTIVES

- To review types of lipid disorders that can cause hypertriglyceridemia
- To learn about the inpatient management of hypertriglyceridemia associated acute pancreatitis
- To learn about pharmacological agents for the treatment of hypertriglyceridemia

	Type I	Type IV	Type V
Elevated lipoproteins	Chylomicrons	VLDL	VLDL Chylomicrons
Cholesterol	Normal	Normal or Increased	Normal
Triglycerides	+++	++	+++
Plasma appearance †	Clear plasma, creamy supernatant	Turbid	Turbid plasma, creamy supernatant
Genotype	LPL deficiency Apo C-II deficiency	FCH Sporadic HTG	Familial HTG
Age of onset (primary form)	Infancy or childhood	Usually adulthood	Usually adulthood
Xanthomas ‡	Eruptive or tuberous	None usually	Eruptive or tuberoeruptive
Other clinical features	Recurrent abdominal pain Pancreatitis Lipemia retinalis Hepatosplenomegaly	Premature CAD Pancreatitis Obesity Glucose intolerance Arthritic symptoms Gall bladder disease Hyperuricemia	Recurrent abdominal pain Pancreatitis Lipemia retinalis Hepatosplenomegaly Peripheral paresthesis Glucose intolerance Hyperuricemia

*Adapted from Reference 12

† Plasma obtained after 12 hours of fasting, left undisturbed in refrigerator overnight

‡Seen only in a minority of patients, frequency increases as plasma lipid levels rise

LPL, lipoprotein lipase; HTG, hypertriglyceridemia; Apo C-II, apolipoprotein CII; CAD, coronary artery disease; FCH, familial combined hyperlipidemia.

Table 3. Familial Hyperlipidemias*

Hypertriglyceride Induced Acute Pancreatitis. Lebenson, J & O. Thomas. 2012. Prof. Luis Rodrigo (Ed.), ISBN: 978-953-307-984-4