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Hypertriglyceridemia-Induced Pancreatitis Prompted by Acute Corticosteroid Treatment: Caution for Clinicians

Running Title: Steroid-Triggered Pancreatitis in Hypertriglyceridemia

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To the Editor:

We report two novel cases of hypertriglyceridemia-induced pancreatitis induced by corticosteroid taper. Both patients had known dyslipidemias, and were later referred to the University of Michigan Lipid Management Clinic unaware of the risks of corticosteroids in their condition(1). These cases highlight the need to be cognizant that even short-term corticosteroids can precipitate hypertriglyceridemia-induced pancreatitis in susceptible individuals.

Patient Presentations:

Characteristics of the two patients are summarized in the **Table.** Patient 1 is a 41-year-old woman with underlying type-IV hyperlipidemia who presented to the Emergency Department (ED) for urticaria after poison oak exposure and was discharged on a 10-day course of prednisone (60mg x1d, 40mg x5d, and 20mg x1d). Four days after beginning her corticosteroid taper, she was hospitalized for acute-onset abdominal pain. Triglycerides (49.0 mmol/L) and lipase (7.45 μkat/L) were elevated, and computed tomography (CT) of the abdomen/pelvis confirmed acute pancreatitis. She denied recent illness or changes in diet, alcohol, medications, or blood glucose. Triglycerides immediately prior to treatment were unknown; her most recent triglycerides were 2.88 mmol/L on gemfibrozil 600mg twice daily, measured 13 days prior to her admission to the hospital. Neither the patient or her inpatient team realized the trigger of her pancreatitis until a retrospective chart review in lipid clinic follow-up several months later.

Patient 2 is a 54-year-old woman with a history of type-V hyperlipidemia and two previous episodes of hypertriglyceridemia-induced pancreatitis, beginning at age 47. She developed a COPD exacerbation and was

prescribed a 7-day course of prednisone 50mg daily. While completing her corticosteroid burst treatment (exact date of prednisone prescription unknown), she developed acute-onset abdominal pain and presented to the ED, where she had elevated levels of amylase (15.2 μkat/L), lipase (46.1 μkat/L), and triglycerides (72.4 mmol/L). Triglyceride levels from two months prior to her admission to the hospital were 7.96 mmol/L on fenofibrate nanocrystals 145mg once daily. She endorsed recent decreased oral intake, but otherwise denied any changes in alcohol, medications, or blood glucose. No linkage between corticosteroids and hypertriglyceridemia-induced pancreatitis was considered by her inpatient team.

Differential diagnosis for chylomicron syndrome precipitation in patients with underlying dyslipidemias include poor diet and/or fat intake, alcohol use, noncompliance with medications, pregnancy and/or worsening diabetes control, systemic estrogen use, and rarely, hypothyroidism or nephrotic syndrome. As noted above, both patients denied these factors as precipitants of their acutely elevated triglyceride levels and resulting pancreatitis. Calculation of the Naranjo Adverse Drug Reaction (ADR) Probability Scale(2) resulted in a score of 5 (see **Supplemental Table**), indicating a "probable" ADR due to corticosteroid use due to the reasonable temporal sequence and lack of alternate reasonable causes of pancreatitis. We note that although it is "probable" by the Naranjo scale that corticosteroids caused acute pancreatitis in these two patients, this score is artificially low due to the lack of: 1) prior conclusive case reports in the dyslipidemic population, 2) trials of prednisone discontinuation/dose reduction/re-administration, 3) antagonist or placebo administration, and 4) prednisone blood level measurement.

Management/Interpretation:

Studies of patients without known dyslipidemias note an increase in triglyceride levels with chronic corticosteroid use. Of note, triglyceride levels on average were <2 mmol/L(3), making corticosteroid-induced pancreatitis unlikely in a non-dyslipidemic population(4). In contrast, the lipid-altering effects of corticosteroids

in patients with baseline hypertriglyceridemia are poorly described. Despite the theoretical linkage, we are unaware of prior reports of a brief course of oral corticosteroids being implicated as the sole trigger of hypertriglyceridemia-induced pancreatitis, except in chemotherapy patients(1). Unfortunately, neither our patients nor their healthcare providers realized recent corticosteroid usage was a potential trigger for pancreatitis. We acknowledge that our diagnoses were made by retrospective histories/chart reviews; however, the temporal course of events strongly support our conclusions, as noted by a Naranjo scale of 5, indicating a "probable" ADR despite a likely underestimated score due to numerous "do not know" responses.

These cases show that a short-term course of oral corticosteroids has the potential to trigger hypertriglyceridemia-induced pancreatitis in susceptible patients. While no evidence-based algorithm exists, several prudent recommendations can be made. Foremost, hyperlipidemic patients should be educated about the risks. If treatment is required, providers should obtain baseline triglyceride and glucose levels, control underlying factors (e.g., diet, alcohol, and diabetes), reduce/discontinue other offending medications (e.g., oral estrogens), and carefully monitor triglycerides. If triglycerides increase >11 mmol/L, discontinuation of oral corticosteroids should be strongly considered(5). The benefits of starting/intensifying triglyceride-lowering medications (e.g., fibrates, EPA/DHA) before/during therapy and/or prophylactic apheresis in severe cases remain unknown. Finally, we recommend against prescribing corticosteroids if baseline triglycerides are >5.5 mmol/L(5), unless required for a life-threatening illness. In conclusion, these cases highlight the importance that health care providers and patients alike be aware of the potential dangers of oral corticosteroid treatment among individuals with dyslipidemias.

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Table. Baseline Characteristics and Testing Results upon Presentation for Acute Pancreatitis

	Patient 1	Patient 2
Baseline Characteristics	41-year-old woman DM, PCOS	54-year-old woman DM, COPD
BMI, kg/m^2	27.9	28.5
Frederickson Phenotype	Type IV	Type IV (prior history of type V)
Baseline Lipid Profile *		
Total cholesterol, mmol/L	5.43	7.37
Triglycerides, mmol/L	2.88	7.96
Lipid-lowering Medications **	Gemfibrozil 600mg BID	Fenofibrate nanocrystals 145mg q-day
Other Relevant Medications	Estrogen OCPs, insulin detemir, dapaglifozin	
Prior Pancreatitis	No	Twice
Acute Presentation		
Corticosteroid Indication	Urticarial rash	COPD flare
Amylase, μkat/L	-	15.2
Lipase, μkat/L	7.45	46.1
Triglycerides, mmol/L	49.0	72.4
CT scan findings	Acute uncomplicated pancreatitis	Not documented

Abbreviations: BID=twice a day; BMI=body mass index; COPD=chronic obstructive pulmonary disease; DM=diabetes mellitus type 2, q-day=once daily; OCP=oral contraceptive pills; PCOS=polycystic ovary syndrome. Other abbreviations in the text

* Documented within one month prior to their acute pancreatitis episode

** Neither patient was on other lipid-altering medications (e.g., statins, fish oils) at the time of their acute pancreatitis episode

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