**SUMMARY (Clinical) 7/11/25**

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**Source:** Macke, C. A., Al-Gadi, I., Bansal, N., Lyons, S. K., & Nella, A. A. (2025). Research Article: Hypertriglyceridemia in New-Onset Type 1 Pediatric Diabetes. *Pediatric Diabetes*, 2025, Article ID 8425032, 7 pages.

**I. Executive Summary**

This research article highlights the occurrence of severe hypertriglyceridemia (HTG), defined as triglyceride (TG) levels above 1000 mg/dL, in pediatric patients newly diagnosed with Type 1 Diabetes Mellitus (T1D), often presenting with diabetic ketoacidosis (DKA). While HTG is common in new-onset diabetes, severe cases in pediatric T1D are rare and not well-characterized. The study presents a single-center experience of five such cases between 2013 and 2022, alongside a review of existing literature. The key findings emphasize the importance of early HTG screening in this population, particularly in the presence of certain risk factors, to mitigate the risk of complications such as acute pancreatitis and to guide optimal management strategies. Insulin deficiency is identified as the primary driver of HTG in these cases, though genetic predisposition may also play a role in some instances.

**II. Main Themes and Most Important Ideas/Facts**

**A. Incidence and Characteristics of Severe HTG in Pediatric T1D**

* **Rarity of Severe HTG:** Severe HTG (TG > 1000 mg/dL) and very severe HTG (TG > 2000 mg/dL) are considered rare in new-onset diabetes, particularly in the pediatric population. The true incidence in pediatric T1D is currently unknown.
* "Severe HTG (defined as TG levels above 1000mg/dL) in pediatric patients with new-onset type 1 diabetes mellitus (T1D) is rare; the true incidence and sequela of this phenomenon have not been well characterized."
* "Severe and very severe HTG...are considered rare in the setting of new-onset diabetes with or without dia-betic ketoacidosis (DKA) and are associated with absolute insu-lin deficiency."
* **Association with DKA:** All five cases presented in this study, and many from the reviewed literature, involved new-onset T1D with DKA. This suggests a strong correlation between severe insulin deficiency (as seen in DKA) and the development of severe HTG.
* **Pathophysiology:** Insulin deficiency in diabetes leads to HTG through two primary mechanisms:

1. **Lipolysis Activation:** Increased free fatty acid (FFA) levels due to activated lipolysis in adipose tissue lead to accelerated formation of very-low-density lipoprotein (VLDL) by the liver.
2. **Decreased LPL Activity:** Reduced lipoprotein lipase (LPL) enzyme activity impairs plasma clearance of VLDL and chylomicrons.

* "Insulin deficiency in diabetes can result in hypertriglyceridemia (HTG), as insulin is an anti-lipolytic agent and regulator of lipoprotein lipase (LPL) enzyme actions."

**B. Complications Associated with Severe HTG**

* **Acute Pancreatitis:** Severe HTG carries a significant risk of acute pancreatitis, with the risk increasing with higher TG levels (5% risk at TG ≥ 1000 mg/dL, 10-20% at TG ≥ 2000 mg/dL in adults). Pancreatitis can be the initial presentation of new-onset diabetes and is a serious complication, potentially leading to shock, circulatory failure, respiratory distress, and multi-organ failure.
* "Severe HTG (TG levels ≥ 1000mg/dL) carries a 5% risk of acute pancreatitis in adults, and this risk rises to 10%–20%with TG ≥ 2000mg/dL [3]."
* "Delayed initiation of pancreatitis treatment increases patient’s morbidity and mortality risk as it can result in grave complications, such as shock, circulatory failure, severe respiratory distress, or multi-organ failure [7, 23]."
* **Diagnostic Challenges:** Abdominal pain is a common symptom of DKA, potentially masking pancreatitis.
* "Concomitant pre-sentation of DKA and pancreatitis presents a challenge for physicians, as a common symptom of DKA is abdominal pain, so pain due to pancreatitis may be falsely attributed to DKA."
* **Laboratory Interference:** Severe HTG can interfere with the accuracy of laboratory electrolyte measurements and HbA1c assays.
* "Other severe HTG-related adverse effects include interference with the reliability of laboratory electrolyte measurements and HbA1c assays, and lipemia retinalis [11–13]."

**C. Management and Treatment**

* **Insulin Therapy and Fasting:** The primary treatment for severe HTG in this context is insulin therapy combined with fasting. Continuous intravenous (IV) insulin infusion is often required, potentially extending beyond DKA resolution, to achieve significant TG reduction.
* "In our patients, insulin therapy combined with fasting was effective in reducing TG to < 1000mg/dL."
* "Most of the patients required continuous IV insulin infusion past DKA clearance, which has also been successful in previous published cases [14]."
* **Antilipidemic Agents:** While most cases of severe HTG are transient and resolve with insulin, some patients, particularly those with a family history of hyperlipidemia, may require long-term antilipidemic agents like fenofibrate and omega-3 acid ethyl esters.
* "Antilipidemic agents are required in select cases, but it is not clear which patients are at highest risk of requiring this treatment."
* "Only 4 out of the 15 patients reported in the literature received oral antilipidemic therapy during the acute phase of illness...Similarly, two of the five patients in this report required antilipidemic treatment at the time of follow up..."
* **Plasma Exchange:** Plasma exchange is rarely necessary and was not required in any of the cases presented in this series.

**D. Recommendations for Screening and Monitoring**

* **Early Lipid Screening:** Current American Diabetes Association guidelines recommend a lipid panel soon after diagnosis and after glycemic control improves. However, this study suggests the benefit of earlier screening, potentially at the time of T1D diagnosis, to identify severe HTG and prevent complications.
* "The cases presented here highlight the ben-efits of earlier lipid screening (before glycemic control improves), as earlier screening can recognize severe HTG, help effectively treat the condition and prevent HTG-induced complications."
* **Suggested Screening Triggers:** The authors recommend a low threshold for HTG screening in pediatric patients with new-onset T1D who present with:
* Strong family history of hyperlipidemia
* Lipemic blood samples (visibly cloudy or milky)
* Protracted abdominal pain
* Persistent acidemia (slow resolution of acidosis or elevated anion gap despite ketosis resolution)
* "We suggest a low threshold for screening for HTG in individuals with strong family history of hyperlipidemia, protracted abdominal pain, slow resolution of acidosis, or lipemic blood samples."
* **Pancreatitis Screening:** For patients with DKA whose abdominal pain does not fully resolve with acidosis, checking lipase and TG levels is suggested to rule out pancreatitis.

**E. Genetic Predisposition**

* While insulin deficiency is the primary cause of HTG in these cases, genetic predisposition to HTG, such as genotype variability affecting the LPL gene, may play a role in some individuals, particularly those requiring long-term antilipidemic therapy or experiencing recurrence of hyperlipidemia.
* "Although insulin deficiency is considered the primary reason for severe HTG in DKA, genetic predisposition for HTG may play a role, complicating the clinical picture."
* "Previous research postulated that genotype variability affecting the LPL gene directs the degree of susceptibility to insulin deficiency-mediated severe HTG [11]..."

**III. Gaps and Future Research**

* The true incidence of severe HTG in new-onset pediatric T1D remains unknown due to current screening practices.
* More studies are needed to guide appropriate lipid screening protocols at the time of pediatric T1D diagnosis.
* Longitudinal data on the need for oral antilipidemic treatment in this population is sparse, and further research is needed to identify which individuals would benefit most from early or more frequent TG screening.
* Further investigation into the genetic factors contributing to severe HTG in pediatric T1D could help in predicting the need for adjunct antilipidemic therapy.

**IV. Conclusion**

Severe hypertriglyceridemia is a serious, though rare, early manifestation of new-onset pediatric Type 1 Diabetes, often complicated by DKA. Its prompt recognition is crucial to prevent severe complications like acute pancreatitis and to guide effective treatment, primarily with IV insulin and fasting. Implementing early and targeted HTG screening in at-risk pediatric patients with new-onset T1D is essential for improved patient outcomes.

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