Type 1 Diabetes Associated with Pegylated Interferon/Ribavirin Therapy in Chronic Hepatitis C

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Published In/Presented At
Sharma, A., & Yozviak, J. (2010, April 28-May 1). Type 1 diabetes associated with pegylated interferon/ribavirin therapy in chronic hepatitis c. Poster presented at: The 33rd Annual Meeting of the Society of General Internal Medicine, Minneapolis, MN.
Type 1 Diabetes Associated with Pegylated Interferon/Ribavirin Therapy in Chronic Hepatitis C

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Learning Objectives:
- To recognize that pegylated interferon/ribavirin (Peg-IFN/RBV) therapy for chronic hepatitis C (HCV) has been associated with the development of numerous autoimmune disorders, including type 1 diabetes.
- Frequent blood glucose monitoring during Peg-IFN/RBV therapy is necessary, with investigation for decreased C-peptide levels and antibodies directed against pancreatic beta cells if hyperglycemia is persistent.

Case Information
- A 55 year old male with genotype 2b chronic HCV, occasional postprandial hyperglycemia, and a family history of type 2 diabetes presented to the emergency department after 17 weeks of pegylated interferon/ribavirin therapy with signs and symptoms of diabetic ketoacidosis (DKA).
- In the preceding weeks, with the exception of mild fasting hyperglycemia, he had tolerated therapy well and had achieved a rapid virologic response (HCV RNA undetectable at week 4). At the time fasting hyperglycemia was noted, the hemoglobin A1C was normal at 5.2%.
- The patient subsequently developed weight loss, malaise, polyuria, and polydipsia. Upon arrival in the emergency department, his blood glucose was 846 mg/dL with positive urine ketones and serum acetone, and an emergency department hospital admission was initiated.

Discussion:
- Chronic Hepatitis C, the most common blood-borne infection in the United States, can lead to hepatic fibrosis that can progress to cirrhosis. Peg-IFN/RBV therapy has become the standard of care and typically cures >50% of those treated.
- Numerous adverse effects are associated with Peg-IFN/RBV, many of which are autoimmune in etiology. Such examples include various forms of inflammatory arthritis, a lupus-like syndrome, psoriasis, leukocytoclastic vasculitis, interstitial pneumonitis, autoimmune hemolytic anemia, immune thrombocytopenic purpura, a variety of thyroid disorders, autoimmune liver disease, and uncommonly, type 1 diabetes.
- There have been several published case reports that associate new onset of diabetes with IFN therapy, which is often, insulin-requiring.
- Alpha IFN have also been associated with the development, or exacerbation, of insulin resistance. IFN therapy may stimulate a counter regulatory hormone secretion (i.e. growth hormone, glucagon), thus resulting in impaired glucose tolerance.
- Alpha IFN may mediate destruction of pancreatic beta-cells by inducing inflammation and activation of T-helper lymphocytes along with over-expression of MHC class 1 antigens in islet cells, leading to injury by CD8+ cytotoxic lymphocytes. This beta-cell injury may be permanent, as many affected patients require insulin for >1 year following cessation of peg-IFN/ribavirin therapy.
- Whereas we do not believe it is realistic to screen for every possible complication of IFN therapy, the potential for autoimmune disorders, including type 1 diabetes, needs to be discussed with prospective treatment candidates and incorporated into the risk-benefit analysis prior to therapy.
- We recommend close laboratory monitoring in all patients undergoing peg-IFN/ribavirin therapy.
- The homeostasis model assessment (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) can be easily calculated to assess for insulin resistance in the setting of fasting hyperglycemia.
- Persistently elevated blood glucose in patients receiving peg-IFN/ribavirin therapy could be a sign of beta cell injury. In these instances, we suggest prompt evaluation including GAD antibody and c-peptide assays to assess for the development of type 1 diabetes, which may have long-term implications.

Table 1. Relevant Patient Data*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Blood Glucose</td>
<td>140 mg/dL (normal 80-110 mg/dL)</td>
</tr>
<tr>
<td>Hemoglobin A1C</td>
<td>5.2% (&lt;7.0%)</td>
</tr>
<tr>
<td>C-Peptide</td>
<td>1.3 ng/mL (0.9-6.9 ng/mL)</td>
</tr>
<tr>
<td>TSH</td>
<td>1.9 μIU/mL (0.35-4.0 μIU/mL)</td>
</tr>
<tr>
<td>Anti-GAD Antibodies</td>
<td>640.9 (Normal &lt;74.0)</td>
</tr>
</tbody>
</table>

*Normal Range in Parentheses