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Successful Hepatitis C Antiviral Therapy Induces Remission of Type 2 Diabetes: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Male, 49
Final Diagnosis: Type 2 diabetes
Symptoms: —
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic

Objective: Unusual clinical course

Background: Type 2 diabetes is a well described extra-hepatic manifestation of hepatitis C infection (HCV). Eradication of HCV has led to improvements in insulin resistance but to date has not been shown to induce remission of diabetes.

Case Report: We report a case of a 49-year-old man with HCV and a 2-year history of T2DM on oral agents. He was initially treated with peg-interferon/ribavirin (peg-IFN/rib) but did not achieve a HCV treatment response. Four years later he was retreated with peg-IFN/rib plus an HCV protease inhibitor (boceprevir). His HbA1c at the start of treatment was 7.9%. Antiviral response to HCV-therapy correlated with a significant improvement in glucose control without a change in diabetes therapy or improvement in adherence. He achieved a sustained virological response and within a year of completing antiviral therapy he no longer required medical therapy for diabetes. Two years after the completion of HCV treatment, the patient has maintained an HbA1c of 5.8% without any diabetes medications.

Conclusions: This case provides evidence of the important relationship between HCV and diabetes and highlights the potential reversibility of glucose abnormalities with successful eradication of HCV. Increased awareness of this association may improve detection of undiagnosed HCV infection, identify patients with reversible causes of diabetes, guide therapeutic decisions for HCV treatment, and improve outcomes in patients with both diseases.

MeSH Keywords: alpha-Fetoproteins • Antiviral Agents • Carcinoma, Hepatocellular • Diabetes Mellitus, Type 2 • Hepatitis C • Insulin Resistance

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Background

The World Health Organization estimates that approximately 185 million people are infected with HCV worldwide [1]. Diabetes is also a global health care challenge. Approximately 347 million individuals worldwide have diabetes, with type 2 diabetes accounting for 90% of all cases [2]. An association between these two chronic diseases was first recognized in 1994 and since then several epidemiological studies have demonstrated an increased prevalence of type 2 diabetes among HCV-infected patients compared with HBV infection, chronic liver disease from other causes, and healthy controls [3–8]. The mechanism by which HCV impairs glucose metabolism is not clear. Although alterations in insulin-signalling pathways have been implicated, the process is likely multifactorial, including host factors and HCV genotype [6].

The presence of insulin resistance and type 2 diabetes in HCV has been associated with poor response to interferon-ribavirin HCV antiviral therapy, acceleration of liver fibrosis, and increased risk of hepatocellular carcinoma (HCC) [9–12]. Several observational studies have demonstrated that eradication of HCV is associated with improved insulin sensitivity and may reduce the long-term risk of diabetes in this population [13–15]. Case reports have described improvements in glycemic control with treatment of HCV with both IFN/Ribavirin and IFN/Ribavirin/telaprevir; however, the improvements were limited to the treatment phase [16,17]. In both these cases, there was evidence of recurrence of diabetes once HCV antiviral therapy ended. This is the first reported case to demonstrate complete remission of diabetes with viral clearance beyond the treatment phase.

Case Report

A 49-year-old man with no history of diabetes was referred to Endocrinology with polyuria, polydipsia, fasting blood sugar of 18 mmol/L, and a hemoglobin A1c (HbA1c) of 10% (Table 1). His past medical history included hemophilia, blood transfusion acquired HCV, non-alcoholic steatohepatitis, and early-stage cirrhosis. He had previously received pegylated-interferon/ribavirin (peg-IFN/rib) treatment for HCV and did not achieve a sustained virological response (SVR). The patient was diagnosed with type 2 diabetes and was started on Metformin 500 mg twice daily and Gliclazide 80 mg twice daily. Within a month, his HbA1c was 7.7% and fasting blood sugars ranged between 5–7 mmol/L. He continued to adhere to the prescribed treatment of oral agents over the next 2 years and maintained an HbA1c between 4.6 and 8.6%

In 2011, he was retreated with a 48-week course of peg-IFN/rib plus a HCV protease inhibitor (boceprevir). His HbA1c at the start of treatment was 7.9%, with no change in diabetes medications. Antiviral response to HCV-therapy correlated with a significant improvement in glucose control based on random glucose levels and HbA1c measurements (Figure 1). He achieved a sustained virological response (free of viremia 6 months following completion of HCV treatment) and within a year of completing antiviral therapy no longer required diabetes medications. More than 2 years after the completion of HCV antiviral treatment, the patient remains aviremic and has maintained an HbA1c of 5.8% without diabetes medication. His weight remained relatively stable during this period with no significant lifestyle changes (Figure 1). In addition to the improvements in glucose metabolism described, we also observed decreasing levels of alpha-fetoprotein (AFP) during treatment, which paralleled the improvements in HbA1c (Figure 2).

Discussion

Despite the extensive literature describing an association, type 2 diabetes is often under-recognized as an extrahepatic manifestation of HCV. Epidemiological studies estimate the prevalence type 2 diabetes among HCV-infected patients to vary between 14.5% and 33% [18]. Insulin resistance has been implicated as the precursor to development of HCV-medicated type 2 diabetes and may be present in up to 70% of HCV-infected patients [19]. This case report illustrates the relationship between HCV and type 2 diabetes, highlights the potential reversibility of glucose abnormalities with successful HCV eradication, and draws attention to the need for further research into the association between impaired insulin signalling and alpha-fetoprotein levels (AFP).

Mechanisms for impaired insulin sensitivity in HCV infection

Despite extensive research in this area, the exact mechanism by which HCV impairs insulin sensitivity and leads to increased burden of diabetes is not well understood and is likely multifactorial. HCV infection is specific to the liver. However, insulin sensitivity appears to be impaired both in the liver and the periphery [20,21]. HCV impairs insulin signaling through direct and indirect mechanisms [22]. HCV directly impacts insulin signaling by interacting with specific proteins such as serine/threonine kinases that subsequently lead to inhibition or increased degradation of insulin signaling molecules [6,23]. HCV may also indirectly cause insulin resistance in the periphery by inducing the production of pro-inflammatory cytokines that impair insulin signaling pathways in uninfected tissues [20]. Changes in metabolic parameters described with chronic HCV infection differ by genotype, suggesting that the mechanisms by which these signaling molecules are impacted are genotype-dependent. Viral steatosis is more common

Table 1. Hematologic and biochemical laboratory measures pre and post HCV-antiviral therapy (IFN/Rib/boceprevir) for HCV genotype 1 b.

Investigations	June 2009	Pre-treatment with IFN/Rib (Oct 2011)	Pre-treatment with Bocepravir (Nov 2011)	12-months after start of treatment (Oct 2012)	24-months after start of treatment (Oct 2013)
HbA1c (%)	10.0	8.6	7.9	4.6	5.8a
Fasting glucose (mmol/L)	18.4	–	9.2	–	–
Random glucose (mmol/L)	–	10.3	10.7	6.4	4.5
Hemoglobin (g/L)	138	133	115	108	138
AST (U/L)	175	168	129	42	24
ALT (U/L)	165	233	175	58	41
GGT (U/L)	297	336	304	156	39
HCV RNA (IU/ml)	4.68×10^6 b	–	1.43×10^6	Not detected	Not detected
Total cholesterol (mmol/L)	5.1 c	4.0 d	–	4.2	3.36 a
HDL-c (mmol/L)	0.9 c	0.9 d	–	1.24	1.50 a
LDL-c (mmol/L)	3.2 c	2.2 d	–	2.5	1.56 a
Triglycerides (mmol/L)	2.0 c	1.8 d	–	1.01	0.66 a
TSH (mU/L)	1.90	1.40	0.89	2.43	–
Free T4 (pmol/L)	12.4	–	–	–	–
Creatinine (umol/L)	74	77	81	79	88
Albumin (g/L)	42	39	38	43	46
AFP (ug/L)	75.4	160.9 e	N/A	2.8 f	2.2
Liver Biopsy (May 2009)	Stage III fibrosis; grade II portal and lobular activity; severe steatosis				
Fibroscan (June 2013)	Cirrhosis (left/caudate lobe hypertrophy; nodular hepatic contour). Fibrosis score of F4.				

a – December 2013; b – January 2009; c – November 2009; d – January 2011; e – July 2012; f – June 2012. HbA1c – hemoglobin A1c; AST-; ALT-; GGT-; HCV – hepatitis C virus; HDL-c – high density lipoprotein cholesterol; LDL-c – low density lipoprotein cholesterol; TSH – thyroid stimulating hormone; Free T4 – free thyroxine; AFP – alpha fetoprotein.

among HCV-genotype 3-infected patients, and, in contrast, there is a higher prevalence of insulin resistance among HCV-genotype 1 and 4 infection [6,24].

HCV treatment, insulin resistance, and glycemic control

Several observational studies have demonstrated that successful treatment of HCV with IFN/Ribavirin leads to improved insulin sensitivity and may reduce the long-term risk of type 2 diabetes [10,13–15]. Tahrani et al. reported a case of improved glycemic control and hypoglycemic episodes requiring cessation of diabetes therapies during treatment with IFNα-Ribavirin (Table 2) [16]. In contrast to our patient, the improvements in glycemic control were not maintained. After 24 weeks of treatment, HCV polymerase chain reaction remained positive and HCV treatment was stopped. Six months post-treatment, the glycemic control had deteriorated based on an HbA1c of 8.2%. The difference between the above-cited case and our patient may be due to the differences in antiviral treatment response and persistent viremia in the patient described above.

In recent years, the treatment of HCV has evolved rapidly with the development of direct-acting antiviral (DAA) therapies (protease inhibitors, NS5a inhibitors, and nucleotide and non-nucleotide polymerase inhibitors). The effect of DAA HCV treatments on insulin resistance and long-term risk of type 2 diabetes has yet to be clearly established. A randomized controlled trial of HCV mono-infected study participants receiving 14 days of monotherapy with the protease inhibitor Danoprevir found that serum HCV RNA and HOMA-IR correlated significantly (Spearman rho=0.379, $p<0.0001$) [25]. At the end of 14 days of Danoprevir monotherapy, the mean decrease in HCV RNA

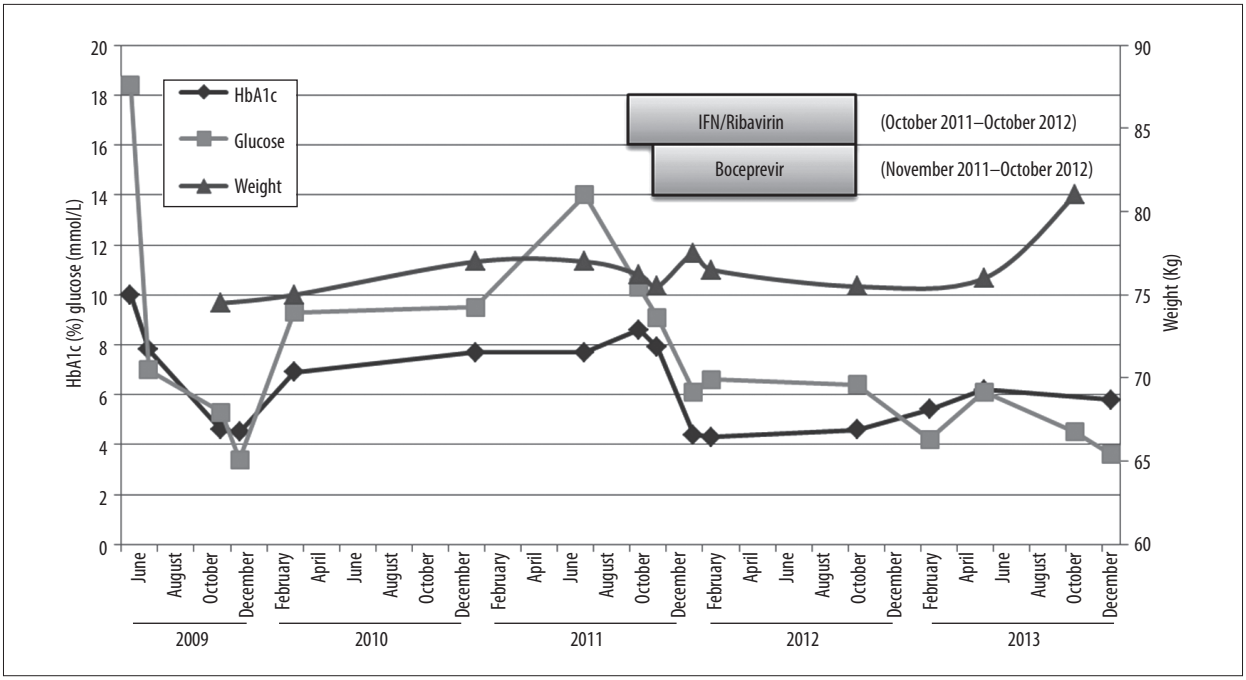

Figure 1. Changes in glucose metabolism with Interferon/Ribavirin/boceprevir treatment for HCV genotype 1b. The above depicts the changes in hemoglobin A1c (blue line) and glucose levels (red line) that were observed in a 49-year-old man with hepatitis C genotype 1b before, during, and after hepatitis C antiviral treatment (Interferon/Ribavirin/boceprevir). Abbreviations: HbA1c-hemoglobin A1c.

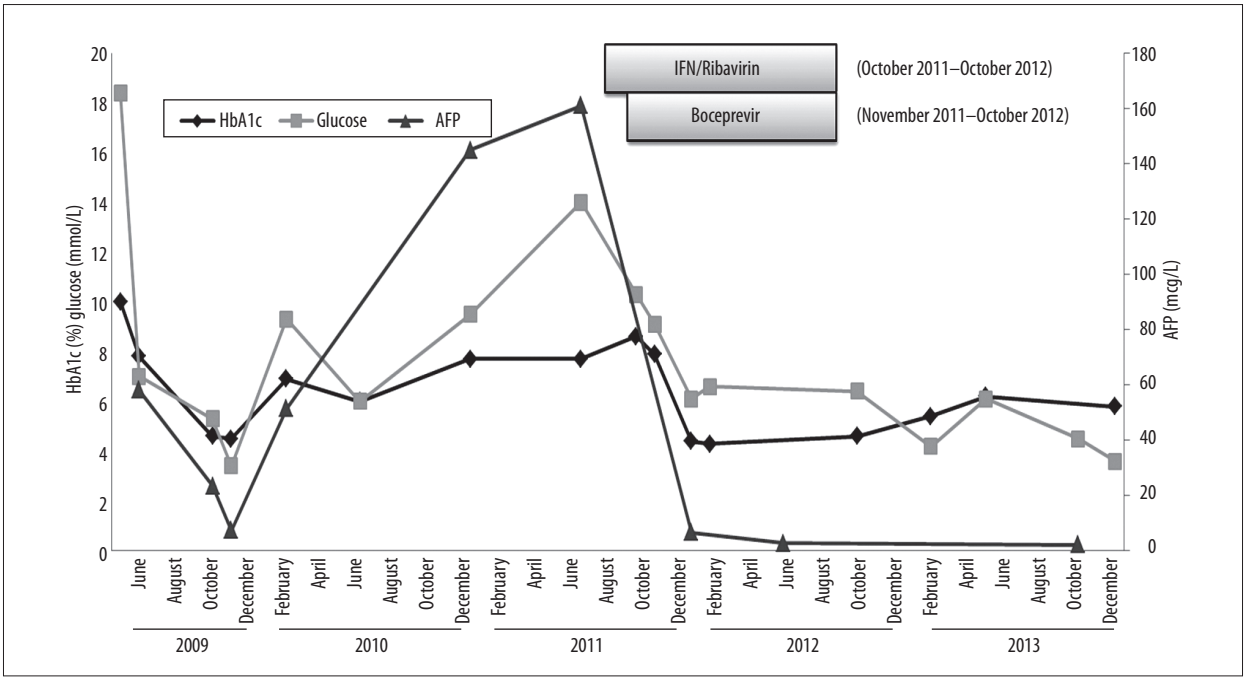

Figure 2. Changes in AFP and glucose levels with Interferon/Ribavirin/boceprevir treatment for HCV genotype 1b. The above depicts the reduction in alpha-fetoprotein levels (red line) that paralleled improvements in glucose metabolism [hemoglobin A1c (green line), glucose levels (blue line)] that were observed in a 49-year-old man with HCV genotype 1b after receiving HCV-antiviral treatment (Interferon/Ribavirin/ boceprevir). Abbreviations: HbA1c hemoglobin A1c; AFP alpha-fetoprotein.

Table 2. Case reports of HCV-infected individuals experiencing improvements in glycemic control with antiviral treatment of HCV.

References	Sex	Age	BMI	HCV and therapy	Treatment outcome	Diabetes treatment and HbA1c (pre-antiviral therapy)	Diabetes outcomes
Tahrani et al. (2006) [15]	M	40	30.8 kg/m^2	24 weeks IFN-α/Rib	No SVR	Lispro (Humalog Mix) and Metformin HbA1c 7.7%	6 months post-treatment: A1c 8.2% on diet alone.
Tallón de Lara et al. (2014) [16]	F	56	44.0 kg/m^2	IFN-α2a/Rib (48 weeks) Telaprevir (12-weeks)	SVR	Sitagliptin 50 mg od Metformin 500 mg od HbA1c not provided	1 month after telaprevir stopped patient resumed diabetes medications

IFN – interferon; Rib – ribavarin; HbA1c – hemoglobin A1c.; SVR – sustained virological response.

was 2.2±1.3 log10 IU/ml (p<0.0001) in patients who received the active drug (n=40), which correlated with a decrease in mean HOMA-IR score by 1.6±1.1 (p<0.0001). In contrast, HCV-RNA and HOMA-IR remained unchanged in placebo recipients.

A recently published case report further suggests that telaprevir, a NS3/4A protease inhibitor, may improve glucose metabolism (Table 2) [17]. In this case, a patient developed recurrent episodes of hypoglycemia shortly after initiating triple therapy (IFN/Ribavirin and telaprevir), which required discontinuation of all diabetes medications. Similar to the previously described case, but in contrast with our patient, improvements in glycemic control were not maintained when antiviral therapy ended, despite achieving an SVR. While the differences in outcomes may be due to host factors, the authors of this case report suggest that the protease inhibitor may have a direct antidiabetic effect. Interestingly, our patient continued to show improvement in glucose metabolism post-treatment, with diabetes therapy being reduced and eventually discontinued over 12 months. This suggests a mechanism of impairment that extends beyond the direct viral effects of HCV or HCV therapy and improvements in glucose metabolism, which may reflect decreased inflammation and liver fibrosis with improved liver function. Further studies are needed to establish the mechanisms by which HCV induces insulin resistance and the effects that different HCV therapies have in improving glycemic outcomes.

HCV, insulin resistance, and AFP

In addition to the improvements in glucose metabolism described, we observed decreasing levels of alpha-fetoprotein (AFP) during treatment, which paralleled the improvements in HbA1c (Figure 2). AFP is an oncofetal protein associated with hepatic malignancies and liver regeneration [26,27]. HCV core protein, inflammation, necrosis, and hepatocellular injury have all been suggested as causes for elevated AFP levels in chronic HCV infection [26–29]. Although type 2 diabetes and insulin resistance have been identified as risk factors for the progression of liver fibrosis and development of hepatocellular carcinoma, the mechanism by which this occurs is not clear [9–12]. The relationship between AFP and insulin resistance was recently examined in a retrospective analysis of 300 HCV-infected patients [30]. This study demonstrated that whole-body insulin resistance and hepatic fibrosis correlated directly with elevated levels of AFP. In addition, this group conducted a pilot study examining the effects of a lifestyle modification program on insulin resistance and AFP levels. Lifestyle modification over a 3-month period correlated with improved insulin resistance and a reduction in AFP levels. The parallel improvements in AFP and glycemic control demonstrated in our patient are likely in part a reflection of resolving inflammation and hepatocellular injury. However, these findings draw attention to the need for further prospective studies to understand the relationship among insulin resistance, AFP, and hepatocarcinogenesis.

Conclusions

This case highlights the interaction between HCV and type 2 diabetes, as well as the potential reversibility of impaired glucose metabolism with viral eradication. It further suggests the need for close monitoring of glucose levels and the potential need for dose adjustments of diabetes therapies during treatment of HCV to prevent hypoglycemia. Studies are needed to delineate the impact of different HCV antiviral therapies on insulin signalling pathways and the potential for improving glucose metabolism. This knowledge will help inform patient care, guide therapeutic selection, and improve liver and metabolic outcomes for HCV-infected patients with type 2 diabetes.

Furthermore, this case highlights the association between insulin resistance and AFP levels. Although the improvements in both parameters with HCV antiviral therapy are in part a reflection of decreased inflammation and liver injury, additional

evaluation for causative relationship(s) among HCV, insulin resistance, AFP, and HCC are necessary.

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Conflicts of interest

None declared.