

Diabetes in treated hepatitis C infection: dodging the sweet sting



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Background

Diabetes mellitus (diabetes) has reached epidemic proportions affecting at least 387 million people worldwide [1] with a considerable burden of complications which culminate in premature cardiovascular disease, renal failure, blindness and neuropathy. Efforts internationally focus on minimizing the impact of diabetes through judicious diabetes care but also on early detection and prevention.

Hepatitis C virus (HCV) affects an estimated 185 million individuals worldwide [2]. Approximately 80% of people infected with HCV progress to chronic infection; of these, 30–40% develop cirrhosis within 25 years [3,4]. Of patients with cirrhosis, one in four will develop hepatocellular carcinoma and/or decompensated liver disease. HCV infection is the main cause for cirrhosis, hepatocellular cancer and liver failure. In Europe and the USA, advanced liver disease secondary to chronic HCV is the foremost indication for liver transplantation.

There are six known genotypes of HCV; in Western nations, genotypes 1, 2 and 3 account for 97% of all infections [5]. Chronic HCV infection is associated not only with insulin resistance [6], which improves after HCV eradication after treatment [7], but also with increased diabetes risk [8].

The consequences of HCV infection constitute a significant illness burden and risk for fatal and/or malignant disease. Interventions for HCV eradication exist, with the standard of care for chronic infection being ‘triple therapy.’ Triple therapy is a proven efficacious intervention for chronic HCV infection, producing a sustained virological response (i.e., undetectable levels of HCV RNA) for at least 6 months following completion of therapy in 98% of people treated [9], reducing rates of both decompensated liver failure and hepatocellular carcinoma [10]. Triple therapy consists of pegylated interferon, ribavirin and a protease inhibitor, either bocepravir or telaprevir. Whilst there are immense health benefits from triple therapy, significant adverse effects exist. A significant adverse effect includes the apparently rare development of Type 1 diabetes mellitus. There are two very recently reported cases of Type 1 diabetes occurring on interferon-based triple therapy for HCV infection [11,12], which highlight the importance for vigilant care, observation and perhaps susceptibility screening in people with chronic HCV infection undertaking triple therapy.

One case, a 54-year-old man with genotype 1a HCV infection, presented acutely with diabetic ketoacidosis 7 weeks after triple therapy commencement (pegylated interferon- α -2a, ribavirin and telaprevir) [11]. glutamic acid decarboxylase (GAD) and islet cell antibodies were both positive, with

KEYWORDS

• diabetes • diabetes prevention • glucose • hepatitis C • interferon • protease inhibitors • Type 1 diabetes

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absent C-peptide, confirming Type 1 diabetes. His HCV RNA viral load counts deteriorated after cessation of triple therapy. Triple therapy was not recommenced, apparently due to uncontrolled hyperglycemia despite insulin therapy.

The second case, reported soon after, was a 23-year-old woman with chronic HCV infection (genotype 1B) who presented with symptoms of hyperglycemia 6 months after triple therapy initiation (pegylated interferon, ribavirin and bocepravir) [12]. GAD antibodies were strongly positive, with low C-peptide. Insulin therapy and education for diabetes self-management were initiated. The presence of an IL-28B polymorphism associated with post-transplantation diabetes following liver transplantation for HCV infection was found [13], raising the question of whether IL-28B genotypes may identify individuals at risk of Type 1 diabetes on interferon-based regimens.

These two case reports follow publication of a Japanese national survey that suggests the rate of Type 1 diabetes following interferon-based therapies is 1.18% [14], a seemingly unacceptably high complication rate. The majority of cases in this survey received interferon for HCV infection treatment. Diabetes onset was often abrupt and of rapid onset after interferon initiation, with high GAD antibodies levels found in the majority of cases. Underreporting is a possible limitation of this study, since cases were collected through a survey of members of the Japanese Diabetes Society; nevertheless no similar data are available from any other country or service. The Japanese data are gravely concerning since, as diabetologists, we would see these as potentially preventable cases of Type 1 diabetes.

Potential mechanisms of Type 1 diabetes induction

Interferon is an immunomodulator therapy associated with precipitating Type 1 diabetes when used in multiple sclerosis [15], hepatitis B virus treatment [16] and dual therapy for hepatitis C infection [17]. It is proposed that interferon induces autoimmune diabetes through the development of pancreatic-associated autoantibodies, which promote immune destruction of islets, resulting in insulin deficiency and ketoacidosis-prone Type 1 diabetes [11].

However, a second mechanism is likely, perhaps acting additively to promote hyperglycemia. Protease inhibitors are known to increase insulin resistance and risk for Type 2 diabetes,

with a wealth of published clinical and laboratory data from studies of the protease inhibitors used to treat HIV infection. For example, a single dose of the protease inhibitor indinavir in healthy volunteers acutely reduces insulin-stimulated glucose uptake [18]. Short-term studies of different protease inhibitors, again in healthy volunteers, suggest differences between different protease inhibitors to increase insulin resistance [19]. Chronic protease inhibitor therapy in HIV is also associated with increased insulin resistance [20]. For a detailed review of the mechanisms of protease inhibitor-induced insulin resistance, readers are referred to several excellent reviews [21,22]. Extensive experience and observations in protease inhibitor therapy in HIV infection have also shown that protease inhibitors promote hypertriglyceridemia, predicting Type 2 diabetes development [23,24]. Thus, protease inhibitors through direct effects on insulin signaling or through hepatic lipid metabolism affect glucose metabolism and contribute to overall diabetes risk. A review of the literature did not reveal any published study examining the effects of bocepravir or telaprevir on any aspect of insulin or glucose metabolism.

The potent pairing of interferon with protease inhibitors effectively eliminates HCV viral load, but at the cost of increasing diabetes risk. This can be expected to be (at least) additive to the increased diabetes risk already observed in chronic HCV infection [8].

Diabetologists in action

As diabetologists, the outcome of Type 1 diabetes complicating HCV infection triple therapy would seem to be an unacceptable one. The current HCV treatment guidelines include only very limited screening for diabetes. For example, treatment guidelines from the National Hepatitis C Program Office, USA, recommend baseline fasting glucose alone [10]. There are currently no recommendations for glucose screening during or after treatment. Furthermore, there are no studies reporting glucose disorders during or after HCV infection triple therapy. Studies of glucose metabolism in people undergoing triple therapy for chronic HCV infection are urgently required, both short and longer term. As diabetologists, we must ask our gastroenterology and infectious disease colleagues how we can share our expertise in diabetes screening, surveillance and intervention in this group who are at greater risk for both Type 1 and Type 2 diabetes.

“The cost of antibody screening is substantially less than that of lifelong insulin-requiring diabetes...”

The possibility of diabetes induction raises questions as to whether there are any means for baseline susceptibility detection. For example, should glycosylated hemoglobin levels supersede baseline glucose as a screen for diabetes? Should GAD and islet antibodies be measured as a susceptibility indicator? Nakamura and co-authors from the Japanese national survey suggest GAD and islet autoantibodies should be performed in all patients being considered for interferon therapy. This would seem reasonable. The cost of antibody screening is substantially less than that of lifelong insulin-requiring diabetes, to say nothing of the burden of daily diabetes care and the consequences of diabetes on physical and mental health and mortality.

A prudent approach in the apparently sophisticated paradigm of individualized medicine would be to evaluate each individual's diabetes risk before, during and after triple therapy for HCV, as detailed in **Figure 1**. An efficient and cost-effective method for this is history (family

history for diabetes, past gestational diabetes), physical examination (obesity) and baseline biochemistry. All are standard care and expected as basic practice. Early detection of glucose disorders could occur with simple measures of fasting glucose or glycosylated hemoglobin during standard 24-week triple therapy. These could be added onto the occasions of guideline-mandated HCV viral load testing at 0, 4, 8, 12, 24 and 36 weeks [10].

Further, as diabetologists with knowledge of Type 1 diabetes pathogenesis, we can contribute our expertise to detect individuals who might be at higher risk of Type 1 diabetes, through detection of islet autoantibodies at baseline and again at 4 weeks of triple therapy. There are no studies to provide evidence for islet autoantibody retesting at 4 weeks, however the Japanese data [14] and one case report [11] suggest hyperglycemia onset occurs soon after interferon initiation. Islet autoantibody-positive individuals might be then considered for interferon-free therapy, which has recently been shown to be efficacious [25,26].

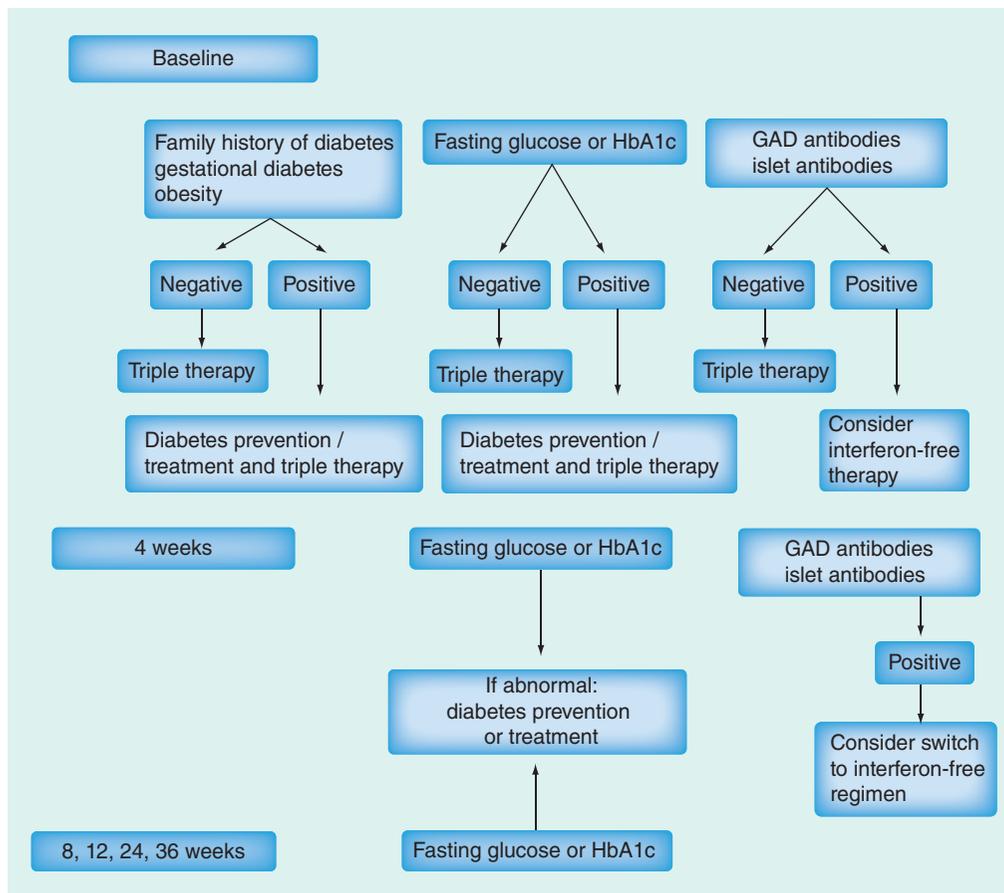


Figure 1. A proposed diabetes risk evaluation and screening algorithm in people being considered for triple therapy for chronic hepatitis C virus infection.

Identifying individuals at risk of diabetes on triple therapy requires consideration not only of the traditional autoimmune markers of diabetes but also of the genes involved in modulating the inflammatory response to interferon. The possibility that individual genetic factors, such as certain IL-28B polymorphisms, can identify increased diabetes risk has already been raised [12]. IL-28B single nucleotide polymorphism testing in HCV treatment is recommended, to inform therapy duration as certain polymorphisms are associated with a rapid sustained virological response [10]. IL-28B acts on interferon-stimulated genes and intracellular inflammation pathways to increase insulin resistance. This raises a future research area for observation as to whether IL-28B genotypes may identify individuals at higher diabetes risk following triple therapy, not only after liver transplantation.

Additional areas for future research include the longitudinal examination of diabetes

incidence and GAD and islet antibody development before and after triple therapy for HCV. The potential for certain IL-28B polymorphisms to inflate diabetes risk also requires investigation. This information could help inform predictive markers for diabetes in HCV infected people and, in turn, optimize screening and treatment regimen selection. As diabetologists, we are well-positioned to assist our gastroenterology and infectious diseases colleagues in identifying individuals at risk for diabetes.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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