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Susceptibility to Type 2 Diabetes Mellitus in Hepatitis C Patients: A Systematic Review

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Key Points

Question: Do patients with Hepatitis C have a higher susceptibility to Type 2 Diabetes Mellitus?

Findings: In this systematic review, multiple recent studies suggest a correlation among hepatitis C infection, insulin resistance, and type 2 diabetes mellitus. The exact biochemical mechanism is unknown; however the proposed pathway is the impairment in insulin signaling. There are works of literature that support the eradication of hepatitis C infection improve glycemic control in diabetic patients.

Meanings: Patients with hepatitis C have a higher risk of developing diabetes mellitus. Initiation of routine monitoring of hemoglobin A1C (HA1C) is beneficial, and for patients with elevated HA1C, early treatment of diabetes can prevent further complications with better clinical outcome.

Introduction

Hepatitis C viral infection (HCV) affects an estimated 71 million people worldwide with a death rate of approximately 399,000 each year from complications such as cirrhosis and hepatocellular carcinoma (Hepatitis, 2017). According to CDC, there are 30,500 cases of acute hepatitis C, with an estimated 2.7-3.9 million chronic cases in 2004 in the United States alone. The prevalence of HCV is high, and it creates a massive burden for the healthcare field worldwide (Viral, 2017).

As the population with hepatitis C is gradually increasing in size, it is essential to know if this condition can lead to chronic diseases other than the ones already known. Various research show a possible link between type 2 diabetes mellitus (T2DM) and HCV with no concrete evidence. There is no current standard protocol of monitoring and treating both diseases. The relationship between T2DM and HCV needs to be investigated on a deeper level to consider changes in clinical practice as both conditions are chronic and they affect patients' overall lifestyle, quality of life, and mortality. This systematic review will focus on discovering the correlation between the two conditions and recommending routine monitoring of HA1C in HCV patients.

Methods/Literature Search

A systematic literature review of recent studies on relevant topics was performed to determine the best available evidence of the correlation between HCV and T2DM. Various components were examined, such as epidemiology, pathology, clinical presentation, assessment, diagnosis, treatment, and prognosis. A search for existing studies on the topic was conducted using PubMed. The keywords used were "hepatitis C" and "diabetes." Without any filters, it yielded 2609 articles. The following filters were applied to narrow down the results; article type

of clinical study, clinical trial, controlled clinical trial, editorial, journal article, meta-analysis, multicenter study, observational study, randomized controlled trial, review, systematic reviews; humans in species category; publication dates of past 5 years; full text availability; English language; core clinical journals and MEDLINE for journal categories; and age group adult 19+ and above. Additional keywords were used to further focus on the topic of interest; "transplant", "carcinoma", "HIV", "hepatitis B" and "type 1" were excluded. Many pieces of research examine the relationship of diabetes post liver transplant secondary to the complication of hepatitis C infection. They are not relevant to the goal of the study. Type 1 diabetes is an early onset disease with a genetic etiology, therefore type 1 diabetes should be excluded as research is to determine if hepatitis C patients are at more risk of developing diabetes, specifically type 2 diabetes. Articles with analysis of chronic diseases along with hepatitis C and complications of hepatitis C other than DM were excluded. A total of 107 articles were reviewed and further narrowed down to 18 based on relevancy and research quality evaluated with Oxford Centre for Evidence-based Medicine's Levels of Evidence and Grades of Recommendation.

Results

Centers for Disease Control and Prevention defines hepatitis C as a liver infection caused by hepatitis C virus. Infection is most common in intravenous drug users due to needle sharing. HCV affects the liver but can lead to other extrahepatic manifestations such as fatigue, diabetes mellitus, glomerulonephritis, mixed cryoglobulinemia, porphyria cutanea tarda, cardiovascular disease, CHF and non-Hodgkin's lymphoma (Viral, 2017).

The exact mechanism of how HCV increases the risk of developing T2DM is unknown. However, there are numerous research suggest the pathophysiology of impairment in the insulin signaling pathway. Aytug et al. examined 42 liver specimens from nonobese and nondiabetic

patient with HCV and found HCV infection lead to postreceptor defect in insulin receptor substrate-1 (IRS-1), as well as insulin signaling defect in downstream hepatic IRS-1 tyrosine phosphorylation, which both contribute to insulin resistance (IR) and the development of T2DM. Kawaguchi and Mizuta concluded that impairment of the tyrosine phosphorylation results in the reduction of PI3K-Akt activation, and HCV genotype 1 core protein was responsible for inducing hepatic IR by suppressing IRS-1 tyrosine phosphorylation. Naing and colleagues found the peroxisome proliferator-activated receptors (PPARs) upregulates glucose synthesis with factors glycerol-3-phosphate dehydrogenase, glycerol kinase, and glycerol transport proteins. As PPARs are the main nuclear receptors in the liver, decreased activity of these receptors due to hepatitis C infection contribute to HCV-induced IR. They also noted immune-mediated factor TNF-alpha lower IRS-1, in turn increase IR as well. Even though the actual underlying biochemistry mechanisms are unknown, a strong correlation between HCV and development of diabetes mellitus has been established with many research throughout the years.

According to Muhammad Memom and his colleagues in their research "Prevalence of Type 2 Diabetes Mellitus in Hepatitis C Virus Infected Population: A Southeast Asian Study," they determined a strong association of T2DM with HCV infection, notably higher in cirrhosis patients. This study was a prospective study conducted in 2009 at Isra University Hospital in Hyderabad. The study included a total sample size of 361 patients with hepatitis C. The inclusion and exclusion criteria were clearly defined. Statistical analysis was performed using Student's t-test, chi-square test, and multiple logistic regression model. The prevalence of T2DM was calculated based on different factors; age, BMI, gender, weight, family history of diabetes, and HCV genotype. As the conclusion, they demonstrated advanced age, increased weight, HCV genotype 3, and cirrhosis are strong predictors for T2DM (Memom, 2013).

Younossi and colleagues used a total of 19,741 individual data derived from the National Health and Nutrition Examination Survey to examine the associations among chronic hepatitis C, metabolic and cardiac outcomes. In multivariate analysis adjusted for age, obesity, non-Caucasian race/ethnicity and smoking, they concluded that HCV is an independent predictor of IR [Odds Ratios (95% CI) = 2.06 (1.19–3.57)] and DM [Odds Ratios = 2.31 (1.18–4.54)].

"Hepatitis C virus infection and development of type 2 diabetes mellitus: Systematic review and meta-analysis of the literature" is a meta-analysis of 33 cases with total systematic review of 544 records. It concluded the prevalence of HCV is higher in patients with T2DM compared to non-diabetic patients. The inclusion and exclusion criteria were thorough and relevant to the topic of interest. However, the researchers only included previous clinical trials, no literature reviews were considered. This article was published on January 11, 2018. It contains useful resources; nonetheless, it might be outdated as the most recent literature included was from February 29, 2016.

"Prevalence of Diabetes Type 2 in Hepatitis C Infected Patients in Kpk, Pakistan" is a case review of a sample size of 1295 total patient with confirmed hepatitis C infected patient of 212. Blood samples were obtained for analysis of HCV, and random blood sugar were used to define diabetes mellitus per World Health Organization's standard. Questionnaires were used to get more detailed patient information, include name, age, gender, location, education background, family history of the disease, and previous treatments. The study summarized that HCV might be a reason that causes T2DM, with a prevalence rate of 26.42%. Case review has low statistical reliability; however, the relatively large sample size is desirable.

A nationwide study with a sample size of 11,126 was conducted in Egypt through data collection with the Egypt Demographic and Health Survey. HCV antibody, HCV RNA were

confirmed through ELISA and Adlatis ElAgen HCV Ab test. Patients' past medical history of diabetes was investigated. Researchers found no evidence of an association between HCV exposure and diabetes but did detect an association between diabetes and chronic HCV infection. The study is large-scaled, nationwide with reliable data. It has significant statistical power (Cuadros, 2015).

Multiple studies illustrated an improvement in glycemic control and renal function in diabetic patients with HCV post antiviral treatments. The study published in 2014 Hepatology Journal by Hsu et al. concluded that antiviral treatment for HCV could improve renal outcome in diabetic patients. Hsu et al. studied a total of 1,411 HCV patients treated with pegylated interferon and fibavirin, 1,411 untreated HCV patients and 5,633 diabetic patients without HCV infection over a period of 8 years. The incidences of end-stage renal disease (ESRD) in treated, untreated, and uninfected population were 1.1% (95% confidence interval [CI], 0.3-2.0%), 9.3% (95% CI, 5.9-12.7%), and 3.3% (95% CI, 2.3-4.3%), respectively. It clearly indicates a significant decrease in risk of ESRD in diabetic patients if HCV is treated properly. It indirectly implies HCV can potentially cause insulin resistance which leads to worsening renal function in diabetic patients.

Vanni et al. summarized in their literature the most current studies on antiviral treatment of HCV and T2DM. They conclude curing HCV results in a reduced incidence of T2DM and overall improvement of clinical outcome. They hypothesize early diagnosis and treatment of HCV infection can lessen T2DM complications.

Discussion

HCV rate increases yearly and affects patients of all genders, races, and ages worldwide. It has known complications of cirrhosis, hepatocellular carcinoma, and many other extrahepatic

manifestations. Chronic HCV has been linked to T2DM due to impaired glucose metabolism, insulin resistance, and other unknown causative mechanisms. This systematic review of recent researches continues to provide support of the suspected correlation of the two conditions. Multiple factors cause the biochemical defect in insulin signaling pathway in HCV patients which lead to IR and T2DM. HCV induces IRS-1 suppression, prevent downstream IRS-1 tyrosine phosphorylation, decrease PPARs activity, and TNF-alpha factor lower IRS-1 function. Patients with HCV have a higher prevalence of developing DM and HCV is an independent predictor of IR. Completion of antiviral treatment for HCV has shown to decrease the complication of T2DM or complete eradication of the disease. The combinations of all the evidence provide a strong indication for protocol changes when it comes to managing patients with both chronic conditions.

Glycosylated hemoglobin test (HA1C) measures average blood glucose control for the past two to three months. An elevated HA1C of 5.7-6.4 indicated prediabetes and 6.5 or higher is diagnostic for DM. Patients with an official diagnosis of HCV should have a routine evaluation of HA1C every three months or six months to monitor for insulin resistance and new onset of prediabetes or DM. Intervention for suspected insulin resistance secondary HCV shall start as soon as possible. Per the American Diabetes Association, the current recommendations of initial diabetes management are adequate patient education and lifestyle modification. Healthcare providers need to be aware of the association between HCV and T2DM, and provide the much-needed education for patients. If the initial interventions are not sufficient for glycemic control, providers will need to consider DM medications depend on patient's other co-morbidities. Prompt intervention and management of both diseases can minimize or prevent

potential health complications, help providers to better manage the chronic conditions clinically, and give patients an overall good health outcome in the long run.

Conclusion

HCV and T2DM have an established correlation and management of both chronic conditions can be challenging for the healthcare provider. Early intervention and prevention of onset of T2DM in HCV patients are crucial in clinical practice. A new protocol of monitoring HA1C every 3 months or 6 months shall be included in the management of HCV patients.

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