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Original article

Association between HCV infection and diabetes type 2 in Egypt: is it time to split up?

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ABSTRACT

Purpose: There is a conflicting evidence about the association between hepatitis C virus (HCV) infection and diabetes mellitus. The objective of this study was to assess this association in Egypt, the country with the highest HCV prevalence in the world.
Methods: The source of data was from the Egypt Demographic and Health Survey conducted in 2008. Using multivariable logistic regression analyses to account for known confounders, the association was investigated at two levels']: (1) HCV exposure (HCV antibody status) and diabetes mellitus and (2) diabetes mellitus and chronic HCV infection (HCV RNA status) among HCV-exposed individuals.
Results: We found no evidence for an association between HCV antibody status and diabetes (adjusted odds ratio [OR] = 0.87; 95% confidence interval [CI], 0.63–1.19). However, among HCV-exposed individuals, we found an evidence for an association between diabetes and active HCV infection (adjusted OR = 2.44, 95% CI, 1.30–4.57).
Conclusions: Although it does not appear that HCV exposure and diabetes are linked, there might be an association between diabetes and chronic HCV infection. The HCV–diabetes relationship may be more complex than previously anticipated. Therefore, a call for an "amicable divorce" to the HCV–diabetes relationship could be premature.

Introduction

Hepatitis C virus (HCV) infection and diabetes mellitus are the major public health challenges with increasing morbidity and mortality disease burden [1, 2]. HCV is a multifaceted infection affecting different processes such as mitochondrial function, insulin resistance, lipid metabolism, and signaling pathways among others [3, 4]. HCV infection can lead to inflammation of the liver, progression to fibrosis, and development of cirrhosis or hepatocellular carcinoma [4]. Diabetes has been also recognized as part of the spectrum of HCV-associated diseases [5]. Diabetes mellitus is a complex disease with pathophysiology that includes increased hepatic glucose production, defects in insulin secretion, and/or insulin resistance [6, 7].

The precise biological mechanisms underlining glucose intolerance and diabetes in HCV-infected individuals are not completely understood. Several hypotheses, however, have been proposed for the development of diabetes mellitus in HCV-infected individuals. Alterations in hepatic lipid and carbohydrate metabolism with HCV infection have been commonly observed, potentially causing fat accumulation in hepatocytes [8, 9]. This intracellular fat accumulation could induce insulin resistance and may lead to the development of diabetes [10]. Moreover, studies have suggested that expression of the HCV core protein can induce hepatic insulin resistance through alterations in signaling in the insulin receptor substrate-1 pathway [11, 12]. Results derived from animal models have also suggested a more direct effect of HCV infection on insulin resistance in the liver through the activity of hepatic tumor necrosis factor-α on the insulin signaling pathway [13].

Emerging epidemiologic evidence has suggested a link between HCV infection and diabetes [5,14–17]. However, most epidemiologic studies reported analyses from data derived from tertiary liver care centers [16, 17]. Such clinic-based studies may suffer from selection bias, and recruited liver patients may not represent the

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early stages of infection or disease present in the general population. Only few population-based studies have been conducted to assess this association, and their results were inconclusive [18–21]. Notably, a recent landmark study on a nationally representative sample of the U.S. population, the National Health and Nutrition Examination Survey (NHANES), failed to identify a statistically significant association between HCV infection and diabetes [22]. The study included more than 15,000 participants, of whom 277 participants were HCV antibody positive [22]. The lack of a clear association between HCV infection and diabetes in this study, along with the accumulating conflicting evidence from other studies [16, 17, 19, 20, 23], casts doubt on the existence of a causal link leading to a call for an "amicable divorce" to this association [7].

A major concern about the U.S.-based study and the other population-based studies has been the relatively small number of HCV infected individuals included in the analyses, because of the low HCV prevalence in the population [16, 20]. For example, HCV prevalence in the U.S. population is only 1.7% [22]. Therefore, there may not have been sufficient statistical power in these studies to characterize the complexity of the association between HCV and diabetes. It is critical, as has been suggested recently [22], to replicate such studies on nationally representative samples in countries with high HCV prevalence where such samples may include a large number of HCV infected individuals.

In the present study, we aimed to examine the association between HCV infection and diabetes in a large nationally representative population-based sample in Egypt, the country with the highest HCV prevalence worldwide (14.7%) [24–26], with genotype 4 being the dominant genotype (responsible for more than 90% of HCV infections) countrywide [26]. This sample offers a rare opportunity to examine this association as it is one of the largest samples ever to study HCV infection [24] and conducted in a country where HCV prevalence is more than 10-fold higher than that in the United States. [24, 25]. The sample included more than 1400 HCV antibody-positive individuals [24], compared to only 277 in the U.S. study [22]. The first objective of our study was to assess the association between diabetes mellitus and HCV exposure (antibody positivity) in Egypt. The second objective was to assess the association between chronic HCV infection (HCV RNA positivity) and diabetes mellitus in the subsample of HCV antibody-positive individuals.

Materials and methods

Conceptual framework

The association between HCV infection and diabetes can be manifested at different levels. At one level, HCV-exposed individuals (i.e., HCV antibody positive) could be at higher risk of developing diabetes. Conversely, diabetic patients could also be more frequently exposed to HCV through medical procedures, and thus have a higher likelihood of becoming infected. Therefore, we assessed the association between diabetes mellitus and HCV antibody serological status in the whole sample (Model 1).

On another level, diabetic patients could be less likely to clear the infection if they are exposed to the virus. Alternatively, individuals with chronic HCV infection (i.e., HCV RNA positive) could be more likely to develop diabetes. Therefore, we also examined the relationship at this level by assessing the association between HCV RNA status and diabetes mellitus among only the subsample of HCV antibody-positive individuals (Model 2).

Data sources

Our source of data was the Egypt Demographic and Health Survey (EDHS) conducted in 2008 [24]. All women and men aged 15 to 59 years present in the sampled households were eligible for the survey, and 11,126 (87.1%) of these individuals were tested for HCV antibody and HCV RNA. The HCV testing protocol included an initial round of testing to detect the presence of antibodies against the virus [24]. A third generation Enzyme Immunoassay (ELISA), Adlatis EIAgen HCV Ab test (Adaltis Inc., Montreal, Canada) was used to test for antibodies against HCV. This test showed 100% of sensitivity and 98.1% of specificity, with a cut-off value (signal-to-cut-off ratio, S/CO) of 1.0 or more to be considered reactive for anti-HCV antibodies, whereas those S/CO less than 1.0 were considered nonreactive [27]. All positives with this test were confirmed by a Chemiluminescent Microplate Immunoassay (CIA) [24]. All confirmed HCV antibody-positive specimens were tested by Quantitative real time PCR (RT-qPCR) for the detection of HCV RNA [24]. Further methodologic details related to specimen handling and laboratory methods used for the detection of HCV antibody and HCV RNA can be found in El-Zanaty et al. [24].

We used the binary answer to the question "has a doctor or other health professional ever told you that you had diabetes?" as the measure for diabetes mellitus. After excluding participants with missing HCV antibody status or diabetes status, the final analyses were conducted on 10,143 participants (Fig. 1).

Statistical analyses

We conducted two separate analyses. In the first model, the dichotomous HCV antibody serological status (indicator of exposure to HCV) was included as independent variable, and diabetes status was the main outcome (model 1). In the second model, diabetes status was included as independent variable, and HCV RNA status (indicator of active infection) among HCV antibody-positive individuals was the main outcome (model 2). To adjust for confounders, several variables known to be associated with HCV infection or diabetes were first analyzed in bivariate analyses. Variables included were age, place of residence (urban or rural), sex, level of education, body mass index (BMI), hypertension, ever had dental treatment, ever had surgery, ever had blood transfusion, ever had received parenteral antischistosomiasis therapy (PAT), and ever been hospitalized. BMI was stratified in three categories: normal (BMI < 25), overweight (BMI $= 25–30$), and obese (BMI > 30) [28].

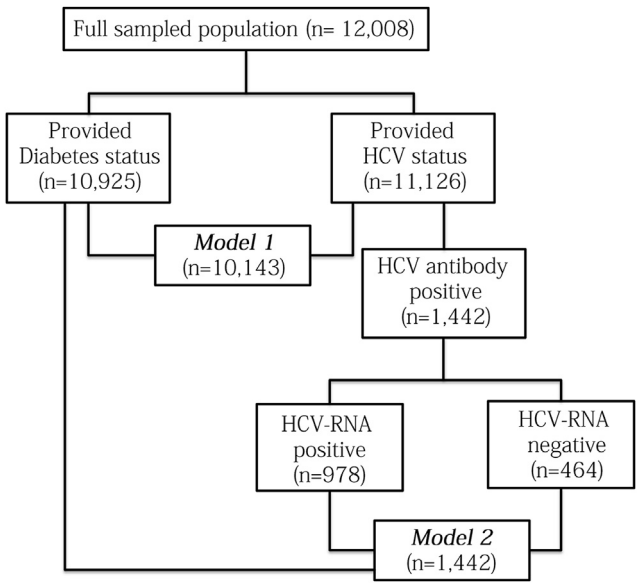

Fig. 1. Determination of study sample.