Incidence of Type 2 Diabetes in Patients With Chronic Hepatitis C Receiving Interferon-Based Therapy

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Type 2 diabetes (T2D) has been associated with hepatitis C virus (HCV) infection as an independent risk factor. The increased insulin resistance induced by the HCV core protein or the treatment with interferon-based therapy (IBT) may have a role (1). It is generally agreed that IBT for patients with chronic hepatitis C (CHC) may trigger short-term insulin resistance. However, the long-term risk of developing T2D for CHC patients with IBT remains unclear. Studies suggested that if viral clearance is achieved after IBT, the risk of T2D might be reduced by two-thirds in CHC patients (2,3). An Italian study argued that a lower insulin resistance at baseline may be the reason for reduced risk of T2D (4). We therefore conducted a retrospective cohort study, using insurance claims data of Taiwan, to examine 1) whether CHC patients are at an elevated risk of developing T2D and 2) whether CHC patients receiving IBT are at a reduced risk of T2D, not only through viral clearance but also through possible alterations of glucose metabolism.

The health insurance of Taiwan is a universal insurance system with 99% of all 23 million residents covered. We used a subset of claims data of 1 million beneficiaries randomly selected from all residents to identify adults (N = 9,094) newly diagnosed with HCV infection or CHC who received IBT from 1 January 2000 to 31 December 2011 as our CHC-IBT cohort. We also randomly selected a cohort with CHC without IBT as the CHC-nonIBT cohort, matched by age and sex. The comparison cohort was randomly selected from a population without CHC or HCV, with the sample size fourfold higher (N = 36,376) than that of the CHC-IBT cohort, matched by age and sex. The mean ages were alike in the CHC cohorts and comparison cohort (mean ± SD age: 55.5 ± 15.4 vs. 55.4 ± 15.6 years).

We used the Kaplan-Meier method to estimate the cumulative incidence of T2D for the three cohorts by the end of 2013 and used the log-rank test to examine the differences. We estimated the incidence of T2D and used Cox regression models to calculate hazard ratio (HR) and adjusted hazard ratio (aHR) after controlling for age, sex, and comorbidities, including hyperlipidemia, hypertension, chronic kidney disease, stroke, malignancy, human immunodeficiency virus infection, hepatitis B virus, alcoholic liver diseases, cirrhosis, cirrhosis-related ascites, esophageal varices, and hepatic encephalopathy.

The cumulative incidence of T2D was the highest in the CHC-nonIBT cohort, followed by the control cohort and CHC-IBT cohort (17.7%, 14.9%, and 11.1%, respectively), with mean follow-up times of 5.35, 5.35, and 5.87 years, respectively (data not shown). The T2D incidence in the CHC-nonIBT cohort was 2.4-fold greater than that in the CHC-IBT cohort (1.72 vs. 0.73 per 100 person-years) (Table 1). The aHRs of T2D for these two cohorts were 1.34 (95% CI 1.24–1.46, P < 0.001) and 0.65 (95% CI 0.51–0.81, P < 0.001), respectively, compared with general population comparisons (Table 1).

Consistent with previous research, our study confirmed that CHC patients...
without IBT were at an elevated risk of T2D compared with non-CHC control subjects. The risk was substantially reduced for CHC-IBT patients. This finding is comparable to that of the study in Japan (3). It is noteworthy that the overall hazard of developing T2D for patients receiving IBT was reduced 35% compared with non-CHC control subjects. It is likely that other mechanisms may be involved apart from viral eradication alone. An animal study reported that the secretion of leptin was significantly lowered in adipose tissue after exposure to interferon-α (5). A direct interferon-dependent decreasing effect on the leptin system may explain the decreased risk of T2D in CHC patients with IBT. It is also possible that interferon regulatory factor 9 (IRF9) proteins, key factors in the interferon-α–dependent inhibition of viral replication and spread, might have a role in attenuating hepatic insulin resistance (5), steatosis, and inflammation through an interaction with peroxisome proliferator–activated receptor-α. However, further studies are needed to clarify this relationship.

The key limitation in this study is that diagnoses used were clinician-initiated, which cannot be assumed to equate to research diagnostic criteria. Data on lifestyle, BMI, and laboratory examinations of the study population were also not provided and not adjusted for in the data analysis. However, study participants drawn from real-world clinical practices rather than from selected research is an advantage.

From this population-based cohort study, we conclude that CHC patients without IBT are at an increased risk of developing T2D. The risk of T2D is lowered greatly for CHC patients who have received IBT. Possible mechanisms should be explored.

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### Author Contributions

M.-C.T. and S.-I.W. designed the study. M.-C.T., F.-C.S., S.-I.W., and R.S. contributed to writing of the manuscript. All authors contributed to collection and/or assembly of data, data analysis, interpretation, revisions, and final approval of the manuscript. S.-I.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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### Table 1—Incidence rate of T2D and related HRs for the CHC-IBT cohort and CHC-nonIBT cohort compared with comparison subjects

|                     | Event | PY  | IR   | HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
|---------------------|-------|-----|------|-------------|---------|----------------------|---------|
| Incidence rates of patients with or without CHC  |       |     |      |             |         |                      |         |
| Comparison (those without CHC as reference)     |       |     |      |             |         |                      |         |
| All CHC                                             | 3,143 | 257,950 | 1.22 | 1.00 (reference) | <0.0001 | 1.00 (reference) | <0.0001 |
|                                                | 882   | 57,317 | 1.54 | 1.26 (1.17–1.36) | <0.0001 | 1.23 (1.14–1.33) | <0.0001 |
| Incidence rates of patients with or without IBT   |       |     |      |             |         |                      |         |
| Comparison (those without CHC as reference)     |       |     |      |             |         |                      |         |
| CHC-nonIBT                                         | 3,143 | 257,950 | 1.22 | 1.00 (reference) | <0.0001 | 1.00 (reference) | <0.0001 |
|                                                | 807   | 47,013 | 1.72 | 1.41 (1.30–1.52) | <0.0001 | 1.34 (1.24–1.46) | <0.0001 |
| CHC-IBT                                            | 75    | 10,305 | 0.73 | 0.60 (0.47–0.75) | <0.0001 | 0.65 (0.51–0.81) | 0.0002 |

Models adjusted by sex, age, occupation, urbanization, income, and comorbidities. PY, person-years; IR, incidence rate, per 100 person-years.