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WORD COUNT	4825	TIME SUBMITTED	17-JAN-2024 06:41AM
		PAPER ID	106200234

Name of Journal: *World Journal of Gastrointestinal Oncology*
Manuscript NO: 88815
Manuscript Type: ORIGINAL ARTICLE

Retrospective Cohort Study

Chinese herbal medicine decreases incidence of HCC in DM patients with regular insulin management

Chinese herbal medicine reduced HCC risk

Hsiang-Chun Lai, Ju-Chien Cheng, Hei-Tung Yip, Long-Bin Jeng, Sheng-Teng Huang

Abstract

BACKGROUND

Type 2 diabetes mellitus (DM) is an independent risk factor for hepatocellular carcinoma (HCC), while insulin is a potent mitogen. Identifying a new therapeutic modality for preventing insulin users from developing HCC is a critical goal for researchers.

AIM

We aimed to investigate whether regular herbal medicine use can decrease HCC risk in DM patients with regular insulin control.

METHODS

We used data acquired from the Taiwanese National Health Insurance Research Database between 2000 and 2017. We identified subjects with DM who were prescribed insulin for >3 months. The herb user group was further defined as subjects prescribed herbal medication for DM for >3 months per annum during the follow-up period. We matched the herb users to non-users at a 1:3 ratio according to age, sex, comorbidities

and index year by propensity score matching. We analysed HCC incidence, HCC survival rates, and the herbal prescriptions involved.

RESULTS

We initially enrolled 657,144 DM patients with regular insulin use from 2000 to 2017 for this study. Among these, 46,849 patients had used a herbal treatment for DM, and 140,547 patients were included as the matched control group. The baseline variables were similar between the herb users and non-users. DM patients with regular herb use had a 12% decreased risk of HCC compared to the control group (adjusted hazard ratio (aHR)=0.88, 95% confidence interval= 0.80, 0.97). The cumulative incidence of HCC in the herb users was significantly lower than that of the non-users. Patients with a herb use of >5 years cumulatively exhibited a protective effect against development of HCC (adjusted HR= 0.82, p value< 0.05). Of patients who developed HCC, herb users exhibited a longer survival time than non-users (aHR= 0.78, P = 0.0001). Additionally, we report the top ten herbs and formulas in prescriptions and summarize the potential pharmacological effects of the constituents. Our analysis indicated that *Astragalus propinquus* (Huang Qi) plus *Salvia miltiorrhiza Bunge* (Dan Shen), and *Astragalus propinquus* (Huang Qi) plus *Trichosanthes kirilowii* Maxim. (Tian Hua Fen) were the most frequent combination of single herbs. Meanwhile, Ji Sheng Shen Qi Wan plus Dan Shen was the most frequent combination of herbs and formulas.

CONCLUSION

This large-scale retrospective cohort study reveals that herbal medicine may decrease HCC risk by 12% in DM patients with regular insulin use.

Key Words: Hepatocellular carcinoma; Diabetes mellitus; Insulin; Herb; Taiwanese National Health Insurance Research Database

Lai HC, Cheng JC, Yip HT, Jeng LB, Huang ST. Chinese herbal medicine decreases incidence of HCC in DM patients with regular insulin management. *World J Gastrointest Oncol* 2023; In press

Core Tip: Type 2 diabetes mellitus (DM) is an independent risk factor for hepatocellular carcinoma (HCC), while insulin is a potent mitogen. In this propensity score-matched population-based cohort study, we aimed to investigate whether regular herbal medicine use can decrease HCC risk in DM patients with regular insulin control. DM patients with regular herb use had a 12% decreased risk of HCC compared to the control group. The cohort with herb use of >5 years cumulatively exhibited a protective effect against development of HCC. Moreover, among patients who developed HCC, herb users exhibited a longer survival time than non-users (adjusted HR= 0.78).

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer, and the third-leading cause of cancer-related deaths worldwide [1]. Regional incidence rates of liver cancer are the highest in East Asia (14.8 per 100,000 person-years), more than double the worldwide incidence rate (7.3 per 100,000 person-years) [2], this is followed by North Africa (13.2 per 100,000 person-years) and South East Asia (9.5 per 100,000 person-years) [2]. Treatment strategies for HCC include surgery (resection or liver transplantation), ablation, intra-arterial therapy, radiotherapy, and systemic therapy (such as tyrosine kinase inhibitor (TKI)). Meanwhile, the Barcelona Clinic of Liver Cancer (BCLC) provides the most commonly applied staging system and guidelines regarding treatment options [3]. Major risk factors for HCC include male gender, chronic hepatitis B virus (HBV), chronic hepatitis C virus (HCV), cirrhosis, alcohol abuse, tobacco use, nonalcoholic fatty liver disease (NAFLD), diabetes mellitus, obesity, and exposure to toxins such as aflatoxins and carbon tetrachloride [4]. In East Asia, chronic HBV infection is the primary risk factor for HCC; however, incidence rates of HBV infection have been decreasing following a universal vaccination policy. Meanwhile,

HCV infection is a more influential factor in Western Europe and America, where subjects with HCV have a 15- to 20-fold increased risk of developing HCC [5]. In terms of treatments, direct-acting antiviral agents have been reported to achieve a higher rate of sustained virological response (SVR) with lower side effects compared to interferon regimens. More specifically, after treatment with direct-acting antiviral agents, HCV patients with SVR had a 78% decreased risk of HCC occurrence compared with non-responders [6]. Henceforth, due to the declining role of viral infections, metabolic etiologies have increasingly become the focus of investigations into HCC occurrence.

Type 2 diabetes mellitus (T2DM) is an independent risk factor for both NAFLD and HCC [7]. It is reported that patients with T2DM have a 2.5- to 4-fold increased risk of developing HCC compared with normal subjects [8]. Treatments for diabetes mellitus (DM) include insulin-sensitizing agents, agents stimulating insulin secretion, insulin supplementation, and treatments to reduce gastrointestinal and urinary glucose absorption. While these medications generally provide adequate control of blood sugar levels, some of them fail to significantly reduce the risk of HCC occurrence. In recent years, studies have demonstrated an elevated risk of HCC incidence in diabetic patients treated with insulin [9]. As insulin is a potent mitogen, it acts to up-regulate various growth factors including insulin-like growth factor 1 (IGF-1), thereby increasing HCC risk [8]. As a complementary and alternative treatment option, traditional Chinese medicine (TCM) has been used for centuries in East Asia, while it has more recently been gaining popularity worldwide. Studies have reported that TCM contains many natural compounds, exerting a variety of beneficial therapeutic effects, including anti-cancer and the balancing of blood sugar levels [10, 11]. Of particular interest here, TCM indicates that *Astragalus membranaceus* (a synonym of *Astragalus propinquus*) has the effect to tonify qi. In contemporary investigations, *Astragalus membranaceus*, which is rich in anti-diabetic compounds including polysaccharides (Astragalus polysaccharides), saponins (Astragalus saponins), and flavonoids (Astragalus flavonoids) has presented anti-HCC effects in cell lines [12, 13].

Researchers have yet to report on the potential of herbal treatments to decrease HCC risk in DM patients with regular insulin use. In addition, it must be noted that the development of carcinogenesis is a relatively long-term process. Thus, we herein aimed to conduct a population-based retrospective cohort study using data from the Taiwan National Health Insurance Research Database (NHIRD) to investigate the potential of regular herb use to decrease HCC risk in DM patients with regular insulin management. We further analyzed the associated TCM prescriptions to provide both clinical guidance and to summarize the potential molecular mechanisms of the herbs and formulas which could act to decrease HCC risk in DM patients with regular insulin management.

MATERIALS AND METHODS

Data source

In Taiwan, over 99% of residents participate in the single-payer National Health Insurance (NHI) program, which was launched in 1995. The medical claim data is stored in the Nation Health Insurance Research Database (NHIRD). In addition to demographic characteristics such as sex, birth date and region of residence, the database contains critical information regarding disease diagnosis, medication usage and other treatments received. Diseases in this database are recorded using codes of the International Classification of Diseases, Ninth & Tenth Revision, Clinical Modification (ICD-9&10-CM). Here, we utilized the NHIRD to investigate the association of herb use and HCC in DM patients. This study was approved by the Institutional Review Board of China Medical University Hospital Research Ethics Committee (CMUH109-REC2-031 (CR-3)). All records and personal information were anonymized prior to analysis, thus the requirement for written informed consent was waived.

Study population and flow chart

We used data acquired from the Taiwanese NHIRD for the period of January 1, 2000 to December 31, 2017. We defined subjects with three or more outpatient visits or one inpatient record of ICD-9-CM code 250 or ICD-10-CM E08-E13 as DM patients. For

this cohort study, DM patients with insulin use for >3 months were the study population. The exposure group in this study included patients with herb use due to DM for >3 months per annum during the follow-up period. DM patients with insulin use never having received herbal treatment within the study period were defined as the non-exposure group. The index date for the exposure group was set at the first day of herb use after insulin prescription, and we assigned a random date after insulin prescription as the index date for non-exposure patients. The index date for the exposure and non-exposure groups were matched, with both post-indexed more than 3 months to account for insulin exposure. Exclusion criteria included patients under 20 years old, with an index date prior to 2000 or after 2017, having any type of cancer aside from HCC, and with HCC diagnosis prior to the index date or within one year after the index date. We matched the herb users to non-users at a 1:3 ratio according to age, sex, comorbidities and index year by propensity score matching. The flow chart illustrating the inclusion process in this study is shown in Figure 1.

Main outcomes and comorbidities

The primary outcome of this study was HCC, as defined by the Registry for catastrophic illness patients. Patients with IC Cards for Severe Illness with ICD-9-CM code of 155 or ICD-10-CM code of C220, C228 were the HCC patients. Death or withdrawal from the program prior to the end of the study period (31 December 2017) was considered as censoring. The related comorbidities included hypertension (ICD-9-CM code 401-405; ICD-10-CM code I10-I15), coronary heart disease (ICD-9-CM code 410-414; ICD-10-CM code I20-I25), ischemic stroke (ICD-9-CM code 433,434; ICD-10-CM code I63, I65, I66, I67, I68, G46.3-G46.8), hemorrhagic stroke (ICD-9-CM code 430-432; ICD-10-CM code I60, I61, I62), hyperlipidemia (ICD-9-CM code 272; ICD-10-CM code E78), renal insufficiency (ICD-9-CM code 585, 586, 588.8, 588.9; ICD-10-CM code N18, N19, N25.8, N25.9), cirrhosis (ICD-9-CM code 571.2, 571.5, 571.6; ICD-10-CM code K70.2, K70.30, K70.31, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.60, K74.69), alcoholic liver damage (ICD-9-CM code 571.0, 571.1, 571.3; ICD-10-CM code K70.0, K70.10, K70.11, K70.40, K70.41, K70.0), nonalcoholic fatty liver disease (NAFLD) (ICD-9-

CM code 571.8; ICD-10-CM code K74.4, K75.81, K76.0, K76.89), hepatitis B virus (HBV) infection (ICD-9-CM code V02.61, 070.20, 070.22, 070.30, 070.32; ICD-10-CM code Z22.51, B16.2, B16.9, B18.1, B19.10, B19.11) and hepatitis C virus (HCV) infection (ICD-9-CM code V02.62, 070.41, 070.44, 070.51, 070.54; ICD-10-CM code Z22.52, B17.10, B17.11, B18.2, B19.20, B19.21). In addition, several medications were included in our analysis, including lipid-lowering drugs (statin and non-statin), aspirin, HBV treatments (Lamivudine, Adefovir, Entecavir, Telbivudine, Tenofovir, Peg-INF α-2a), HCV treatments (Harvoni, Sovaldi, Zepatier, Maviret, Epclusa, Viekirax+Exviera, Daklinza, Daklinza+Sunvepra, Interferon+Ribavirin), and oral antidiabetic drugs (OADs) (Biguanides, Sulfonamide, alpha glucosidase inhibitors (AGI), Thiazolidinediones, Dipeptidyl peptidase 4 (DPP4) inhibitors, Glucagon-like peptide-1 (GLP-1) receptor agonist, Sodium-glucose cotransporter 2 (SGLT2) inhibitors and glinides).

Statistical analysis

For the categorical variables of baseline characteristics, we represented the number and the percentage. The mean and standard deviation (SD) of age were presented. The differences between the two groups were shown by standard mean difference (SMD). A significant difference was shown for SMD >0.1. We calculated the incidence rate by dividing the number of events for each 1,000 person-years and the hazard ratio (HR) through the Cox proportional hazard. A 95% confidence interval (CI) and p-value were also indicated. We further illustrated the cumulative incidence curve as calculated by the Kaplan-Meier method and compared by the log-rank test for statistical significance. All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC). A significance level was set at p-value <0.05.

RESULTS

Baseline characteristics and comorbidities of study participants

In this study, we enrolled a total of 657,144 DM patients with regular insulin use identified within the period of 2000 and 2017. Of these patients, 46,849 had used herbal treatments for DM management, while 140,547 were included as the matched control

group. After propensity matching, the baseline variables were similar between the herb users and non-users (SMD < 0.1) (Table 1). Nearly half of the study patients were older than 60 years of age. The top three comorbidities identified in this cohort study were hyperlipidaemia, hypertension, and coronary heart disease, while the proportions of all comorbidities in the study group and the control group were similar. In addition, medications used by the herb users and non-users demonstrated no differences (Table 1).

Chinese herbal medicine decreased HCC risk among DM patients with insulin management

The association between herbal management and HCC is shown in Table 2. The incidence rate of HCC among the herb users was 2.07 per 1,000 person-years, while it was 1.93 per 1,000 person-years among non-users. After adjustment for the variables noted in Table 1, the adjusted HR of HCC was 0.88 (95%CI=0.80, 0.97; p-value=0.001) for herb users compared to the control group. As illustrated in Figure 2, the cumulative incidence of HCC in herb users was significantly lower than that of the non-users (p-value=0.0078), while male patients had a higher risk of HCC relative to female patients (adjusted HR=1.77; 95%CI=1.62, 1.94; p-value<0.001). In addition, older patients exhibited an elevated risk of developing HCC. Comorbidities including cirrhosis (adjusted HR=4.28; 95%CI=3.80, 4.82; p-value<0.001), NAFLD (adjusted HR=1.24; 95%CI=1.09, 1.42; p-value<0.001), HBV infection (adjusted HR=2.59; 95%CI=2.32, 2.90; p-value<0.001) and HCV infection (adjusted HR=4.56; 95%CI=4.09, 5.08; p-value<0.001) were identified as risk factors of HCC. Similarly, patients with HBV and HCV treatments exhibited increased risks of HCC, by 3.69-fold (95%CI=3.21, 4.25; p-value<0.001) and 1.47-fold (95%CI=1.14, 1.88; p-value<0.001) respectively. Of the patients using a GLP-1 receptor agonist and SGLT2 inhibitors, the adjusted HR of HCC were 0.40 (95%CI=0.24, 0.68; p-value<0.001) and 0.79 (95%CI=0.64, 0.98; p-value=0.010), respectively.

Chinese herbal medicine users achieved a longer survival time compared to non-herb users among patients who developed HCC

By analysing herb usage during the study period, patients with a herb use of >5 years cumulatively exhibited a protective effect against development of HCC (adjusted HR= 0.82, p value< 0.05; p-value=0.003). In patients who used herbs for <1 year, 1-2.9 years, and 3-4.9 years, the adjusted HR of <1 for developing HCC failed to reach statistical significance (Table 3). In the cohort of patients who developed HCC, herb users exhibited a longer survival time in days compared to non-users (adjusted HR= 0.78, *P* = 0.0001) (Figure 3).

The top ten herbs and formulas of prescriptions

Data regarding the top ten single herbs and herbal formulas used by patients, and summaries of the potential pharmacological effects of the constituents are presented in Table 4. Patients with prescriptions of *Rheum palmatum* L. (Da Huang), *Salvia miltiorrhiza Bunge* (Dan Shen), *Trichosanthes kirilowii* Maxim. (Tian Hua Fen), and *Scrophularia ningpoensis* Hemsl. (Xuan Shen) exhibited lower risks of HCC, with statistical significance (adjusted HR=0.79-0.87; p-value<0.05). In terms of herbal formulas, patients with prescriptions of Ji Sheng Shen Qi Wan, Liu Wei Di Huang Wan, Shu Jing Huo Xie Tang, Xue Fu Zhu Yu Tang, Qi Ju Di Huang Wan, Bai Hu Jia Ren Shen Tang, and Zhi Gan Cao Tang exhibited lower risks of HCC, with an adjusted HR 0.77-0.86, with statistical significance (p-value<0.05). The network analysis of the top thirty most prescribed herbs and formulas is presented in Figure 4. The analysis illustrates that *Astragalus propinquus* (Huang Qi) plus *Salvia miltiorrhiza Bunge* (Dan Shen), and *Astragalus propinquus* (Huang Qi) plus *Trichosanthes kirilowii* Maxim. (Tian Hua Fen) were the most frequent combination of single herbs. Meanwhile, Ji Sheng Shen Qi Wan plus Dan Shen was the most frequent combination of herbs and formulas.

DISCUSSION

Summary of findings

2 Although previous studies have demonstrated that DM patients with insulin management have an increased risk of HCC, this is the first large-scale cohort study indicating the efficacy of herbs at decreasing the HCC risk by 12% among DM patients,

after adjusting for sex, age, various drug uses and major comorbidities (adjusted HR=0.88; 95%CI=0.8, 0.97; p-value=0.001). Furthermore, among patients who developed HCC during the study period, herbal medicine users exhibited a longer survival time in days compared to non-users (adjusted HR= 0.78, P = 0.0001).

HCC general risk factors

Similar to previous reports, our study reveals that males had an elevated risk of developing HCC as compared to females (adjusted HR=1.77; 95%CI=1.62, 1.94; p-value<0.001) [14]. Additionally, approximately 50% of our cohort patients were over 60 years of age, noting that HCC risk steadily increases with age. While the diagnosed onset age of HCC varies in different parts of the world, Yang *et al* reported a median onset age above 60 years [4], which is similar to our findings. Meanwhile, our stratified analysis reveals that cirrhosis patients had the highest risk of developing HCC compared to other comorbidities (adjusted HR=4.28; 95%CI=3.8, 4.82; p-value<0.001). A study by Fattovich *et al* reported a 4-fold elevated risk of developing HCC in cirrhosis patients compared to those with chronic hepatitis [15]. With viral infection or alcohol intake, a damaged liver will undergo regeneration and tissue recovery. The repeated hepatocyte and hepatic stellate cellular proliferation may trigger cancer-related fibroblasts and lead to cirrhosis as well as HCC proliferation [16]. Furthermore, between 15% and 30% of cirrhosis patients develop T2DM due to perturbed glucose utilization and decreased insulin removal by the liver [17]. Hyperglycemia and hyperinsulinemia status may also result in development of HCC. Of note, our study identified HBV and HCV infections as major risk factors of developing HCC. The worldwide incidence of HCV-related HCC is 12–17 per 1,000 person-years, which is similar to our finding (15.10 per 1,000 person-years) [5]; on the other hand, incidence of HBV-related HCC varies by region [15]. In our study, HBV and HCV treatments were adopted in accordance with patient preference, and following NHI payment guidelines. HBV treatments were covered for patients with HBV DNA≧2,000IU/mL with 5-fold elevated liver enzymes or decompensated liver status, while HCV treatments were covered for patients positive for anti-HCV for >6 months with cirrhosis ≧F2 or positive for HCV RNA. We

hypothesize that the liver status of patients in the HBV and HCV treatment groups were generally more severe, thus causing the elevated risk of HCC incidence noted in our study.

Association between DM, OADs and HCC risk compared to other studies

DM is a metabolic disorder associated with hyperglycemia, hyperinsulinemia, and insulin resistance. Due to metabolic disturbances, DM is noted as an independent risk factor for various types of cancer, including breast, colorectal, endometrial, pancreatic, gallbladder, renal, and liver cancers [18]. It has been reported that T2DM patients have a 2.5- to 4-fold risk of developing HCC compared with normal subjects [8], the possible underlying mechanism of which is associated with insulin resistance related to hyperinsulinemia. Hyperinsulinemia increases IGF-1, causing IGF-1 and insulin receptor substrate-1 overexpression, thereby activating hepatoma cell proliferation [19]. Insulin supplementation is indicated in T2DM and gestational DM patients; however, although insulin supplements can achieve satisfactory control of blood sugar levels, mounting evidence suggests an elevated risk of HCC in diabetic patients. According to a previous study, both higher daily insulin dosage and longer treatment duration increase the risk of HCC in patients treated with insulin by adjusted odds ratio from 1.9 to 3.73 [8]. More specifically, sulfonylureas, which promote insulin secretion, pose a 2.6-fold increased risk of developing HCC [20]. Our report reveals a similar result whereby sulfonylureas increased HCC risk (adjusted HR=1.08), but without statistical significance.

The biguanide metformin is an oral anti-hyperglycemic agent which has been identified as a potential hepatoprotective drug against HCC development [21]. Metformin activates AMPK and inhibits the downstream mTOR pathway, which plays a key role in preventing hepatocarcinogenesis [22]. Indeed, previous studies have reported a metformin treatment group with a 43-76% reduced risk of HCC and reduced overall mortality risk [8, 9]; however, our subgroup analysis showed no difference between biguanides users and non-users (adjusted HR= 1.16; 95%CI=0.84, 1.61; p-value=0.368). Meanwhile, glucagon-like peptide-1 (GLP-1) is an insulin secretagogue

which ameliorates liver fat accumulation and the inflammatory microenvironment, acting to prevent NAFLD progression to non-alcoholic steatohepatitis (NASH). In our study, GLP-1 receptor agonists decreased HCC risk (adjusted HR= 0.4; 95%CI=0.24, 0.68; p-value<0.001). Previous studies have demonstrated that GLP-1 receptor agonists induce autophagy *via* elevating the transforming growth factor beta-1 (TGF-β1) level and reducing migration *via* suppression of the stress-activated protein kinase/c-Jun N-terminal kinase pathway [23, 24], which is further supported by our findings. However, it should be noted that GLP-1 receptor agonists elevate the insulin level in patients, thereby potentially elevating the risk of HCC. Thus, more high-quality clinical evidence is required to clarify the association between GLP-1 receptor agonist and HCC occurrence. In addition, SGLT2 inhibitors are a new class of OAD which act to decrease glucose reabsorption in the renal proximal tubules. SGLT2 has been shown to attenuate the development of NASH and induce cell cycle arrest and apoptosis in an animal model [25]. Our report reveals a decreased HCC risk (adjusted HR= 0.79; 95%CI=0.64, 0.98; p-value=0.010) in SGLT2 inhibitor users; however, there is a lack of clinical data regarding SGLT2 inhibitors as a protector or inducer of carcinogenesis.

Possible mechanisms in Chinese herbal medicine for preventing HCC among DM patients

Although many OADs have been developed, insulin continues to play a prominent role in the clinical setting as it is applied to such conditions as chronic DM, type 1 DM, chronic kidney disease, and gestational DM. Thus, identifying a new therapeutic modality is critical to preventing insulin users from developing HCC. As such, many of the herbs applied in TCM contain natural compounds which have been demonstrated to exert both anticancer and antidiabetic effects without causing hyperinsulinemia [10, 11]. Table 4 Lists and summarizes the possible pharmacological effects of the ten most prescribed herbs and formulas identified in our study. Importantly, previous studies have indicated that these herbs and formulas contain active compounds involved in the inhibition of HCC progression. A majority of them have been shown to induce apoptosis both *in vivo* and *in vitro* in HCC cell line studies, while *Corydalis yanhusuo* [26] and *Anemarrhena asphodeloides* [27] (present in Zhi Bai Di Huang Wan and Bai Hu Jia Ren

Shen Tang) have been noted to induce autophagy. In addition, *Pueraria montana* and *Paeonia lactiflora* (present in Jia Wei Xiao Yao San and Ma Zi Ren Wan) inhibit HCC invasion and metastasis. Aside from *Corydalis yanhusuo*, the other top ten herbs and formulas have been reported to exert antidiabetic effects, primarily by ameliorating insulin resistance *via* various molecular pathways. As previously reported, *Rheum palmatum* [28], *Astragalus propinquus* [29] and *Magnolia officinalis* [30] prevent pancreas β-cell death and control blood sugar levels. Meanwhile, *Salvia miltiorrhiza* [31, 32] and *Magnolia officinalis* [33] inhibit IGF-1, a tumor carcinogen, indicating their potential to inhibit HCC proliferation. Furthermore, *Scutellaria baicalensis* [34], *Ophiopogon japonicas* [35] and *Anemarrhena asphodeloides* [36] have been demonstrated to modulate gut microbiota in high-fat-diet animal models. Collectively, the present study and previous investigations indicate that the herbs identified herein are associated with both anticancer and antidiabetic effects without causing hyperinsulinemia, although further investigation is warranted.

Limitations

The NHIRD used in this study provides a large sample size, covering over 99% of Taiwan's residents with a low loss of follow-up, and provides sufficient power for subgroup analyses to demonstrate convincing outcomes after adjusting for potential confounding factors. However, several limitations need to be considered. First, the NHIRD does not offer information on potential confounding factors such as body mass index, environmental/chemical exposure, alcohol/tobacco consumption, or history of family illness. Thus, we have attempted to adjust for the alcohol confounding factor by considering alcoholic liver disease, revealing no statistical significance between the two cohorts. Second, clinical data were lacking in terms of laboratory data and imaging results, making it difficult to investigate DM control quality, and stages of cirrhosis and HCC. Among the demographic characteristics in our patients, the proportion with cirrhosis, alcoholic liver damage and HBV/HCV infection were not significantly different between the groups, suggesting that the background risk of liver cancer occurrence was likely similar for both groups. Third, the NHIRD only records herbal

prescriptions manufactured by good manufacturing practice (GMP)-certified pharmaceutical companies; hence, herbs purchased outside of the National Health Insurance (NHI) program were not analyzed in this study. However, self-paid herbs are relatively expensive, at approximately $300 to $400 USD per month, while we identified patients with >3 months of herbal prescriptions per annum during the study period, thus the chance of patients purchasing herbs not covered by NHI should be minimal. Fourth, due to the nature of retrospective cohort studies, bias may exist in our results. More specifically, it is reasonable to suggest that patients with a longer survival time may have received herbal treatment for a correspondingly longer period, thus warranting a prospective study to confirm our results. To minimize these limitations, we defined only patients with long-term (>3 months) use of insulin and herbs, and patients diagnosed with HCC according to the Registry for Catastrophic Illness Database. We also reviewed the possible mechanisms underlying herbal effects on both anti-HCC and reversal of insulin resistance to bridge our results. Taken together, our study reveals several notable findings, while the prescription patterns identified in this large-scale cohort study provide valuable clinical guidance, and warrant further clinical studies and pharmacological investigation.

CONCLUSION

As DM patients using insulin have an increased risk of developing HCC, identifying a new therapeutic modality to prevent or mitigate this risk is of critical importance. This is the first large-scale cohort study revealing that regular herbal medicine prescriptions can effectively decrease the risk of HCC in DM patients using insulin. Furthermore, herbal prescriptions may extend the survival time for those DM patients with HCC. Future large-scale cohort studies or prospective studies are recommended to further support our results.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is the fifth most commonly occurring cancer globally. Type 2 diabetes mellitus (DM) is independent risk factor for hepatocellular carcinoma (HCC), while insulin is a potent mitogen. Identifying a new therapeutic modality for preventing insulin users from developing HCC is a critical goal for researchers.

Research motivation

Previous reports have indicated the potential of herbal treatments to decrease HCC risk in DM patients. However, the development of carcinogenesis is a relatively long-term process. Thus, we herein aimed to conduct a population-based retrospective cohort study using data from the Taiwan National Health Insurance Research Database (NHIRD) to investigate the potential of regular herb use to decrease HCC risk in DM patients with regular insulin management.

Research objectives

The objective of this study was to evaluate whether regular herbal medicine use can decrease HCC risk in DM patients with regular insulin control.

Research methods

We used data acquired from the Taiwanese NHIRD between 2000 and 2017. We identified subjects with DM who were prescribed insulin for >3 months. The herb group was further defined as subjects prescribed herbal medication for DM for >3 months per annum during the follow-up period. We analysed HCC incidence, HCC survival rates, and the herbal prescriptions involved.

Research results

We enrolled 657,144 DM patients with regular insulin use from 2000 to 2017 in this study. Among these, 46,849 patients had used herbal treatment for DM, and 140,547 patients were included as the matched control group. The baseline variables were similar between the herb users and non-users. DM patients with regular herb use had a

12% decreased risk of HCC compared to the control group (adjusted hazard ratio (aHR)=0.88, 95% confidence interval= 0.80, 0.97). The cumulative incidence of HCC in herb users was significantly lower than that of the non-users. Patients with herb use for >5 years cumulatively exhibited a protective effect against development of HCC (adjusted HR= 0.82, p value< 0.05). Of patients who developed HCC, herb users exhibited a longer survival time than non-users (aHR= 0.78, *P* = 0.0001). Our analysis indicated that *Astragalus propinquus* (Huang Qi) plus *Salvia miltiorrhiza Bunge* (Dan Shen), and *Astragalus propinquus* (Huang Qi) plus *Trichosanthes kirilowii* Maxim. (Tian Hua Fen) were the most frequent combination of single herbs. Meanwhile, Ji Sheng Shen Qi Wan plus Dan Shen was the most frequent combination of herbs and formulas.

Research conclusions

This large-scale retrospective cohort study reveals that herbal medicine may decrease HCC risk by 12% in DM patients with regular insulin use. Furthermore, herbal prescriptions may extend the survival time for those DM patients who develop HCC.

Research perspectives

Since herbal prescriptions are relatively cheap and commonly used, large-scale cohort studies or prospective studies are required to support our results.

ACKNOWLEDGEMENTS

We are grateful to Health Data Science Center, China Medical University Hospital for providing administrative, technical and funding support. The authors would like to thank James Waddell for the proofreading and revision of our manuscript.

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