Integrative traditional Chinese medicine therapy reduces the risk of diabetic ketoacidosis in patients with type 1 diabetes mellitus

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ABSTRACT

Ethnopharmacological relevance: Life-long insulin is the standard treatment for type 1 diabetes mellitus (T1DM). The role of traditional Chinese medicine (TCM) in T1DM is still not clear. The aim of this study is to explore the prescription pattern of TCM and its impact on the risk of diabetic ketoacidosis (DKA) in patients with T1DM.

Materials and methods: We retrieved samples from the registry for catastrophic illness patients from the National Health Insurance Research Database (NHIRD). Based on a frequency (1:4) matched case-control design, patients with T1DM in 2000–2011 were designated as cases (TCM users) and controls (non-TCM users). TCM treatment for patients with T1DM was analyzed. The incidence of DKA and the annual costs of emergency visits and hospitalizations were evaluated for all causes.

Results: Overall, 416 subjects were TCM users, whereas a total of 1608 matched subjects were classified as non-TCM users. The most common Chinese herbal formula and single herb is Liu-wei-di-huang-wan (Six-ingredient pill of Rehmannia) and Huang-qi (Radix Astragali; Astragalus membranaceus (Fisch.) Bunge, Astragalus membranaceus var. mongholicus (Bunge) P.K.Hsiao), respectively. Compared with non-TCM users, we found a 33% reduction in DKA incidence for all TCM users (aHR 0.67, 95% CI 0.56–0.81, p < 0.000) and a 40% reduction for users receiving TCM treatment for more than 180 days (aHR 0.58, 95% CI 0.41–0.82, p < 0.01). There were no significant differences between TCM users and non-users in the frequency and medical costs of emergency visits and hospitalizations.

Conclusions: Integrative TCM use may reduce the risk of DKA in patients with T1DM. Our results suggest that TCM may have a substantial positive impact on the management of TIDM.

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1. Introduction

Diabetes mellitus (DM) is the most common metabolic disease and is characterized by a partial or complete deficiency of insulin related to the destruction of pancreatic β cells. Type 1 diabetes mellitus (T1DM) in particular is manifested at a young age and may require life-long insulin treatment depending on the residual pancreatic function (Barker et al., 2014). According to reports from the International Diabetes Federation, there are an estimated 542,000 children living with T1DM (International Diabetes Federation, 2013). Moreover, approximately 86,000 children under 15 years of age develop T1DM annually, and the annual incidence rate is estimated to be 3% worldwide (International Diabetes Federation, 2013). The biannual sex-specific incidence rate per 100,000 inhabitants in Taiwan was 5.88 and 6.92 for male and female younger than 15 years, respectively (Lin et al., 2014).

Complications of T1DM, such as diabetic ketoacidosis (DKA),

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remain a major concern in the treatment of T1DM (Gan et al., 2012). A previous epidemiologic study based on the National Health Insurance Research Database (NHIRD) revealed that diabetic ketoacidosis (DKA) contributed to 24.6% of all hospital admissions among Taiwanese patients with T1DM in 2007–2008 (Lin et al., 2014). DKA remained the most common complication of T1DM leading to hospitalization after the onset of disease. Although insulin replacement is the primary therapy for T1DM, complementary and integrative therapies that reduce complications associated with T1DM remain of interest.

Previous studies on traditional Chinese medicine (TCM) have been largely limited by their research approaches, which include questionnaire- and observation-based surveys (Dannemann et al., 2008; Fabian et al., 2011; Haliloglu et al., 2011). Moreover, reports on parents or children attempting to use TCM as a complementary medicine for T1DM may have been underestimated (Chien et al., 2007). In the TCM system, diabetes has been defined as "Xiao-Ke", a sign of Yin-Yang imbalance, yin vacuity with fire flaming upward and Qi vacuity (Li and Xu, 2006). Literally, "Xiao-Ke" means that the patient experiences dryness, thirst and a thin body contour due to exhaustion. TCM is very common in Asian countries. Our previous study revealed that 31.2% of the Taiwanese population covered by the National Health Insurance (NHI) program had conducted at least one TCM outpatient visit in 2010 (Yen et al., 2013). The Taiwanese NHI program has been reimbursing TCM costs since 1996 and covered more than 99% of Taiwanese population (Huang et al., 2014; Yen et al., 2013). Notably, many of the Taiwanese public hospitals and university-affiliated teaching hospitals offer TCM clinics. Of these hospitals and clinics, 93.7% are contracted with the NHI Program. Such a large population-based cohort provides advantages include enormous sample size and lack of selection and participation bias (Hsing and Ioannidis, 2015). For example, we have found that integration of TCM therapy may reduce the risk for cerebral vascular accidents in patients with type 2 diabetes mellitus (Lee et al., 2016).

Integrating TCM with glucose control and the management of complications from diabetic kidney disease (DKD) and atherosclerotic cardiovascular disease (ASCVD) has been suggested as an innovative treatment strategy for DM care (Fu and Liu, 2012; Zhang and Jiang, 2012). The current study aimed to evaluate whether supplementing standard medical treatments with TCM can reduce DKA among patients with T1DM. In addition, we characterized the Chinese herbal medicine that these patients received.

2. Methods

2.1. Data source

Data were analyzed from the National Health Insurance Research Database (NHIRD) in Taiwan. The NHIRD consists of records for all outpatient and hospitalization incidents for of all NHI beneficiaries as well as details of the administered treatments and drugs or Chinese herbal medicines prescribed. The NHIRD registry and original data are comprised of demographic characteristics, outpatient and inpatient visits, diagnostic codes, assessments, procedures, prescriptions and medical expenditures for reimbursements. All diseases in the NHIRD are classified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD also established a registry for catastrophic illness patients database (RCIPD), which includes approximately 30 disease categories, such as T1DM, cancer (Fleischer et al., 2016), schizophrenia, end-stage renal disease and rheumatoid arthritis (Huang et al., 2015). Patients with T1DM who received complete clinical and laboratory evaluation followed by

Table 1

Demographic data of adjunctive TCM users and matched non-TCM users among patients with type 1 DM from 2000 to 2011 in Taiwan.

	TCM users N=416		Non-TCM users N=1608		
	n	%	n	%	P-value
Men	187	45.0	734	45.7	0.90
Average age, year (SD)	24.8	(13.3)	24.1	(12.8)	0.33
Medical history					
Hypertension	26	6.25	3	3.92	0.04*
Hyperlipidemia	116	27.9	426	46.5	0.57

* $P < 0.05$.

Table 2

Frequency distribution of various TCM therapies for type 1 DM.

Treatment methods	Clinical visits	%
Herbal remedies	25,571	83.3
Acupuncture	3555	7.67
Manipulative therapy	2310	7.53
Acupuncture and herbal remedies	266	0.87
Manipulative therapy and herbal remedies	183	0.60
All clinical visits	30,685	100

careful and routine review by endocrinologists commissioned by the National Health Insurance Administration were granted catastrophic illness certificates. Therefore, the accuracy of the T1DM diagnoses in this study is highly reliable, which reduces the potential for sampling bias. With the advantage of almost total coverage of patients with T1DM and electronic resource forms for insurance claim data, we were able to investigate the effects of TCM treatment for all patients with T1DM in the registry. The description of therapeutic actions and indications of the Chinese herbal formulas (Scheid et al., 2009) and single herbs (Bensky et al., 2004) are based on Chinese medical theory. Herbal formulas were listed in pin-yin name and English name. Ingredients of the herbal formulas and the single herbs were listed in pin-yin name, Latin name and botanical plant name. Full botanical names comply with the *International Plant Names List* (IPNI; http://www.ipni.org) and *The Plant List* (http://www.theplantlist.org/) (Chan et al., 2012). This study was approved by the Research Ethics Committee of China Medical University and Hospital (CMUH104-REC2-115).

2.2. Study population

This study was based on a case-control design. All of the cases were selected from the registry for catastrophic illness patients database (RCIPD) from the NHIRD from 1998 to 2011. In Taiwan, T1DM is considered a catastrophic illness in the health insurance system. All research subjects were evaluated and reviewed by the NHI administration. Holders of catastrophic illness certificates (CICs) are eligible for exclusion from extra insurance charges and co-payments. Therefore, CICs registration is a valid and reliable source of data for T1DM retrieval. Moreover, because waiving the co-payment is required for admission, emergency visits, and outpatient services, this certification is only applied when detailed and specific clinical data are met, e.g., regular insulin use with a history of diabetic ketoacidosis, a positive glucagon test, or the presence of glutamic-acid-decarboxylase (GAD) antibodies (Lu et al., 2014). The CICs are canceled if a patient dies. Consequently, T1DM data retrieved based on CICs are considered complete.

A T1DM adjunctive TCM user was defined as an individual