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Research Paper

Integrating traditional Chinese medicine healthcare into diabetes care by reducing the risk of developing kidney failure among type 2 diabetic patients: A population-based case control study

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ABSTRACT

Ethnopharmacological relevance: Our previous study indicated that the traditional Chinese medicine (TCM) formula *Liu-Wei-Di-Huang-Wan*, which consists of six type of herbs, namely *Rehmannia glutinosa* (Gaertn.) DC., root, dried; *Cornus officinalis* Siebold & Zucc., fructus, dried; *Dioscorea oppositifolia* L., root, dried; *Alisma plantago-aquatica* subsp. *orientale* (Sam.) Sam., tuber, dried; *Paeonia* × *suffruticosa* Andrews, bark, dried; *Poria cocos* (Fr.) Wolf., sclerotium, dried, is the most frequently prescribed herbal formula used to treat type 2 diabetes patients. The aim of the study was to evaluate the integration of TCM into diabetes care in terms of how it reduces the risk of developing kidney failure.

Materials and Methods: The Taiwan's National Health Insurance Research Database (NHIRD) provided detailed information of health care services for each patient and covers 98% of all Taiwan residents as of 2007. Case and control subjects were selected from the NHIRD. Two multivariable logistic regression models were constructed in order to explore two types of exposure assessments including prescription of TCMs (model 1) and prescription of different estimated dosages of *Liu-Wei-Di-Huang-Wan* (model 2).

Results: Using logistic regression model 1, having used TCMs was independently associated with a decreased risk of kidney failure by multivariable analysis (OR=0.69, 95% CI: 0.61–0.77). Using logistic regression model 2, there was no difference between non-*Liu-Wei-Di-Huang-Wan* TCM users and *Liu-Wei-Di-Huang-Wan* TCM users in terms of the risk of developing kidney failure. Furthermore, there was also no linear dose–response trend when we used exposure to prescribed *Liu-Wei-Di-Huang-Wan* as a continuous variable (for non-*Liu-Wei-Di-Huang-Wan* TCM users, OR=0.68, 95% CI: 0.60–0.77; for TCM users consuming 1–30 g of *Liu-Wei-Di-Huang-Wan*, OR=0.69, 95% CI: 0.54–0.87; for >30 g of *Liu-Wei-Di-Huang-Wan*, OR=0.84, 95% CI: 0.49–1.44).

Conclusions: Integrating TCM healthcare into diabetes care was found to be associated with a decreased risk of developing kidney failure. Having recognized the use of TCM, exploring any potential interactions and adverse effects, and integrating both technologies into a holistic treatment system may be beneficial to the relief of diabetic nephropathy on patients with type 2 diabetes.

1. Introduction

Diabetes mellitus is a chronic metabolic disease and is the most frequently reported cause of kidney failure (Perneger et al., 1994a). Due to having a long asymptomatic preclinical phase, asymptomatic hyperglycemia is likely to go undetected (Harris and Eastman, 2000) resulting in a high incidence of nephropathy when type 2 diabetes mellitus is diagnosed (Laakso, 1999). An increasing prevalence of diabetes mellitus is a worldwide trend (Jiang et al., 2012; Wild et al.,

Abbreviations: NHIRD, National Health Insurance Research Database; TCM, traditional Chinese medicine

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2004) and is a wake-up call because of the impact that kidney failure will have on the economic and sociomedical development of nations in the near future (Zhang et al., 2010). Preventing the development of kidney failure has therefore become an important therapeutic challenge for many clinicians.

Traditional Chinese medicine (TCM) has been an important part of health care in Taiwan for many years and continues to have growing popularity in Taiwan and many other Asian countries; TCM is fully reimbursed under the current Taiwanese National Health Insurance (NHI) system (Hsieh et al., 2008; Zhong et al., 2013). TCM doctors are specialized practitioners who use meticulous approaches to gather clinical symptoms and signs, which are then used to make diagnoses and decide on treatment strategies; these approaches follow rules of induction and are guided by empirical experience over many hundreds of years. Moreover, clinical treatment based on these strategies is used to optimize the body's ability to function normally and to treat discomfort and/or complications when patients are suffering from diabetes; this contrasts with Western medicine, which concentrates on battling hyperglycemia (Huang et al., 2013; Poon et al., 2011). Thus, using numerous blood sugar profiles in order to interpret the therapeutic effects of TCM treatment is not a useful approach. Rather, a comparison of the therapeutic effectiveness of TCMs in terms of improving diabetic nephropathy between case and control groups, or alternatively randomized control trials, is needed to explore the effectiveness of TCMs. Although several recent studies have explored the biological activity and potential therapeutic effects of several TCMs in terms of their ability to treat diabetes or chronic kidney disease (Covington, 2001; Jiang et al., 2014; Li et al., 2014; Peng et al., 2005; Zhang et al., 2014), it remains necessary to compare diabetic nephropathy outcomes when diabetic care is carried out with and without the concurrent use of TCMs.

Our previous study indicated that the TCM formula *Liu-Wei-Di-Huang-Wan*, which consists of six type of herbs, namely *Rehmannia glutinosa* (Gaertn.) DC., root, dried; *Cornus officinalis* Siebold & Zucc., fructus, dried; *Dioscorea oppositifolia* L., root, dried; *Alisma plantago-aquatica* subsp. *orientale* (Sam.) Sam., tuber, dried; *Paeonia* × *suffruticosa* Andrews, bark, dried; *Poria cocos* (Fr.) Wolf., sclerotium, dried, is the most frequently prescribed herbal formula used to treat type 2 diabetes patients (Huang et al., 2013). *Liu-Wei-Di-Huang-Wan* is prescribed mainly to target a kidney yin deficiency pattern, which is identified by TCM doctors via four diagnostic methods (inspection; listening and smelling; inquiry; pulse-feeling and palpation); the specific symptoms of diabetic patients are self-perceived dizziness, sore back, fatigue, irritability, dark scanty urine, a pale face with flushed red cheeks, a red peeled tongue and a rapid pulse. According to the ancient TCM theory, the kidneys are associated with “the gate of vitality” and “the sea of essence”, which in concept are more a way of describing a set of interrelated parts rather than a specific anatomical organ. However, the clinical evidence regarding the effectiveness of this unique approach to diagnosis and treatment in terms of the pathological process associated with diabetic nephropathy is uncertain/lacking. Consequently, in this study, our aim was to measure the risk of kidney failure when diabetic care is carried out with and without the concurrent use of TCMs and, further, to estimate the risk of kidney failure between *Liu-Wei-Di-Huang-Wan* users and non-TCM users. The results of this study should provide valuable information that will help patients with kidney failure who could potentially benefit from TCM healthcare and/or the prescription of *Liu-Wei-Di-Huang-Wan*. This, in turn, will strengthen further the patient–physician relationship when treating diabetes and diabetic nephropathy. Moreover, it is well known that the consumption of NSAID and of herbs containing aristolochic acid is a risk factor for kidney failure (Lai et al., 2009, 2010; Martena et al.,2007; Mazer and Perrone, 2008; Murray and Brater, 1993; Perneger et al., 1994b; Vanhaelen et al., 1994), and, as a result, we have excluded these potential confounders in order to strengthen the validity of our results.

2. Materials and methods

2.1. Data resources

Taiwan launched a single-payer National Health Insurance Program on March 1, 1995. As of 2007, 22.60 million of Taiwan's 22.96 million population was enrolled in this program. The database of this program contains registration files and original claim reimbursement data. The National Health Insurance Research Database (NHIRD) is extracted from this system by the Bureau of National Health Insurance, Taiwan (BNHI) and is maintained by the National Health Research Institutes, Taiwan (NHRI); it is provided to scientists in Taiwan for research purposes. This database provides a platform for exploring the pharmaco-epidemiological profiles of TCM therapeutics that are prescribed by licensed TCM doctors in daily practice in Taiwan. This study was designed as a population-based case control study analyzing one-million random sample selected from the 22 million beneficiaries of the National Health Insurance scheme in Taiwan. All data were obtained from the NHIRD and consisted of patient's gender, patient's date of birth, all records of clinical visits and hospitalizations of the patient, prescribed drugs and dosages (both conventional medicines and herbal products), special treatments (such as dialysis, and renal transplant), the dates of the above, and three major diagnoses coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) format (Centers for Disease Control and Prevention, 2014; National Health Research Institutes in Taiwan, 2014). The identification number of each insured person was transformed and encrypted during the extraction process and therefore patient privacy was protected.

2.2. Definitions of cases and controls

The process of selection of cases and controls from the random sample of one million individuals was performed according to the flow chart shown in Fig. 1. In the beginning, we included all patients that (1) had at least three outpatient visits with a diabetes diagnosis within 1 year or (2) had one or more hospital admission with a diabetes diagnosis (n=40,163). Next we selected all type 2 diabetic patients with kidney failure over the period 1998–2008 in Taiwan, including patients with end stage renal disease (ESRD) that is patients requiring dialysis therapy or renal transplant. We defined a diagnosis of chronic kidney disease (CKD) as being that of the *International Classification of Diseases, Ninth Revision* codes 580–589, 250.4, 274.1, 403.01, and 404.02, which are consistent with the definition of CKD stages 1–5 according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) (National Kidney Foundation, 2002).

There were 4645 prevalent cases of kidney failure among the type 2 diabetic population during the period 1997–2008 in the database. We waited for one year to enroll patients with newly developed kidney failure after January 1998, and as a result 4584 cases were collected. To prevent indication bias due to individuals taking herbs after the development of CKD, we deliberately excluded cases with kidney failure diagnosed as CKD before July 1, 1997, which allowed at least 6 months for the patient to accumulate a consumed dose. Moreover, cases having had a history of kidney failure before diagnosis of type 2 diabetes were also excluded. We then selected subjects without kidney failure from among type 2 diabetic patients as the control group, fulfilling the same process of setting inclusion and exclusion criteria as the case group mentioned above. The reimbursement database contained all details for prescribed