

근골격계 질환에 대한 양약 및 한약 병용의 간과 신장에 대한 안전성: 후향적 관찰 연구

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Hepatic and Renal Safety of Concurrent Use of Conventional and Herbal Medications for Musculoskeletal Disorders: A Retrospective Observational Study

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This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant no. HI20C1405).

RECEIVED June 21, 2022

ACCEPTED June 28, 2022

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Objectives This study aimed to investigate whether the concurrent use of conventional and herbal medications affects liver and kidney function, by examining blood test data.

Methods We retrospectively reviewed the electronic medical records of 590 inpatients with musculoskeletal diseases between 2013 and 2017. We investigated cases of drug-induced liver injury (DILI) according to the Roussel Uclaf Causality Assessment Method criteria and cases of drug-induced kidney injury (DIKI) based on the Kidney Disease Improving Global Outcomes definition.

Results One case (0.17%) of DILI and one case (0.17%) of DIKI were identified. Significant improvements in serum laboratory data were observed after the concurrent use of both types of medications ($p < 0.05$). The kappa coefficients ranged from 0.26 to 0.72, indicating that the values after the concurrent use of conventional and herbal medications showed a fair similarity to the baseline values of the patients. The linear regression test showed that female sex and high body mass index (BMI) were risk factors for an increase in the serum blood levels of liver function parameters.

Conclusions The concurrent use of conventional and herbal medications for musculoskeletal disorders is relatively safe; however, clinicians should exercise caution when prescribing these medications to female patients and patients with a high BMI because of their potential effect on hepatic function. (*J Korean Med Rehabil* 2022;32(1):131-140)

Key words Drug-induced kidney injury, Chemical and drug induced liver injury, Herbal medication, Musculoskeletal disorder, Retrospective studies

Introduction>>>>

Herbal medicines have been used for thousands of years in East Asia and are now actively consumed worldwide for the treatment and prevention of diseases. A survey in Korea revealed that 61.1% of the total Korean population took herbal medicines in 2016¹⁾. In a systematic review conducted in the United Kingdom, the average 1-year prevalence of the use of complementary and alternative medicine was 41.1%²⁾.

A survey conducted by the Ministry of Health and Welfare in Korea showed that, among Korean medicine consumers, the first to seventh most common diseases treated in Korean medicine clinics were all musculoskeletal disorders, and more than half of the patients with these conditions also had previously or concurrently visited Western medicine clinics³⁾. It can be inferred that it is common for patients to concurrently use both types of medications, as reported in a retrospective chart review on musculoskeletal disorders in Korea (prevalence rate 35.9%, 2,475 of 6,894 inpatients)⁴⁾.

Recently, the hepatic safety of herbal medications was investigated in terms of the occurrence of drug-induced liver injury (DILI), and it was concluded that herbs are relatively safe⁵⁾, as the incidence rate of DILI was similar to that with conventional medications (~ 1%)^{6,7)}. Meanwhile, with respect to drug-induced kidney injury (DIKI) due to herbal medications, large-scale studies conducted in Korean medicine hospitals reported that taking herbal medicines does not have significant adverse effects on renal function⁸⁻¹⁰⁾.

However, there are relatively fewer reports on the safety of the concurrent use of conventional and herbal medications, despite the increasing popularity of this practice. In a retrospective Korean study that screened for DILI among inpatients who were administered both herbal and conventional medications for at least 14 days between 2006 and 2010, 5 of the 892 patients (0.56%) were identified to have DILI¹¹⁾. In another study, the prevalence rate of DILI was 2.3% of the 256 total patients with a

broad range of diseases¹²⁾. Considering that the main diseases requiring the concurrent use of conventional and herbal medicines are musculoskeletal disorders, there is a need to investigate the safety of the practice in this patient population, with attention to the fact that non-steroidal anti-inflammatory drugs (NSAIDs) are the main drugs causing DILI and DIKI^{7,13)}.

In this study, we retrospectively reviewed changes in liver and renal function based on blood test results, and investigated the incidence of DILI and DIKI in inpatients with musculoskeletal disorders and injuries to examine the safety of the concurrent use of conventional and herbal medications.

Materials and Methods>>>>

1. Patients

Patients who were admitted to Kyung Hee University Korean Medicine Hospital between January 1, 2013, and December 31, 2017, were included in this study. The total number of included patients was 590.

The inclusion criteria were as follows: (1) hospitalization for at least 7 days, (2) a musculoskeletal disorder or injury as the main diagnosis (International Statistical Classification of Diseases and Related Health Problems 10th revision codes: M01-M99, S01-S99, or T01-T10), (3) administration of both conventional and herbal medications for >7 days during the hospitalization period, (4) available blood test results for assessing hepatic and renal function at admission and at discharge (i.e., before and after taking both conventional and herbal medications), and (5) age >19 years.

The exclusion criteria were as follows: (1) a history of liver or kidney disease before the hospitalization period, such as viral hepatitis or chronic kidney failure, and (2) chief complaints other than musculoskeletal diseases.

2. Data collection

The need for informed consent from patients was waived owing to the retrospective nature of this study. After obtaining approval for the study from the Kyung Hee University Korean Medicine Center Institutional Review Board (KHMCIRB 2018-08-002-001), we retrospectively collected and analyzed related laboratory data by examining the electronic medical records (EMRs) of patients who satisfied the inclusion and exclusion criteria. Two authors (SY Kim and H Kim) collected and analyzed the data, and the procedure was monitored and approved by another author (WS Chung). The clinical chemistry data collected before and after taking herbal medications included aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total bilirubin (TB), direct bilirubin (DB), blood urea nitrogen (BUN), and creatinine.

On the basis of the examination and analysis of the blood test data, cases of DILI and DIKI were identified. The identified cases were reviewed by analyzing the diagnosis, sex, age, length of hospital stay, type of administered conventional and herbal medications, and major changes in clinical symptoms. When relevant liver or kidney injury was detected, the following items were investigated using EMRs to identify the definite cause: (1) recent patient history, including exposure to contrast medium or immunosuppressants, and (2) results of other evaluations including urine analysis, urine microscopy, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), radiography (abdominal or pelvic), and biopsy.

3. Ascertainment of DIKI and DILI

1) Evaluation and analysis of DILI

The DILI cases were identified using the updated Roussel Uclaf Causality Assessment Method (RUCAM) criteria for liver injury, as follows: (a) an increase of $> 5 \times$ upper limit of normal (ULN) in ALT or (b) an increase of $> 2 \times$ ULN in ALP¹⁴.

The injuries of the patients were classified into three types based on the R ratio ($[\text{ALT}/\text{ULN}]/[\text{ALP}/\text{ULN}]$): R ratio > 5 and $\text{ALT} > 2 \times \text{ULN}$, hepatocellular liver injury; $2 < \text{R ratio} < 5$ and both ALT and $\text{ALP} > 2 \times \text{ULN}$, mixed liver injury; and R ratio < 2 and $\text{ALP} > 2 \times \text{ULN}$, cholestatic liver injury.

Each case was evaluated for the likelihood of DILI and judged as ‘excluded (0),’ ‘unlikely (1-2),’ ‘possible (3-5),’ ‘probable (6-8),’ or ‘highly probable (> 8)’ according to the RUCAM score. On the basis of the evaluation, the characteristics of cases with DILI were further analyzed for those that were judged ‘possible,’ ‘probable,’ and ‘highly probable.’ The characteristics of cases were extracted, including diagnosis, sex, age, length of hospital stay, and type and dosage of the prescribed conventional and herbal medications.

2) Evaluation and analysis of DIKI

Kidney injury was classified according to the Kidney Disease Improving Global Outcomes (KDIGO) definition. Acute kidney injury (AKI) was defined as any of the following: an increase in serum creatinine (SCr) by ≥ 0.3 mg/dL (≥ 26.5 mmol/L) within 48 h; or an increase in SCr to ≥ 1.5 times the baseline value, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 mL/kg/h for 6 h. The patients were classified as having stage I, II, or III kidney injury¹⁵. Kidney disease was evaluated according to SCr and urine output. When SCr above the ULN was detected, the urine output of those cases was referred from the EMRs.

For patients with kidney injury, other evaluations including urine analysis, urine microscopy, ultrasound, CT, MRI, radiography (abdominal or pelvic), and tissue biopsy were performed to determine whether the injury was acute or chronic, and whether it was prerenal, renal, or postrenal.

The characteristics of the patients with DIKI were abstracted, including diagnosis, sex, age, length of hospital stay, body mass index (BMI), type and dosage of the prescribed conventional and herbal medications, and risk factors for AKI, as suggested by KDIGO.

4. Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, NY, USA) was used for statistical calculations. The Shapiro-Wilk test was used to ascertain the normality of the distribution of continuous data. Continuous data are presented as median and interquartile range, whereas categorical data are expressed as frequencies. The Wilcoxon signed-rank test or paired t-test was performed to compare changes in clinical chemistry values between admission and discharge. The non-inferiority test and Cohen's kappa test were conducted to assess the similarity of the data between admission and discharge.

Linear regression analysis was performed to identify predictors of changes in blood test results between before and after taking the two types of medications. Statistical significance was set at $p < 0.05$.

Results>>>>>

1. General characteristics of patients

The patients' characteristics are summarized in Table I. The data from 590 patients (161 men and 429 women) who satisfied the inclusion and exclusion criteria were analyzed after the review of EMRs.

2. Identification of DILI cases at admission

Among the initial 590 patients, 3 patients with liver injury based on the updated RUCAM criteria were identified at admission. The characteristics of these cases are summarized in Table II. One case was excluded because the liver injury detected at admission was found to be caused by liver metastases during hospitalization. The DILI of the other two cases was assumed to be associated with the use of conventional drugs, especially NSAIDs, and the subsequent discontinuation of the suspected drug led to the normalization of liver enzyme levels.

3. Identification of DILI cases at discharge

Only one case of newly developed DILI (0.17%) during hospitalization was identified (Table III). The type of DILI in this case was categorized as mixed (R value=3.62) based on the RUCAM score. It was suspected to have been caused by a herbal medication composed of various herbs (Table IV), and was judged to be a 'probable' DILI with a RUCAM score of 7. The types of conventional medicines used by the patient were antihyperlipidemic agents and antidiabetics. The classification of patients according to the results of liver function tests at admission and discharge is presented in Table V.

Table I. Characteristics of the Study Population and Injury Groups at Discharge

Characteristics	Study population (n=590)	Liver injury group (n=1)	Kidney injury group (n=1)
Age (yr)	60 (50-73)	60	89
Sex (n)	Male	161 (27.3)	0
	Female	429 (72.7)	1
Length of hospital stay (days)	18 (12-29)	22	28
Height (cm)	160 (155-166)	163	148
Weight (kg)	60 (53-68)	63	45

Age, length of hospital stay, height, and weight data are presented as median and interquartile range. The numbers of patients according to sex are presented as number and percentage.

Table II. Characteristics of Drug-Induced Liver Injury Cases at Admission

Patient (sex/age)	BMI (kg/m ²) (height/weight)	Main impression	Length of hospital stay (days)	Medication and dosage (per day)	Past history and progression	Laboratory data at admission					Follow-up
						AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	
P1 (F/32 yr)	22.27 (160 cm/ 57 kg)	Sprain and strain of the cervical spine	40	Aceclofenac 100 mg, tizanidine hydrochloride 1 mg, Ranitidine 75 mg, Tripotassium dicitrato bismuthate 100 mg, Sucralfate 300 mg	After a traffic accident, she was admitted to the local orthopedics department and took drugs for 3 weeks. After stopping the drugs at admission to our hospital, she was prescribed hepatotonic drugs.	138	332	73	117	57	Recovery
P2 (F/44 yr)	21.10 (157 cm/ 52 kg)	Backache NOS, thoracic region	8	Antibiotics, muscle relaxants, analgesics*	Before admission, she took drugs for muscle pain prescribed at other hospitals. In consultation with the gastroenterology department, multiple liver metastases were found.	206	142	388	264	46	Unknown (dropout)
P3 (M/75 yr)	21.22 (175 cm/ 65 kg)	Spinal stenosis, cervical region	23	Telmisartan 80 mg, rosuvastatin calcium 20.8 mg, almagate 1.5 g, dexamethasone 1 mg, diclofenac 50 mg, piroxicam 40 mg, cimetidine 400 mg	After surgery for spinal stenosis 10 days before admission, he took an overdose of analgesics by himself. Hepatotoxic drugs were discontinued after admission.	96	167	334	204	77	Recovery

BMI: body mass index, AST: aspartate transaminase, ALP: alkaline phosphatase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, CK: creatinine kinase, F: female, NOS: not otherwise specified, M: male.

*The ingredient is unknown because the patient stopped taking drugs owing to elevation of liver enzymes before admission.

Table III. Identification of a Newly Developed Drug-Induced Liver Injury Case during the Hospital Stay

Patient (sex/age)	BMI (kg/m ²) (height/weight)	Impression	Length of hospital stay (days)	R value	Type of liver injury	Time to injury	Herbal medication (RUCAM score*)	Conventional medication (RUCAM score)
P1 (F/60 yr)	23.71 (163 cm/63 kg)	Spinal stenosis, lumbar region	26	3.62	Mixed	19 days	<i>Chunglijagam-tang</i> gagam [†] (7)	Alogliptin 25 mg (1), rosuvastatin 10 mg (3)

BMI: body mass index, RUCAM, Roussel Uclaf Causality Assessment Method, F: female.

*The RUCAM score was assessed as follows: ≥ 9 , highly probable; 6-8, probable; 3-5, possible; 1-2, unlikely; and ≤ 0 , no relationship to the drug.

[†]The herbal drug was administered as a decoction composed of multiple herbs.

Table IV. Composition of the Herbal Medication Used in a Liver Injury Case

Patient (sex/age)	Prescribed herbal medication components (RUCAM score*)
P1 (F/60 yr)	<i>Longanae Arillus</i> 4 g, <i>Radix Rehmanniae</i> 4 g, <i>Radix Asparagi</i> 4 g, <i>Radix Ophiopogonis</i> 4 g, <i>Radix Angelicae Sinensis</i> 4 g, <i>Radix Paeoniae Alba</i> 4 g, <i>Rhizoma Dioscoreae</i> 4 g, <i>Fructus Corni</i> 4 g, <i>Poria cocos</i> 4 g, <i>Atractylodis Rhizoma Alba</i> 4 g, <i>Moutan Radicis Cortex</i> 4 g, <i>Alismatis Rhizoma</i> 4 g, <i>Anemarrhenae Rhizoma</i> 4 g, <i>Phellodendri Cortex</i> 4 g, <i>Glycyrrhizae Radix et Rhizoma</i> , <i>Licorice</i> 2 g, <i>Atractylodis Rhizoma</i> 8 g, <i>Magnoliae Cortex</i> 6 g, <i>Fraxini Cortex</i> 4 g (7)

RUCAM: Roussel Uclaf Causality Assessment Method, F: female.

*The RUCAM score was assessed as follows: ≥ 9 , highly probable; 6-8, probable; 3-5, possible; 1-2, unlikely; and ≤ 0 , no relationship to the drug.

4. Identification of DIKI cases

Of the 590 patients, 1 (0.17%) had AKI according to KDIGO. This case corresponded to the 7-day diagnostic window for AKI and was classified as stage I (Table VI).

The composition of the herbal medication administered in this DIKI case is shown in Table VII.

5. Comparison of laboratory serum data before and after taking conventional and herbal medications

In the comparison of the blood test results of patients between before and after taking herbal medicines, the AST, ALT, GGT, ALP, BUN, and creatinine levels were significantly lower after taking medications ($p < 0.05$). The

Table V. Classification of Patients according to Liver Function Test Results at Admission and Discharge

Liver function status at admission	n	Liver function status at discharge	n
Liver injury	3	Liver injury	0
		No liver injury	2
		Dropout	1*
No liver injury	588	Liver injury	1
		No liver injury	587
		Dropout	0
Total	591	Total	590

*One patient was found to have liver metastases during hospitalization. The normal ranges for liver function tests were as follows: alanine aminotransferase (ALT) ≤ 50 U/L; aspartate aminotransferase ≤ 50 U/L; and alkaline phosphatase (ALP) 30-120 U/L. Liver injury was defined according to the updated Roussel Uclaf Causality Assessment Method criteria, as follows: (a) an increase of $> 5 \times$ upper limit of normal (ULN) in ALT or (b) an increase of $> 2 \times$ ULN in ALP.

mean levels of TB and DB were lower after the administration of medications, but the difference was not significant ($p > 0.05$) (data not shown).

6. Simple linear regression for serum blood test items

In the simple linear regression analysis, the changes in GGT, TB, DB, and ALP levels were higher in women. The changes in ALP levels were higher in patients with a higher BMI (Table VIII).

7. Multiple linear regression for serum blood test items

Women had a higher tendency than men to show changes in GGT, TB, DB, and ALP levels. Patients with a higher BMI had a greater change in ALP level.

Table VI. Identification of a Kidney Injury Case within the Hospital Stay

Patient (sex/age)	BMI (kg/m ²) (height/weight)	Impression	Length of hospital stay (days)	SCr baseline (mg/dL)	Peak SCr (mg/dL)	KDIGO Staging	Renal risk factor	Herbal medication	Conventional medication and dosage (per day)	Follow-up
P2 (F/89 yr)	20.54 (148 cm/45 kg)	Other osteoporosis with pathological fracture, multiple sites	28	0.6	1.3	Stage I	Advanced age Female sex Chronic disease (hypertension)	<i>Hyeongbangjihwang-tang</i> *	Losartan 100 mg, Amlodipine 5 mg Diltiazem HCl 90 mg Famotidine 40 mg Nicorandil 10 mg Aspirin 100 mg Nebivolol 5 mg Tramadol 37.5 mg Acetaminophen 325 mg Celecoxib 200 mg Zolpidem tartrate 5 mg	Recovery

BMI: body mass index, SCr: serum creatinine, KDIGO: Kidney Disease Improving Global Outcomes, F: female.

*The herbal drug was administered as a decoction composed of multiple herbs.

Table VII. Composition of the Herbal Medication Used in a Kidney Injury Case

Patient (sex/age)	Prescribed herbal medication components
P2 (F/89 yr)	<i>Rehmanniae Radix Preparata</i> 8 g, <i>Osterici seu Notopterygii Radix et Rhizoma</i> 4 g, <i>Corni Fructus</i> 8 g, <i>Araliae Continentalis Radix</i> 4 g, <i>Poria Sclerotium</i> 8 g, <i>Schizonepetae Spica</i> 4 g, <i>Alismatis Rhizoma</i> 8 g, <i>Saposhnikoviae Radix</i> 4 g, <i>Plantaginis Semen</i> 4 g, <i>Moutan Radicis Cortex</i> 4 g

F: female.

Table VIII. Results of Simple Linear Regression for the Serum Blood Test Items

Dependent variable	Independent variable		Simple linear regression				
			B estimate	95% CI for B	<i>t</i>	p-value	Adjusted <i>R</i> ²
ΔAST	Sex	Female	0				
		Male	0.119	-3.020 to 3.258	0.075	0.941	-0.002
	Age	0.010	-0.074 to 0.095	0.242	0.809	-0.002	
	Length of hospital stay	-0.008	-0.044 to 0.028	-0.434	0.665	-0.02	
ΔALT	Sex	Female	0				
		Male	3.054	-1.243 to 7.351	1.396	0.163	0.002
	Age	0.026	-0.090 to 0.143	0.447	0.655	-0.002	
	Length of hospital stay	-0.011	-0.060 to 0.039	-0.442	0.674	-0.002	
ΔGGT	Sex	Female	0				
		Male	-13.140	-21.036 to -5.245	-3.271	0.001*	0.022
	Age	0.115	-0.103 to 0.334	1.036	0.301	0.000	
	Length of hospital stay	-0.003	-0.093 to 0.086	-0.075	0.941	-0.002	
ΔTB	Sex	Female	0				
		Male	-0.180	-0.284 to -0.075	-3.402	0.001*	0.067
	Age	0.000	-0.004 to 0.003	-0.244	0.808	-0.006	
	Length of hospital stay	0.001	-0.001 to 0.004	1.031	0.304	0.000	
ΔDB	Sex	Female	0				
		Male	-0.052	-0.090 to -0.014	-2.727	0.007*	0.054
	Age	-0.001	-0.002 to 0.000	-1.686	0.095	0.016	
	Length of hospital stay	0.001	0.000 to 0.002	1.791	0.076	0.019	
ΔALP	Sex	Female	0				
		Male	-6.465	-11.447 to -1.483	-2.551	0.011*	0.014
	Age	0.046	-0.089 to 0.182	0.672	0.502	-0.001	
	Length of hospital stay	-0.016	-0.069 to 0.038	-0.578	0.564	-0.002	
ΔBUN	Sex	Female	0				
		Male	-0.750	-1.894 to 0.394	-1.287	0.199	0.001
	Age	-0.016	-0.047 to 0.015	-1.027	0.305	0.000	
	Length of hospital stay	0.001	-0.012 to 0.015	0.156	0.876	-0.002	
ΔCr	Sex	Female	0				
		Male	0.011	-0.069 to 0.091	0.263	0.793	-0.002
	Age	0.000	-0.002 to 0.003	0.416	0.678	-0.001	
	Length of hospital stay	-0.001	-0.002 to 0.000	-1.362	0.174	0.002	
BUN	Sex	Female	0				
		Male	0.005	-0.005 to 0.015	0.971	0.332	0.000

Δ: change, B estimate: regression coefficient, CI: confidence interval, Adjusted *R*²: assessment of goodness of model fit, AST: aspartate transaminase, BMI: body mass index, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, TB: total bilirubin, DB: direct bilirubin, ALP: alkaline phosphatase, BUN: blood urea nitrogen, Cr: creatinine.

Discussion>>>>

This was a retrospective observational study that investigated the safety of the concurrent use of conventional and herbal medications with respect to liver and renal function, mainly in patients with musculoskeletal diseases and injuries. The main finding of this study was that the concurrent use of both types of medications is relatively safe, as shown by the low incidence rate of DILI according to RUCAM (0.17%, 1 case) and that of DIKI according to KDIGO (0.17%, 1 case) among a total of 590 patients. Furthermore, a statistically significant decrease was observed in the levels of blood test items related to hepatic and renal function (AST, ALT, GGT, ALP, BUN, and creatinine), although the non-inferiority test using categorized data suggested that this decrease was not clinically significant. The kappa coefficients of the serum laboratory data ranged from 0.26 to 0.72, indicating that the values before and after the concurrent use of conventional and herbal medications had a fair similarity. Therefore, it can be inferred that the concurrent use of conventional and herbal medications did not result in clinically significant changes in liver and renal function in patients with musculoskeletal disorders and injuries.

The DILI incidence rate of 0.17% corresponds to the results of previous studies. A safety study on the concurrent use of conventional and herbal medications reported an incidence of 0.56% (5 of 892 patients)¹¹. Studies on herbal medication—induced DILI showed similar results. One retrospective study conducted in Japan reported that the incidence of DILI caused by herbal medicine was 0.24% (6 of 2,496 cases)¹⁶ and another study from Germany reported an incidence of 0.93% (14 of 1,507 cases)¹⁷. Moreover, systematic reviews conducted in Korea concluded that the incidence of DILI after treatment with herbal medications was <1%^{18,19}. Furthermore, a large-scale study on herb-induced liver injury in 4,578 patients with musculoskeletal diseases, first published in 2015 and updated in 2019 with the updated RUCAM criteria^{4,20}, de-

tected DILI in only 3 patients (0.07%).

In the DILI case in the current study, the patient was identified to have taken conventional medications, including antihypertensive drugs and antidiabetics, which could have increased the levels of liver function parameters as an adverse effect²¹. In the DIKI case, the patient used conventional medications, including antibiotics, antihypertensive drugs (especially angiotensin II receptor antagonists), and NSAIDs, which are all known to potentially cause kidney injury²².

From the results of previous studies and the current study, it can be inferred that the use of herbs, regardless of the concurrent use of conventional medicines, does not increase the risks of DILI and DIKI.

To identify factors that influenced the levels of the blood test items during the administration of both types of medications, a multiple linear regression analysis was performed. Women had a higher tendency than men to show changes in GGT, TB, DB, and ALP levels. This seems to be related to the finding of a previous study that female patients experience greater difficulty in recovering from liver damage and are thus more susceptible to DILI²³. Moreover, the change in ALP level was higher in patients with a higher BMI. Although the increase in the levels of these serum components did not lead to the occurrence of DILI or DIKI, clinicians need to be cautious when prescribing herbal medications in addition to conventional medicines in female patients or patients with a high BMI, and should monitor patients as closely and as frequently as possible.

The hypothesis of this study, based on empirical data, was that the concurrent use of conventional and herbal medications does not cause a deterioration in the liver and renal function of patients with musculoskeletal diseases and injuries. This study is relevant for the following reasons: (1) it surveyed patients with musculoskeletal diseases and injuries as the primary diagnoses, which are the most common diagnoses seen in Korean medicine clinics that easily lead to the concurrent use of herbal medicines with conventional medications, and (2) it used var-

ious appropriate statistical methods, including non-inferiority, Cohen's kappa, and multiple regression tests, to analyze the data before and after taking both types of medications from various perspectives.

This study had the following limitations: (1) no control group was used, which could have consisted of patients taking either conventional medications alone or herbal medications alone, and (2) the exact herb that possibly caused hepatic or renal injury could not be identified because herbal medicines are usually prescribed in the form of a mixture of several different herbs.

To confirm the safety of the concurrent use of conventional and herbal medications in patients with musculoskeletal diseases and injuries, we retrospectively reviewed the EMRs of inpatients in a Korean medicine hospital. From the data of 590 cases, the incidence of both DILI and DIKI was found to be 0.17%. Further studies are warranted on the possibility of liver and kidney injuries with each herbal medication. In addition, toxicity from the interaction between conventional and herbal medicines should be identified to firmly prove the safety of taking herbal medications.

Acknowledgments>>>>>

The authors thank Jae-Hyun Park, Hokyung Chang, and Hansol Lee from Kyung Hee University Korean Medicine Hospital for providing assistance in the analysis process.

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