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Yo Jyo Hen Shi Ko (YHK) Improves Transaminases in Nonalcoholic Steatohepatitis (NASH): A Randomized Pilot Study

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NASH is a common condition with a rising incidence. There is progression to cirrhosis in some cases and the potential for mortality or requirement of liver transplantation. Currently, there is no approved therapy for NASH. The natural compound YHK has both anti-inflammatory and antifibrotic properties, and can lead to improvement in transaminases in viral hepatitis. Improvement in transaminases may correlate with improved histology in NASH and hence may impact on the natural history. We sought to determine the effects of YHK on NASH. We performed a randomized, double-blind, placebo-controlled pilot study to determine the effects of YHK on transaminases and on quality of life (QoL) in patients with biopsy-confirmed NASH and a persistently abnormal ALT or AST. Eight patients were randomized to YHK or placebo for 8 weeks. The ALT and AST were measured at baseline and weeks 4, 8, and 12. SF-36 surveys were serially completed. All five patients in the YHK group but none in the placebo group had a marked decrease in ALT at both week 4 and week 8 compared to baseline. After discontinuing YHK the ALT returned toward baseline at week 12. The mean decrease in ALT compared to baseline was significantly greater in the YHK group than in the placebo group at both week 4 (-42.8 ± 23.2 vs. -6.3 ± 6.7 U/L; $P = 0.036$) and week 8 (-45.4 ± 23.4 vs. 6.0 ± 24.6 U/L; $P = 0.036$). There was also a nonsignificant decrease in AST in the YHK group compared to placebo. QoL was not affected and no severe adverse events were reported. In this controlled pilot study we found the novel nutraceutical agent YHK to be effective at reducing ALT values in patients with NASH. YHK is well tolerated. Further studies are justified to assess the impact of YHK in the natural history of NASH.

KEY WORDS: nonalcoholic steatohepatitis (NASH); Yo Jyo Hen Shi Ko (YHK); treatment.

Nonalcoholic steatohepatitis (NASH) is common, rising in incidence, and an important cause of chronic liver disease (1). This entity is typically more common in females and is often associated with truncal obesity, diabetes mellitus type 2, and dyslipidemia (2). Patients typically present with asymptomatic elevations of transaminases or alkaline phosphatase. Occasionally, late presentations include features of advanced liver disease (3, 4).

The first principles of management of patients with NASH are the modifications of risk factors with exercise and dietary modification. Medical therapy has included weight loss agents, cytoprotective agents, antioxidants, antihyperlipidemics, antidiabetics, and anti-inflammatories, with mixed effects on transaminases and hepatic histology, surrogate markers for disease activity in trials of therapies in NASH (3, 5). However, to this point there is no definitive medical therapy for patients with NASH.

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Traditional herbal remedies have been used for thousands of years. These preparations are usually derived from several different medicinal plant species, and it is apparent that some of the ingredients have active pharmacological properties (6). A number of these agents have data to support their use in various types of liver diseases, which are common in regions of the world where herbal medicines are popular (6–8). One such formula is Yo Jyo Hen Shi Ko (YHK; Kyotsu Jigyo, Inc., Japan), which is derived from *Panax pseudoginseng*, *Eucommia ulmoides*, *Polygonati rhizoma*, and *Glycyrrhiza glabra*. It has been reported in animal models to have activity as an antifibrotic agent (9, 10), to be protective against experimentally induced hepatic injury (11, 12), and to improve transaminases in patients with viral hepatitis (13, 14).

This pilot study was done to determine the effect of YHK on transaminase levels in patients with biopsy-proven NASH and a persistently elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level. In addition, we sought to study the effect of YHK on the quality of life in patients with NASH, as well as to determine any adverse events related to this medication.

METHODS

Protocol. This randomized, double-blind, placebo-controlled trial was designed to determine the effect of YHK vs. placebo on transaminases in patients with biopsy-proven NASH and a persistently abnormal AST or ALT. Ethics approval was approved from the Research Ethics Board at The University of Western Ontario on October 20, 2003. The study took place from November 2003 until June 2004. Patients with biopsy-proved NASH and an AST and/or ALT value elevated above the normal limit for a minimum of 3 months were recruited from the hepatology clinic at our institution. At the initial (screening) visit, each patient underwent a detailed medical history and physical examination, including measurement of the body mass index (BMI). Blood tests included complete blood count, electrolytes, blood urea nitrogen, creatinine, AST, ALT, alkaline phosphatase, γ-glutamyl transferase, albumin, bilirubin, international normalized ratio, thyroid stimulating hormone, magnesium, calcium, and hepatitis B and hepatitis C serology. In addition, each patient completed a "practice" standardized quality of life questionnaire (SF-36) (15). If either AST or ALT was elevated for more than 3 months and at screening, then the patient returned within 1 week for enrollment. At that time, AST and ALT were again measured, and a baseline SF-36 was completed. The patient was then randomized to receive either YHK (two 250-mg tablets [500 mg] three times daily) or an identical placebo for 8 weeks. Each patient returned for follow-up at weeks 4 and 8, after which the study medication was discontinued. The final visit was at week 12, 4 weeks after treatment ended. At each visit, AST and ALT were measured, an SF-36 was completed, and adverse events were recorded.

Enrollment Criteria. The inclusion criteria were as follows: age between 18 and 75 years, a minimum of 3 months of elevated AST and/or ALT above the normal limit, consumption of less than 20 g alcohol per week, the ability to give informed consent, and the presence of NASH on liver biopsy based on accepted criteria (3, 16). Exclusion criteria consisted of the presence of overuse of alcohol (>20 g/week), evidence of viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, α-1 antitrypsin deficiency, primary sclerosing cholangitis, or primary biliary cirrhosis, a history of any other hepatic, gastrointestinal, renal, cardiovascular, neurological, or hematological disorder, a history of psychiatric disorder which might impair the ability of subjects to provide written informed consent, pregnancy, breastfeeding, or lack of effective birth control in women of child-bearing age. In addition, subjects were excluded if they were using any herbal treatments or dietary supplements other than multivitamin/mineral formulations, had any change in medications in the 4 weeks preceding trial entry, or participated in any clinical trial within 6 weeks before study entry.

Masking. The YHK or identical placebo was prepackaged and coded prior to delivery to our research office, to ensure complete double-blinding of the study coordinator, investigators, and patients. The blinding code was not broken until all patients had completed the study.

Outcome Measures. The primary outcome measures were the effects on hepatic transaminases (AST and ALT) in patients with NASH treated with YHK compared to placebo. The secondary outcome measure was the effect of YHK on quality of life in patients with NASH.

Statistics. Two-tailed Mann-Whitney *U* tests were used to compare the mean change in AST, ALT, and physical and mental component summary measures of the SF-36 surveys at weeks 4, 8, and 12 in the YHK group vs. the placebo group compared to the baseline. The 95% confidence intervals were also calculated for these differences.

RESULTS

Analysis. A total of 13 patients were recruited for the study. Four of these patients were excluded after screening transaminases were normal. One patient was excluded after discontinuing methotrexate (which was used for rheumatic disease) immediately after enrollment, in response to a marked elevation in transaminases found on his baseline bloodwork. This left a total of eight patients, five in the YHK group and three in the placebo group, all of whom completed the study and follow-up visits. The full demographic characteristics of the study participants are detailed in Table 1.

All patients in the YHK group and none in the placebo group had a decrease in ALT values to normal levels at weeks 4 and 8 compared to baseline, with an increase back toward baseline off study medication at week 12 (Figure 1). The mean decrease in ALT compared to baseline was significantly greater in the YHK group than in the placebo group at weeks 4 and 8, but not significantly different off medication at week 12 (Table 2). Although there was a decrease in the mean AST values in the YHK group, this did not reach statistical significance compared to placebo (Table 3).

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS IN THE YHK AND PLACEBO GROUPS

	YHK	*Placebo*
Number of patients	5	3
Sex (F/M)	4/1	1/2
Age (years; mean ± SD)	56 ± 7	47 ± 12
BMI (kg/m^2; mean ± SD)	32.7 ± 2.0	34.0 ± 4.3
Metabolic disorders (*n*)		
Type 2 diabetes mellitus	3	1
Dyslipidemia*	2	0
Baseline laboratory data (mean ± SD)		
ALT (U/L)	69.8 ± 24.5	81.0 ± 21.9
AST (U/L)	67.6 ± 48.1	53.0 ± 4.6
ALP (U/L)	78.4 ± 23.5	100.7 ± 62.7
Bilirubin (mg/dl)	0.89 ± 0.51	0.84 ± 0.45
Albumin (g/dl)	3.98 ± 0.48	4.07 ± 0.42
INR	1.04 ± 0.06	1.00 ± 0.10

*Both dyslipidemic patients were also diabetic.

Quality of Life. For each SF-36 survey, a physical component summary (PCS) measure and a mental component summary (MCS) measure were calculated. The effect of YHK vs. placebo on both the PCS and the MCS measures was variable between patients at each time interval (Figures 2 and 3). There was no statistically significant differences in the change in either of these measures in the YHK group vs. the placebo group at any of the time intervals (weeks 4, 8, and 12) compared to baseline.

Adverse Events. Adverse events in both the YHK and the placebo groups were mild and similar between the two groups (Table 4).

DISCUSSION

Medical therapy for NASH has been disappointing to date. Although a number of treatments have been studied, nothing has yet been proven to prevent the progression to advanced liver disease, and the only recommended therapies are dietary modification and weight loss (3).

The nutraceutical compound YHK has been reported in animal studies to have antifibrotic properties (9, 10), to be protective against experimentally induced hepatic injury (11, 12), and to improve transaminases in patients with viral hepatitis (13, 14). In this pilot study treating patients with biopsy-proven NASH and persistently elevated transaminases, patients assigned to the YHK group had a statistically significant reduction in ALT values compared to the placebo group, as well as a nonsignificant reduction in AST during treatment. Impressively, all patients in the treatment group but none in the placebo group had a normalization of their ALT values during therapy and a rise again in ALT after stopping therapy, indirect evidence of an anti-inflammatory effect with the drug. Although there was no difference in quality of life between the YHK-treated patients and those taking placebo, the YHK group did not have a reduced quality of life compared to the placebo group. In addition, there were no serious side effects in the patients taking YHK, demonstrating its safety and tolerability at the prescribed dose of two 250-mg tablets three times daily, a dose similar to that commonly used in Japan (where YHK is available as a nutritional supplement) and studied in previous research of YHK in liver diseases (13, 14).

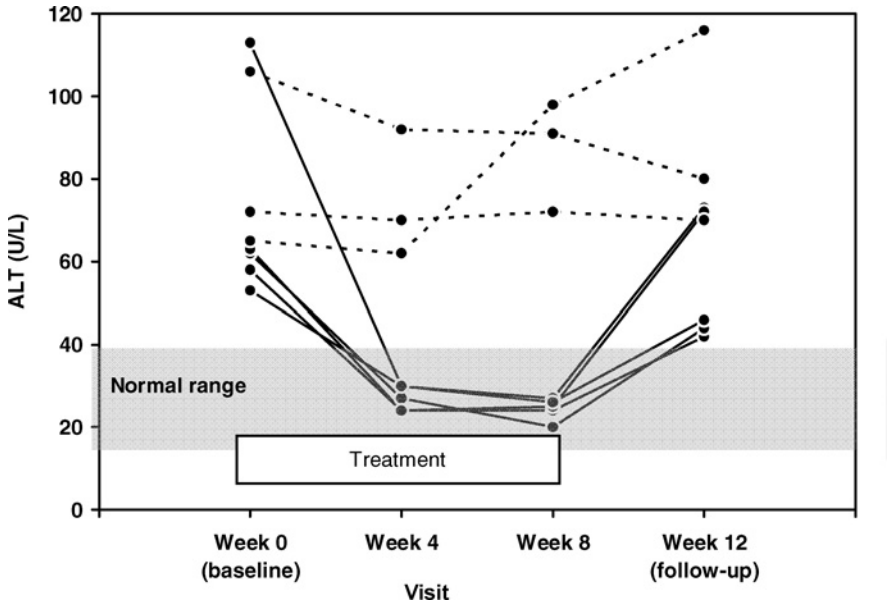

Fig 1. ALT in individual patients at each visit in YHK (solid lines) and placebo (dotted lines) groups.

TABLE 2. COMPARISON OF MEAN CHANGE IN ALT IN THE YHK AND PLACEBO GROUPS AT WEEKS 4, 8, AND 12 (FOLLOW-UP) RELATED TO BASELINE MEAN ALT IN EACH GROUP

Time interval for comparison	*Mean change in ALT (U/L)*		*Difference in ALT in YHK vs. placebo (95% confidence interval)*	P *value*
	YHK	*Placebo*		
Week 4–baseline	−42.8	−6.3	−36.5 (−71.7 to −1.9)	0.036
Week 8–baseline	−45.4	6.0	−51.4 (−93.9 to −8.9)	0.036
Week 12–baseline	−14.4	7.7	−22.1 (−70.3 to 26.2)	0.571

Herbal remedies have been used for thousands of years, and significant research has been done to isolate and identify the active ingredients in these agents. However, there are still many unanswered questions surrounding the pharmacology of herbal products. Nonetheless, more is becoming known about the active ingredients in and mechanisms of action of these preparations (17).

YHK is composed of four main ingredients: *Panax pseudoginseng*, *Eucommia ulmoides*, *Polygonati rhizoma*, and *Glycyrrhiza glabra*. Trilinolein, isolated from *Panax pseudoginseng*, has been shown to have an antioxidant effect when used to treat circulatory disorders (18, 19). Dozens of compounds have been isolated from *Eucommia ulmoides*, with antioxidant and anticomplement effects and a capability to increase numbers of T lymphocytes and natural killer cells (20). The water-soluble extract of *Polygonati rhizoma* has an inhibitory effect on hepatic glucose output in animal models of diabetes, leading to reduced fasting glucose, reduced glycosylated hemoglobin, and improved glucose tolerance. In addition, a reduction of triglyceride levels in diabetic rats with hypertriglyceridemia has been seen (21). These mechanisms may be also be important in patients with NASH, particularly those complicated by the presence of diabetes or dyslipidemia. Glycyrrhizin, the aqueous extract of *Glycyrrhiza glabra*, has received the most attention in the treatment of liver disorders. There are studies demonstrating an improvement in transaminases in patients with viral hepatitis (22–24) as well as a decrease in the development of cirrhosis and hepatocellular carcinoma in patients with hepatitis C (25) receiving glycyrrhizin. The hepatic anti-inflammatory effects of glycyrrhizin may be related to an increase in hepatic lymphocyte activation (26), an inhibition of the lytic pathway of complement (27), and a decrease in production of interleukin-10 by liver dendritic cells (28).

The results of this study are limited in a number of ways. The small number of patients allowed the assignment of only a few patients to each group. Individual variations in results may have had large effects when combining the data for analysis. However, the consistency of results between patients in each group is encouraging, particularly when looking at the effect of YHK on transaminase levels. In addition, little can be firmly established about the safety and effects on quality of life with YHK with such a small sample size.

The relatively short time period utilized for this study allowed only for measurement of transaminases as surrogate markers of disease activity, and did not permit an analysis of more important end points in this slowly progressive disease, such as the progression/quantity of fibrosis, the development to cirrhosis, and its complications including the need for liver transplant, or death. The use of decreases in transaminases themselves as markers of disease improvement in NASH is also of uncertain value. Although there are a number of reports showing a correlation between decreased transaminase levels and improved histology after treatment (29–32), this finding is not uniform (33). In addition, a long-term study of untreated NASH patients demonstrated that transaminase levels did not predict changes in histology over time (34).

Despite the shortcomings of this study, the significant improvement in ALT value without any serious adverse events or deterioration in quality of life in patients with

TABLE 3. COMPARISON OF MEAN CHANGE IN AST IN THE YHK AND PLACEBO GROUPS AT WEEKS 4, 8, AND 12 (FOLLOW-UP) RELATED TO BASELINE MEAN AST IN EACH GROUP

Time interval for comparison	*Mean change in AST (U/L)*		*Difference in AST in YHK vs. placebo (95% confidence interval)*	P *value*
	YHK	*Placebo*		
Week 4–baseline	−23.2	2.3	−25.5 (−74.4 to 23.3)	0.143
Week 8–baseline	−18.2	18.7	−36.9 (−80.6 to 6.9)	0.071
Week 12–baseline	−13.0	20.3	−33.3 (−99.1 to 32.4)	0.571

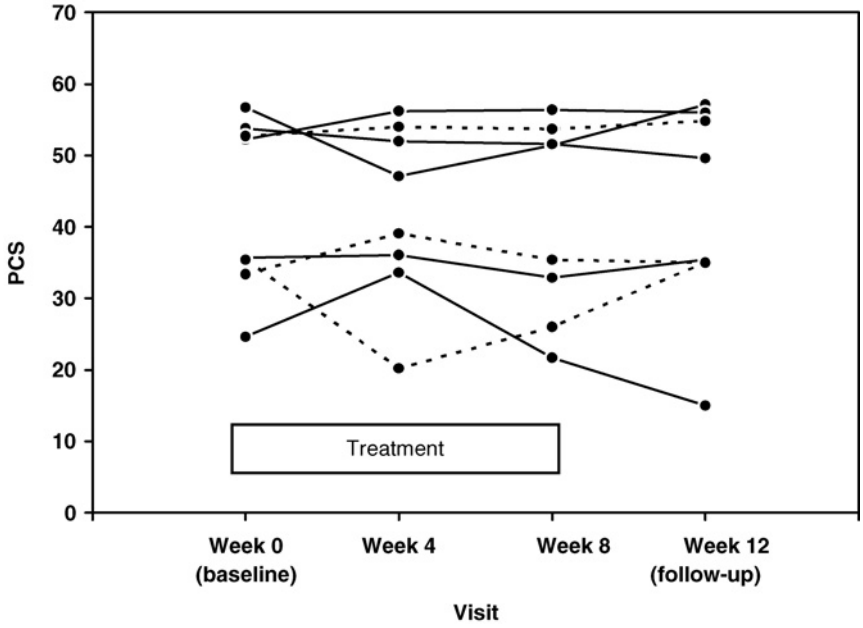

Fig 2. Physical component summary (PCS) measure on SF-36 quality of life surveys in individual patients at each visit in YHK (solid line) and placebo (dotted line) groups. A greater PCS measure indicates a higher quality of life at that point in time.

NASH treated with YHK is encouraging. A larger study with a longer treatment period and follow-up with more clinically relevant end points is warranted to confirm the utility of YHK in NASH, its effects on quality of life and safety. Traditional medical therapies for NASH have not yet been proven to be effective, and nutraceutical agents are becoming more attractive to many patients (17). Further research into the specific pharmacologic effects of the

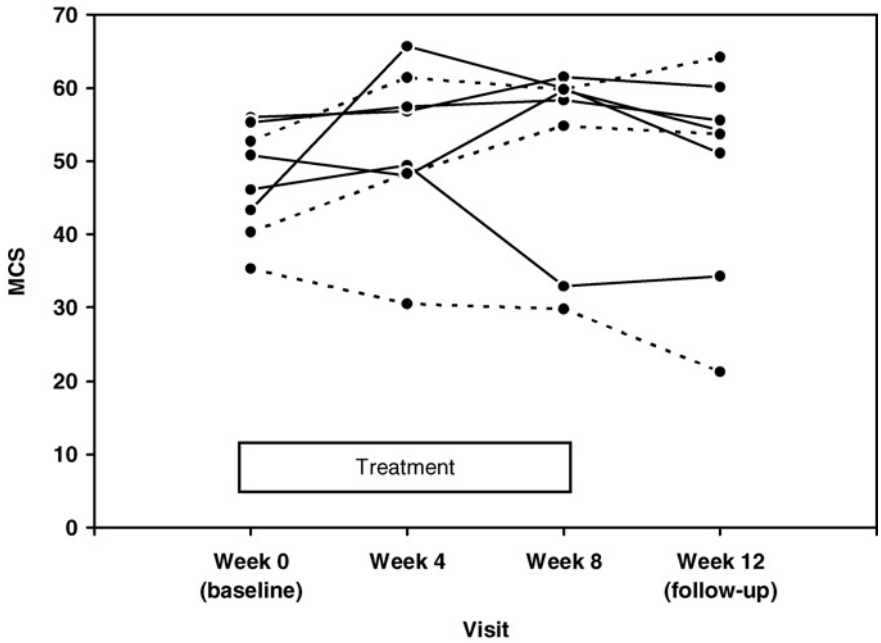

Fig 3. Mental component summary (MCS) measure on SF-36 quality of life surveys in individual patients at each visit in YHK (solid line) and placebo (dotted line) groups. A greater MCS measure indicates a higher quality of life at that point in time.

TABLE 4. ADVERSE EVENTS IN THE YHK AND PLACEBO GROUPS

	YHK (n = *5*)	*Placebo* (n = *3*)
Abdominal pain	1	2
Back pain	1	0
Chest pain	2	0
Diarrhea	1	0
Fatigue	1	0
Flatus	1	0
Headache	2	1
Heartburn	0	1
Nausea	1	0
Upper respiratory infection	1	1

active ingredients of YHK in patients with NASH may ultimately lead to targeted therapies for this disorder.

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