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Original Article

Overview of RCT for Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis

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Objective: This study aimed to get information on the current status of therapies to date for non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis (NASH).
Methods: All randomized clinical controlled trial (RCT)-derived papers for NAFLD or NASH were reviewed via PubMed Database.
Results: 39 RCTs met the review criteria, of which 15 and 24 papers were for NAFLD and NASH, respectively. 83% of the papers were released since 2006, and 30 studies were conducted for western medicines, antioxidants and lifestyle intervention whereas nine trials were done using herbal medicine or acupuncture which showed positive outcome.
Conclusions: NAFLD and NASH are new epidemic disorders which can be a target of traditional Oriental medicine. This study will be helpful for the Oriental medicine-based strategies or therapeutic development for them.

Key Words : Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, randomized controlled trial, traditional Korean medicine, herbal drug

Introduction

Non-alcoholic fatty liver disease (NAFLD) is regarded as the hepatic manifestation of metabolic syndrome, which is characterized as fat infiltration in hepatic tissue not due to excessive alcohol consumption[1,2]. Most patients with NAFLD have few or no symptoms, maintaining fatty liver without disturbing liver function; however some patients infrequently progress to outright hepatic inflammation, so-called non-alcoholic steatohepatitis (NASH)[3].

Recently, NAFLD and NASH have become an important medical issue because of their epidemic proportions in developed countries, however no therapeutics for them exist[4,5]. Two studies reported that the prevalence of NAFLD in Japanese adults and adolescents were 9.3% and 4.5% respectively[6,7] and three studies presented the prevalence around 11~15% of NAFLD in Chinese[8-10]. One study using 6,600 subjects of the general Korean population revealed a 16.1% (male 21.6% and female 11.2%) NAFLD prevalence in 2006[11].

A change of lifestyle leading to over-nutrition, insulin resistance and a highly disordered metabolic milieu increases the prevalence of NAFLD and NASH, however the etiology of those disorders are still unclear[12]. Accordingly, the development of therapeutics is extremely urgent, and many therapeutic

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candidates such as antioxidants or antidiabetic drugs have been investigated[13,14]. Based on long experience with herbal medicines, NAFLD and NASH could be a promising target of traditional Oriental medicine.

In order to refer to the current status of therapeutic development in Oriental medicine-based strategies for those disorders, the present study produced an overview of randomized clinical controlled trials (RCTs) for NAFLD or NASH via PubMed Database.

Methods

1. Data source and collection

Systematic literature searches were conducted using electronic PubMed Database. Studies were screened using the following inclusion criteria: (a) human subjects, (b) use of a control procedure, (c) subjects randomized among treatment conditions, and (d) question for efficacy of any therapeutic or remedies for NAFLD and NASH. The initial assessment using the inclusion criteria was made by reading abstracts. Articles that appeared to meet the criteria were then read in full.

2. Data synthesis and analysis

A total of 42 and 80 papers for NAFLD and NASH were reviewed respectively, and of them 39 were finally selected. Data considering clinical questions, study design, patient characteristics, and outcomes were extracted. The RCTs were heterogeneous in aspect of therapeutics or purposes. Hence, this study decided not to pool the data from specific sections statistically.

Results

1. General pattern of RCTs

The first RCT was published in 2000, which evaluated the efficacy of oral betaine glucuronate for 191 patients with NASH[15]. Over 83% of the papers were released since 2006. 25 of 39 studies were conducted in the USA (9), China (9), Italy (4) and France (3), respectively. The average number of subjects was 70 (range from 8 to 247), and the average trial period was 8.9 months (range from 2 to 24).

2. Clinical questions for NAFLD and NASH

Among the 39 studies, 15 were for NAFLD and 24 for NASH, respectively (Fig. 1-A). Regarding NAFLD, 5 herbal medicines, 3 lifestyle modifications, 2 hypolipidemics, 2 antidiabetics, 2 antioxidants, and 1 food supplement were investigated (Fig. 1-B). For the NASH, 6 antidiabetics, 4 herbal medicines including acupuncture, 4 ursodeoxycholic acids (UDCA), 3 hypolipidemics, 3 antioxidants, 2 lifestyle modifications, and 2 food supplements were investigated (Fig. 1-C).

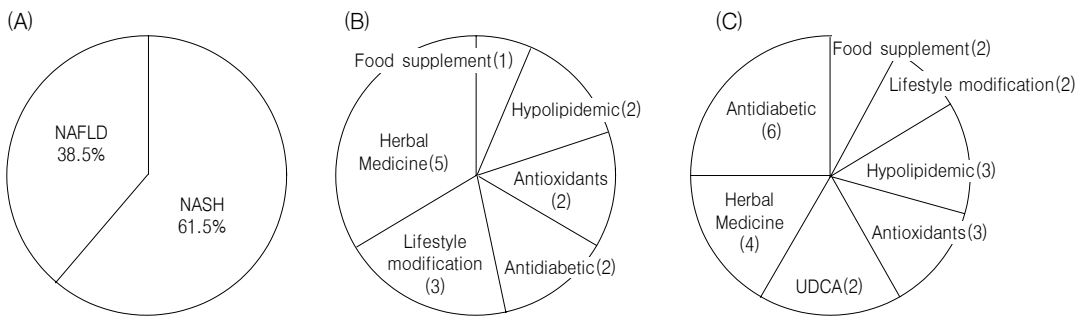

Fig. 1.

3. Analysis of study outcomes including herbal medicines and acupuncture

Except two studies (treatment using metformin[16] and alpha-tocopherol plus ascorbic acid[17]), all studies for NAFLD showed positive results. Carnitine complex, lifestyle modifications including weight reduction, antidiabetic, and hypolipidemic drugs were included. 19 of 24 studies for NASH showed positive results. Hypolipidemic drugs, antidiabetic and UDCA were simultaneously positive and negative depending on the trials.

Nine studies belonged in complementary therapy using Oriental medicine and acupuncture (Table 1). All of these studies showed effectiveness of therapy compared with placebo and proved their safety.

Discussion and conclusion

According to the change of lifestyle leading to metabolic syndrome, the prevalence of NAFLD and NASH has increased rapidly and become an important medical issue. Nevertheless, no effective therapeutics have yet been established[12], and thus many clinical investigations, including herbal medicines, have been performed recently. In order to get information about the current status of therapeutic development, this study surveyed and reviewed all RCTs for NAFLD and NASH via PubMed database.

A total of 39 RCT-derived papers were selected, consisting of 15 for NAFLD and 24 for NASH, respectively. Very heterogeneous therapeutics were studied, including lifestyle modifications, hypolipidemics, antidiabetics, antioxidants, food supplements, and herbal medicines. NAFLD and NASH are known to be strongly associated with metabolic syndrome (diabetes, obesity, combined hyperlipidemia, and hypertension) and insulin resistance[27]. Accordingly, lifestyle modification, hypolipidemic and antidiabetic drugs were mainly investigated. All studies focusing on lifestyle intervention with diet therapy were effective[28,29], whereas the results using hypolipidemic and antidiabetic drugs were partially conflicted[16,30]. These results indicate the importance of diet therapy and modification of lifestyle.

Oxidative stress is considered as a potential factor of pathogenesis of NAFLD and in NASH progress[31]. Several studies were conducted using vitamin E or vitamin C as antioxidants, and their clinical efficacy was controversial[17,32]. For UDCA, a well-known a cytoprotective and anti-cholestatic agent, four studies

Table 1. Summary of anti-NAFLD or NASH RCT studies using Oriental medicines

Author	Therapeutics	Outcomes
Li L. *et al*.[18]	Qianggan Capsule	Effective and safe for patient with NAFLD
Lou SY. *et al*.[19]	Yiqi Sanju Formula	Improved clinical symptoms and laboratory tests
Ji G. *et al*.[20]	Danning tablet	Improved NAFLD of damp-heat syndrome type
Gu CL. *et al*.[21]	Tiaozhi yanggan decoction	Effective and highly safe in treating NAFLD
Ji G. *et al*.[22]	Danning tablet	Effective for NAFL patients of damp-heat Syndrome type AND better than UDCA
Chande N. *et al*.[23]	Yo Jyo Hen Shi Ko	Reducing ALT values in patients with NASH
Zhang SJ. *et al*.[24]	QuYuHuaTanTong Luo Decoction	Effective for treating non-alcoholic steatohepatitis
Wang YL. *et al*.[25]	Yiqi Huoxue Recipe	Good effect in treating NASH
Meng SX[26]	Acupuncture	BL 23, CV 4, KI 3, and SP 6 -effect on NASH

were tried against NASH which showed two positive as well as two negative outcomes[33-36]. In fact, vitamin E, vitamin C and UDCA have been used for patients with various hepatic injuries. Those remedies have a partial therapeutic property against NASH. Because NASH may progresses into fibrosis, cirrhosis (20%), liver failure (9%) or hepatocellular carcinoma (1%), therapeutic developments against NASH are clinically urgent[37].

On the other hand, herbal medicines have been brought to the attention of investigators in treatment of NAFLD or NASH. Eight studies were done for the efficacy of herbal medicines against NAFLD or NASH[18-25]. Seven were conducted in China and the other in Canada[23]. One acupuncture study also showed a positive result in NASH treatment[26]. In particular, two studies presented that the efficacy of Danning tablets was better than UDCA[20,22]. These results indicate the potential of Oriental medicine as therapeutics for NAFLD or NASH. Although a few studies on NFALD or NASH using herbal medicine have been done[38-40], no RCT-based study had been conducted in Korea yet.

NFALD or NASH will likely be more prevalent in the future and be potential targets of traditional Korean medicine. The author hopes that this study can provide helpful information in the process of therapeutic development using Oriental medicine.

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