Natural history and epidemiology of non-alcoholic fatty liver disease in Korea

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Non-alcoholic fatty liver disease (NAFLD) is a heterogeneous disease that may range from simple steatosis (non-alcoholic fatty liver, NAFL) to non-alcoholic steatohepatitis (NASH) which can progress to advanced fibrosis and cirrhosis and is currently one of the most common chronic liver diseases in Korea and worldwide. Furthermore, in parallel with the increasing prevalence of obesity, type 2 diabetes and metabolic syndrome, the prevalence of NAFLD is expected to increase. However, data about the incidence, prevalence and natural history of NAFLD are diverse depending on the characteristics of study population and screening tests - hepatic imaging studies, histology and liver enzymes. Herein, the natural history and epidemiology of NAFLD are shortly reviewed and summarized using many recent articles, esp. Korean data.

Keywords: Non-alcoholic fatty liver disease; epidemiology; incidence; prevalence; natural history

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a heterogeneous disease that may range from simple steatosis (non-alcoholic fatty liver, NAFL) to non-alcoholic steatohepatitis (NASH) which can progress to advanced fibrosis and cirrhosis. NAFLD is one of the most common liver diseases in Korea nowadays affecting 18.7-28.1% of the nondiabetic general population. The major risk factors for NAFLD are central obesity, type 2 diabetes mellitus, dyslipidemia, and the associated metabolic syndrome. The prevalence of obesity and metabolic syndrome in Korea National Health and Nutrition Examination Survey (KNHANES) has substantially increased during the past decade, and so the prevalence of NAFLD in Korea is expected to increase. Furthermore, the increasing prevalence of NAFLD will increase clinical burden with extra-hepatic health problems because patients with NAFLD have the positive relation to cardiovascular risk factors and Framingham risk score. Therefore, the acquisition of knowledge about the natural history and epidemiology of NAFLD is an important issue, and we will review shortly the recent data regarding this issue, esp. including Korean data.

Natural History of NAFLD

The natural history of NAFLD is not yet fully demonstrated but recent data have added a tantalizing clue on it.
It is generally accepted that the majority of patients with NAFLD may have stable course or remission and only a small portion of patients may progress and the disease progression depends on the histological status of NAFLD at the time of presentation. As aforementioned, NAFLD can be histologically divided into NAFL and NASH. Generally, patients with NAFL have a benign prognosis, whereas patients with NASH can have progressive liver disease, finally leading to cirrhosis and hepatocellular carcinoma (HCC). It is notable that according to a report, even most patients with NASH have relatively benign course, with 10-15% histological progression and only about 2% progressing to decompensated cirrhosis. However, the proportion of patients with progressive disease varies depending on the data. It is also well recognized that several risk factors such as obesity, diabetes mellitus, degree of inflammation and fibrosis on initial biopsy, weight gain and age, have been associated with disease progression, whereas controlled weight reduction has been associated with disease regression.

A very recent report showed that of the 66 patients who have NAFLD by ultrasonography at baseline, as many as 24 patients (36.4%) had no evidence of NAFLD at 7 years follow-up, even though mostly depending on modest weight reduction. According to a paired biopsy study with 103 patients and mean interval between biopsies of 3.2 years, liver fibrosis stage apparently progressed in 37%, remained stable in 34% and regressed in 29%. Furthermore, 12.6% (13/103) patients with fibrosis had no fibrosis. In this study, diabetes and initial fibrosis stage were the independent risk factors associated with higher rate of fibrosis progression. A systematic review of risk factors for fibrosis progression in 221 NASH patients showed that 37.6% had progressive fibrosis over a mean follow-up interval of 5.3 years. In this study, age and inflammation on initial biopsy are independent predictors of progression to advanced fibrosis and other traditional parameters (e.g. obesity, diabetes, hypertension) were not statistically significant predictors.

Other long-term follow-up study of patients with NAFLD and elevated liver enzymes covered most aspects of natural history of NAFLD. In this study, about 20% among patients with NAFL will progress to NASH with early fibrosis and about 15% among patients with NASH and early fibrosis will progress to cirrhosis and/or decompensation over the 8-13 years. The predictors of fibrosis progression are weight gain and presence of portal tract fibrosis. About 7% of patients with compensated cirrhotic NASH will develop HCC within 10 years. In patients with NASH and cirrhosis, the 10-year liver related mortality is around 15% and all-cause mortality about 20% (Fig. 1). This study demonstrated that patients with NASH progressed to cirrhosis have a substantial risk for hepatic decompensation, development of HCC and death. Another study showed that liver-related mortality of NASH patients were 17.5% compared to only 2.7% in patients with NAFL over a median follow-up of 18.5 years.

The risk of HCC development seems to be somewhat lower in NASH-related cirrhotic patients than in those with HCV-re-
lated cirrhosis, with 11.3% for NASH and 30.5% for HCV at 5 years and 12.8% for NASH and 20.3% for HCV at 3.2 years.\textsuperscript{21,22} However, the overall survival is similar, probably associated with increased cardiovascular death in patients with NASH (the 5-year survival rates were 75.2% for NASH and 73.8% for HCV, respectively).\textsuperscript{21} In western countries, a rise in incidence of HCC associated with NAFLD has been observed in recent years. Although data about the natural history of NAFLD in Korea is lacking, a retrospective and hospital-based study of Korean patients with HCC compared etiologies between two periods (1993-1995 and 2000-2002) demonstrated that the prevalence of cryptogenic HCC was increased from 2.3% to 5.4% during the observational period, and from this study it might be carefully inferred that NAFLD and/or its risk factors contribute to the recent increase of cryptogenic HCC prevalence in Korea.\textsuperscript{23}

A long-term follow-up study of Swedish patients with biopsy proven NAFLD demonstrated that survival of patients with NASH was lower than expected in comparison with general population.\textsuperscript{12} Recent meta-analysis found that NAFLD was associated with increased overall mortality, originated from cardiovascular disease (CVD) and liver-related disease, and an increased risk of type 2 diabetes.\textsuperscript{24} In this meta-analysis, however, CVD mortality was not different between NAFL and NASH.

**Epidemiology of NAFLD**

1. Incidence

The incidence of NAFLD is not yet clearly determined because of difficulties in estimation, esp. for general population. Several reasons for difficulties are a substantial loss in long-term follow-ups of healthy people from general population, insufficiency of a reference method for the assessment of NAFLD, and a paucity of information of metabolic parameters. So, only a few studies are available about the incidence of NAFLD.

Susuki et al\textsuperscript{25} prospectively investigated the incidence of NAFLD based on elevated liver enzymes from data obtained as part of routine health care for employees in a Japanese government office and they reported that the incidence of high aminotransferases was 31 per 1,000 person-years. Hamaguchi et al\textsuperscript{26} performed a prospective observational study in the setting of a medical health checkup program in a general hospital, and they observed 308 (9.8%) new cases of NAFLD among 3147 participants who did not have NAFLD at baseline during follow-up for a mean time of only 1.1 years.

The incidence of fatty liver in the general Italian population was estimated by the Dionysos study at two new cases/100 people/year, indicating the 15.3% incidence rate among 144 patients without NAFLD at baseline during a follow-up period of 8.5 years.\textsuperscript{27} Zelber-Sagi et al\textsuperscript{17} evaluated a representative sample of the general population without alcohol related liver disease and primary NAFLD. During the 7-year follow-up, they observed 28 (19.0%) new cases of NAFLD among 147 subjects.\textsuperscript{17}

Recently three Korean studies evaluated the incidence of NAFLD defined by ultrasonographic examination. Kim et al\textsuperscript{28} investigated the incidence of NAFLD in 2895 healthy subjects (1502 men, 1393 women) with mean age of 47 years attending medical check-up, and they observed 374 (19.3%) new cases of NAFLD among 1938 subjects during 5 years. In a cohort of Korean male workers aged 30-59 years attending health check-ups, an incidence rate of 37 per 1000 person-years was reported.\textsuperscript{29} In a large cohort of non-diabetic healthy Korean adults participated in a health
check-up program, new cases of NAFLD are developed in 13% (644/4954) during a 5-year follow-up.\textsuperscript{30} According to these data, metabolic syndrome, weight gain, or insulin resistance were associated with NAFLD incidence. According to these data, the current incidence of NAFLD in Korea is about 13-19% in general population.

2. Prevalence

There are relatively large data available about the prevalence of NAFLD despite it varies depending on characteristics of study population and screening tests - hepatic imaging studies, histology and liver enzymes and it is clear that NAFLD is an increasing common problem in Korea and worldwide. The results of recent epidemiologic Korean studies about the prevalence of NAFLD are summarized in Table 1. It showed that the current prevalence of NAFLD in Korea was 18.7-28.1% in general population and 51.4% in living liver donors. A systematic review revealed that the estimated worldwide prevalence of NAFLD ranges from 3.1 to 51% in general populations.\textsuperscript{31} Using proton magnetic resonance spectrography in the United States, the prevalence of hepatic steatosis (5.5% or more fat) was estimated 31\%.\textsuperscript{32} The several population based studies using ultrasonography demonstrated that the prevalence of NAFLD in general population from 9.3 to 29.5\% in Asia,\textsuperscript{33,34} 17.1\% in Mexico,\textsuperscript{35} 30\% in Israel,\textsuperscript{36} 20\% in Romania,\textsuperscript{37} 22.6\% in Italy.\textsuperscript{38} The prevalence of NAFLD diagnosed by elevated liver enzymes was much lower than by imaging studies, ranged from 2.8\% in United States\textsuperscript{39} to 9.3\% in Japan.\textsuperscript{25}

In patients with morbid obesity (body mass index ≥ 35kg/m\textsuperscript{2}), type 2 diabetes, and dyslipidemia, the prevalence of NAFLD is much higher than in general population. Two studies of morbidly obese patients undergoing bariatric surgery revealed that the prevalence of NAFL was 47\%, NASH 27-42\% and cirrhosis 2.9-3.9\%.\textsuperscript{40,41} Two review articles showed that among patients who were morbidly obese and undergoing bariatric surgery the prevalence of NAFLD was about 76\% (range 33-99\%), NASH 37\% (range 9.8-72.5\%), fibrosis 23\% (range 7.3-49\%), and cirrhosis 5.8\% (1.6-10\%).\textsuperscript{42,43} Among diabetic patients, the prevalence of ultrasonographic NAFLD was 40-69.5\%.\textsuperscript{44,46} In addition to a higher prevalence of NAFLD in patients with type 2 diabetes, they appear to have more advanced liver disease, including NASH and cirrhosis.\textsuperscript{42} Dyslipidemia including hypertriglyceridemia, hypercholesterolemia, or both is also associated with NAFLD, found in 20\%-92\% of patients with NAFLD. It is notable that most of these patients had other components of the metabolic syndrome.\textsuperscript{16}

On the other hand, there is no information available on the prevalence of NASH in general population, as large population-based studies can be hardly performed, because a liver biopsy, the current gold standard of NASH diagnosis and staging, is invasive and cannot be applied as a screening tools. For lacking anything better, we can estimate the

<table>
<thead>
<tr>
<th>Reference, Year</th>
<th>Population (n)</th>
<th>Prevalence of NAFLD (%)</th>
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<tbody>
<tr>
<td>Diagnosis of NAFLD, by ultrasound</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim (2004)\textsuperscript{2}</td>
<td>General population (N=768)</td>
<td>23.4</td>
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<tr>
<td>Park (2006)\textsuperscript{3}</td>
<td>General population (N=6648)</td>
<td>18.7</td>
</tr>
<tr>
<td>Bae (2010)\textsuperscript{4}</td>
<td>General population (N=99969)</td>
<td>28.1</td>
</tr>
<tr>
<td>Sinn (2012)\textsuperscript{5}</td>
<td>General population (N=5878)</td>
<td>27.4</td>
</tr>
<tr>
<td>Diagnosis of NAFLD, by biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee (2007)\textsuperscript{6}</td>
<td>Living liver donors (N=589)</td>
<td>51.4, (2.2% NASH)</td>
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</table>
prevalence of NAFL and NASH using liver biopsy in general population or low-risk groups from reports of biopsy samples of apparently healthy liver transplant donors or series of autopsy with non-liver related death. Studies of living liver donors showed the prevalence of NAFLD ranged from about 15% to 52% similar in both Eastern and Western population, but that of NASH was somewhat lower in Eastern countries (1.1-2.2%) including Korea than in Western countries (3-15%). An autopsy study of 351 non-alcoholic patients showed that a prevalence of NASH was 2.7% among normal weight subjects, while it increased to 12.2% among diabetic patients and 18.5% among severely obese patients.

3. Risk factors associated with NAFLD

Well-known risk factors related to NAFLD are age, sex, race, obesity (esp. central obesity), type 2 diabetes, dyslipidemia and metabolic syndrome. A part of them will be shortly described herein and some parts are above-mentioned. The prevalence of NAFLD among adults increases with age. This may be parallel with increasing prevalence of insulin resistance and metabolic syndrome with age. The peak prevalence of NAFLD was earlier in men (fourth decade) than women (sixth decade).

Similarly to Western studies, Park et al showed that the prevalence of NAFLD increased gradually among Korean women aged 20-49 years and spiked suddenly once age exceed 50 years. Earlier studies of patients with NAFLD suggested a female preponderance but more recent studies, including population-based studies, showed that NAFLD affects both genders equally or a higher proportion of men. A Korean study showed the prevalence of NAFLD were higher in men than in women below 50 years, but the prevalence did not differ significantly according to gender above 50 years. The difference with regards to the influence of age on the prevalence of NAFLD between the genders may be attributed by protective effects of estrogen and less visceral fat in women. Racial and ethnic difference in prevalence of NAFLD are evaluated in some reports. In a study using proton magnetic resonance spectrography, Browning et al found a lower prevalence of NAFLD among African Americans (median 24%) than non-Hispanic whites (median 33%) or Hispanics (45%). Caldwell et al showed the prevalence of NASH is much lower in African American decent than in European American descent. These differences may be explained less visceral fat and a different lipoprotein metabolism in African Americans.

Obesity and metabolic syndrome including diabetes were closely linked to prevalence of NAFLD. Sinn et al showed the prevalence of NAFLD increased ranging from 15.2% to 100% in accordance with the increased numbers of observed metabolic components of the Adult Treatment Panel III criteria. As described previously, in Korean population the prevalence of obesity and type 2 diabetes is increasing, and so the prevalence of NAFLD appears to increase.

Conclusion

Korean data about the natural history of NAFLD is not yet available, so we have no choice but to infer from data of other countries. Even though the majority of patients with NAFLD may have stable course or remission and only a small portion of patients may progress, patients with NASH progressed to cirrhosis have a substantial risk for hepatic decompensation, development of HCC and death. It is also notable that NAFLD itself is associated with increased cardiovascular death. Well-known risk factors associated with NAFLD progression include obesity, diabetes mellitus, degree
of inflammation and fibrosis on initial biopsy, weight gain and age, whereas controlled weight reduction has been associated with disease regression. The natural history of NAFLD is summarized in Figure 1.

Nowadays, NAFLD is one of the most common liver diseases in Korea and worldwide and the prevalence of NAFLD is expected to increase further in parallel with increasing prevalence of obesity, type 2 diabetes and metabolic syndrome. The prevalence of NAFLD and NASH is much higher in patients who have the metabolic syndrome than in general population and the risk to disease progression is increasing in accordance with the increasing numbers of metabolic components. Overall, the current incidence and prevalence of NAFLD in Korea is about 13-19% and 19-28% in general population respectively, and the prevalence of NASH in Korea is 2.2% in living liver donors but is not determined yet in general population. Further well-designed prospective studies about the natural history and epidemiology of NAFLD, esp. in general Korean population, are required.

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