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Current Topic Concerning Non-Obese Non-Alcoholic Fatty Liver Disease (NAFLD)

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has been most common liver disease, which is prevalent for 25% worldwide. NAFLD with BMI <25 (non-obese NAFLD) is not a rare disease than expected. The prevalence of non-obese NAFLD for general population is 5.1% from 23 studies. NAFLD incidence among non-obese people was 24.6 per 1000 person-years. Currently, prevalence of non-NAFLD among NAFLD group in Europe vs East Asia are 50% vs 38%. For retrospective cohort study for NAFLD, the risk of T2DM vs hypertension was 11.7 vs 7.99, respectively, and hazard ratio (HR) was 1.09 for older age and 2.87 for T2DM.

Keywords: ***Non-alcoholic fatty liver disease (NAFLD); Non-obese NAFLD; Chronic liver diseases (CLDs); Sarcopenic obesity (Sa-O); NAFLD fibrosis score (NFS)***

Non-alcoholic fatty liver disease (NAFLD) has been the most common liver disease, which is prevalent for 25% worldwide [1]. In the US, NAFLD and its subtype (non-alcoholic steatohepatitis) are observed for 30% and 5% of the population, respectively. The main causes of NAFLD are binge eating and decreased activity. Therefore, NAFLD is thought to have usually obesity. However, NAFLD with BMI <25 (non-obese NAFLD) is not a rare disease than expected. NAFLD seems to be recently a significant disease with public health burden, which affect obese patients as well as patients with normal weight. A certain subset of them shows elevated risk of all-cause mortality and harmful outcome compared with obese patients. NAFLD development in lean patient would be related with metabolic phenotype, including insulin resistance, sarcopenia and visceral fat tissue [2].

The prevalence of non-obese NAFLD in 93 studies (n=10,576,383, 24 countries) was summarized [3]. As a result, top 3 countries were Sweden 70.9%, Mexico 69.8%, and Austria 67.8% within NAFLD patients. Furthermore, they were Europe 51.3%, Central America 56.6%, South Asia 40.9% and East Asia 37.8%. For East Asia, non-obese NAFLD ratio is Japan

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39.1%, Korea 37.4%, China 44.3%, Taiwan 36.3%, Hong Kong 36.4%, respectively. The prevalence of lean NAFLD in the general population was 5.1% from 23 studies (n=113394). NAFLD incidence among non-obese people was 24.6 per 1000 person-years [4]. Non-obese NAFLD was formerly thought to be common in Asian countries. However, it is more frequent in Europe and US. Prevalence of non-NAFLD among NAFLD group in Europe vs East Asia are 50% vs 38% [3]. It is from multi-factorial reasons, such as eating habits, intestinal flora, genetic factor and others.

The characteristics of non-obese NAFLD cases were examined in 762 NAFLD patients [5]. The results revealed that many cases have visceral fat accumulation and insulin resistance. Moreover, when the body weight was divided into three groups of non-obesity / obesity / severe obesity, the median age of male was 49.9 / 46.8 / 40.5 ($p<0.01$) and females were 60.2 / 59.6 / 48.5 ($p<0.01$) years old, respectively. For its characteristic point, low skeletal muscle mass was observed. Advanced fibrosis was found more frequent in severely obese men, with the ratio of 31.0%/41.6%/60.9% ($p<0.01$), respectively [5]. In contrast, the trend showed opposite in severely obese women with the ratio of 51.4%/62.9%/33.7% ($p<0.01$), respectively. Skeletal muscle mass was proved to be lower significantly in the female non-obese group.

NAFLD cases (n=404) were divided into three groups by the BMI value, which were non-obese, obese and severe obese as <25, 25 to <30 and ≥ 30 [6]. Furthermore, their detail data were compared with those of 253 non-NAFLD. As a result, the ratio of non-obese NAFLD was 25.7%/27.6% in men/women. Non-obese NAFLD group showed lower muscle strength and muscle mass than obese groups. Abdominal visceral fat area ≥ 100 cm^2 was observed in 59.3%/43.8% in men/female, which were less than obese groups. By multivariate analysis, some factors related to liver fat accumulation in non-obese group were proved to be HbA1c, visceral fat area, leptin and myostatin. Consequently, non-obese NAFLD cases seem to have pathophysiological factors such as not only reduced muscle mass/strength and impaired glucose tolerance, but also muscle atrophy (presarcopenia).

The problem of pre-sarcopenia may be related to increasing trend of NAFLD, which probably includes chronic liver diseases (CLDs) and liver cirrhosis (LC). As CLD patients increase these days, some LC patients may be found with impaired hepatic function and obesity. They may present sarcopenic obesity (Sa-O), involving both obesity and sarcopenia [7]. Sa-O includes complicated pathophysiological mechanisms, such as insulin resistance, oxidative stress, inflammation, involvement of cytokines, impaired hormonal function and decreased physical activity.

T2DM may contribute the progression of NAFLD, and also predict development to liver fibrosis and mortality. A cross-sectional study was investigated in diabetes center and primary care clinic [8]. Out of 449 T2DM cases, 78.7% (344/436) of cases showed NAFLD, of which 13.1% (45/344) showed the findings of increased liver stiffness. The Odds Ratio (OR) for increased controlled attenuation parameter (CAP) (NAFLD) was 1.08 in elevated ALT, 2.64 in obesity (BMI ≥ 27.5 kg/m^2), 4.36 in metabolic syndrome. On the other hand, OR for increased liver stiffness was 1.06 in highest AST, 1.02 in CAP value and 4.56 in concomitant hypertension, respectively.

As regards to the prognosis, there are several reports on analyzing much data concerning NAFLD. A meta-analysis examined some aspects of the prognosis for non-obese NAFLD patients [3]. As a result, the mortality rate of non-obese NAFLD patients was 12.1 / 1000 person-years, and the prognosis was poor compared to those of obese NAFLD patients (7.5 / 1000

person-years). A retrospective cohort study for long years was investigated, in which totally 223 patients were included for 19.5 years in median [9]. The risk of T2DM vs hypertension was 11.7 vs 7.99, respectively, which are compared with general population. By multivariate analysis, the hazard ratio (HR) was 1.09 for older age and 2.87 for T2DM. Moreover, the factors significantly related to the clinical events included hepatic steatosis, advanced liver fibrosis and rather mild hepatic steatosis.

A Retrospective study for NAFLD was investigated, in which lean cases (n=170) existed out of 446 cases confirmed by the histopathological diagnosis method [10]. Lean NAFLD cases showed lower values of liver function tests, glucose and lipid metabolic markers, histological scoring and NAFLD fibrosis score (NFS) compared with non-lean NAFLD. By multivariate analysis of lean NAFLD, the value of NFS ≥ -1.455 would become the independent predictor for developing severe fibrosis. Consequently, lean NAFLD patients with NFS ≥ -1.455 will be carefully monitored and followed up. Furthermore, liver fibrosis (stage 3-4: HR 4.33), aging (HR 1.10), and hypertension (Hr 2.25) have been reported as prognostic factors in non-obese NFALD patients [11].

In summary, current topics concerning non-obese NAFLD were described and discussed in this article. Such patients seem to be rather common and are properly managed from now. Various information mentioned here will be hopefully references for future clinical practice.

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