Identification of individuals with non-alcoholic fatty liver disease by the diagnostic criteria for the metabolic syndrome

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Abstract

AIM: To clarify the efficiency of the criterion of metabolic syndrome to detecting non-alcoholic fatty liver disease (NAFLD).

METHODS: Authors performed a cross-sectional study involving participants of a medical health checkup program including abdominal ultrasonography. This study involved 11 714 apparently healthy Japanese men and women, 18 to 83 years of age. NAFLD was defined by abdominal ultrasonography without an alcohol intake of more than 20 g/d, known liver disease, or current use of medication. The revised criteria of the National Cholesterol Education Program Adult Treatment Panel III were used to characterize the metabolic syndrome.

RESULTS: NAFLD was detected in 32.2% (95% CI: 31.0%-33.5%) of men (n = 1874 of 5811) and in 8.7% (95% CI: 8.0%-9.5%) of women (n = 514 of 5903). Among obese people, the prevalence of NAFLD was as high as 67.3% (95% CI: 64.8%-69.7%) in men and 45.8% (95% CI: 41.7%-50.0%) in women. Although NAFLD was thought of as being the liver phenotype of metabolic syndrome, the prevalence of the metabolic syndrome among subjects with NAFLD was low both in men and women. 66.8% of men and 70.4% of women with NAFLD were not diagnosed with the metabolic syndrome. 48.2% of men with NAFLD and 49.8% of women with NAFLD weren't overweight [body mass index (BMI) ≥ 25 kg/m²]. In the same way, 68.6% of men with NAFLD and 37.9% of women with NAFLD weren't satisfied with abdominal classification (≥ 90 cm for men and ≥ 80 cm for women). Next, authors defined it as positive at screening for NAFLD when participants satisfied at least one criterion of metabolic syndrome. The sensitivity of the definition “at least 1 criterion” was as good as 84.8% in men and 86.6% in women. Separating subjects by BMI, the sensitivity was higher in obese men and women than in non-obese men and women (92.3% vs 76.8% in men, 96.1% vs 77.0% in women, respectively).

CONCLUSION: Authors could determine NAFLD effectively in epidemiological study by modifying the usage of the criteria for metabolic syndrome.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common clinical condition with histological features that resemble those of alcohol-induced liver injury, but occurs in patients who do not drink an excessive amount of alcohol (ethanol > 20 g/d)[1,2]. This disease is often associated with obesity[3], type 2 diabetes mellitus[4,5], dyslipidemia[6], and hypertension[7]. Each of these abnormalities carries a cardiovascular disease risk, and together they are often categorized as the insulin resistance syndrome or the metabolic syndrome[8,9].

NAFLD is now considered to be the hepatic representation of the metabolic syndrome[10-12].

Conventional radiology studies used in the diagnosis of fatty liver include ultrasound (US), computed tomography, and magnetic resonance (MR) imaging. Other than these radiological studies, we have no sensitive and low invasive screening method for NAFLD. Alanine aminotransferase (ALT) > 30 IU/L was usually used as the cut off level of screening NAFLD[13,14]. This threshold had a sensitivity of 0.92 for detecting the fatty-fibrotic pattern proven by ultrasound among obese children[15]. However, ALT was within normal limits in 69% of those who had increased liver fat[16]. Similarly, in the Dallas Heart Study, 79% of the subjects with a fatty liver (liver fat content > 5.6%) had normal serum ALT[17]. This implies that a normal ALT does not exclude steatosis. Aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) also correlate with liver fat content independent of obesity[18], but are even less sensitive than serum ALT.

It was well known that NAFLD was associated with the metabolic syndrome and patients with NAFLD tend to be accompanied with the abnormal component of the metabolic syndrome. However, the efficiency of the criterion of metabolic syndrome for detecting NAFLD has not yet been clarified. We aimed to clarify the efficiency and perform a cross sectional study among apparent healthy Japanese.

MATERIALS AND METHODS

Study design

We performed a cross-sectional study involving partici-
Statistical analysis

The R version 2.9.0 (available from http://www.r-project.org/) was used for statistical analyses. Two groups of subjects were compared by using the unpaired $t$-test and the chi-square test, and a $P < 0.05$ was accepted as a significant level.

RESULTS

Basic characteristics of study population

The metabolic syndrome defined by revised NCEP-ATP III definition was detected in 15.0% (95% CI: 14.1%-16.0%) of men ($n = 873$ of $5811$) and in 5.1% (95% CI: 4.5%-5.7%) of women ($n = 300$ of $5903$). The metabolic syndrome defined by IDF definition was detected in 8.2% (95% CI: 7.5%-9.0%) of men ($n = 479$ of $5811$) and in 4.3% (95% CI: 3.8%-4.8%) of women ($n = 254$ of $5903$) (Table 1). Among obese people, the metabolic syndrome defined by revised NCEP-ATP III definition was detected in 30.7% (95% CI: 30.0%-31.4%) of men and in 27.1% (95% CI: 26.3%-27.9%) of women, respectively (Table 1).

Association of NAFLD with gender difference, or body fat accumulation

NAFLD was detected in 32.2% (95% CI: 31.0%-33.5%) of men ($n = 1874$ of $5811$) and in 8.7% (95% CI: 8.0%-9.5%) of women ($n = 514$ of $5903$). The prevalence of NAFLD in men was four times higher than those in women (Table 1). Among obese people, the prevalence of NAFLD was as high as 67.3% (95% CI: 64.8%-69.7%) in men and 45.8% (95% CI: 41.7%-50.0%) in women (Table 1). NAFLD was associated with body fat accumulation strongly both in men and women.

When we separated by quartile the subjects according to their BMI or abdominal circumference, half of NAFLD men and three quarters of NAFLD women were classified in the superior quartile. The prevalence of NAFLD in the superior quartile was higher in women than in men. The prevalence of individuals who met two or more of the MS criteria other than waist circumference was increased according to the increase of BMI or abdominal circumference (Figure 1B).

| Men | Total $n$ (%) | Obese $n$ (%) | Non-obese $n$ (%) |
|-----|---------------|---------------|-------------------|
| Number | 5811 | 1441 | 4370 |
| NAFLD | 1874 (32.2) | 703 (48.8) | 871 (20.7) |
| 5 criteria of the metabolic syndrome | | | |
| Increased abdominal circumference | 791 (13.6) | 703 (48.8) | 88 (2) |
| Elevated fasting glucose level | 1967 (33.8) | 704 (48.9) | 1263 (26.9) |
| Elevated blood pressure | 1294 (22.3) | 575 (39.9) | 719 (16.5) |
| Decreased HDL cholesterol level | 1736 (29.9) | 654 (45.4) | 1082 (24.8) |
| Elevated triglyceride level | 1063 (18.3) | 484 (33.6) | 579 (13.2) |
| ALT $> 30$ | 1269 (21.8) | 607 (46.5) | 592 (14.7) |
| MS defined by rNCEP-ATP II | 873 (15) | 578 (40.1) | 295 (6.8) |
| MS defined by IDF | 479 (8.2) | 443 (30.7) | 36 (0.8) |
| At least 1 criterion | 3688 (63.3) | 1291 (89.6) | 2397 (55.7) |
| At least 2 criteria | 1955 (33.6) | 957 (66.4) | 998 (22.9) |
| At least 1 criterion or ALT $> 30$ IU/L | 3885 (66.9) | 1337 (92.8) | 2548 (58.3) |
| Women | | | |
| Number | 5903 | 563 | 5340 |
| NAFLD | 514 (8.7) | 258 (45.8) | 256 (4.8) |
| 5 criteria of the metabolic syndrome | | | |
| Increased abdominal circumference | 878 (14.9) | 430 (76.4) | 448 (8.4) |
| Elevated fasting glucose level | 679 (11.5) | 176 (31.3) | 503 (9.4) |
| Elevated blood pressure | 578 (9.8) | 185 (32.9) | 393 (7.4) |
| Decreased HDL cholesterol level | 1320 (22.4) | 265 (47.1) | 1055 (19.8) |
| Elevated triglyceride level | 195 (3.3) | 73 (13) | 122 (2.3) |
| Elevated ALT (ALT $> 30$ IU/L) | 200 (3.4) | 78 (13.9) | 122 (2.3) |
| MS defined by rNCEP-ATP II | 300 (5.1) | 174 (30.9) | 126 (2.4) |
| MS defined by IDF | 254 (4.3) | 162 (28.8) | 92 (1.7) |
| At least 1 criterion | 2374 (40.2) | 511 (90.8) | 1863 (34.9) |
| At least 2 criteria | 853 (14.5) | 353 (61.1) | 498 (9.3) |
| At least 1 criterion or elevated ALT | 2430 (41.2) | 515 (91.5) | 1915 (35.9) |

NAFLD: Nonalcoholic fatty liver disease; US: Abdominal ultrasonography; BMI: Body mass index; HDL: High density lipoprotein; MS: Metabolic syndrome; rNCEP-ATP III: Revised National Cholesterol Education Program Adult Treatment Panel III definition; IDF: International diabetes federation definition; ALT: Alanine aminotransferase.
Figure 1  We separated the subjects by quartile according to their body mass index or abdominal circumference. A: The bar indicated the prevalence (%) of individuals with NAFLD; B: Individuals who meet two or more of the MS criteria other than waist circumference according to BMI or waist circumference quartiles. 2 MS criteria means individuals who meets two or more of the MS criteria other than waist circumference. NAFLD: Nonalcoholic fatty liver disease; BMI: Body mass index; MS: Metabolic syndrome.
Role of the criteria of the metabolic syndrome in detecting or diagnosing NAFLD in obese or non-obese population

Although NAFLD was associated with obesity or body fat accumulation strongly, the population that was neither overweight (BMI ≥ 25 kg/m\(^2\)) nor had elevated abdominal circumference was not small (Figure 2). Actually, 48.2% of men with NAFLD and 49.8% of women with NAFLD were not overweight (BMI ≥ 25 kg/m\(^2\)). Similarly, 68.6% of men with NAFLD and 37.9% of women with NAFLD did not satisfy increased abdominal circumference classification. Half of the NAFLD group was classified as non-obese, but the prevalence of NAFLD among the non-obese population was lower. These facts mean an effective method is needed to detect NAFLD among the non-obese population. Then, we separated the subjects into two groups, obese group or non-obese group, and investigated the efficacy of the criteria of metabolic syndrome for detecting NAFLD in each group.

Among the criteria for metabolic syndrome, the criterion of abdominal circumferences (≥ 80 cm) had high sensitivity (87.6%) for detecting NAFLD in women who were overweight (BMI ≥ 25 kg/m\(^2\)) (Table 2). In other words, abdominal circumference was effective for detecting NAFLD in obese women. However, the criterion of abdominal circumference had low sensitivity (36.3%) in non-obese women. The sensitivity of abdominal circumference (≥ 90 cm) was very low (5.8%) in non-obese men. Even in obese men the sensitivity was not high (55.3%). Other criteria for metabolic syndrome had higher sensitivity in obese men and women than in the non-obese population but sensitivity never exceeded 60%.

As a screening tool for NAFLD, the sensitivity of elevated ALT (ALT > 30 IU/L) was 49.7% in men, which exceeded the sensitivity of the criteria of metabolic syndrome, but it was 17.7% in women, which was lower than all metabolic syndrome criteria were. On the other hand, the specificity of elevated ALT was as high as 90.6% in men and 98.0% in women, but the criteria of metabolic syndrome had equally high specificity.

Next, we defined it as positive at screening for NAFLD

| BMI (kg/m\(^2\)) | Men       | Women     |
|------------------|-----------|-----------|
| BMI ≥ 25 kg/m\(^2\) and NAFLD | 16.7%     | 4.4%      |
| BMI < 25 kg/m\(^2\) and NAFLD | 15.6%     | 4.3%      |
| BMI < 25 kg/m\(^2\) and nonNAFLD | 59.6%     | 86.1%     |
| < 90 cm and NAFLD | 22.1%     | 3.3%      |
| < 90 cm and nonNAFLD | 64.3%     | 81.8%     |

| Men       | Women     |
|-----------|-----------|
| Waist ≥ 90 cm but nonNAFLD | 3.5%      |
| Waist ≥ 90 cm and NAFLD | 10.1%     |
| Waist < 90 cm and NAFLD | 62.1%     |

Figure 2 This figure indicates the prevalence of non-alcoholic fatty liver disease and alcoholic fatty liver disease with or without patients being overweight (BMI ≥ 25 kg/m\(^2\)) or having elevated abdominal circumferences (≥ 90 cm for men and ≥ 80 cm for women). Data was expressed as prevalence (%). NAFLD accompanied with being overweight occurred in 51.8% of NAFLD men (970/1874) and 50.2% of NAFLD women (258/514). NAFLD accompanied by elevated abdominal circumference occurred in 31.4% of NAFLD men (588/1874) and 62.1% of women (319/514). NAFLD: Non-alcoholic fatty liver disease; BMI: Body mass index.
when participants satisfied at least one or two components of metabolic syndrome. The sensitivity of the definition “at least 1 criterion” was 84.8% in men and 86.6% in women. Separating subjects with BMI, the sensitivity was higher in obese men and women than in non-obese men and women (92.3% vs 76.8% in men, 96.1% vs 77.0% in women, respectively).

The prevalence of subjects with NAFLD who also had the metabolic syndrome is indicated in Figure 3. Although NAFLD was thought of as being the liver phenotype of metabolic syndrome, the prevalence of the metabolic syndrome among subjects with NAFLD was low both in men and women. Among men with NAFLD, 66.8% were not diagnosed with the metabolic syndrome defined by revised NCEP-ATP III definition, and 79.0% were not diagnosed with the metabolic syndrome as defined by revised IDF definition. Even in women, 70.4% and 67.5%, respectively, were not diagnosed with metabolic syndrome by revised NCEP-ATP III definition and revised IDF definition. These results mean that a large number of participants diagnosed with the metabolic syndrome have NAFLD, but a large number of participants with NAFLD were not diagnosed with the metabolic syndrome, whether we used revised NECP-ATP III criteria or IDF criteria.

**DISCUSSION**

In this study, we clarified the impact of the criteria of the metabolic syndrome for diagnosing NAFLD in a healthy population. The metabolic syndrome was associated with abdominal obesity and its criteria include waist circumference, and NAFLD was reported to be associated with abdominal obesity. However, our results indicated there was no significant difference between BMI and waist circumferences as the strength of association with NAFLD or the accumulation of metabolic syndrome criteria.

The presence of multiple metabolic disorders such as diabetes mellitus, obesity, dyslipidemia and hypertension is associated with a potentially progressive, severe liver disease. Previous reports demonstrated that prevalence of NAFLD increased to 10%-80% in individuals with obesity, 35%-90% in individuals with type 2 diabetes mellitus, 30%-56% in individuals with hypertension, and 26%-58% in individuals with dyslipidemia. Another study in a Japanese population showed that prevalence of NAFLD increased to 43% in individuals with impaired fasting glucose and 62% in individuals with type 2 diabetes mellitus. Some studies estimate the prevalence of NAFLD be up to 15%-30% of the general population, and the prevalence of metabolic syndrome was estimated to be up to 25% of the general population. In those patients with the metabolic syndrome, liver fat content is significantly increased up to 4-fold higher than those without the metabolic syndrome, and the incidence of NAFLD has been shown to be increased 4-fold in men and 11-fold in women with the metabolic syndrome. Our data clearly indicated that 21% to 33% of sub-
The MS was defined by revised NCEP-ATP III definition

Among subjects with NAFLD, 33.2% was diagnosed as MS, and 66.8% was not diagnosed as MS

The MS was defined by IDF definition

Among subjects with NAFLD, 21.0% was diagnosed as MS, and 79.0% was not diagnosed as MS

Figure 3 The prevalence of subjects with or without the metabolic syndrome among 1874 men and 514 women with non-alcoholic fatty liver disease. Data was expressed as prevalence (%). The metabolic syndrome (MS) was diagnosed using revised IDF. Among men with NAFLD, 66.8% and 79.0% were not diagnosed with the MS defined by revised NCEP-ATP III definition and revised IDF definition, respectively. In women, 70.4% and 67.5%, respectively, were not diagnosed with the MS by revised NCEP-ATP III definition and revised IDF definition. IDF: International Diabetes Federation; NCEP-ATP III: National Cholesterol Education Program Adult Treatment Panel III; NAFLD: Non-alcoholic fatty liver disease.

NAFLD with the MS
NAFLD without the MS

Men

Women

NAFLD with the MS
NAFLD without the MS

Among subjects with NAFLD, 33.2% was diagnosed as MS, and 66.8% was not diagnosed as MS

Among subjects with NAFLD, 29.6% was diagnosed as MS, and 70.4% was not diagnosed as MS

NAFLD with the MS
NAFLD without the MS

Men

Women

NAFLD with the MS
NAFLD without the MS

Among subjects with NAFLD, 21.0% was diagnosed as MS, and 79.0% was not diagnosed as MS

Among subjects with NAFLD, 32.5% was diagnosed as MS, and 67.5% was not diagnosed as MS

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Subjects with NAFLD, depending on gender and the criteria used, were diagnosed with the metabolic syndrome. Several previous studies reported how many subjects with NAFLD were diagnosed with the metabolic syndrome, but almost all previous studies were hospital studies. Three population based studies mentioned the prevalence of subjects with NAFLD who were diagnosed with the metabolic syndrome among the general population. In these studies, the prevalence of the metabolic syndrome among subjects with NAFLD was 17% to 36% depending on gender and the criteria used. The reported prevalence was similar to ours.

There has been no report regarding the sensitivity and specificity of the metabolic syndrome for detecting NAFLD. Among the criteria for metabolic syndrome, the criterion of abdominal circumference had high sensitivity in obese women. However, it had low sensitivity (36.3%) in non-obese women and was very low (5.8%) in non-obese men and low (55.3%) in obese men. Other than the criterion of abdominal circumference, none of the sensitivities exceeded 60%. In our study, the specificity of elevated ALT (ALT > 30 IU/L) was 90.6% in men and 98.0% in women. However, the sensitivity was as low as 47.9% in men and 17.7% in women. The specificity of elevated ALT was significantly higher among obese subjects than among non-obese subjects, and sensitivity was higher among obese subjects than among non-obese subjects.

When we investigated the predictability of each component of metabolic syndrome such as abdominal circumference, fasting blood sugar, serum lipid, and blood pressure, each component had high specificity but low sensitivity, similar to elevated ALT. Therefore, we defined it as screening positive for NAFLD, when subjects satisfied at least one criterion of metabolic syndrome; the sensitivity was 84.8% in men and 86.6% in women. Additionally, we defined it as positive when subjects satisfied at least one criterion of metabolic syndrome or elevated ALT. The sensitivity of “at least 1 criterion or elevated ALT” was 90.4% in men and 87.4% in women. However, the specificity of “at least 1 criterion or elevated ALT” was lower -44%-63%.
The result of our study means that we could identify NAFLD effectively in epidemiological study by modifying the usage of the criteria for metabolic syndrome. It is clinically critical evidence that a large part of patients with NAFLD were not diagnosed with the metabolic syndrome, when we used today’s definition for the metabolic syndrome. However, our subject population consisted only of Japanese, thus, the generalizability of our study to non-Japanese populations is uncertain. It is one of our study limitations that we used abdominal ultrasonography for diagnosing NAFLD, although the validation ultrasonography had a sensitivity of 91.7% and a specificity of 100%.

COMMENTS

Background
It is well known that non-alcoholic fatty liver disease (NAFLD) is associated with the metabolic syndrome and patients with NAFLD tend to also have the metabolic syndrome.

Research frontiers
The impact of overlap between NAFLD and the metabolic syndrome has not been evaluated yet.

Innovations and breakthroughs
It is clinically critical evidence that a large number of patients with NAFLD were not diagnosed with the metabolic syndrome in a healthy Japanese population.

Applications
The authors could identify NAFLD effectively by modifying the usage of the criteria for metabolic syndrome.

Peer review
It is a relatively large population study. The conclusion is consistent with recent observations showing the dissociation between NAFLD and other parameters of metabolic syndrome. The readers of this journal will be interested in the findings of this study.

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