

# PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

## Nonobese Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) refers to a group of conditions characterized by hepatic steatosis in the absence of significant alcohol consumption. NAFLD is seen commonly in patients with metabolic abnormalities associated with obesity, such as type II diabetes, dyslipidemia, and metabolic syndrome. Evidently, however, not all obese subjects develop NAFLD and, more importantly, NAFLD can be found in nonobese individuals. Although NAFLD occurring in nonobese subjects has been reported in children and adults of all ethnicities, it appears to be recognized more frequently in Asians, even when strict ethnicity-specific body mass index criteria are used to define obesity. Studies based on liver biopsies suggest that the prevalence of nonalcoholic steatohepatitis and fibrosis does not differ significantly between nonobese NAFLD and NAFLD in obese patients. Visceral obesity as opposed to general obesity, high fructose and cholesterol intake, and genetic risk factors (eg, palatin-like phospholipase domain-containing 3) may be associated with nonobese NAFLD. In general, nonalcoholic steatohepatitis is associated with increased mortality, primarily from cardiovascular causes, independent of other metabolic factors. Although data regarding the mortality impact of nonobese NAFLD are not as mature, it may be important to identify high-risk nonobese NAFLD patients and manage their metabolic profile. Currently, lifestyle modification to reduce visceral adiposity, including dietary changes and physical activity, remains the standard of care in patients with nonobese NAFLD.

**Keywords:** Nonalcoholic Fatty Liver Disease; Nonalcoholic Steatohepatitis; Nonobese; Nonoverweight; Body Mass Index; Lean; Hepatic Steatosis.

Nonalcoholic fatty liver disease (NAFLD) is defined by the presence of steatosis in the liver without an alternate identifiable cause such as significant alcohol consumption. NAFLD encompasses a broad spectrum of pathology ranging from simple steatosis unaccompanied by inflammation or fibrosis to nonalcoholic steatohepatitis (NASH), and to cirrhosis and hepatocellular carcinoma.<sup>1,2</sup> The global increase in the prevalence of obesity, type II diabetes, and metabolic syndrome has led to an increasing incidence of NAFLD.<sup>3</sup> NAFLD has been recognized as the most common liver disease in the Western world, with an estimated prevalence of 20% to 30%.<sup>4</sup> The increase of NAFLD has become a significant public health

concern because NAFLD is associated with increased mortality from liver-related and liver-unrelated causes.<sup>5,6</sup>

Obesity is a common clinical phenotype associated with NAFLD, which is linked to metabolic syndrome and related comorbidities, including type II diabetes, hypertension, and dyslipidemia. Clearly, not all obese subjects develop NAFLD<sup>7</sup> and NAFLD also can be found in nonobese patients.<sup>8</sup> NAFLD may represent a group of conditions in which several pathogenetic processes may be in play that may be disparate between obese and nonobese patients, despite similar clinical and histopathologic presentation. Better understanding of the NAFLD occurring in a nonobese subject, for which we propose the term *nonobese NAFLD* or nonobese fatty liver disease, goes beyond a pursuit of academic curiosity. Questions of obvious practical importance may include the following: (1) what is the clinical significance of nonobese NAFLD as a liver disease, and (2) if nonobese NAFLD is a clinically significant condition, what are indicators to identify patients at risk? In this review, we attempt to address these questions by summarizing what is known and what remains unknown about nonobese NAFLD in the literature.

### Prevalence

Globally, the reported prevalence of nonobese NAFLD varies widely, ranging from 3% to 30%. The variability may be attributed to differences in study subject selection, diagnostic modalities, and lifestyle and dietary customs of the specific population. The prevalence data on nonobese NAFLD between the East and West are not directly comparable at least in part because of the different body mass index (BMI) cut-off values for

**Abbreviations used in this paper:** BMI, body mass index; CETP, cholesteryl ester transfer protein; CI, confidence interval; MONW, metabolically obese but normal weight; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PNPLA3, palatin-like phospholipase domain-containing 3; SAD, sagittal abdominal diameter; SREBP, sterol-regulatory element-binding protein; TM6SF2, transmembrane 6 superfamily member 2.

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Asians. The recommended BMI cut-off value for Asians for being overweight is 23 to 25 kg/m<sup>2</sup> and for obesity is greater than 25 kg/m<sup>2</sup>, in contrast to 25 to 30 kg/m<sup>2</sup> and greater than 30 kg/m<sup>2</sup>, respectively, for subjects of other races.<sup>9</sup>

The prevalence of nonobese NAFLD described in the literature is summarized in Table 1. Although different studies used different BMI cut-off values, we attempt to align the definition of nonobese NAFLD to BMI less than 30 kg/m<sup>2</sup> for Western studies and BMI less than 25 kg/m<sup>2</sup> for Eastern studies. Among patients with non-obese NAFLD, lean NAFLD was defined as NAFLD in the population with a BMI less than 25 kg/m<sup>2</sup> for the Western studies and a BMI less than 23 kg/m<sup>2</sup> for Eastern studies. Most of the population-based studies that reported the prevalence of nonobese NAFLD in the West were conducted in the United States. The Dallas Heart Study measured the hepatic triglyceride content with proton nuclear magnetic resonance spectroscopy.<sup>10</sup> The prevalence of steatosis (defined as a hepatic triglyceride content > 5.5%) in subjects who were non-obese (BMI < 30 kg/m<sup>2</sup>) was 17%, compared with 34%

in the overall study subjects.<sup>10</sup> The prevalence was not significantly different between nonobese Caucasians and nonobese Hispanics (20% vs 26%; *P* = .12), whereas it was significantly lower in nonobese African Americans (11%).<sup>10</sup> The Multi-Ethnic Study of Atherosclerosis reported that the prevalence of nonobese NAFLD (BMI < 30 kg/m<sup>2</sup>), as assessed by computed tomography, was 11%, including 9% among Caucasians, 6% among African Americans, and 18% among Hispanic Americans.<sup>11</sup>

The most generalizable data to the US population may come from the National Health and Nutrition Examination Survey (NHANES). Based on the NHANES III data collected from 1988 to 1994, 2 studies reported the prevalence of ultrasonography-detected hepatic steatosis to be 7% (moderate-severe hepatic steatosis)<sup>12</sup> and 21% (mild-severe hepatic steatosis)<sup>13</sup> among lean (BMI < 25 kg/m<sup>2</sup>) participants without evidence of other liver disease. When the data were re-analyzed using a BMI cut-off value of 30 kg/m<sup>2</sup>, the prevalence increased to 27% (unpublished data). Finally, a northern Italian study (the Dionysus Study) used ultrasonography to determine steatosis in 257 subjects.<sup>14</sup> The prevalence of lean

**Table 1.** Prevalence of Lean NAFLD and Nonobese NAFLD

Study	Population	N	Detection	BMI cut-off value, kg/m <sup>2</sup>	Prevalence	
					Nonobese NAFLD	NAFLD
<b>Western</b>						
<b>Lean NAFLD</b>						
Bellentani et al, <sup>14</sup> 2000	Italy, community-based (nonobese)	257	US	<25	16.4%	
Kim and Kim, <sup>13</sup> 2012	US population-based (NHANES III)	11,277	US	<25	21.2%	34.0%
<b>Nonobese NAFLD</b>						
Browning et al, <sup>10</sup> 2004	US population-based (The Dallas Heart Study)	2287	MRS	<30	16.7%	31%
Foster et al, <sup>11</sup> 2013	US, population-based (MESA)	3056	CT	<30	11.3%	17.0%
<b>Eastern</b>						
<b>Lean NAFLD</b>						
Fan et al, <sup>22</sup> 2005	China, population-based	3175	US	<23	3.3%	20.8%
Das et al, <sup>8</sup> 2010	India, community-based	1911	US, liver biopsy	<23	5.1% (lean)	8.7% (0.2% cirrhosis)
Sinn et al, <sup>16</sup> 2012	Korea, community-based (nonobese, nondiabetic)	5878	US	<25	6.9% (nonobese)	
				≥18.5, <23	16.0% (lean)	
				≥18.5, <25	27.4% (nonobese)	
<b>Nonobese NAFLD</b>						
Omagari et al, <sup>20</sup> 2002	Japan, community-based (nonobese, nondiabetic)	3432	US	<25	12.5%	21.8%
Kim et al, <sup>21</sup> 2004	Korea, community-based (nonobese, nondiabetic)	768	US	18.5–24.9	16.1%	34.4% (BMI 25-30)
Chen et al, <sup>23</sup> 2006	Taiwan, population-based	3245	US	<25	4.2%	11.5%
Park et al, <sup>24</sup> 2006	Korea, community-based	6648	US	<25	9.8%	18.7%
Dassanayake et al, <sup>25</sup> 2009	Sri Lanka, population-based (Ragama Health Study)	2985	US	<25	16.7%	32.6%
Fu et al, <sup>26</sup> 2009	Taiwan, community-based (adolescents)	220	US	<85th percentile	16.0%	39.8%
Kwon et al, <sup>15</sup> 2012	Korea, community-based	29,994	US	<25	12.6%	20.1%
Xu et al, <sup>18</sup> 2013	China, community-based	6905	US	<25	7.3%	
Lankarani et al, <sup>27</sup> 2013	Iran, population-based	819	US	<25	9.2%	21.5%
Wei et al, <sup>19</sup> 2015	Hong Kong, community-based	911	MRS	<25	19.3%	28.8%

CT, computed tomography; MESA, Multi-Ethnic Study of Atherosclerosis; MRS, magnetic resonance spectroscopy; US, ultrasonography.

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