Non-obese Fatty Liver Disease

- NAFLD has been recognized as the most common liver disease in the Western world, with an estimated prevalence of 20% to 30%.

- 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.

- not all obese subjects develop NAFLD and, more importantly, NAFLD can be found in non-obese individuals.

- NAFLD may represent *a group of conditions* in which *several pathogenetic processes* may be in play that may be disparate between *obese and non-obese* patients, *despite similar* clinical *and* histopathologic presentation.

Questions

- (1) what is the clinical significance of non-obese NAFLD as a liver disease,
- (2) if non-obese NAFLD is a clinically significant condition, what are indicators to identify patients at risk?

Prevalence

- **Globally,** the reported prevalence of non-obese 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.

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recommended BMI cut-off value for Asians

- For overweight = 23 to 25 kg/m^2 (other races=25-30).
- for obesity is >25 kg/m^2, (other races > 30)

definition of non-obese NAFLD

- BMI < 30 kg/m^2 for Western studies.
- BMI < 25 kg/m^2 for Eastern studies.
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lean NAFLD

- BMI < 25 kg/m^2 for the Western studies
- BMI < 23 kg/m^2 for Eastern studies.

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Study	Population	N	Detection	BMI cut-off value, kg/m²	Nonobese NAFLD	NAFLD
Western						
Lean NAFLD						
Bellentani et al,[14] 2000	Italy, community-based (nonobese)	257	US	<25	16.4%	
Kim and Kim,[13] 2012	US population-based (NHANES III)	11,277	US	<25	21.2%	34.0%
Nonobese NAFLD						
Browning et al,[10] 2004	US population-based (The Dallas Heart Study)	2287	MRS	<30	16.7%	31%
Foster et al,[11] 2013	US, population-based (MESA)	3056	CT	<30	11.3%	17.0%
Eastern						
Lean NAFLD						
Fan et al,[12] 2005	China, population-based	3175	US	<23	3.3%	20.8%
Das et al,[8] 2010	India, community-based	1911	US, liver biopsy	<23 <25	5.1% (lean) 6.9% (nonobese)	8.7% (0.2% cirrhosis)
Sinn et al,[16] 2012	Korea, community-based (nonobese, nondiabetic)	5878	US	18.5, <23 18.5, <25	16.0% (lean) 27.4% (nonobese)	
Nonobese NAFLD						
Omagari et al,[20] 2002	Japan, community-based (nonobese, nondiabetic)	3432	US	<25	12.5%	21.8%
Kim et al,[21] 2004	Korea, community-based (nonobese, nondiabetic)	768	US	18.5–24.9	16.1%	34.4% (BMI 25-30)
Chen et al,[23] 2006	Taiwan, population-based	3245	US	<25	4.2%	11.5%
Park et al,[24] 2006	Korea, community-based	6648	US	<25	9.8%	18.7%
Dassanayake et al,[25] 2009	Sri Lanka, population-based (Ragama Health Study)	2985	US	<25	16.7%	32.6%
Fu et al,[26] 2009	Taiwan, community-based (adolescents)	220	US	<85th percentile	16.0%	39.8%
Kwon et al,[15] 2012	Korea, community-based	29,994	US	<25	12.6%	20.1%
Xu et al,[18] 2013	China, community-based	6905	US	<25	7.3%	
Lankarani et al,[27] 2013	Iran, population-based	819	US	<25	9.2%	21.5%
Wei et al,[19] 2015	Hong Kong, community-based	911	MRS	<25	19.3%	28.8%

Histology

- There are only **limited data** on the histology of non-obese NAFLD.

- morphologic features of **non-obese NAFLD** and **obesity-associated NAFLD** are presumed to be ***indistinguishable*** from each other.
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- In a **Belgian** study that included **1777** patients undergoing a ***liver biopsy*** for *chronic liver disease*, ***non-diabetic non-obese NAFLD*** (BMI < 30 kg/m^2) was found in *2.8%.*

- Of those, ***NASH*** and ***fibrosis*** were present in *61%* and *55%*, respectively, and there was *less* ***inflammation*** and ***fibrosis*** compared with obese NAFLD patients.

- There were 2 other European studies that reported the presence of *NASH* in ***50% and 65%*** of ***lean NAFLD*** patients, even when a lower BMI (<25 kg/m^2) cut-off value was used to select those patients.

- In these studies, the ***severity*** of ***inflammation*** and ***fibrosis*** *did not differ significantly* between ***non-obese NAFLD*** and ***obese NAFLD***.

A recent international study :

among 1090 patients with histology-confirmed NAFLD :

- 11.5% were lean NAFLD.
- 88.5% were overweight or obese NAFLD

- Patients with **lean NAFLD** had a **lower** degree of **steatosis** and **less** advanced **fibrosis**, but **more** severe **lobular inflammation** than the obese NAFLD

Asian studies

- also have reported that NASH *frequently* is found in non-obese NAFLD.
- In a Indian study ,NASH in **31%** and cirrhosis in **2.4%** among lean-NAFLD patients .
- Another study from Bangladesh ,**NASH** (53% vs 47%) and **fibrosis** (20% vs 19%) was *similar* between patients with ***non-obese NAFLD*** and those with ***obese NAFL***D.
- A Chinese study , transient elastography showed that **2.6%** of non-obese NAFLD patients and **5.1%** of obese-NAFLD patients had *suspected advanced fibrosis* , although ***liver stiffness*** was **slightly lower** in non-obese NAFLD patients (4.6 vs 5.6 kPa; $P < .001$).

Asian studies

- In a **histology-based** study , *non-obese NAFLD* had a **lower** *steatosis* grade ,*hepatocellular ballooning* compared with obese NAFLD.

- no difference in the histologic severity of NASH or fibrosis .

Risk Factors for Non-obese Fatty Liver Disease

- Features of the **metabolic syndrome** commonly associated with **obesity** *do not affect all obese* **individuals**, sparing approximately *10% to 30%.*

- These **metabolic healthy** but obese patients, despite having ***excessive body fat***, have normal blood pressure and glucose metabolism, a favorable lipid profile, and low visceral and hepatic fat.

- On the opposite end of the ***spectrum***, some individuals with a normal BMI have *metabolic abnormalities* similar to those characteristically *associated with obesity.*
- This subset of patients is called metabolically obese but normal weight (MONW), and show metabolic profiles characteristic of insulin resistance.

- The WHO recommends BMI as a *surrogate marker* for ***physiological changes*** accompanying excess weight and obesity.

- impact of obesity **varies widely** at a given BMI , because factors such as age, sex, ethnicity, **diet**, and **genetics** play an important pathophysiological role in determining the metabolic abnormalities associated with obesity.

- Clearly, BMI is a **crude marker** of *adiposity* compared, for example, with reference tests such as *dual energy X-ray* absorptiometry

- BMI also *fails* to address body fat distribution.
- Specifically, visceral abdominal adiposity, which is associated with the metabolic syndrome, is thought to be a key link to NAFLD.
- So, common anthropometric measurements such as the waist circumference may *not be sufficient* in assessing metabolic risks, it may not distinguish visceral vs subcutaneous adipose tissue.

- **Visceral adipose** tissue accounts for only **7% to 15%** of total body fat; however, it plays a far more important role than subcutaneous fat in the *pathogenesis of insulin resistance*.

- Portal venous blood contains **free fatty acids** and **cytokines** secreted by **visceral adipose** tissue, which is thought to drive the development of NAFLD.

- body fat distribution ***rather than*** *total body fat content* may be much ***more important*** in the development of *non-obese NAFLD.*

- Visceral adipose tissue area was associated with incident non-obese NAFLD in a *dose-dependent manner*.

- significant inverse association between ***non-obese NAFLD*** and the **subcutaneous adipose** tissue area independent of visceral adiposity.

- subcutaneous fat is that it **may act** as **a reservoir** for metabolically neutral surplus lipids and **might protect** subjects *against nonobese NAFLD* by *storing away excess calories.*

- When **subcutaneous** adipose tissue storage becomes **saturated**, fat deposits occur in other areas such as **visceral adipose** tissue and hepatocytes.

- Recently, sagittal abdominal diameter (SAD) has been proposed as an anthropometric indicator for visceral adiposity.
- SAD is measured by the anteroposterior diameter of the abdomen in the supine position, which *displaces subcutaneous fat laterally by gravity*.

- ***SAD*** may have a *stronger correlation* with *visceral adiposity* than ***BMI*** or ***waist circumference,*** particularly among *non-obese* (*BMI < 25 kg/m²*) and *younger* (*age <50 y*) subjects *compared* with *older obese subjects.*

- *In contrast*, waist circumference may be **better** correlated with *subcutaneous adiposity* than with *visceral adiposity*.

- is SAD is superior to other anthropometric measures in predicting visceral obesity in non-obese NAFLD?

- Asians **generally** have a **higher percentage** of *body fat* and *visceral fat* (skinfold thickness) **compared with** people of **other races** of the same age, sex, and even BMI.

- ***Lower BMI cut-off*** values have been suggested for the ***definition of metabolic syndrome*** in *Asian* individuals **because** of *higher total body* and *visceral* fat at any given BMI compared with those of other races.

Metabolic Risk Factors

- metabolic **risk factors** associated with insulin resistance are relevant for non-obese NAFLD **as they** are for obese NAFLD.
- Kwon et al suggested that the association with components of metabolic syndrome was ***stronger*** ***for*** ***non-obese NAFLD*** than for ***obese NAFLD***.
- non-obese NAFLD had **higher** adjusted prevalence ratios for certain components (high TG levels for both genders, high BP, impaired fasting glucose level, and low HDL cholesterol for women) of metabolic syndrome than those with obese NAFLD.

- Finally, several cohort studies have shown an association between weight gain within a non-obese BMI range and an incident non-obese NAFLD.
- **weight gain** is an *independent predictor* of development of NAFLD at the 7-year follow-up evaluation.

Table 3. Risk Factors for Nonalcoholic Fatty Liver Disease in the Nonobese

Study	Region	Risk factors for nonobese NAFLD
Omagari et al,[20] 2002	Japan, community-based (nonobese, nondiabetic)	Triglyceride, fasting glucose, percentage body fat
Kim et al,[21] 2004	Korea, community-based (nonobese, nondiabetic)	Male, waist circumference, triglyceride, HOMA (<23), age, BMI, HOMA (23–25)
Chen et al,[23] 2006	Taiwan, population-based	Age, ALT, triglyceride
Das et al,[8] 2010	India, community-based	BMI, biceps skin-fold thickness (BMI < 25)
Kim and Kim,[13] 2012	US, population-based (nonobese)	Waist circumference, diabetes, HDL cholesterol
Sinn et al,[16] 2012	Korea, community-based (nonobese, nondiabetic)	Age, HOMA, triglyceride, HDL cholesterol, waist circumference, overweight (BMI > 23), ALT, uric acid, metabolic syndrome
Wei et al,[19] 2015	Hong Kong, community-based	BMI, waist circumference, glycated hemoglobin, HOMA-IR, ferritin, PNPLA3 polymorphism

Dietary Composition

- studies suggest that a high cholesterol diet is linked to non-obese NAFLD.

- although dietary intake of total energy, fat (including polyunsaturated fatty acids), and carbohydrates was markedly higher in obese NAFLD patients

- cholesterol intake was significantly higher in nonobese NAFLD patients than their obese NAFLD counterparts.[71,72]

- High cholesterol intake may cause nonobese NAFLD, even when the total caloric intake may **not be excessive.**

- There has **not** been a **dietary intervention study to** lower cholesterol intake for the treatment of non-obese NAFLD.

- Cholesterol absorption inhibitors, such as ezetimibe, may reduce **liver injury** in noN-obese NAFLD (In obese NASH patients, ezetimibe can not significantly reduce liver fat).

Fructose ingestion

- Consumption of soft drinks with added sugar, especially *corn syrup fructose,* has been linked to NAFLD.

- NAFLD patients consumed almost twice the amount of soft drinks as controls.

- non-obese NAFLD occurs at a younger age than obese-NAFLD .

- young adults tend to consume more soft drinks than older adults, fructose ingestion may play a larger role in patients with non-obese NAFLD than in obese NAFLD

Genetic Risk Factors

- Although visceral obesity, dietary preference, and insulin resistance are *the most prevalent risk factors* for **non-obese NAFLD**, **hepatic fat** varies ***substantially among*** subjects with equivalent adiposity, indicating that *other factors* contribute to non-obese NAFLD.

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- Intrafamilial aggregation and interethnic variations in susceptibility suggest that genetic factors may be important in nonobese NAFLD.

- a variant allele (rs738409) of palatin-like phospholipase domain-containing 3 (PNPLA3) was associated **strongly** with *hepatic triglyceride* content.

- The variant is associated **not only** with hepatic fat accumulation **but also** with susceptibility to *more aggressive forms of NAFLD*, such as NASH, fibrosis, and HCC.

cholesteryl ester transfer protein (CETP)

- may be important in the pathogenesis of NAFLD.
- CETP plays a **critical role** in reverse cholesterol transport, the process by which cholesterol moves from peripheral tissue back to the liver.

- risk of NAFLD associated with the CETP polymorphisms was most pronounced in non-obese individuals.
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Prognosis:

- Prognosis of non-obese NAFLD have been **scarce until now**.

- a *higher overall mortality* than patients with obese NAFLD ,over a follow-up period of 11 years, despite presenting with a healthier metabolic profile such as lower insulin resistance.

Treatment

- weight loss with lifestyle modification.
- *loss of at least 3% to 5%* of body weight may be **necessary** to improve nonobese NAFLD.

In Asian patients whose mean BMI was 25 kg/m²

- 97% of patients who ***lost more than 10%*** of their body weight achieved resolution of NAFLD,
- #40% of patients with a ***3% to 5%*** weight loss of their body weight did.
- A study showed that improvement in liver histology from **weight reduction** by **lifestyle modification** was similar between potential living liver donors with non-obese NAFLD and those with obese NAFLD.
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- increased physical activity is an important component of lifestyle modification in patients with non-obese NAFLD irrespective of visceral obesity or insulin resistance.

Conclusions

- Non-obese NAFLD occurs in **children** and **adults** of all ethnicities, although it appears to be ***more common*** among Asians.

Likely risk factors for non-obese NAFLD :

- **visceral** instead of general obesity,
- **body weight gain** even within normal weight limits,
- **high fructose** and **high cholesterol** intake,
- **genetic** risk factors (eg, PNPLA3).

- prevalence of NASH and advanced fibrosis does *not* differ ***significantly*** between non-obese NAFLD and obese NAFLD.

- Although the ***natural history*** of non-obese NAFLD has *not* been studied widely, it is important to identify individuals ***at risk for nonobese NAFLD***, who lack the easily recognizable phenotype of obesity.

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- Currently, lifestyle modification, including diet and physical activity targeting visceral adiposity, remains the *mainstay in the management* of patients with non-obese NAFLD,
- pharmaceutical agents being studied for NAFLD in general also may be effective for non-obese NAFLD in the future.