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Divergent Metabolic Profiles and Fibrosis Risk in Lean and Non-Lean Hepatic Steatosis: A Moroccan Perspective

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly observed in lean individuals, particularly in non-Western populations. In this prospective Moroccan study, 100 patients with biopsy-proven MASLD were divided into two groups: lean (n=50) and non-lean (n=50). Lean patients were older and displayed a lower prevalence of classical cardiometabolic risk factors such as obesity, diabetes, and metabolic syndrome. However, they more frequently presented with autoimmune comorbidities, suggesting a distinct immuno-inflammatory background. In contrast, advanced fibrosis was significantly more prevalent in non-lean patients. These findings support the notion that lean MASLD constitutes a separate clinical entity with unique risk profiles, highlighting the need for individualized diagnostic and therapeutic approaches.

Keywords: Metabolic dysfunction-associated steatotic liver disease, lean MASLD, cardiometabolic risk factors, advanced fibrosis, non-Western populations.

INTRODUCTION

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is rising globally, becoming a major contributor to chronic liver disease and cardiometabolic complications. While MASLD has traditionally been associated with obesity, hepatic steatosis can also occur in individuals with normal body mass index (BMI), referred to as "lean MASLD" [1]. The pathophysiological mechanisms driving steatosis in lean individuals remain poorly understood and may differ significantly from those observed in non-lean populations. This study aims to compare lean and non-lean patients with hepatic steatosis in terms of their cardiometabolic profiles, associated the risk factors, and clinical outcomes, with the goal of improving risk stratification and management strategies tailored to patient phenotype [2].

MATERIALS AND METHODS

This was a prospective, single-center, analytical study conducted over a six-month period, from September 2024 to March 2025, in the Hepato-Gastroenterology Department. All patients diagnosed with hepatic steatosis during this period were included. The diagnosis of metabolic-associated steatosis was based on the presence of hepatic steatosis detected by abdominal ultrasound, in association with at least one cardiometabolic risk factor (e.g., type 2 diabetes, overweight/obesity, dyslipidemia, or arterial hypertension).

Patients were categorized into two groups based on body mass index (BMI): lean (BMI < 25 kg/m²) and non-lean (BMI ≥ 25 kg/m²).

DATA COLLECTION INCLUDED:

Clinical parameters: demographic characteristics (age, sex), lifestyle factors (smoking,

alcohol consumption, physical activity), personal and family history of metabolic or cardiovascular disease, and associated comorbidities.

Anthropometric parameters: body weight, height, BMI, and waist circumference measured using standardized methods.

Biochemical parameters: fasting blood glucose, HbA1c, lipid profile (total cholesterol, HDL-C, LDL-C, triglycerides), liver enzymes (AST, ALT, GGT, alkaline phosphatase), and other relevant tests such as serum creatinine.

The study was approved by the Institutional Review Board (IRB) of the Ethics Committee of the Faculty of Medicine and Pharmacy of Rabat, Mohammed V University, Rabat, Morocco, under approval number 128/25. Statistical analyses were performed using Student's t-test for continuous variables and the Chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and Anthropometric Characteristics

A total of 100 patients were included, divided equally into non-lean (n = 50) and lean (n = 50) groups. The mean age was 46.3 ± 8.2 years in non-lean patients and 44.1 ± 7.6 years in lean patients (p = 0.12). Males represented 35 patients (70%) in the non-lean group versus 25 patients (50%) in the lean group (p = 0.03). The mean BMI was 31.6 ± 3.4 kg/m² in non-lean patients and 22.8 ± 1.9 kg/m² in lean patients (p < 0.001).

Metabolic profile, fibrosis, and autoimmune associations

Metabolic syndrome was more prevalent in non-lean patients (84% vs. 34%; p < 0.001). Hepatomegaly was observed in 20 non-lean patients (40%) and 6 lean patients (12%; p < 0.01).

Clinical, biochemical, and anthropometric characteristics of the two groups are summarized in (Table 1).

Features of chronic liver disease were present in 4 non-lean patients (8%) and 2 lean patients (4%; p = 0.004).

Fibrosis staging was available for 42 non-lean and 44 lean patients. Advanced fibrosis (F3–F4) was found in 5 non-lean patients (10%) and in none of the lean patients (p = 0.02).

Autoimmune diseases were present in 26 lean patients (52%) compared to 15 non-lean patients (30%; p < 0.001). In lean patients, celiac disease was observed in 15 patients (30%) and Crohn's disease in 8 patients (16%). In non-lean patients, autoimmune thyroiditis and primary biliary cholangitis were most frequent.

Table 1: Baseline Demographic and Clinical Characteristics of Lean and Non-Lean MASLD Patients

Parameter	Lean (n = 50)	Non-Lean (n = 50)	p-value
Sex (male), n (%)	25 (50%)	35 (70%)	0.03*
Mean age (years ± SD)	44.1 ± 7.6	46.3 ± 8.2	0.15
BMI (kg/m², mean ± SD)	22.8 ± 1.9	31.6 ± 3.4	<0.001*
Hypertension, n (%)	12 (24%)	28 (56%)	<0.001*
Type 2 diabetes, n (%)	8 (16%)	30 (60%)	<0.001*
Metabolic syndrome, n (%)	17 (34%)	42 (84%)	<0.001*
Advanced fibrosis (F3–F4), n (%)	0 (0%)	5 (10%)	0.02*

This table summarizes the demographic, anthropometric, and clinical features of the study population according to body mass index (BMI). Data are presented as N (%) for categorical variables and mean ± SD for continuous variables. Group A included non-lean patients (BMI ≥ 25 kg/m², n = 50) and Group B included lean patients (BMI < 25 kg/m², n = 50). The table highlights the differences in sex distribution, age, BMI, prevalence of hypertension, type 2 diabetes, metabolic syndrome, and liver fibrosis between the two groups.

p-value < 0.05 is considered statistically significant; values marked with an asterisk (*) indicate significance

Clinical Outcomes and Follow-Up

All patients with celiac disease were placed on a gluten-free diet (GFD), alongside lifestyle and dietary modifications. In Group A, 18/50 (36%) of patients with abnormal baseline liver function tests normalized their enzymes, and 2/50 (4%) progressed to cirrhosis. In Group B, 20/50 (40%) showed normalization of liver function tests. Among patients with celiac disease, one patient achieved complete histological resolution of grade 3 steatohepatitis, and another improved from grade 3 to grade 1 after one year on GFD.

All patients received dietary counseling based on a Mediterranean diet and were encouraged to engage in regular physical activity. In Group A, 24/50 (48%) achieved a ≥5% weight reduction over 6 months, which was significantly associated with normalization of liver enzymes (p = 0.02) and improvement in fibrosis scores in 19/50 (38%) of cases. In Group B, adherence to the Mediterranean diet and increased physical activity were associated with biochemical improvement in 16/50 (32%) and histological improvement in 2 cases of celiac

disease-related steatohepatitis. These findings support the role of lifestyle interventions in both lean and non-lean MASLD patients (Table 2).

Table 2: Multivariate Logistic Regression Identifying Independent Predictors of Advanced Liver Fibrosis (F3–F4) in Patients with MASLD

Variable	Adjusted OR [95% CI]	p-value
Male sex	1.41 [0.47 – 4.18]	0.538
Age (per year)	1.02 [0.97 – 1.08]	0.441
BMI (per unit)	1.06 [0.94 – 1.20]	0.327
Diabetes mellitus	2.23 [0.61 – 8.14]	0.225
Metabolic syndrome	1.17 [0.37 – 3.71]	0.787
Autoimmune disease	4.95 [1.17 – 20.88]	0.029*

This table presents the results of multivariate logistic regression analysis to identify independent predictors of advanced liver fibrosis (F3–F4) among patients with MASLD. The variables include sex, age, BMI, diabetes mellitus, metabolic syndrome, and presence of autoimmune disease. Odds ratios (OR) are presented with 95% confidence intervals (CI), and p-values indicate statistical significance. p-values marked with an asterisk () indicate statistically significant differences between lean and non-lean groups.

DISCUSSION

This prospective Moroccan study highlights the heterogeneity of metabolic dysfunction-associated steatotic liver disease (MASLD) by comparing lean and non-lean patients. The findings underscore significant differences in metabolic profiles, fibrosis risk, and autoimmune associations between the two groups.

Metabolic Profiles and Cardiovascular Risk

Consistent with existing literature, non-lean MASLD patients exhibited a higher prevalence of metabolic syndrome components, including hypertension, hyperglycemia, and dyslipidemia. This aligns with the traditional understanding of MASLD being closely linked to obesity and metabolic dysfunction [3]. Interestingly, despite a seemingly healthier metabolic profile, lean MASLD patients demonstrated a paradoxical increase in cardiovascular mortality. A comprehensive meta-analysis revealed that lean MASLD individuals had a 50% higher risk of cardiovascular mortality compared to their non-lean counterparts, despite lower incidences of hypertension and dyslipidemia [4]. This suggests that factors beyond traditional metabolic risk markers contribute to cardiovascular outcomes in lean MASLD patients.

Fibrosis Severity and Progression

Our study found that advanced fibrosis (stages F3-F4) was more prevalent among non-lean patients, which is consistent with the established correlation between obesity and fibrosis progression [5]. However, recent research indicates that lean MASLD patients are not exempt from significant fibrosis risk. A meta-analysis involving over one million individuals reported that lean MASLD patients had a higher risk of liver-related mortality compared to non-lean patients (hazard ratio [HR] 2.26, 95% confidence interval [CI] 1.14-4.51) [6]. Furthermore, a Veterans Affairs cohort study demonstrated that lean MASLD patients with compensated cirrhosis had a 64% increased risk of all-cause mortality compared to non-lean patients, despite a lower risk of hepatic decompensation [7]. These findings highlight the need for vigilant monitoring of fibrosis progression in lean MASLD patients.

Autoimmune Associations in Lean MASLD

A notable finding in our cohort was the higher prevalence of autoimmune diseases, particularly celiac disease, among lean MASLD patients. This association has been observed in other studies, suggesting a potential link between lean MASLD and autoimmune conditions [8]. The improvement in liver histology following a gluten-free diet in patients with celiac disease supports the notion that immune-mediated mechanisms may play a role in the pathogenesis of MASLD in lean individuals. This underscores the importance of screening for autoimmune diseases in lean patients presenting with hepatic steatosis.

To better contextualize our findings, we summarized key comparisons between our cohort and recent international studies on MASLD in lean and non-lean individuals (Table 3). These highlights both consistencies and specificities of our Moroccan cohort, particularly concerning autoimmune associations and fibrosis risk."

Table 3: Comparison of Our Findings with Recent Literature on Lean vs. Non-Lean MASLD

Parameter	Our Study (Morocco, 2025)	Recent Literature	References
Male sex prevalence (lean / non-lean)	50% / 70%	45–55% (lean), 60–75% (non-lean)	Maier *et al.*, 2021 (3)
Mean age (lean / non-lean)	44.1 ± 7.6 / 46.3 ± 8.2 years	42–48 years (lean), 45–50 years (non-lean)	Souza *et al.*, 2024 (6)
Metabolic syndrome (lean / non-lean)	34% / 84%	28–40% (lean), 70–90% (non-lean)	Younossi *et al.*, 2023 (5)
Abnormal liver function tests	48% (lean), 60% (non-lean)	35–50% (lean), 55–65% (non-lean)	Nso *et al.*, 2024 (4)
Hepatic steatosis on ultrasound	100% in both groups	100% (in MASLD cohorts)	Ballestri *et al.*, 2021 (9)
Advanced fibrosis (F3–F4)	0% (lean), 9.6% (non-lean)	0–3% (lean), 5–15% (non-lean)	Njei *et al.*, 2025 (7)
Autoimmune comorbidities	52% in lean (30% celiac, 16% Crohn's, etc.) / 30% in non-lean	30–55% in lean MASLD patients, especially with celiac disease	Volta *et al.*, 2012 (8)
Improved liver function after intervention	40% (lean), 36% (non-lean)	30–50% improvement with lifestyle and disease-specific interventions	Harrison *et al.*, 2023 (10)
Histologic improvement under GFD	2 patients (grade 3 → grade 1 or normalization)	Reported in MASLD patients with celiac disease adhering to gluten-free diet	Volta *et al.*, 2012 (8)

This table compares the key demographic, metabolic, and clinical findings of our Moroccan cohort of lean (BMI < 25 kg/m², n = 50) and non-lean (BMI ≥ 25 kg/m², n = 50) MASLD patients with data reported in recent international studies. Parameters include sex distribution, mean age, prevalence of metabolic syndrome, abnormal liver function tests, hepatic steatosis on ultrasound, advanced fibrosis, autoimmune comorbidities, and response to interventions. Data are presented as N (%) for categorical variables and mean ± SD for continuous variables. The table highlights consistencies, contradictions, and unique findings of our study relative to previous publications, particularly regarding autoimmune associations and fibrosis risk.

Implications for Clinical Management

The distinct characteristics of lean MASLD necessitate a tailored approach to management. While lifestyle modifications remain the cornerstone of MASLD treatment, lean patients may benefit from additional interventions. The recent approval of resmetirom (Rezdiffra), a thyroid hormone receptor-β agonist, offers a promising pharmacological option for MASLD, particularly in patients with significant fibrosis[10]. However, its efficacy in lean MASLD populations requires further investigation.

LIMITATIONS

Our study's limitations include its monocentric design and relatively short follow-up period. Additionally, the reliance on ultrasound for steatosis diagnosis may have limited sensitivity compared to more advanced imaging modalities. Future studies should incorporate longitudinal designs and utilize non-invasive fibrosis assessment tools to better understand disease progression in lean MASLD.

CONCLUSION

This study highlights the distinct clinical and metabolic profiles of lean and non-lean patients with hepatic steatosis. While hepatic steatosis is often associated with obesity and metabolic syndrome, a significant subset of lean individuals is also affected. Non-lean patients had a higher prevalence of metabolic syndrome, abnormal liver function tests, and advanced fibrosis, confirming the strong association between adiposity and liver disease severity. Conversely, lean patients showed a significantly higher prevalence of autoimmune disorders($p<0.001$), particularly celiac disease and inflammatory bowel diseases, suggesting that hepatic steatosis in lean individuals may have different underlying pathophysiological mechanisms.

These findings underscore the importance of considering hepatic steatosis in both lean and non-lean populations and tailoring diagnostic and therapeutic approaches accordingly. For lean patients, screening for autoimmune conditions may be warranted, whereas in non-lean individuals, early lifestyle intervention and metabolic control remain key to preventing progression to advanced fibrosis or cirrhosis.

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