

Better Beta-cell Function despite Insulin Resistance and Less Fibrosis Characterizes Nonalcoholic Fatty Liver Disease in Lean Subjects

Abstract

Introduction: Information, particularly on insulin resistance (IR) and histological pattern, about nonalcoholic fatty liver disease (NAFLD) in lean subjects (NAFLD-L) is still insufficient, in contrast to NAFLD in overweight/obese subjects (NAFLD-O). NAFLD-L was evaluated and compared against NAFLD-O for IR in a community cohort (CC) and both IR and liver histology in a tertiary cohort (TC). **Materials and Methods:** The present cross-sectional study was done simultaneously in the CC ($n = 425$) of “Population Health and Demographic Surveillance project” and TC ($n = 276$) belonging to the same healthcare referral hierarchy, without any comparison between them. Both the cohorts underwent evaluation, including transient elastography and dual-energy X-ray absorptiometry. Frequently sampled intravenous glucose tolerance test (FSIVGTT) for IR and beta-cell function (BCF), and liver histology were done in TC only. **Results:** NAFLD-L, in comparison to NAFLD-O, had a higher amount of android fat relative to gynoid (android/gynoid fat ratio) (median 1.38 vs. 1.22, respectively, $P = 0.03$), similar IR (by FSIVGTT) (median 2.47 vs. 2.18 mM.mu/l*2, respectively, $P = 0.76$) and better BCF (median 90.46 vs. 86.63 mu/mM, respectively, $P = 0.03$). Higher fibrosis stages/cirrhosis were detected only in NAFLD-O. NAFLD-L and NAFLD-O had similar prevalence of “definite nonalcoholic steatohepatitis” (14% vs. 11%, respectively, $P = 0.08$). **Conclusion:** Similar IR and NASH prevalence in NAFLD-L and NAFLD-O suggest uniform pathophysiology. The metabolic advantage of having better BCF could have been negated by preferential accumulation of more insulin-resistant android fat in NAFLD-L.

Keywords: Beta-cell function, fatty liver, insulin resistance, lean, metabolic dysfunction, steatohepatitis

Introduction

Classically nonalcoholic fatty liver disease (NAFLD) in overweight/obese people (NAFLD-O) is associated with excess and dysfunctional body fat along with varying degrees of insulin resistance (IR). However, NAFLD in lean subjects (NAFLD-L), previously regarded as an outlier, is an emerging yet understudied health concern.^[1-4] Registry-based retrospective data, defining leanness ignoring waist circumference (WC), predominant use of “homeostatic model assessment for IR” (HOMA-IR) for assessment of IR, and heterogeneous histological data lead to an incomplete understanding of NAFLD-L against NAFLD-O.^[5-7] Toward resolving this issue, the recent Delphi consensus on fatty liver (FL) disease acknowledged the “metabolic dysfunction” as the central pathophysiological

mechanism and renamed it as “metabolic dysfunction-associated steatotic liver disease (MASLD)” irrespective of anthropometric diversity.^[8] However, ambiguity on “metabolic dysfunction” still remained as the consensus on this issue did not reach “supermajority” defined as more than 67% uniformity in opinion.^[8] This keeps the road to explore the pattern of metabolic dysfunction open, more so in NAFLD-L. We worked with the traditional nomenclature of NAFLD as our study was conducted before this Delphi consensus.

Indian population, having anthropometric uniqueness with dominance of leanness along with rising prevalence of obesity, represents a natural resource for studying NAFLD-L and comparison with NAFLD-O.^[9] Focused national program for NAFLD recently adopted by India shows the necessity to consider NAFLD a public health concern in countries like India where obesity and leanness coexist.^[10]

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Kausik Das¹,
Anamitra Barik²,
Souveek Mitra³,
Ranajoy Ghosh⁴,
Rajesh Kumar Rai²,
Partha S. Mukherjee³,
Abhijit Chowdhury⁵

¹Department of Hepatology, School of Digestive and Liver Disease, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India, ²Health and Demographic Surveillance Body, Suri, West Bengal, India, ³John C. Martin Centre for Liver Research and Innovation (jcmli.edu.in), Indian Institute of Liver and Digestive Sciences, Kolkata, West Bengal, India, ⁴Division of Gastrointestinal and Liver Pathology, School of Digestive and Liver Disease, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India, ⁵Division of Disease Biology, John C. Martin Centre for Liver Research and Innovation (jcmli.edu.in), Indian Institute of Liver and Digestive Sciences, Kolkata, West Bengal, India

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Address for correspondence:

Prof. Kausik Das,
Department of Hepatology,
School of Digestive and Liver
Disease, Institute of Post
Graduate Medical Education
and Research, 244, A. J. C.
Bose Road, Kolkata - 700 020,
West Bengal, India.
E-mail: kausikdasmal@gmail.
com

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We have recently explored the risk of significant NAFLD related to “metabolic unhealthiness” in a leanness-dominant community.^[11] The present study was subsequently performed using two extreme ends of a healthcare hierarchy serving the same ethnic–geographic territory: the community cohort (CC), the peripheral part of the hierarchy, and a tertiary cohort (TC), the apex of the hierarchy. Our objective was to study NAFLD-L compared against NAFLD-O (a) to understand the characteristics of NAFLD-L, including IR in the community, using CC, and (b) to understand the IR and histological characteristics of NAFLD-L using TC who were regarded to have significant disease necessitating referral to tertiary health care.

Materials and Methods

Study design

Our cross-sectional study was done in CC and TC, two nonoverlapping cohorts belonging to the same healthcare hierarchy and geographic territory, without any comparison between them. This ensured ethnic and cultural homogeneity, avoiding potential confounding influences of lifestyle and dietary practice [Figure 1]. CC was selected from free-living population of a “health and demographic surveillance system (HDSS)” of Birbhum Population project (BIRPOP) (<https://www.shds.co.in/about-birpop/>) in West Bengal, India.^[12] TC was recruited from patients attending two hierarchical referral hospitals for liver disease, Hepatology Outpatient Departments of the School of Digestive and Liver Disease, Institute of Post Graduate Medical Education and Research (IPGMER), Kolkata, India, and the Indian Institute of Liver and Digestive Diseases (IILDS), Sonarpur, Kolkata, India. Evaluation was done using a uniform protocol [Figure 1]. The study was performed in two consecutive phases: community-based work in CC in the first phase (November 2016 to October 2017) and tertiary-care evaluation in TC in the second phase (February 2018 to January 2019).

Study subjects

CC was selected from 351 villages (12,557 households/54,583 persons) under “BIRPOP” HDSS.^[12] A 1:3 systematic sampling in subjects aged ≥ 18 years ($n = 36638$) yielded 12,214 subjects, 57% ($n = 6984$) of whom consented. Finally, 88% ($n = 6134/6984$) of responders were evaluated. Subjects with NAFLD ($n = 425$) constituted the CC and were analyzed [Figure 1]. Subjects with biopsy-proven NAFLD ($n = 276$), selected from the consecutive patients ($n = 315$) referred with a diagnosis of NAFLD to the said tertiary care facilities, constituted TC [Figure 1]. Each subject provided informed consent.

Evaluation

Community subjects were surveyed by trained field surveyors with a minimum of 3 years of experience in large-scale surveys and anthropometric assessments, supervised by investigators. Transient elastography (TE) for liver stiffness measure (LSM)/controlled attenuation parameter (CAP), dual-energy X-ray absorptiometry (DEXA) for body fat distribution, and blood sampling were done in subjects with ultrasound diagnosis of FL/NAFLD ($n = 425$ and 305 in community and tertiary care, respectively) within 1 week of enrollment. Tertiary care NAFLD subjects ($n = 305$) underwent additional detailed evaluation for IR and beta-cell function (BCF) with “frequently sampled intravenous glucose tolerance test” (FSIVGTT) and standard indication-driven liver biopsy (LB) within 1 week of inclusion. Indications for LB were (a) elevated LSM by TE (>7 kPa) suggesting $>F0$ fibrosis, (b) presence of metabolic syndrome (MS) as per definition provided, (c) elevated liver enzyme alanine aminotransferase (ALT) more than 1.5 times the defined upper limit of normal (ULN), and (d) NAFLD fibrosis score >0.676 .^[13,14]

Study tools

FL was assessed on ultrasound using standard definition.^[15] TE was performed with FibroScan® (Echosense, Paris) using standard protocol.^[16] DEXA (model iDXA, GE LUNAR 17) images were analyzed using enCORE software version 18 (GE Medical Systems Lunar, Madison, Wisconsin, USA) for total body/android/gynoid fat and lean body mass (kg). The Android/gynoid fat mass ratio was calculated.^[17] Minimal model (MINMOD) protocol with “MinMod software” (MINMOD Millennium Inc., Pasadena, CA, USA) was used for FSIVGTT to get IR ($\text{mM} \cdot \text{mu}/\text{l} \cdot 2$) and BCF (mu/mM).^[18] HOMA, updated version 2 (HOMA2), the computer-based nonlinear model, for IR (HOMA2-IR) and for BCF (HOMA2-Beta), closely paralleling FSIVGTT, was computed using the HOMA2 calculator, version 2.2.3, provided by the University of Oxford, Diabetes Trials Unit (<https://www.rdm.ox.ac.uk/about/our-clinical-facilities-and-mrc-units/DTU/software/homa/download>; accessed on December 17, 2020).^[19]

Definitions

- NAFLD definition: Presence of FL on ultrasound and/or $>5\%$ steatosis on histology along with absence of significant alcohol intake (<20 g/day for women and <30 g/day for men for the previous 2 years) and other causes of steatosis.^[13,14]
- Anthropometry: Body mass index (BMI) categories specific for Asians, i.e. $\leq 22.9/23-27.5/>27.5$ kg/m^2 , were taken as normal weight/overweight/obese, respectively.^[20] Abdominal obesity (AO) was defined using WC cutoff for South Asians ($\geq 90/\geq 80$ cm in male/female).^[20] Subjects having BMI ≤ 22.9 kg/m^2 with no AO were

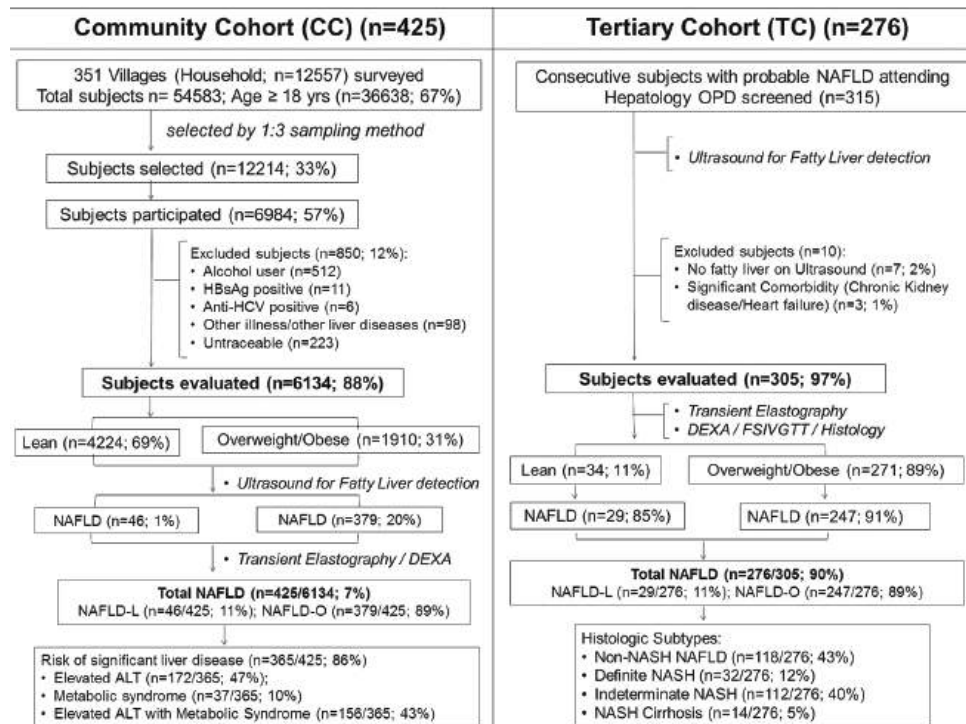


Figure 1: Study flow diagram showing evaluation of community and tertiary cohorts. Lean subjects had a body mass index (BMI) ≤ 22.9 kg/m² and had no abdominal obesity. Overweight/obese subjects had a BMI >23 kg/m². NAFLD: Nonalcoholic fatty liver disease, NAFLD-L: NAFLD in lean subjects, NAFLD-O: NAFLD in overweight/obese subjects, OPD: outpatient department, DEXA: Dual-energy X-ray absorptiometry, FSIVGTT: Frequently sampled intravenous glucose tolerance test, NASH: Nonalcoholic steatohepatitis

defined as lean and ≥ 23 kg/m², irrespective of WC, as overweight/obese. Lean and overweight/obese subjects with NAFLD were categorized as NAFLD-L and NAFLD-O, respectively

- Biochemical and metabolic dysfunctions: ULN for ALT was taken as 30 and 19 U/L for male and female, respectively.^[12] Impaired fasting glucose, diabetes, MS, dyslipidemia, and hypertension were defined according to the modified form of the National Cholesterol Education Program Adult Treatment Panel criteria^[14]
- Histological definitions: Histological findings and subtypes were defined as per the nonalcoholic steatohepatitis clinical research network (NASH-CRN) and liver forum case definitions working group descriptions, respectively.^[21,22] Steatosis was graded as S0 ($<5\%$)/S1 ($5\%-33\%$)/S2 ($33\%-66\%$)/S3 ($>66\%$). Lobular inflammation ($\text{nil}/<2/2-4/>4$ foci per $20\times$ field) was graded as A0/A1/A2/A3, respectively. NAFLD activity score (NAS) was calculated.^[21] Fibrosis stages (F0/F1A/F1B/F1C/F2/F3/F4) were assessed. Histological subtypes, as defined by “Liver Forum Case Definitions Working Group”, were “non-NASH NAFLD” having steatosis $\geq 5\%$ and inflammation $\leq$ Grade 1 without any fibrosis; “definite NASH” having NAS ≥ 5 with/without fibrosis (F0–F3); “indeterminate NASH” having steatosis $\geq 5\%$, mild lobular inflammation (no or <2 foci/ $20\times$ hp), and none/rare ballooning ($\leq$ Grade 1) with/without

fibrosis (F0–F3); “NASH cirrhosis” included “NASH with cirrhosis”, “steatosis ($\geq 5\%$) with cirrhosis,” and “indeterminate NASH with cirrhosis.”^[22]

Statistical analysis

Categorical data were presented as numbers (n) with percentage (%) and continuous data as median and interquartile range (25th and 75th percentile values). Subjects included in the final analysis did not have missing data for any variable. Two groups were compared by Mann–Whitney U and Chi-square with exact tests for continuous and categorical variables, respectively. Corrections for multiple comparisons were done with Benjamini–Hochberg method for control of false discovery rate.^[23] $P < 0.05$ (two-sided) was considered statistically significant. Effect size (ES) for continuous variables of metabolic significance was calculated as Cohen’s d /Hedges’ g with 95% confidence intervals (95% CIs), corrected for unequal sample size and nonnormal/skewed data (Hedges’ correction), to assess their magnitude of impact on NAFLD-L and NAFLD-O, independent of statistical significance of the differences.^[24] Cohen’s d /Hedges’ g (95% CI) was presented using a forest plot for the variables – android/gynoid fat mass ratio; IR and BCF measured by HOMA2-IR and HOMA2-Beta in CC; and IR and BCF measured by FSIVGTT in TC. In the absence of relevant data in the literature to compare, ES was regarded as

Table 1: Characteristics of lean and overweight/obese subjects with nonalcoholic fatty liver disease of community cohort

Variables	All subjects (n=6134)	NAFLD-L (n=46)	NAFLD-O (n=379)	P*
Age (year)	39 (29–50)	40 (32–51)	44 (35–50)	0.46
Men, n (%)	2649 (43)	28 (61)	157 (41)	0.01
Adiposity characteristics, median (IQR)				
Android fat mass (kg)	45.60 (41.90–50.50)	37.10 (31.10–42.90)	48.45 (44.60–51.75)	0.02
Gynoid fat mass (kg)	36.30 (26.80–41.40)	26.80 (23.30–30.90)	38.25 (34.15–45.30)	0.02
Android/gynoid fat mass ratio	1.33 (1.20–1.39)	1.38 (1.33–1.39)	1.22 (1.12–1.40)	0.03
Metabolic and biochemical characteristics				
HOMA-IR, median (IQR)	1.56 (1.14–2.25)	1.61 (1.11–1.98)	2.37 (1.62–3.20)	0.01
HOMA2-IR, median (IQR)	1.21 (0.79–1.92)	1.05 (0.78–1.16)	1.40 (1.04–1.90)	0.006
HOMA2-beta, median (IQR)	109.30 (79.80–149.20)	93.30 (70.70–107.90)	95.70 (70.70–133.50)	0.42
MS, n (%)	1883 (31)	17 (37)	349 (92)	0.003
Diabetic, n (%)	1069 (17)	14 (30)	164 (43)	0.02
Dyslipidemia, n (%)	3994 (65)	26 (56)	277 (73)	0.01
Hypertension, n (%)	1467 (24)	19 (41)	170 (45)	0.64
ALT (IU/L), median (IQR)	26 (20–34)	32.5 (26–47)	34 (23–53)	0.99
Elevated ALT, n (%)	3589 (58)	33 (72)	295 (78)	0.31
AST (IU/L), median (IQR)	27 (22–33)	32 (26–38)	30 (24–41)	0.54
GGT (IU/L), median (IQR)	25 (18.81–32.21)	26 (19–43)	31 (22–47)	0.27

*P-values (two-sided) <0.05 were taken as significant and were adjusted for multiple comparisons by using the Benjamini and Hochberg method. NAFLD: Nonalcoholic fatty liver disease, NAFLD-L: NAFLD in lean subjects, NAFLD-O: NAFLD in overweight/obese subjects, IQR: Interquartile range presented as 25th and 75th percentile values, HOMA-IR: Homeostatic model assessment of insulin resistance, HOMA2-IR: Homeostatic model assessment updated version 2 for insulin resistance, HOMA2-Beta: Homeostatic model assessment updated version 2 for beta-cell function, MS: Metabolic syndrome, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase

small ($d = 0.2$), medium ($d = 0.5$), and large ($d \geq 0.8$) as per Cohen's classification.^[24]

As the sample sizes were not calculated *a priori*, we did *post hoc* power analysis for the given sample sizes and alpha level of significance using software G*Power (version 3.1.9.6, Universität Düsseldorf, Germany). For the CC, the power of the study corresponding to the observed ES (Cohen's d /Hedges' g –0.9) of the variable “android-to-gynoid fat mass ratio” was 84%. For the TC, the power of the study corresponding to the observed ES (Cohen's d /Hedges' g –0.66) of the variable “BCF by FSIVGTT” was 87%.

Analyses were done using software SPSS (IBM Corp., released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA: IBM Corp.).

Ethical approval

Study complied with the ethical principles of 1964 Helsinki Declaration and its amendments and was approved by Institutional Ethics Committee of Institute of Post Graduate Medical Education and Research, 244, A. J. C. Bose Road, Kolkata, India (Approval letter Memo No. Inst/IEC/294/777 dated July 3, 2014) as well as by Institutional Ethic Committee of Indian Institute of Liver and Digestive Diseases, Sonarpur, Sitala (East), 24 Pgs (North), Kolkata, India (Approval letter Memo No. IILDS/EC/001 dated July 18, 2018).

Results

Cohort characteristics

The majority of the community subjects evaluated were lean ($n = 4224/6134$; 69%), and 1% ($n = 46/4224$) of them had NAFLD [Figure 1]. Overall, NAFLD was present in 7% ($n = 425/6134$) of community subjects and that constituted the CC ($n = 425$).

Tertiary care subjects with ultrasonographic diagnosis of FL ($n = 305$) were evaluated further with TE, DEXA, and histology. Subjects with histologically proven NAFLD constituted the TC ($n = 276$).

Characteristics of CC [Table 1]: NAFLD-L constituted 11% ($n = 46/425$) of all NAFLD [Figure 1]. Diabetes, dyslipidemia, and overall MS were more frequent in NAFLD-O than NAFLD-L [Table 1]. Eighty-six percent ($n = 365/425$) of NAFLD were at risk of having significant liver disease, as suggested by elevated liver enzymes ($n = 172$), MS ($n = 37$), or both ($n = 156$) [Figure 1].

Characteristics of tertiary cohort: Males constituted 50% ($n = 138/276$). NAFLD-L and NAFLD-O constituted 11% ($n = 29/276$) and 89% ($n = 247/276$) of all NAFLD, respectively [Figure 1]. Conversely, 85% ($n = 29/34$) of lean and 91% ($n = 247/271$) of overweight/obese with ultrasound-detected FL had histologically confirmed

Table 2: Metabolic and histologic comparison between lean and overweight/obese subjects with histology-proven nonalcoholic fatty liver disease of the tertiary care cohort

Variables	All subjects with NAFLD (n=276), n (%)	NAFLD-L (n=29), n (%)	NAFLD-O (n=247), n (%)	P*
Age (year); median (IQR)	40 (33–49)	46 (34–54)	40 (33–48)	0.11
Men	138 (50)	24 (83)	114 (46)	0.003
Adiposity characteristics, median (IQR)				
Android fat mass (kg)	51.70 (46.50–59.60)	43.70 (39.50–47.10)	53.80 (47.70–60.20)	0.01
Gynoid fat mass (kg)	46.90 (35.60–55.00)	32.00 (30.40–36.60)	50.10 (39.40–55.50)	0.007
Android-to-gynoid fat mass ratio	1.17 (1.07–1.29)	1.35 (1.29–1.39)	1.15 (1.04–1.24)	0.009
Biochemical and metabolic characteristics, median (IQR)				
HOMA2-IR	1.30 (0.82–1.99)	1.14 (0.73–1.87)	1.30 (0.87–1.99)	0.39
Insulin resistance (mM/ μ L $\times$ 2) [†]	2.23 (1.20–3.30)	2.47 (1.19–14.80)	2.18 (1.29–3.29)	0.75
Beta-cell function (μ /mm) [†]	87.23 (56.78–142.30)	90.46 (59.90–272)	86.63 (53.22–138.15)	0.03
Metabolic syndrome	233 (84)	10 (34)	223 (90)	0.002
Diabetic	68 (25)	11 (38)	57 (23)	0.08
Dyslipidemia	214 (77)	17 (59)	197 (80)	0.01
CAP (dB/m), median (IQR)	299.50 (260–334)	266 (253–338)	303 (267–334)	0.04
ALT (IU/L), median (IQR)	48 (31–76)	51 (31–60)	48 (31–78)	0.85
AST (IU/L), median (IQR)	40 (29–59)	40 (28–54)	40.50 (29–60)	0.72
GGT (IU/L), median (IQR)	44 (30–57)	44 (33–69)	44 (30–56)	0.64
Histological characteristics				
Steatosis (%), median (IQR)	30 (10–50)	20 (10–40)	30 (10–50)	0.02
Steatosis (higher grade) ($\geq$ S2) ^{‡,§}	125 (45)	9 (31)	116 (47)	0.02
NAS, median (IQR) [‡]	3 (1–4)	2 (1–4)	3 (1–4)	0.07
NAS $\geq$ 5 [‡]	32 (12)	4 (14)	28 (11)	0.57
Hepatocyte ballooning [‡]	111 (40)	9 (31)	103 (42)	0.04
Lobular inflammation (moderate to severe) ^{‡,}	18 (6)	2 (7)	16 (6)	0.44
Fibrosis stages [‡]				
F0	166 (60.14)	19 (65.52)	147 (59.51)	0.026
F1	63 (22.83)	8 (27.59)	55 (22.27)	
F2	25 (9.58)	2 (6.90)	23 (9.31)	
F3	8 (2.90)	0	8 (3.24)	
F4	14 (5.10)	0	14 (5.67)	
Megamitochondria [‡]	9 (3)	1 (3)	8 (3)	0.32
Mallory–Denk bodies [‡]	18 (6)	4 (14)	14 (6)	0.01
Apoptotic hepatocyte [‡]	50 (18)	8 (27)	42 (17)	0.02
Lipogranuloma [‡]	8 (3)	0	8 (3)	0.03
Histological subtypes [¶]				
Non-NASH NAFLD	118 (43)	16 (55)	102 (41)	0.08
Definite NASH	32 (12)	4 (14)	28 (11)	
Indeterminate NASH	112 (40)	9 (31)	103 (42)	
NASH cirrhosis	14 (5)	0	14 (6)	

*P-values (two-sided) <0.05 were taken as significant and were adjusted for multiple comparisons by Benjamini and Hochberg method,

[†]IR and beta-cell function were measured by FSIVGTT using MINMOD, [‡]As defined by NASH-CRN,^[23] [§] $\geq$ S2: Steatosis>33%, ^{||}Lobular inflammation (moderate to severe): $\geq$ 2 foci per 20 $\times$ optical field, [¶]Histological subtypes were defined as per classification provided by liver forum case definitions working group.^[24] NASH: Nonalcoholic steatohepatitis, NAFLD: Nonalcoholic fatty liver disease, NAFLD-L: NAFLD in lean subjects, NAFLD-O: NAFLD in overweight/obese subjects, IQR: Interquartile range presented as 25th and 75th percentile values, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, CAP: Controlled attenuation parameter (noninvasive assessment of liver fat), IR: Insulin resistance, HOMA2-IR: Homeostatic model assessment updated version 2 for IR, FSIVGTT: Frequently sampled intravenous glucose tolerance test, MINMOD: Minimal model, NASH-CRN: Nonalcoholic steatohepatitis clinical research network

NAFLD [Figure 1]. Dyslipidemia was the most common metabolic abnormality ($n = 214/276$; 77%), followed by diabetes ($n = 68/276$; 25%) [Table 2]. MS was present in

84% ($n = 233/276$) [Table 2]. Dyslipidemia and MS were more frequent in NAFLD-O than NAFLD-L [Table 2]. NAS $\geq$ 5, “definite NASH” and “NASH cirrhosis” were

present in 12% ($n = 32/276$), 12% ($n = 32/276$), and 5% ($n = 14/276$), respectively [Table 2].

Adiposity and insulin resistance profile of nonalcoholic fatty liver disease in lean subjects vis-a-vis nonalcoholic fatty liver disease in overweight/obese subjects

NAFLD-L, compared to NAFLD-O, had a higher amount of android fat relative to gynoid (android/gynoid fat ratio), measured by DEXA, both in CC (median 1.38 vs. 1.22, respectively, $P = 0.03$) and TC (median 1.35 vs. 1.15, respectively, $P = 0.009$) [Tables 1 and 2]. Furthermore, ES (Cohen's d [Hedges' g]) for android/gynoid fat ratio showed medium (0.54 in TC) to large (0.90 in CC) effects toward NAFLD-L [Figure 2].

NAFLD-L had relatively lower HOMA2-IR than NAFLD-O in CC [Table 1] but with small ES (Cohen's d [Hedges' g]; -0.31) [Figure 2]. Physiologically robust test, FSIVGTT, in TC, showed comparable IR in NAFLD-L and NAFLD-O (median 2.47 vs. 2.18, respectively; $P = 0.76$) [Table 2]. Distribution of ES (Cohen's d [Hedges' g]) for IR (FSIVGTT) across the line of "no effect" suggested IR to have an effect of similar magnitude on NAFLD-L and NAFLD-O [Figure 2].

FSIVGTT in TC showed better BCF in NAFLD-L than in NAFLD-O (median: 90.46 vs. 86.63 $\mu\text{M}/\text{M}$ in NAFLD-L and NAFLD-O, respectively, $P = 0.03$; Table 2). Furthermore, ES (Cohen's d [Hedges' g]) for BCF (FSIVGTT) showed a medium effect (0.66) toward NAFLD-L [Figure 2].

Histology of nonalcoholic fatty liver disease in lean subjects vis-a-vis nonalcoholic fatty liver disease in overweight/obese subjects [Table 2]

NAFLD-L had less steatosis than NAFLD-O (median steatosis 20% vs. 30%, respectively) [Table 2]. NAFLD-L and NAFLD-O had comparable NAS (median 2 vs. 3, respectively, $P = 0.07$) and proportion of the subjects with NAS ≥ 5 (14% vs. 11%, respectively) [Table 2]. However, NAFLD-L had less ballooning than NAFLD-O (31% vs. 103 42%, respectively, $P = 0.04$) [Table 2]. Higher fibrosis stages/cirrhosis were detected only in NAFLD-O [Table 2]. Ancillary features of liver injury (megamitochondria/Mallory–Denk bodies/apoptotic hepatocyte/lipogranuloma) were less prevalent [Table 2]. However, NAFLD-L had higher frequencies of Mallory–Denk bodies and apoptotic hepatocytes than NAFLD-O, whereas all the lipogranuloma detected were in NAFLD-O [Table 2]. Overall, the prevalence of "definite NASH" was lower ($n = 32/276$; 12%) than "indeterminate NASH" ($n = 112/276$; 40%) in our cohort [Table 2]. NAFLD-L and NAFLD-O had comparable prevalence of histologic subtypes, including "definite NASH" (14% vs. 11%, respectively; $P = 0.08$) despite less advanced fibrosis in NAFLD-L [Table 2].

Discussion

The primary observations of our study are relevant in improving contemporary pathophysiological understanding of disease and subsequent approach to management in

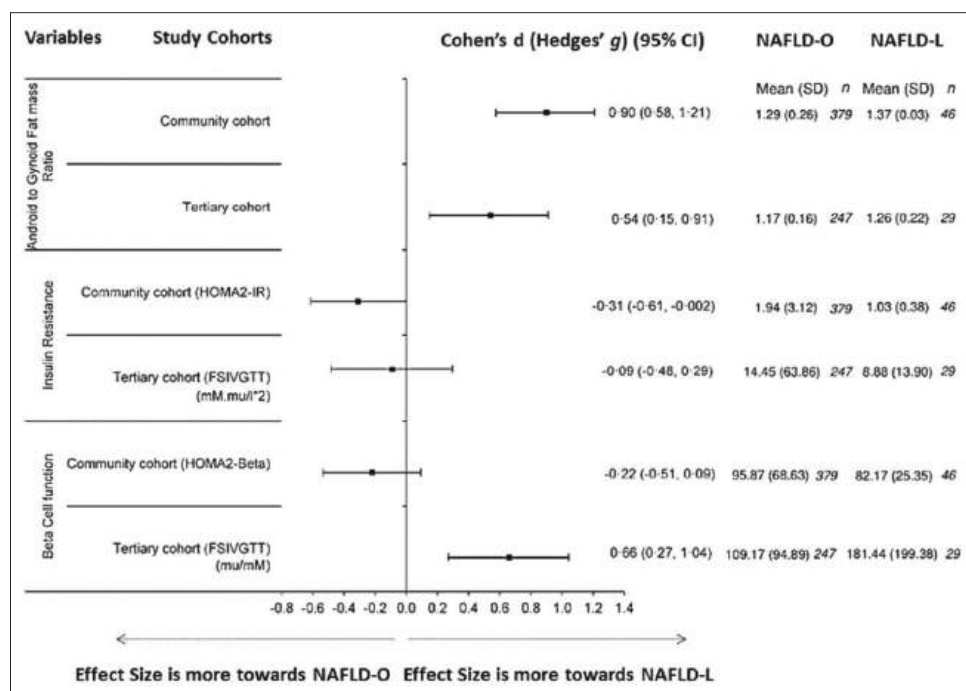


Figure 2: Forest plot showing the effect Sizes of metabolic factors in lean versus overweight/obese subjects with nonalcoholic fatty liver disease. Cohen's d (Hedges' g): a measure of effect size, is defined as the standardized mean difference between the groups, calculated with Hedges' correction for unequal sample size and skewed data. CI: Confidence interval, SD: Standard deviation, n : Sample size, NAFLD-O: Nonalcoholic fatty liver disease in overweight/obese subjects, NAFLD-L: Nonalcoholic fatty liver disease in lean subjects, HOMA2-IR: Homeostatic model assessment (HOMA) updated version 2 for insulin resistance (IR), HOMA2-Beta: HOMA2 for beta-cell function, FSIVGTT: Frequently sampled intravenous glucose tolerance test

NAFLD-L. First, NAFLD-L has similar IR but better BCF compared to NAFLD-O. Second, the prevalence of the “definite NASH” was similar in the two groups despite the absence of advanced fibrosis in NAFLD-L. Third, NAFLD-L had higher android fat than gynoid compared to NAFLD-O.

The spread of the study, adoption of a “habitation to hospital” approach for evaluation of relevant abnormalities, enabled us to pick up the subjects from two ends of the disease care continuum, i.e., community and tertiary care within the same healthcare hierarchy. This geographical colocalization of the two cohorts with different disease risk backgrounds ensured elimination of potential confounding by cultural–ethnic influences and represented the broad real-life spectrum of NAFLD. In addition, this also ensured simultaneous use of a public health approach in the community and a more detailed pathophysiological approach in tertiary care to fulfill the objective of comparing NAFLD-L against NAFLD-O. Other methodological strengths of our study were the adoption of a stringent anthropometric definition of leanness (exclusion of AO in addition to the BMI definition), the usage of physiologically robust assessment of IR by FSIVGTT, and histological case definitions proposed to ensure uniformity and comparability across the studies. A cost of the stringent definition of leanness in our study was the reduction in the number of lean subjects available while making it anthropometrically “pure.” Assessment of IR by two methods, one with easy applicability in the field (HOMA2-IR) and another with pathophysiological robustness (FSIVGTT), increased the relevance of the IR data.

Observations from the present study contribute to the understanding of subtle physiological alterations and pathophysiological characteristics of NAFLD in lean subjects in the midst of reported discordances.^[5–7] The evidence that we present from a large community as well as a TC would argue that NAFLD-L is aligned with NAFLD-O in the same spectrum of pathophysiological mechanisms centered around IR, differing only in severity, reflected as better BCF in NAFLD-L but persistent IR with impending beta-cell dysfunction in NAFLD-O.^[25] Thus, glucotoxicity and lipotoxicity related to beta-cell dysfunction are expected to be less severe in NAFLD-L.^[25] This could explain the observed differences in severity of clinically apparent metabolic dysfunction in the forms of MS and dyslipidemia. However, this metabolic advantage could have been negated by preferential accumulation of more insulin-resistant android fat, despite the absence of anthropometric obesity, in NAFLD-L, and thereby inducing IR comparable to NAFLD-O.^[26] This upholds the well-known pathophysiological linkage between IR and NAFLD and suggests that IR could be a logical central therapy target in NAFLD-L, as it is in classical NAFLD-O. Thus, our findings on one hand justify the concept of “metabolic dysfunction” as a central mechanism for the recently proposed “MASLD” and on the other hand provide

clues to the uniqueness of this “metabolic dysfunction” in lean subjects with MASLD, i.e., NAFLD-L.

We observed an overall trend toward the presence of histologically less severe disease and comparable frequency of “definite NASH” in NAFLD-L and NAFLD-O. This makes NAFLD-L and NAFLD-O indistinguishable in terms of histological inflammatory activity, whereas NAFLD-L could be at a lower risk of having advanced fibrosis. Over and above, the observation of histologically mild disease in the majority of NAFLD subjects biopsied underscores the need for refinement of the indications for histological assessment and the need for adoption of a strategy of screening “high-risk” subjects using noninvasive biomarkers for further invasive assessment.^[27]

We acknowledge that our study had some limitations. First, a relatively low participation rate (57%) for screening in the selected community subjects. This was mostly because of unwillingness to comply with the stepwise evaluation plan, along with occupational commitment and lack of incentive in the study, as addressed in a meta-analysis of community Diabetes screening studies showing a decreasing rate of response with increasing steps of evaluation.^[28] The present observational study, without any therapeutic intervention, proceeded with this real-life response pattern unlike any therapeutic or clinical drug trials. Second, apparently, we had a lower proportion of the subjects with biopsy-proven NAFLD in NAFLD-L group (11%, $n = 29/276$). However, this was in concordance with the proportion of nonobese NAFLD (12.9%) reported from Southeast Asia.^[4] Third, we could not evaluate the community and TCs during the same time period because of constraints in workforce, resources, and logistic issues. Fourth, we could not define NAFLD or NASH as “MASLD” or “metabolic dysfunction-associated steatohepatitis (MASH)” in our study, as these terminologies were adopted recently after we undertook the present study.^[8]

Our CC, the lowest stratum of the healthcare hierarchy, having a low prevalence (1%) of noninvasively diagnosed NAFLD in lean subjects, could explain the proportion of NAFLD-L in TC, the highest stratum of the same healthcare hierarchy. This real-life impact of community prevalence of NAFLD-L on the burden of the tertiary care facility was appreciated because of using two extreme ends of the same healthcare hierarchy in our study.

Given the fact that the pathophysiological pattern remains the same regardless of the nomenclature, NAFLD or MASLD, our present observations, along with others, might be useful to enrich the newly evolving nomenclature of “MASLD” and “MASH” in terms of pathophysiological understanding and clinical outcome, particularly in lean or nonobese subjects.^[29]

Conclusion

NAFLD-L constituted one-tenth of all NAFLD in the community. NAFLD-L showed pathophysiological

similarity with NAFLD-O, in terms of the pattern of IR and histological subtypes. The metabolic advantage of having a lower prevalence of MS and better BCF is counterbalanced by preferential accumulation of more insulin-resistant android fat in NAFLD-L. This observation could strengthen the biological concept behind the development of the new terminology “MASLD” and be utilized to further explore pathophysiologic and therapeutic aspects of NAFLD/MASLD in lean subjects.

Author contributions

- The corresponding author takes the responsibility for the integrity of the work as a whole. This manuscript has been read and approved by all the authors that the requirements for authorship have been met. Each author believes that the manuscript represents honest work. All the authors had access to the data, and all of them share the responsibility for the submission for publication. Individual contributions of the authors are provided
- Kausik Das contributed to development of concept, design the study, literature search, clinical and invasive evaluations in TC, review of liver histology, data acquisition, data management, statistical analysis, interpretation of result, manuscript preparation, editing and review, and approval of final version of manuscript; Anamitra Barik contributed to design the study, field work for CC evaluation, CC data acquisition, data management, interpretation of CC data, manuscript review, and approval of final version of manuscript; Souveek Mitra contributed to literature search, clinical and invasive evaluations in TC, TC data acquisition, manuscript review, and approval of final version of manuscript; Ranajoy Ghosh contributed to assessment of liver histology, biochemical laboratory works, histologic data acquisition, review of histological data analysis, manuscript review, and approval of final version of manuscript; Rajesh K Rai contributed to design the study, field work for CC evaluation, CC data acquisition, data management, interpretation of CC data, manuscript review, and approval of final version of manuscript; Partha S. Mukherjee contributed to design the study, field work for CC evaluation, CC data acquisition, data management, interpretation of CC data, manuscript review, and approval of final version of manuscript; Abhijit Chowdhury contributed to development of concept, design the study in CC, clinical evaluations in community and TCs, manuscript editing and review, and approval of final version of manuscript.

Data availability

Original data (de-identified participant data) in the Excel spreadsheet format may be provided on personal communication with the corresponding author after publication of the article.

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Conflicts of interest

There are no conflicts of interest.

References

1. Fan JG, Saibara T, Chitturi S, Kim BI, Sung JJ, Chutaputti A, *et al.* What are the risk factors and settings for non-alcoholic fatty liver disease in Asia-Pacific? *J Gastroenterol Hepatol* 2007;22:794-800.
2. Das K, Das K, Mukherjee PS, Ghosh A, Ghosh S, Mridha AR, *et al.* Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. *Hepatology* 2010;51:1593-602.
3. Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, *et al.* Nonalcoholic fatty liver disease in lean individuals in the United States. *Medicine (Baltimore)* 2012;91:319-27.
4. Ye Q, Zou B, Yeo YH, Li J, Huang DQ, Wu Y, *et al.* Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020;5:739-52.
5. Young S, Tariq R, Provenza J, Satapathy SK, Faisal K, Choudhry A, *et al.* Prevalence and profile of nonalcoholic fatty liver disease in lean adults: Systematic review and meta-analysis. *Hepatol Commun* 2020;4:953-72.
6. Shalimar, Elhence A, Bansal B, Gupta H, Anand A, Singh TP, *et al.* Prevalence of non-alcoholic fatty liver disease in India: A systematic review and meta-analysis. *J Clin Exp Hepatol* 2022;12:818-29.
7. Tan EX, Lee JW, Jumat NH, Chan WK, Treeprasertsuk S, Goh GB, *et al.* Non-obese non-alcoholic fatty liver disease (NAFLD) in Asia: An international registry study. *Metabolism* 2022;126:154911.
8. Rinella ME, Lazarus JV, Ratzliff V, Francque SM, Sanyal AJ, Kanwal F, *et al.* A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 2023;78:1966-86.
9. India State-Level Disease Burden Initiative Collaborators. Nations within a nation: Variations in epidemiological transition across the states of India, 1990-2016 in the global burden of disease study. *Lancet* 2017;390:2437-60.
10. Sarin SK, Prasad M, Ramalingam A, Kapil U. Integration of public health measures for NAFLD into India's national programme for NCDs. *Lancet Gastroenterol Hepatol* 2021;6:777-8.
11. Mukherjee PS, Ghosh S, Mukhopadhyay P, Das DK, Sarkar P, Majumdar S, *et al.* Stepwise evaluation for the risk of metabolic unhealthiness and significant non-alcoholic fatty liver disease in India. *Lancet Reg Health Southeast Asia* 2023;12:100142.
12. Ghosh S, Barik A, Majumdar S, Gorain A, Mukherjee S, Mazumdar S, *et al.* Health and demographic surveillance system profile: The Birbhum population project (Birbhum HDSS). *Int J*

- Epidemiol 2015;44:98-107.
13. Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol* 2010;53:372-84.
 14. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64:1388-402.
 15. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, *et al.* The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology* 2002;123:745-50.
 16. European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del Hgado. EASL-ALEH clinical practice guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015;63:237-64.
 17. Stults-Kolehmainen MA, Stanforth PR, Bartholomew JB, Lu T, Abolt CJ, Sinha R. DXA estimates of fat in abdominal, trunk and hip regions varies by ethnicity in men. *Nutr Diabetes* 2013;3:e64.
 18. Bergman RN. Lilly lecture 1989. Toward physiological understanding of glucose tolerance. Minimal-model approach. *Diabetes* 1989;38:1512-27.
 19. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004;27:1487-95.
 20. World Health Organization. Regional Office for the Western Pacific. The Asia-Pacific Perspective: Redefining Obesity and its Treatment. Sydney: Health Communications Australia; 2000. Available from: <https://iris.who.int/handle/10665/206936>. [Last accessed on 2025 Dec 10].
 21. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, *et al.* Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005;41:1313-21.
 22. Siddiqui MS, Harrison SA, Abdelmalek MF, Anstee QM, Bedossa P, Castera L, *et al.* Case definitions for inclusion and analysis of endpoints in clinical trials for nonalcoholic steatohepatitis through the lens of regulatory science. *Hepatology* 2018;67:2001-12.
 23. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *J Clin Epidemiol* 2014;67:850-7.
 24. Sullivan GM, Feinn R. Using effect size-or why the P value is not enough. *J Grad Med Educ* 2012;4:279-82.
 25. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options. *JHEP Rep* 2019;1:312-28.
 26. Jensen MD. Role of body fat distribution and the metabolic complications of obesity. *J Clin Endocrinol Metab* 2008;93:S57-63.
 27. Long MT, Nouredin M, Lim JK. AGA clinical practice update: Diagnosis and management of nonalcoholic fatty liver disease in lean individuals: Expert review. *Gastroenterology* 2022;163:764-74.e1.
 28. Khunti K, Mani H, Achana F, Cooper N, Gray LJ, Davies MJ. Systematic review and meta-analysis of response rates and diagnostic yield of screening for type 2 diabetes and those at high risk of diabetes. *PLoS One* 2015;10:e0135702.
 29. Wu T, Ye J, Mo S, Ye M, Li X, Li Q, *et al.* Impact of nomenclature as metabolic associated steatotic liver disease on steatotic liver disease prevalence and screening: A prospective population survey in Asians. *J Gastroenterol Hepatol* 2024;39:1636-47.