Nonalcoholic Fatty Liver in Lean Individuals: Clinicobiochemical Correlates of Histopathology in 157 Liver Biopsies from Healthy Liver Donors

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Background: **Generally diagnosis of non-alcoholic fatty disease is made on imaging, however, mild steatosis is difficult to diagnose on imaging. Liver biopsy is the procedure of choice but is not carried out as it is an invasive procedure. We describe our experience of 157 liver biopsies in living liver donors with normal body mass index (BMI) <23 kg/M^2 (lean).** ***Materials and methods:*** **The study was conducted at a tertiary care center in north India. Data of lean living donors who underwent a liver biopsy before donation were analyzed. Data are presented as percentage, mean, or median (25–75 interquartile range).** ***Results:*** **Of 718 donors who had a liver biopsy before donation, 157 (21.8%) donors were lean (BMI < 23 kg/M^2). Seventy-eight percent of lean donors had no or only one metabolic risk factor. Fifty-three (33.7%) of lean donors had nonalcoholic fatty liver (NAFL) in liver biopsy. When donors with NAFL were compared to donors with normal histology, donors with NAFL had significantly higher aspartate transaminase (26.6 ± 7.5 versus 23.7 ± 5.4, p = 0.007), alanine transaminase (33.4 ± 11.7 versus 27.8 ± 10.7, p = 0.003), and gamma glutamyl transpeptidase [25 (16–40.5) versus 18 (14–23), p = 0.003]. Only triglycerides (TGs) were statistically different among metabolic factors in lean NAFL and normal histology groups, 97 (70–161) versus 86 (62.5–114.7), p = 0.043. A total of 30% donors in the lean NAFL group had TGs >150 mg/dl as compared with 12.5% in the normal histology group, p = 0.009. Other metabolic risk factors were not statistically different.** ***Conclusion:*** **One third of lean donors had NAFL. Among all metabolic risk factors, only higher TGs levels showed a significant association with NAFL. (J Clin Exp Hepatol 2021;11:544–549)**

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Nonalcoholic fatty liver disease (NAFLD) is a spectrum of nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma.[1,2] NAFLD-related liver disease requiring liver transplantation is increasing gradually. NAFLD is associated with obesity and metabolic risk factors; however, it may occur in lean persons also who have normal body mass index (BMI). Imaging modalities such as ultrasound or computed tomography (CT) are not reliable for milder degrees of steatosis, thus underestimating true prevalence of NAFLD.[1,3,4] Liver biopsy is the gold standard for diagnosis of NAFLD;[1] however, it is not feasible always due to invasive nature and risk of complications. There are less data available on lean individuals with NAFLD and that is further limited by no availability of liver biopsy in most of studies. The earlier studies from India have shown that NAFLD is common.[5–9] As we work at a liver transplantation center and living donor liver transplantation is more common than deceased donor liver transplantation, donor liver biopsies during presurgery work up provide us opportunity to study NAFLD in apparently healthy individuals with near normal liver enzymes. We describe a profile of NAFL in lean liver donors diagnosed during work up.

MATERIAL AND METHODS

This study was conducted at a tertiary care center in north India. The study included all liver donors who underwent a liver biopsy before actual donation from July 2010 to

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Abbreviations: ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; CT: computed tomography; GGT: gamma glutamyl transpeptidase; GRWR: graft-to-recipient weight ratio; HDL: high-density lipoprotein; IR: insulin resistance; LAI: liver attenuation index; MR: magnetic resonance; NAFL: nonalcoholic fatty liver; NAFLD: nonalcoholic fatty liver disease; PNPLA3: patatin-like phospholipase domain-containing protein 3; TG: triglyceride; USG: ultrasound
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January 2018. Data were retrospectively analyzed from a prospective collected database. Institute's ethical committee approved the study. The indications for liver biopsy were one or more of following: low estimated remnant volume (<35%) and/or graft-to-recipient weight ratio (GRWR) (0.6–0.8) for prospective recipients, liver attenuation index (LAI) < 5 (difference of liver and splenic attenuation on noncontrast abdominal CT), BMI ≥ 28, and presence of 2 or more metabolic risk factors. The donors with BMI < 23 kg/M^2 (cut-off for normal BMI in Asian Indians)[10] were considered as lean. Donors with <2 metabolic risk factors underwent biopsy only if they had a low GRWR or remnant 30–35%; donors with >35% remnant or GRWR > 0.8 were not taken for biopsy if they had none or only one metabolic risk factors. All the donors had detailed work up that includes liver function tests, complete blood counts, renal function tests, fasting blood sugar, lipid profile, hepatitis B surface antigen, and hepatitis C antibodies. Prospective donors with history of significant alcohol (>20 g/day) intake were not evaluated further. A noncontrast CT abdomen was carried out as a noninvasive modality to assess donor steatosis in the first phase of donor evaluation. LAI was calculated as attenuation index of the liver minus attenuation index of the spleen, which was measured at minimum of 25 different regions of interest. Metabolic risk factors were defined as serum triglycerides (TGs) >150 mg/dl, serum high-density lipoprotein (HDL) <40 mg/dl (males) or <50 mg/dl (females), impaired glucose tolerance (>100 mg/dl) or presence of diabetes, blood pressure >130/85 mmHg, or on antihypertensive treatment.[10] Liver biopsy was carried out under ultrasound guidance by a hepatologist or interventional radiologist after taking informed consent. NAFL was defined as per standard definition (>5% steatosis on liver biopsy). We do not accept donors for donation if a biopsy during evaluation shows >20% steatosis (right lobe) or >30% steatosis (left lobe), nonalcoholic steatohepatitis (defined by NAFLD activity score), or fibrosis. Thus, all these donors either had NAFL (with equal to or less than 30% steatosis) or had normal histology. The following staining was used in histology: hematoxylin and eosin, Masson's trichrome, Pearl's stain, and Orcein stain.

Statistical Methods

Data are presented as number, mean ± standard deviation, or median (25–75 interquartile range). Two groups (NAFL and normal histology) were compared with Fisher's exact test (categorical variables), student's t test (parametric data), or Mann-Whitney tests (nonparametric data). A univariate and multivariate analysis was carried out to look for factors significantly associated with NAFLD. A two-tailed *P* value < 0.05 was considered significant.

RESULTS

A total of 718 donors had a liver biopsy before donation, and 157 (21.8%) donors were lean (BMI < 23 kg/M^2). Seventy-eight percent (n = 123) of these donors had no or one metabolic risk factor, and biopsy was carried out due to low GRWR or remnant <35%. Fifty-three (33.7%) of lean donors had NAFL in liver biopsy. When lean donors with NAFL were compared with lean and normal histology donors, the lean individuals with NAFL group showed significantly higher aspartate transaminase (AST), alanine transaminase (ALT), and gamma glutamyl transpeptidase (GGT) as shown in Table 1. Only TGs were statistically different among metabolic factors in lean individuals with NAFL and normal histology groups, both as categorical (TGs > 150/dl) and continuous data as shown in Tables 1 and 2. A total of 30% donors in the lean NAFL group had TGs > 150 mg/dl as compared with 12.5% in the normal histology group, p = 0.009. Other metabolic

Table 1 Comparison of No NAFL and NAFL Groups Among Lean Donors.

Parameter	Whole group (n = 157)	No NAFL (n = 104)	NAFL (n = 53)	*P* value between no NAFL and NAFL
Age (years)	32.1 ± 10.1	31.3 ± 9.9	33.5 ± 10.4	0.208
Male:female	94:63	60:44	34:19	0.493
BMI kg/M^2	21.0 ± 1.5	20.9 ± 1.5	21.3 ± 1.2	0.119
AST IU/L	24.7 ± 6.3	23.7 ± 5.4	26.6 ± 7.5	0.007
ALT IU/L	29.7 ± 11.4	27.8 ± 10.7	33.4 ± 11.7	0.003
ALP IU/L	83.1 ± 27.6	81. ± 29.2	86.4 ± 24.1	0.275
GGT IU/L	19 (14.5–29)	18 (14–23)	25.0 (16.0–40.5)	0.003
Triglycerides mg/dl	94 (64–128)	86 (62.5–114.7)	97 (70–161)	0.043
Fasting blood sugar mg/dl	90.6 ± 14.9	90.4 ± 15.0	92.5 ± 16.7	0.426
High-density lipoprotein mg/dl	43.6 ± 12	44.6 ± 11.0	41. ± 13.7	0.153
Low-density lipoprotein mg/dl	98.4 ± 33.2	97.0 ± 31.2	101.2 ± 37.1	0.454

BMI: body mass index; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; GGT: gamma glutamyl transpeptidase; NAFL: nonalcoholic fatty liver.

Table 2 Comparison of Metabolic Risk Factors Between NALF and No NAFL Groups Among Lean Donors.

Parameter	No NAFL (n = 104)	NAFL (n = 53)	*P* value
Impaired fasting glucose	16 (16.6%)	11 (20.7%)	0.502
Hypertension or blood pressure >130/85 mm Hg	1 (0.9%)	1 (1.8%)	1.000
Triglycerides >150 mg/dl	13 (12.5%)	16 (30.1%)	0.009
High-density lipoprotein <40 (males) or <50 (females) mg/dl	55 (52.8%)	34 (64.1%)	0.233
Presence of 2 or more metabolic risk factors	16 (15.3%)	18 (33.9%)	0.013

NAFL: nonalcoholic fatty liver.

risk factors such as HDL, BMI, fasting blood sugar, and presence of hypertension or blood pressure >130/85 mm Hg were not different between the two groups. None of lean donors had diabetes. Serum uric acid levels were available for 32 of the NAFLD group and 60 of the normal histology group, which were not significantly different: 4.5 ± 1.4 versus 4.5 ± 1.0 mg/dl, respectively, p = 1.0. Indication of liver biopsy was low GRWR or remnant with either no or only one metabolic risk factor in majority (n = 123), 35 of these had NAFL (28.4%). The distribution of metabolic risk factors was as following in normal histology and lean NAFL groups: none in 37 (35.5%) and 13 (24.5%), 1 risk factor in 51 (49%) and 22 (41.5%), 2 risk factors in 13 (12.5%) and 14 (26.4%), and 3 risk factors in 3 (2.8%) and 4 (7.5%) patients, respectively. The indication of biopsy was presence of 2 or more metabolic risk factors in 34 patients, and 52% of these had NAFL on biopsy. Seventeen donors had magnetic resonance (MR)–based fat estimation also, in addition to liver biopsy. Six of these had normal MR fat estimation, while 11 had >5% fat estimation, which was true in biopsy. The lean group was also compared with donors with BMI > 23 kg/m^2. The nonlean group (BMI > 23 kg/m^2) showed significantly higher age, BMI, ALT, TGs, fasting blood sugar, low-density lipoprotein, and low HDL (Table 3). One-third patients in lean group had NAFL, while half of the patients had NAFL in non-lean group, it is expected given increasing prevalence of obesity in non-lean group, however, the proportion of NAFL in lean with ≥2 metabolic risk factors (18/34) was similar to NAFL in overweight or obese. Table 4 shows univariate and multivariate analysis for presence of NAFL; the only significant association was higher TGs. It should be noted that due to selection bias (healthy liver donors), diabetes and hypertension are likely to be underrepresented in this study population.

DISCUSSION

We describe biopsy findings of 157 lean donors and one third of them had NAFL. The present study is different from the majority of other studies as it used liver biopsy to diagnose NAFLD in apparently healthy individuals with normal liver enzymes. We found several interesting observations; one third of lean individuals had NAFL on biopsy. While NAFL was present in 28% of donors with no or one metabolic risk factor, the proportion of NAFL increased to 52% in presence of 2 or more metabolic risk

Table 3 Comparison of Lean and Non-lean (BMI > 23 kg/m^2) Groups.

Parameter	Whole group (n = 718)	Lean (n = 157)	Non-lean (n = 561)	*P* value between lean and non-lean
Age (years)	35.2 ± 10.4	32.1 ± 10.1	36.1 ± 10.3	0.000
Male:female	338:380	94:63	244:317	0.000
BMI kg/M^2	25.9 ± 3.6	21.0 ± 1.5	27.3 ± 2.8	0.000
AST IU/L	25.2 ± 7.2	24.7 ± 6.3	25.3 ± 7.5	0.308
ALT IU/L	31.7 ± 12.3	29.7 ± 11.4	32.3 ± 12.5	0.020
ALP IU/L	86.5 ± 28.6	83.1 ± 27.6	87.5 ± 28.8	0.086
GGT IU/L	20 (15–29)	19 (14.5–29)	20 (15–29)	0.271
Triglycerides mg/dl	108 (77–150)	94 (64–128)	111 (81–157)	0.000
Fasting blood sugar mg/dl	93.9 ± 19.5	90.6 ± 14.9	94.8 ± 20.5	0.017
High-density lipoprotein mg/dl	41.9 ± 12.0	43.6 ± 11.9	41.4 ± 11.9	0.045
Low-density lipoprotein mg/dl	105.1 ± 30.3	98.4 ± 33.2	107.0 ± 29.2	0.002
NAFL	334	53 (33.7%)	281 (50%)	0.000

BMI: body mass index; AST: Aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; GGT: gamma glutamyl transpeptidase; NAFL: nonalcoholic fatty liver.

Table 4 Univariate and Multivariate Analysis for Presence of Nonalcoholic Fatty Liver*.

	Univariate logistic regression		Multivariate logistic regression	
	Odds ratio (95% confidence interval)	*P*-value	Odds ratio (95% confidence interval)	*P*-value
Age	1.02 (0.99–1.05)	0.210	1.01 (0.97–1.05)	0.537
Male gender	1.28 (0.65–2.54)	0.476	1.26 (0.59–2.68)	0.557
BMI	1.2 (0.95–1.52)	0.134	1.14 (0.88–1.46)	0.318
Fasting blood sugar	1.02 (0.99–1.04)	0.150	1.01 (0.99–1.04)	0.413
TG	1.01 (1–1.01)	0.007	1.01 (1–1.01)	0.038
HDL	0.98 (0.95–1.01)	0.117	0.99 (0.95–1.02)	0.389

*Only 2 donors had hypertension, so hypertension is not included in analysis. TG: triglyceride; HDL: high-density lipoprotein; BMI: body mass index.

factors even when BMI was not different as all were lean. This is similar to a previous report from our center that a liver biopsy should be performed in presence of 2 or more metabolic risk factors in prospective liver donors to diagnose NAFLD.[9] Several studies have defined lean as BMI < 25 kg/m^2 (including studies from India) and have shown 3.7–27.4% prevalence of NAFLD in lean individuals from different regions of the world.[11] Thus, these studies include overweight patients (BMI >23 to <25 kg/m^2) and should not be considered true lean population. The present study has included donors with normal BMI only. As expected, lean persons had a lower incidence of NAFL (33%) when compared with overweight or obese individuals (50%). However, lean individuals with NAFL had a higher number of metabolic risk factors than lean individuals with normal histology even if the BMI was similar in two groups. Almost one third had NAFL in the present study despite having normal BMI; this confirms that Asians and Indians are predisposed to metabolic risk factors as shown by earlier studies.[12–14] Table 5 shows other important studies and Indian data on lean individuals with NAFL.[8,13,15–23] As shown by the studies included in Table 4, the presence of lean NAFL is associated with insulin resistance, metabolic risk factors, and genetic factors. A recent meta-analysis of 33 observational studies (n = 205 307 individuals) from 14 countries showed a prevalence of 9.7% for NAFLD (95% confidence interval 7.7–11.8%) in lean individuals. A total of 30 studies used ultrasound, 2 used CT, and only one used MR-based fat estimation for diagnosis of NAFLD. The prevalence of lean NAFLD with diabetes, hypertension, and metabolic syndrome was 0.6%, 1.8%, and 1.4% respectively.[24] The meta-analysis found that metabolic risk factors were related to lean NAFLD, similar to findings of the present study. In addition to metabolic risk factors (BMI, waist circumference, low HDL, higher TGs, higher blood pressure, and sugar values), following parameters were significantly different when compared with lean non-NAFLD: a higher age, liver enzymes (AST, ALT, GGT), smoking, physical inactivity, and male gender.[24]

Earlier it was thought that NAFL is benign while nonalcoholic steatohepatitis (NASH) is progressive, however a meta-analysis by Singh *et al*[25] showed that progression to NASH or fibrosis may happen in NAFL also, although rate of fibrosis progression is slow as compared with NASH.

The merits of the present study include a large histology-based (which can not be obtained for apparently healthy individuals with normal liver enzymes in settings other than donor work up) sample size in uncommon population (lean NAFL); limitations of the present study include nonavailability of waist circumference; hence, we were not able to show exact incidence of metabolic syndrome in the study population, although it does not affect primary outcomes of the study (presence or absence of NAFL in lean individuals). Although the present study is retrospective, it is single time study and being retrospective does not affect the results, as all the data are available at an electronic hospital database. The present study might have excluded some donors due to limitations of door selection process; thus, some prospective lean donors with significant steatosis on radiology or with high liver enzymes might have been missed and the actual prevalence of NAFLD in lean individuals may be higher or lower (as the donor cohort is representative of general population). Other limitations include absence of ultrasound, elastography, glucose tolerance test, and measurements of insulin resistance. As donors with nonalcoholic steatohepatitis or fibrosis were not accepted for donation, we do not have data on how many lean individuals had nonalcoholic steatohepatitis or fibrosis. As liver biopsy was performed in presence of near normal enzymes, how many donors had high enzymes to begin with is not known. It is not a random population sample, but doing biopsy in a random population sample is not possible due to ethical issues. There may be some selection bias for

Table 5 Studies on NAFL in Lean Individuals*.

Author[ref]	N of lean, % of NAFLD among lean	Diagnosis based on	Predictors of lean NAFL
Younossi[15]	4457, 9.6%	USG	Younger age, female sex, and a decreased likelihood of having IR and hypercholesterolemia
Feng[16]	731, 18.3%	USG	Lean patients with NAFLD had significantly higher visceral adiposity index than overweight-obese controls, higher chances of having diabetes, hypertension, and metabolic syndrome
Das[8]	1911 total, 90 of 164 with NAFLD were lean, 5.1% of lean had NAFLD	USG/CT	On multivariate analysis, in the lean group, increased BMI and biceps skin-fold thickness predicted NAFLD
Wei[17]	701, 19.2%	Magnetic resonance spectroscopy	Higher weight, high hemoglobin A1c, insulin resistance, hyperferritinemia, and the PNPLA3 G allele
Xu[18]	6905, 7.27% at baseline, 8.88% developed NAFLD during follow-up	USG	Age, gender, BMI, waist circumference, triglyceride, high-density lipoprotein cholesterol, serum uric acid, hemoglobin, and platelet count were independently associated with presence and development of NAFLD
Sinn[19]	5,878, 27.4%	USG	Higher number of metabolic components, higher IR
Nishioji[20]	391 with normal BMI, 60 (15.3%) had NAFLD	USG	G allele of PNPLA3 rs738409 and weight gain ≥10 kg after age 20 had a joint effect on the risk of NAFLD in the normal weight
Kumar[21]	Among 205 patients with NAFLD, 27 (13.2%) were lean	USG	89% of lean individuals with NAFLD were dyslipidemic; the mean BMI of lean individuals with NAFLD was significantly higher than that of unselected lean healthy controls
Sharma[22]	50 lean individuals with NAFLD with raised ALT	USG	Insulin resistance and dyslipidemia were prevalent in 12% and 25% non-overweight patients, respectively
Bhat[13]	30 of 150 individuals with NAFLD were lean	USG	48% had IR in lean
Shah[23]	69 (27.6%) of 250 individuals with NAFLD were lean	USG and Fibroscan	Diabetes is common among lean individuals with NAFLD

IR: insulin resistance; PNPLA3: patatin-like phospholipase domain-containing protein 3; USG: ultrasound; NAFLD: nonalcoholic fatty liver disease; ALT: alanine transaminase; BMI: body mass index; CT: computed tomography; NAFL: nonalcoholic fatty liver.
*Most of studies have defined lean as BMI < 25 kg/m^2.

biopsy, but it should be noted that 78% (123/157) had liver biopsy due to low GRWR or remnant and not due to metabolic risk factors. The presence of mild steatosis (<20%) did not affect recipient outcomes as discussed in a larger sample size from our center,[26] but findings on the present study are important for general hepatology practice. The present study is not directly comparable with the studies mentioned in the meta-analysis as <20% steatosis is generally not picked by ultrasound or CT with good accuracy, also the age-group is relatively young in the present study. The present study shows that prevalence of NAFLD in lean individuals is much higher than what is reported in world literature, as imaging is not able to pick up mild steatosis. Therefore, in patients with metabolic syndrome and raised liver enzymes/hepatomegaly, MR fat estimation may be considered to diagnose NAFL if ultrasound is normal. As NAFLD is associated with coronary artery disease (independent of metabolic risk factors) and other comorbidities, detailed counseling of these patients is important.[27,28] In addition, as NAFL has been shown to progress to nonalcoholic steatohepatitis/fibrosis, the incidence of NAFL in lean and young (mean age: 33 years in the NAFL group) healthy individuals is a matter of concern.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

N.S. and A.D. designed the concept and helped in writing the draft. N.S.C. wrote the first draft. D.G., A.R., P.B., and S.T. contributed data and helped in draft writing. N.S., S.S., and A.S. critically revised the draft.

CONFLICTS OF INTEREST

The authors have none to declare.

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