Nonalcoholic Fatty Liver Disease in Lean Subjects: Associations With Metabolic Dysregulation and Cardiovascular Risk—A Single-Center Cross-Sectional Study

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INTRODUCTION: Although a milder metabolic phenotype of nonalcoholic fatty liver disease (NAFLD) in lean patients (body mass index [BMI] <25 kg/m²) compared to overweight/obese patients with NAFLD is assumed, the relevance of NAFLD among lean subjects remains a matter of debate. We aimed to characterize the metabolic/cardiovascular phenotype of lean patients with NAFLD.

METHODS: In total, 3,043 subjects (cohort I) and 1,048 subjects (cohort II) undergoing screening colonoscopy between 2010 and 2020 without chronic liver disease other than NAFLD were assigned to one of the following groups: lean patients without NAFLD, lean NAFLD, overweight NAFLD (BMI 25–30 kg/m²), and obese NAFLD (BMI >30 kg/m²). Diagnosis of NAFLD was established using ultrasound (cohort I) and controlled attenuation parameter (cohort II).

RESULTS: The prevalence of lean patients with NAFLD was 6.7%/16.1% in the overall cohort I/II and 19.7%/40.0% in lean subjects of cohort I/II. Compared with lean subjects without NAFLD, lean patients with NAFLD had a higher prevalence of dyslipidemia, dysglycemia, and the metabolic syndrome, together with a higher median Framingham risk score in both cohorts (all \( P < 0.001 \)). On multivariable analyses, NAFLD in lean subjects was associated with higher odds of metabolic syndrome (adjusted odds ratio cohort I: 4.27 [95% confidence interval (CI): 2.80–6.51], \( P < 0.001 \); cohort II: 2.97 [95% CI: 1.40–6.33], \( P < 0.001 \)), and higher Framingham risk score (regression coefficient B cohort I: 1.93 [95% CI: 0.95–2.92], \( P < 0.003 \); cohort II: 1.09 [95% CI: 0.81–2.10], \( P = 0.034 \)), among others. Only 69.8% of lean patients with NAFLD in cohort I and 52.1% in cohort II fulfilled the novel criteria for metabolic associated fatty liver disease.

DISCUSSION: NAFLD in lean patients is associated with the metabolic syndrome and increased cardiovascular risk. Novel metabolic associated fatty liver disease criteria leave a considerable proportion of patients unclassified.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A557; http://links.lww.com/CTG/A558; http://links.lww.com/CTG/A559

INTRODUCTION
Nonalcoholic fatty liver disease (NAFLD) is recognized as the most prevalent chronic liver disease worldwide, being highly prevalent in patients with diabetes mellitus (DM) (1), obese patients (body mass index [BMI] ≥30 kg/m²) (2), and patients with dyslipidemia (3). Although this entity is mostly affecting overweight (BMI ≥25 kg/m²) and obese patients, NAFLD has increasingly been recognized with a prevalence of ~13% in lean individuals (BMI <25 kg/m²) and ~5% in the general population (4,5). Several pathophysiological mechanisms are being discussed as potential explanation for NAFLD in lean individuals including a decreased capacity for storing fat in adipose tissue and an

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increased de novo lipogenesis in the liver, among other factors (6). From a clinical perspective, NAFLD in lean patients has been associated with a lower risk of insulin resistance (IR) among other components of the metabolic syndrome (MetS) when compared with overweight/obese patients with NAFLD (7,8), as confirmed in a recent meta-analysis (4). However, because most studies focus on the comparison with overweight/obese patients with NAFLD, less is known about the relevance of NAFLD in lean individuals when compared with lean controls (9). Therefore, we aimed to clarify the impact of NAFLD in lean subjects for cardiovascular risk and metabolic dysregulation.

METHODS

Patients
In total, 5,907 consecutive subjects from a single-center cohort study of patients undergoing screening colonoscopy for colorectal cancer in Austria (SAKKOPI) between 2010 and 2020 were screened for inclusion in this cross-sectional study. Because screening colonoscopy is supported and recommended for everyone starting at the age of 50 years, this study aimed to collect a representative cross-sectional sample of the Austrian population. Importantly, no regulations existed on which patients were included in the study (e.g., type of insurance or comorbidities). An even distribution of educational levels supports representativeness across all social classes (see Supplementary Material, Supplementary Digital Content 1, http://links.lww.com/CTG/A557). Two independent cohorts were established using ultrasound (July 2010–January 2017, cohort I) and transient elastography (FibroScan; Echosens, Paris, France) with controlled attenuation parameter (CAP; January 2017–February 2020, cohort II) to diagnose NAFLD. Patients were excluded if they reported changes in their metabolic phenotype indicated by weight gain or loss $5 kg within the past 6 months, significant alcohol consumption ($20 g/d for women and $30 g/d for men), and in case of established liver disease (i.e., viral hepatitis, autoimmune hepatitis, Wilson disease, hereditary hemochromatosis, and $1 antitrypsin deficiency). For both cohorts, lean patients (BMI $25 kg/m²) without NAFLD were compared with lean patients with NAFLD. Finally, these patients were compared with overweight patients (BMI 25–30 kg/m²) and obese patients (BMI >30 kg/m²) with NAFLD.

As previously described, participants were examined on 2 consecutive days (10), including ultrasound ± transient elastography and laboratory characterization including Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and an
oral glucose tolerance test (OGTT). In addition, participants completed a questionnaire about lifestyle and dietary habits.

**Diagnosis of NAFLD**

In cohort I, NAFLD was diagnosed using ultrasound. Specifically, liver steatosis was considered absent if the echogenicity was homogenous and similar or slightly higher than that of the renal parenchyma. Liver steatosis was defined as significantly increased echogenicity in relation to the renal parenchyma on ultrasound. The severity of sonographic steatosis was not graded (11). In cohort II, NAFLD was diagnosed using abdominal ultrasound and transient elastography with liver stiffness and CAP measurements performed by experienced operators. All measurements were performed after a minimum fasting period of at least 3 hours. The M- and XL-probe was chosen based on the recommendation of the device. The patients were lying in a dorsal position with the right arm in abduction, and measurements were performed in the right lobe of the liver through intercostal spaces. Notably, only reliability CAP measurements (CAP interquartile range [IQR]/median < 0.3) were considered, as previously described (12). Hepatic steatosis was defined as CAP > 248 dB/m (12,13).

**Definitions**

Components of the MetS were defined according to the IDF/AHA/NHLBI consensus definition (see Supplementary Material, Supplementary Digital Content 1, http://links.lww.com/CTG/A557) (14). Furthermore, DM was defined as either a blood glucose of ≥200 mg/dL after 2 hours after the OGTT or fasting blood glucose (FBG) ≥ 126 mg/dL, HbA1c ≥ 6.5%, or previously prescribed antidiabetic medication including insulin (15). Impaired fasting glucose (IFG) was defined as FBG 100–125 mg/dL in nondiabetic individuals. Impaired glucose tolerance (IGT) was defined as a blood glucose of 140–199 mg/dL after 2 hours after OGTT.

### Table 1. Patient characteristics of patients in cohort I stratified according to their BMI and presence of NAFLD: lean patients (BMI < 25 kg/m²) without NAFLD, lean patients with NAFLD, overweight patients (BMI 25–30 kg/m²) with NAFLD, and obese patients (BMI ≥30 kg/m²) with NAFLD

|                  | A Lean w/o NAFLD (n = 892) | B Lean NAFLD (n = 205) | C Overweight NAFLD (n = 636) | D Obese NAFLD (n = 505) | P             |
|------------------|-----------------------------|------------------------|----------------------------|------------------------|---------------|
|                  |                             |                        |                            |                        | 1 vs 2 2 vs 3 2 vs 4|
| Age, yr          | 56.7 ± 9.9                  | 60.3 ± 10.2            | 61.3 ± 9.5                 | 61.6 ± 9.8             | <0.001 0.214 0.115 |
| Male sex         | 305 (34.2%)                 | 116 (56.6%)            | 433 (68.1%)                | 304 (60.2%)            | <0.001 0.003 0.375 |
| Metabolic characterisation |                 |                        |                            |                        |               |
| MetS²            | 66 (8.1%)                   | 54 (31.0%)             | 302 (54.1%)                | 368 (80.5%)            | <0.001 <0.001 <0.001 |
| Visceral obesity | 113 (13.8%)                 | 47 (26.9%)             | 366 (65.2%)                | 451 (97.2%)            | <0.001 <0.001 <0.001 |
| WC, cm           | 84.0 ± 7.9                  | 91.1 ± 7.4             | 100.5 ± 6.9                | 113.5 ± 10.0           | <0.001 <0.001 <0.001 |
| Dyslipidemia      | 170 (19.1%)                 | 80 (39.0%)             | 338 (53.1%)                | 333 (65.9%)            | <0.001 <0.001 <0.001 |
| Triglycerides, mg/dL | 83 (64–106)            | 107 (82–141)           | 128 (93–175)               | 139 (108–185)          | <0.001 <0.001 <0.001 |
| HDL-C, mg/dL     | 70 ± 19                     | 62 ± 23                | 54 ± 14                    | 50 ± 14                | <0.001 <0.001 <0.001 |
| LDL-C, mg/dL     | 141 ± 38                    | 146 ± 41               | 148 ± 38                   | 145 ± 36               | 0.136 0.517 0.670 |
| Dysglycemia      | 387 (43.7%)                 | 128 (63.0%)            | 470 (74.5%)                | 412 (82.1%)            | <0.001 0.002 <0.001 |
| Prediabetes      | 342 (38.6%)                 | 103 (50.7%)            | 352 (55.8%)                | 247 (49.2%)            | 0.002 0.209 0.712 |
| DM               | 45 (5.1%)                   | 25 (12.3%)             | 118 (18.7%)                | 165 (32.9%)            | <0.001 0.034 <0.001 |
| IFG              | 191 (22.7%)                 | 66 (37.1%)             | 242 (47.2%)                | 179 (53.1%)            | <0.001 0.020 0.001 |
| IGT              | 90 (13.0%)                  | 33 (23.6%)             | 129 (30.2%)                | 80 (28.3%)             | 0.001 0.131 0.304 |
| OGTT >2 hr, mg/dL | 116 ± 29                   | 127 ± 40               | 133 ± 40                   | 137 ± 44               | 0.001 0.113 0.018 |
| HOMA-IR          | 1.16 (0.82–1.65)            | 1.49 (1.06–2.17)       | 2.21 (1.62–3.15)           | 3.21 (2.16–4.98)       | <0.001 <0.001 <0.001 |
| IR               | 61 (8.1%)                   | 28 (19.2%)             | 184 (41.5%)                | 218 (66.5%)            | <0.001 <0.001 <0.001 |

**Cardiovascular characterisation**

| Hypertension     | 436 (48.9%)                 | 128 (62.4%)            | 498 (78.3%)                | 448 (88.7%)            | <0.001 <0.001 <0.001 |
| Systolic BP, mm Hg | 122 ± 16                   | 129 ± 18               | 132 ± 16                   | 139 ± 19              | <0.001 0.033 <0.001 |
| CCS              | 33 (3.7%)                   | 15 (7.5%)              | 56 (8.8%)                  | 46 (9.3%)             | 0.020 0.544 0.439 |
| FRS score, points | 7 (4–11)                   | 11 (7–18)              | 14 (9–22)                  | 17 (11–27)            | <0.001 <0.001 <0.001 |
| SCORE, %         | 1.3 (0.5–3.5)               | 2.8 (1.1–7.1)          | 3.8 (1.8–7.0)              | 4.0 (1.8–7.9)         | <0.001 0.014 0.003 |

BMI, body mass index; BP, blood pressure; CCS, chronic coronary syndrome; DM, diabetes mellitus; FRS, Framingham risk score; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; OGTT, oral glucose tolerance test; SCORE, Systematic Coronary Risk Estimation; WC, waist circumference.

*Only* patients were considered if data on all components of the MetS were available in the individual patient.
OGTT in non-diabetic individuals. Prediabetes was defined as IFG or IGT in nondiabetic individuals or HbA1c 5.7%–6.4% (15). Dysglycemia was defined as the presence of either prediabetes or DM. IR was defined as a HOMA-IR ratio of ≥2.5 (16). Levels of systolic blood pressure (BP), FBG, blood glucose after OGTT, HbA1c, HOMA-IR, triglycerides, cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were only considered for comparison among BMI groups in the absence of specific medication that could have artificially influenced individual levels. Chronic coronary syndrome was defined as a history of myocardial infarction, coronary artery disease, coronary artery bypass graft, or coronary stent. The Framingham risk score (FRS) was calculated to assess 10-year cardiovascular risk (17), and the Systematic Coronary Risk Estimation established by the European Society of Cardiology and the European Association of Preventive Cardiology (18) was used to confirm these associations. The Fib-4 score with a cutoff of >3.25 was used to diagnose advanced fibrosis (F≥3) (19). See Supplementary Methods (Supplementary Digital Content 1, http://links.lww.com/CTG/A557) for statistics and ethical statement.

**RESULTS**

**Patient cohort**

In total, 3,043 individuals were included in cohort I, of which 892 were lean and did not have NAFLD (29.3% of the overall cohort and 81.3% of lean subjects), 205 were lean and diagnosed with NAFLD (6.7% of the overall cohort and 19.7% of lean subjects), and 636 (20.9% of the overall cohort)/505 (16.6% of the overall cohort) patients were overweight or obese with NAFLD (Figure 1). In cohort II, 1048 patients with valid CAP measurements were included: 254 lean subjects without NAFLD (24.2% of the overall cohort and 60.0% of lean subjects), 169 lean patients with NAFLD (16.1% of the overall cohort and 40.0% of lean subjects), 317 overweight patients with NAFLD (30.2% of the overall cohort), and 154 obese patients with NAFLD (14.7% of the overall cohort). Considering all individuals, overall NAFLD prevalence was 44.2% in cohort I and 61.1% in cohort II. Of note, CAP identified 258 additional patients with NAFLD in cohort II because NAFLD prevalence would have been 44.4% if ultrasound was only used for cohort II (see Supplementary Results, Supplementary Digital Content 2, http://links.lww.com/CTG/A558).

**Metabolic characterization**

At first, we compared lean patients with NAFLD (n = 205) with lean subjects without NAFLD (n = 892) in cohort I. Lean patients with NAFLD were more often male (56.6% vs 34.2%, P < 0.001) and had a higher prevalence of visceral obesity (26.9% vs 13.8%, P < 0.001; Table 1). Dyslipidemia was more prevalent (39.0% vs 19.1%, P < 0.001) with higher levels of triglycerides (107 [IQR: 82–140] vs 83 [IQR: 64–106] mg/dL, P < 0.001) and lower levels of high-density lipoprotein cholesterol (62 ± 23 vs 70 ± 19 mg/dL, P < 0.001). Importantly, dysglycemia was found in 63.0% vs 43.7% of patients (P < 0.001), because lean patients with NAFLD had a higher prevalence of DM (12.3% vs 5.1%, P < 0.001) and prediabetes (50.7% vs 38.6%, P = 0.002; Figure 2). Results for cohort II were similar with dyslipidemia (30.2% vs 12.6%, P < 0.001) and dysglycemia (41.4% vs 24.8%, P < 0.001) being significantly different among groups despite being less prevalent than in the overall cohort (Table 2). Next, we specifically analyzed parameters of glucose metabolism in lean patients without DM and found a higher proportion of patients with IFG (37.1% vs 22.7%, P < 0.001), IGT (23.6% vs 13.0%, P = 0.001), a higher mean blood glucose after OGTT (127 ± 40 vs 116 ± 29 mg/dL, P = 0.001), and higher median HOMA-IR (1.49 [IQR: 1.06–2.17] vs 1.16 [IQR: 0.82–1.65], P < 0.001), corresponding to 19.2% vs 8.1% of these patients with IR (P < 0.001) in cohort I. Again, results were similar in cohort II.

In both cohorts, a higher proportion of lean patients with NAFLD suffered from the MetS (26.9% vs 13.8% in cohort I and 14.4% vs 4.5% in cohort II, both P < 0.001). Specifically, 22.5%, 6.2%, 1.8%, and 0.1% (cohort I) and 17.0%, 4.0%, 0.4%, and 0.0% (cohort II) of lean patients without NAFLD exhibited 2, 3, 4, or 5 components of the MetS (Figure 3). These proportions were significantly larger in lean NAFLD (26.4%, 26.4%, 4.6%, and 0.0% with 2, 3, 4, or 5 components in cohort I and 33.5%, 9.0%, 5.4%, and 0.0% in cohort II, respectively).

On multivariable logistic regression analyses correcting for age, sex, and waist circumference, lean patients with NAFLD had a higher risk of MetS (adjusted odds ratio [aOR] for cohort I: 4.27 [95% confidence interval (CI): 2.80–6.51], P < 0.001 and aOR for cohort II: 2.97 [95% CI: 1.40–6.33], P < 0.001; Tables 3 and 4). This association remained significant for dyslipidemia (aOR cohort I: 1.65 [95% CI: 1.55–3.19], P < 0.001 and aOR cohort II: 2.24 [95% CI: 1.33–3.78], P < 0.001) and dysglycemia (aOR cohort I: 1.57 [95% CI: 1.08–2.27], P = 0.017 and aOR cohort II: 1.62 [95%
Table 2. Patient characteristics of patients in cohort II stratified according to their BMI and presence of NAFLD: lean patients (BMI < 25 kg/m²) without NAFLD, lean patients with NAFLD, overweight patients (BMI 25–30 kg/m²) with NAFLD, and obese patients (BMI ≥30 kg/m²) with NAFLD

| B         | Lean w/o NAFLD (n = 254) | Lean NAFLD (n = 169) | Overweight NAFLD (n = 317) | Obese NAFLD (n = 154) | P          |
|-----------|--------------------------|----------------------|-----------------------------|-----------------------|------------|
| Age, yr   | 56.7 ± 8.2               | 59.6 ± 8.6           | 60.1 ± 8.5                  | 60.1 ± 7.8            | 0.001      |
| Male sex  | 83 (32.7%)               | 89 (52.7%)           | 233 (73.5%)                 | 93 (60.4%)            | <0.001     |
| Metabolic characterization |                      |                      |                            |                       |            |
| MetS³     | 11 (4.5%)                | 24 (14.4%)           | 116 (37.8%)                 | 109 (71.2%)           | <0.001     |
| Visceral obesity | 23 (9.3%)               | 24 (14.4%)           | 144 (46.9%)                 | 142 (92.8%)           | 0.111      |
| WC, cm    | 81.2 ± 8.6               | 86.9 ± 7.5           | 98.0 ± 7.6                  | 110.4 ± 11.1          | <0.001     |
| Dyslipidemia | 32 (12.6%)              | 51 (30.2%)           | 123 (38.8%)                 | 79 (51.3%)            | <0.001     |
| Triglycerides, mg/dL | 80 (61–102)         | 99 (74–139)          | 113 (92–152)                | 128 (94–176)          | <0.001     |
| HDL-C, mg/dL | 69 ± 16                 | 63 ± 14              | 54 ± 13                     | 51 ± 11               | <0.001     |
| LDL-C, mg/dL | 143 ± 39                | 151 ± 37             | 154 ± 35                    | 155 ± 35              | 0.068      |
| Dysglycemia | 63 (24.8%)              | 70 (41.4%)           | 186 (58.7%)                 | 113 (73.4%)           | <0.001     |
| Prediabetes | 56 (22.0%)              | 58 (34.3%)           | 144 (45.4%)                 | 74 (48.1%)            | 0.005      |
| DM         | 7 (2.8%)                 | 12 (7.1%)            | 42 (13.3%)                  | 39 (25.3%)            | 0.035      |
| IFG        | 30 (11.9%)               | 39 (23.6%)           | 123 (40.9%)                 | 66 (49.6%)            | 0.002      |
| IGT        | 19 (8.1%)                | 26 (17.8%)           | 43 (15.7%)                  | 29 (25.2%)            | 0.004      |
| OGTT >2 hr, mg/dL | 109 ± 28               | 122 ± 34             | 126 ± 39                    | 131 ± 43              | <0.001     |
| HOMA-IR    | 0.99 (0.76–1.32)         | 1.33 (0.98–1.82)     | 1.86 (1.35–2.42)            | 2.87 (1.92–4.18)      | <0.001     |
| IR         | 4 (1.6%)                 | 15 (8.9%)            | 68 (23.0%)                  | 78 (59.5%)            | 0.002      |
| Cardiovascular characterization |                      |                      |                            |                       |            |
| Hypertension | 150 (59.1%)             | 128 (75.7%)          | 260 (82.0%)                 | 142 (92.2%)           | <0.001     |
| Systolic BP, mm Hg | 130 ± 17                | 136 ± 18             | 138 ± 16                    | 143 ± 17              | 0.001      |
| CCS        | 6 (2.4%)                 | 5 (3.0%)             | 21 (6.6%)                   | 10 (6.5%)             | 0.706      |
| FRS score, points | 5 (3–9)               | 8 (6–14)             | 13 (7–22)                   | 14 (9–22)             | <0.001     |
| SCORE, %   | 1.4 (0.6–3.5)           | 2.5 (1.2–5.5)        | 3.8 (1.7–8.2)               | 3.6 (1.8–7.1)         | <0.001     |

BMI, body mass index; BP, blood pressure; CCS, chronic coronary syndrome; DM, diabetes mellitus; FRS, Framingham risk score; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; OGTT, oral glucose tolerance test; SCORE, Systematic Coronary Risk Estimation; WC, waist circumference.

*Only patients were considered if data on all components of the MetS were available in the individual patient.

Cl: 1.04–2.52], P = 0.035). Importantly, NAFLD in lean non-diabetic subjects was associated with prediabetes (aOR cohort I: 1.52 [95% CI: 1.04–2.22], P = 0.032 and aOR cohort II: 1.61 [95% CI: 1.01–2.56], P = 0.045).

Metabolic dysregulation increased with BMI when lean patients with NAFLD were compared to overweight and obese patients with NAFLD, indicated by higher prevalence of the MetS (31.0% vs 54.1% vs 80.5% for cohort I and 14.4% vs 37.8% vs 71.2% for cohort II). However, the prevalence of IGT in non-diabetic subjects was not significantly different among BMI groups (23.1% vs 30.2% vs 28.8% for cohort I and 17.8% vs 15.7% vs 25.2% for cohort II).

Cardiovascular risk assessment
Lean patients with NAFLD had a higher prevalence of arterial hypertension (cohort I: 62.4% vs 48.9%, P < 0.001 and cohort II: 75.7% vs 59.1%, P < 0.001) when compared with lean subjects without NAFLD. Notably, 10-year cardiovascular risk was higher in lean patients with NAFLD (median FRS in cohort I: 11 [IQR: 7–18] vs 7 [IQR: 4–11] points, P < 0.001 and median FRS in cohort II: 8 [IQR: 6–14] vs 5 [IQR: 3–9], P < 0.001). For both cohorts, an association between NAFLD in lean individuals and FRS remained significant, independent of age, sex, and waist circumference (adjusted regression coefficient B in cohort I: 1.93 [95% CI: 0.95–2.92], P < 0.001 and adjusted regression coefficient B in cohort II: 1.09 [95% CI: 0.81–2.10], P = 0.034). Again, the prevalence of chronic coronary syndrome and arterial hypertension increased in the overweight NAFLD and obese NAFLD group, together with higher FRS values in both cohorts.

Metabolic associated fatty liver disease
In cohort I, of 205 lean patients with NAFLD, 143 (13.0% of lean individuals and 69.8% of lean NAFLD) fulfilled the recently
proposed definition of metabolic associated fatty liver disease (MAFLD) (16). In cohort II, of 169 patients with NAFLD, 88 (20.8% of lean individuals and 52.1% of lean NAFLD) fulfilled MAFLD criteria (Table 5). Of note, although arterial hypertension and prediabetes were subcriteria that were frequently fulfilled, the other criteria were less frequently met (see Supplementary Table 1, Supplementary Digital Content 3, http://links.lww.com/CTG/A559). See Supplementary Material (see Figure 3.

**Table 3.** Multivariable binary logistic regression analysis (A) and multivariable linear regression analysis (B) of cohort I investigating factors associated with NAFLD in different BMI strata compared with lean patients (BMI < 25 kg/m²) without NAFLD

|                  | Lean w/o NAFLD | Lean NAFLD | Overweight NAFLD | Obese NAFLD |
|------------------|----------------|------------|------------------|-------------|
| **A**            |                |            |                  |             |
| Metabolic syndrome<sup>a</sup> | Reference 1.06 (1.07 to 1.52), \(P = 0.075\) | 1.91 (1.37–2.65), \(P < 0.001\) | 3.44 (2.22–5.31), \(P < 0.001\) | 1.86 (1.16–2.98), \(P = 0.010\) |
| Hypertension     | Reference 1.06 (1.07 to 1.52), \(P = 0.075\) | 1.91 (1.37–2.65), \(P < 0.001\) | 3.44 (2.22–5.31), \(P < 0.001\) | 1.86 (1.16–2.98), \(P = 0.010\) |
| Dyslipidemia     | Reference 0.77 (0.55 to 1.10), \(P = 0.098\) | 0.54 (0.33–0.89), \(P = 0.014\) | 0.60 (0.37–1.00), \(P = 0.050\) | 0.63 (0.36–1.10), \(P = 0.117\) |
| Dysglycemia      | Reference 0.77 (0.55 to 1.10), \(P = 0.098\) | 0.54 (0.33–0.89), \(P = 0.014\) | 0.60 (0.37–1.00), \(P = 0.050\) | 0.63 (0.36–1.10), \(P = 0.117\) |
| Prediabetes<sup>b</sup> | Reference 1.06 (1.07 to 1.52), \(P = 0.075\) | 1.91 (1.37–2.65), \(P < 0.001\) | 3.44 (2.22–5.31), \(P < 0.001\) | 1.86 (1.16–2.98), \(P = 0.010\) |
| DM               | Reference 1.06 (1.07 to 1.52), \(P = 0.075\) | 1.91 (1.37–2.65), \(P < 0.001\) | 3.44 (2.22–5.31), \(P < 0.001\) | 1.86 (1.16–2.98), \(P = 0.010\) |
| **B**            |                |            |                  |             |
| OGTT > 2 hr<sup>b</sup> | Reference 0.81 (0.60 to 1.10), \(P = 0.207\) | 0.54 (0.33–0.89), \(P = 0.014\) | 0.60 (0.37–1.00), \(P = 0.050\) | 0.63 (0.36–1.10), \(P = 0.117\) |
| HOMA-IR<sup>b</sup> | Reference 0.77 (0.55 to 1.10), \(P = 0.098\) | 0.54 (0.33–0.89), \(P = 0.014\) | 0.60 (0.37–1.00), \(P = 0.050\) | 0.63 (0.36–1.10), \(P = 0.117\) |
| Framingham risk score | Reference 0.83 (0.60 to 1.14), \(P = 0.256\) | 0.54 (0.33–0.89), \(P = 0.014\) | 0.60 (0.37–1.00), \(P = 0.050\) | 0.63 (0.36–1.10), \(P = 0.117\) |

Analyses were adjusted for age, sex, and waist circumference. Displayed values are adjusted odds ratios and adjusted regression coefficient B with 95% confidence intervals.

BMI, body mass index; FBG, fasting blood glucose; DM, diabetes mellitus; HOMA-IR, Homeostasis Model of Insulin Resistance; NAFLD, nonalcoholic fatty liver disease; OGTT, oral glucose tolerance test.

<sup>a</sup>Analysis was not adjusted for waist circumference because this parameter is part of the definition of the metabolic syndrome.

<sup>b</sup>Patients with DM were excluded from the calculation.
Supplementary Digital Content 1, http://links.lww.com/CTG/A557) for fibrosis, transaminase levels, and dietary patterns.

**DISCUSSION**

NAFLD in lean subjects is increasingly investigated because of open questions regarding pathophysiological mechanisms, uncertainty in risk stratification, and patient management (20). We previously demonstrated differences in glucose tolerance, PNPLA3 genetic variants, and the metabolome compared with healthy lean controls (21). Here, we provide further and more detailed evidence on the relevance of NAFLD in lean patients regarding their metabolic and cardiovascular phenotype from a single-center cross-sectional study. Importantly, we report on a large and homogenous cohort of comprehensively characterized patients undergoing screening endoscopy, thus providing a representative sample of the general population around age 60 years using transient elastography with CAP for the first time to characterize lean white patients with and without NAFLD. Specifically, we add up evidence on an altered glucose and lipid metabolism, resulting in a strong association with dyslipidemia and dysglycemia.

Although the association of NAFLD with components of the MetS is well-established, the relevance of NAFLD in lean individuals remains a matter of debate. Several reasons exist why high-quality evidence from studies comparing lean patients with NAFLD with lean controls is scarce: First, considerable differences in the study populations, case definitions, diagnosing modalities, and study designs exist, consecutively limiting comparability and increasing heterogeneity (9,20). Second, most of published studies investigating the clinical phenotype largely report on Asian populations (22–25), with only 3 cross-sectional studies from white cohorts (7,21,26). However, differences in the metabolic phenotype among ethnicities result in the need for separate analysis (27–29). This has been shown by a stimulating study of Weinberg and colleagues (30) reporting a lower prevalence of cirrhosis, cardiovascular diseases, and diabetes in Asian patients irrespective of the BMI category, when compared with other ethnicities in a multicenter study from the United States.

Third, most studies focus on describing prevalence and epidemiology of NAFLD because of heterogeneity in patient characterization, summarized by 3 recently published meta-analyses (4,5,9). However, all 3 meta-analyses present convincing data on a milder metabolic phenotype in lean patients with NAFLD compared with overweight/obese patients with NAFLD. Nevertheless, fewer studies exist on the comparison between lean patients with NAFLD and healthy subjects. Although one of the above-mentioned meta-analyses recently summarized data on this comparison (9), subanalyses on lean individuals only included the previously mentioned 3 studies reporting on white patients (7,21,26). Specifically, our previous study (21) and the study by Erkan et al. (26) represented selected patient cohorts with a limited number of patients, which cannot be regarded representative for the general population. Noteworthy, all other studies included data from Asian cohorts with different case definitions and ethnic background and only used ultrasound for diagnosis of NAFLD (9).

On the contrary, we confirm the strong association of NAFLD with the MetS and its components, especially with dyslipidemia and dysglycemia, in 2 not otherwise preselected cohorts of white. Although we miss young adults, our cohorts with patients around age 60 years represent the patient population where the presence of NAFLD might be considerably more important for prognosis, risk stratification, and patient management than in younger patients.

Although data on the association with increased IR—probably because of an altered steroid synthesis in increased visceral adipose tissue (31)—do exist (7,21,24,25), we specifically report a higher prevalence of IGT as reflected by a pathological OGTT. This is of special interest because prediabetic patients might
benefit from early and consequent lifestyle modifications because no medical therapies exist to prevent disease progression to DM (32). The relevance of this association is supported by evidence of both the role of IR for disease progression in NAFLD and the role of NAFLD in the disease progression of DM (33,34).

Despite existing broad evidence from cohorts not stratifying according to BMI—supporting an increased cardiovascular and liver-related mortality in patients with NAFLD, the relevance of NAFLD in lean individuals for cardiovascular and liver-related mortality has drawn less attention (35,36). Specifically, a 2019 study by Golabi et al. (37) compared lean patients with NAFLD with lean controls and observed a higher cardiovascular mortality in lean NAFLD. Despite its longitudinal character, this study applied an inconsistent definition of NAFLD using ultrasound, fatty liver index, and the index of nonalcoholic steatohepatitis. Both scores based on laboratory parameters were derived using only ultrasound as a reference, introducing additional inaccuracy in the diagnosis of NAFLD and nonalcoholic steatohepatitis (38). In our cross-sectional study, we used the FRS as an established score to assess 10-year cardiovascular risk (17). We could confirm that the presence of NAFLD in lean individuals is associated with an increased cardiovascular risk regardless of age, sex, or waist circumference applying the FRS, which can be regarded as the most frequently used score to deal with this topic (39). Our findings were confirmed by estimating the cardiovascular risk using the Systematic Coronary Risk Estimation developed by the European Society of Cardiology, and in 2 separate cohorts, indicating that the metabolic disturbances caused by or leading to NAFLD might indeed translate into an increased cardiovascular risk already in lean patients.

A strength of our study is the use of both ultrasound and CAP to diagnose NAFLD because most of studies on this topic solely rely on ultrasound (7,21,26). Although the prevalence of NAFLD in the general population is estimated to increase with age, being approximately 40% in elderly individuals (~60 years) (40), it has to be acknowledged that ultrasound is an imperfect marker with lower sensitivity for mild (<20% of hepatocytes) or microvesicular steatosis (41,42). Thus, stratifying according to ultrasound might assign a considerable proportion of lean patients with mild NAFLD to the lean and healthy group. This does not only attenuate the number of lean patients with NAFLD but also increase the prevalence of metabolic disorders in this lean and healthy group.

On the contrary, CAP is a novel parameter with high accuracy for mild steatosis (>5% of hepatocytes) and thus a higher sensitivity for the diagnosis of NAFLD (13). The use of CAP in cohort

| Table 5. Prevalence of lean individuals meeting criteria proposed for metabolic associated fatty liver disease (MAFLD) in cohort I (A) and cohort II (B) |
|-----------------|-----------------|-----------------|-----------------|
|                  | Lean w/o NAFLD (n = 892) | Lean NAFLD (n = 205) | P |
| DM               | 45 (5.1%)        | 25 (12.3%)       | <0.001 |
| WC ≥102/88 cm    | 104 (12.3%)      | 42 (23.3%)       | <0.001 |
| BP ≥130/85 mm Hg | 399 (47.1%)      | 106 (58.9%)      | 0.004 |
| Triglycerides ≥150 mg/dL | 63 (7.4%) | 38 (21.1%) | <0.001 |
| HDL-C <40/50 mg/dL | 106 (12.5%) | 40 (22.2%) | 0.001 |
| Prediabetes      | 342 (40.4%)      | 103 (57.2%)      | <0.001 |
| HOMA-IR ≥2.5     | 52 (6.1%)        | 24 (13.3%)       | 0.001 |
| hsCRP >0.2 mg/L  | 83 (9.8%)        | 35 (19.4%)       | <0.001 |
| MAFLD —          |                 | n = 143 (69.8%)  |

|                  | Lean w/o NAFLD (n = 254) | Lean NAFLD (n = 169) | P |
| DM               | 7 (2.8%)                 | 12 (7.1%)            | 0.035 |
| WC ≥102/88 cm    | 22 (8.9%)                | 24 (15.3%)           | 0.049 |
| BP ≥130/85 mm Hg | 144 (58.3%)              | 115 (73.2%)          | 0.002 |
| Triglycerides ≥150 mg/dL | 13 (5.3%) | 30 (19.1%) | <0.001 |
| HDL-C <40/50 mg/dL | 23 (9.3%) | 23 (14.6%) | 0.100 |
| Prediabetes      | 56 (22.7%)               | 58 (36.9%)           | 0.002 |
| HOMA-IR ≥2.5     | 4 (1.6%)                 | 15 (9.6%)            | <0.001 |
| hsCRP >0.2 mg/L  | 23 (9.3%)                | 13 (8.3%)            | 0.737 |
| MAFLD —          | 88 (52.1%)               |

BP, blood pressure; DM, diabetes mellitus; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; NAFLD, nonalcoholic fatty liver disease; WC, waist circumference.

*aOr specific treatment.
II resulted in reliable detection of patients with mild hepatic steatosis and assigning them to the lean NAFLD rather than the lean and healthy group. Thus, the higher prevalence of lean NAFLD in cohort II is likely to be explained by the higher sensitivity of CAP compared with ultrasound. Because individuals with mild steatosis and a milder phenotype of associated metabolic alterations were included in the lean NAFLD group of cohort II, the lower prevalence of metabolic alterations in cohort II and less differences among lean patients with NAFLD and lean controls can be sufficiently explained. The confirmation of the observed associations between NAFLD and MetS/cardiovascular risk in cohort II even strengthens our results because it highlights their importance even in less advanced metabolic disturbance.

Despite a recent meta-analysis proposed a >60% prevalence of nonobese NAFLD in Austria being representative for central Europe, the data used were taken from a selected patient cohort and cannot be regarded representative for the general population, which is in strong contrast to this study (5). In addition, although the NAFLD prevalence of ~60% in cohort II might seem high, we want to point out that no comparable study on the prevalence of NAFLD (i.e., hepatic fat droplets in ≥5% of hepatocytes) in the general Western population using CAP as a more sensitive diagnostic tool for hepatic steatosis exists. Although an Asian study reported a NAFLD prevalence of 18% using CAP ≥30 dB/m to diagnose NAFLD, their results can hardly be compared with this study because of the different cutoff used, differences in Ethnicity, lifestyle, and case definition, as well as concerns regarding the reliability of CAP measurements in this study (43).

Despite the term NAFLD interchanged with MAFLD recently (16), only ~52%–70% of our patients with NAFLD meet these proposed criteria. Although this is a big step forward in nomenclature, several authors have already raised their concerns about this definition. Younossi et al. (44) highlighted that the heterogeneous nature of NAFLD might not be fully covered by the new MAFLD criteria. This is supported by a study of Lin et al. (45) further investigating the NHANES population where they found that 620 of 4,347 patients with NAFLD (14.3%) did not meet the MAFLD criteria (46). Although metabolic parameters were lower or less frequent in these patients, some still had severe steatosis and/or advanced fibrosis (assessed noninvasively) despite the absence of components of the metabolic syndrome (47). In addition, it is yet unclear whether the new definition can identify lean patients at increased risk for cardiovascular events or liver-related morbidity and how patients who do not meet these criteria should be managed. Although the new nomenclature of MAFLD can facilitate diagnosis and patient education, the utility of this new definition in lean patients still needs to be confirmed (48).

Although we investigated lifestyle and dietary habits in these patients, we could not find a consistent association with NAFLD in lean patients across both cohorts. This can be explained by difficulties and inaccuracies when using questionnaires on food frequency and lifestyle habits and does not rule out that established associations between NAFLD and dietary patterns (e.g., high-fructose intake) or a low level of physical activity may also contribute to the risk profile of lean patients with NAFLD (49).

This study has several limitations. First, this study was a single-center, cross-sectional study reporting on associations, which do not imply causality. Therefore, our data can only support conclusions from recent meta-analyses demonstrating a benign phenotype compared with obese NAFLD. Unfortunately, longitudinal data on cardiovascular or liver-related events and survival could not be analyzed. Second, data on liver histology representing the gold standard for NAFLD-diagnosis were not available. Although reliance on ultrasound and CAP might be associated with lower accuracy in correctly diagnosing NAFLD, this allowed us to gain a representative sample of the general population aged ~60 years undergoing colorectal cancer screening colonoscopy, but not because of suspicion of chronic liver disease. Thus, we successfully mitigate selection bias which has to be acknowledged in studies reporting on patients undergoing liver biopsy for assessment of NAFLD severity. Third, despite the undisputed relevance of genetic factors in the pathogenesis of NAFLD, we aimed to focus on routinely available clinical components for NAFLD and designed the study deliberately with the exclusion of genetic factors (50).

In conclusion, we demonstrate a distinct cardiometabolic phenotype of lean NAFLD in 2 independent cohorts undergoing screening endoscopy, showing a strong association with prediabetes and 10-year cardiovascular risk. Thus, future studies are needed to further investigate the pathophysiological background but also to sharpen the definition of lean NAFLD and define algorithms for patient management.

CONFLICTS OF INTEREST

Guarantor of the article: Christian Datz, MD.
Specific author contributions: G.S. and C.D.: conception and design. G.S., U.H.-S., and C.D.: administrative support. G.S., S.B., S.W., L.S., U.H.-S., D.N., E.A., and C.D.: data curation. G.S., B.W., D.N., E.A., and C.D.: data analysis and interpretation. G.S. and C.D.: drafting of the article. All authors: final approval of the article.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

✓ Lean subjects with nonalcoholic fatty liver disease (NAFLD) have a milder metabolic phenotype compared with overweight or obese subjects with NAFLD.
✓ The relevance of NAFLD in lean individuals can still be regarded as a matter of debate.

WHAT IS NEW HERE

✓ NAFLD is frequently observed in lean individuals with a prevalence of 20%–40%.
✓ NAFLD in lean individuals shows a strong association with the metabolic syndrome and its components, especially with glycemic dysregulation.
✓ NAFLD is associated with an increased cardiovascular risk in lean subjects.
✓ Only 52%–70% of lean patients with NAFLD meet the recently proposed definition of metabolic associated fatty liver disease.

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